ИНФОРМАЦИЯ ЗА:
Наименование на заболяването
Класически прогресивна супрануклеарна парализа
Определение на заболяването
Класическата прогресивна супрануклеарна парализа, която е известна още като Richardson синдром, е най-честият клиничен вариант на Прогресивната супрануклеарна пареза. Това рядко с късно начало невродегенеративно заболяване се манифестира с постурална нестабилност, прогресивна ригидност, супрануклеарна погледна пареза и лека деменция.
Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)
G23.1
Код на заболяването по Orpha code
ORPHA240071
Епидемиологични данни за заболяването в Република България
Предполага се честота, сходна на тази в останалата част на Европа т.е. 1-9 / 100 000.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Nath, U., Ben-Shlomo, Y., Thomson, R. G., Lees, A. J., Burn, D. J. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology 60: 910-916, 2003. 2. Donker Kaat, L., Boon, A. J. W., Azmani, A., Kamphorst, W., Breteler, M. M. B., Anar, B., Heutink, P., van Swieten, J. C. Familial aggregation of parkinsonism in progressive supranuclear palsy. Neurology 73: 98-105, 2009.
Епидемиологични данни за заболяването в Европейския съюз
1-9 / 100 000; Превалирането се оценява на около 1/16,600.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Nath, U., Ben-Shlomo, Y., Thomson, R. G., Lees, A. J., Burn, D. J. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology 60: 910-916, 2003. 2. Donker Kaat, L., Boon, A. J. W., Azmani, A., Kamphorst, W., Breteler, M. M. B., Anar, B., Heutink, P., van Swieten, J. C. Familial aggregation of parkinsonism in progressive supranuclear palsy. Neurology 73: 98-105, 2009.
Оценка на съответствието на заболяването с дефиницията за рядко заболяване съгласно § 1, т. 42 от допълнителните разпоредби на Закона за здравето
Заболяването е с разпространение под 5/ 10 000 души от населението на Европейския съюз.

Критерии за диагностициране на заболяването

Диагностициране на заболяването (дефиниция на случай):

Признаците и симптомите на заболяването: ПСП обикновено е с начало през шестото или седмото десетилетие от живота с развитието на постурална нестабилност с падания, забавени вертикални погледни сакади и когнитивно нарушение. Прогресивно пациентите развиват други очни проблеми (сухи и зачервени очи, замъглено зрение, спонтанно неволево затваряне на очите, фотофобия), дизекзекутивен синдром с импулсивност, забавен говор, супранулеарна погледна пареза, нарушение в гълтането. Nicholl и колеги (2003) описват и форма на ПСП, характеризираща се с фатална дихателна хиповентилация при двама пациенти с кръвнородствена връзка на родителите. При двамата пациенти се установява H1/H1 хаплотип, който се асоциира с ПСП.

Етиологията и патогенезата: ПСП е 4R таупатия, съставена от преобладаване на четири повтора (екзон 10 полозитивни) тау изоформи и характерен биохимичен профил (дублет тау 64 и тау 69). MAPT H1c специфичен хаплотип е рисков фактор за развитие на заболяването. ПСП се характеризира също с дефицити в няколко невротрансмитерни системи (в това число допаминергична, холинергична, габаергична). Не са известни факторите, които отключват тау-невродегенерацията.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Nath, U., Ben-Shlomo, Y., Thomson, R. G., Lees, A. J., Burn, D. J. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology 60: 910-916, 2003.
2. Tuite, P. J., Clark, H. B., Bergeron, C., Bower, M., St George-Hyslop, P., Mateva, V., Anderson, J., Knopman, D. S. Clinical and pathologic evidence of corticobasal degeneration and progressive supranuclear palsy in familial tauopathy. Arch. Neurol. 62: 1453-1457, 2005.
3. Nicholl, D. J., Greenstone, M. A., Clarke, C. E., Rizzu, P., Crooks, D., Crowe, A., Trojanowski, J. Q., Lee, V. M.-Y., Heutink, P. An English kindred with a novel recessive tauopathy and respiratory failure. Ann. Neurol. 54: 682-686, 2003.
4. Litvan, I., Baker, M., Hutton, M. Tau genotype: no effect on onset, symptom severity, or survival in progressive supranuclear palsy. Neurology 57: 138-140, 2001.
5. de Yebenes, J. G., Sarasa, J. L., Daniel, S. E., Lees, A. J. Familial progressive supranuclear palsy: description of a pedigree and review of the literature. Brain 118: 1095-1103, 1995

Алгоритми за диагностициране на заболяването

Алгоритми за диагностициране на заболяването: Съгласно Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция.

Анамнезата: ПСП обикновено е с начало през шестото или седмото десетилетие от живота с развитието на постурална нестабилност с падания, забавени вертикални погледни сакади и когнитивно нарушение. Прогресивно пациентите развиват други очни проблеми (сухи и зачервени очи, замъглено зрение, спонтанно неволево затваряне на очите, фотофобия), дизекзекутивен синдром с импулсивност, забавен говор, супранулеарна погледна пареза, нарушение в гълтането.

Диференциалната диагноза на заболяването: Паркинсонова болест; други атипични паркинсонови заболявания, като мултиситемна атрофия и кортикобазалната дегенерация; Niemann-Pick заболяването тип C ; Whipple заболяването.

Лабораторни, образни и хистологични изследвания: Piccini и колеги (2001) показват при PET изследване значително намаление на натрупването в кауда и путамен на (18)F-dopa, наред със значима редукция на глюкозния метаболизъм в стриатум, латерална и медиална препоторна кора и дорзална префронтална кора. ПСП се характеризира невропатологично с глиоза с астроцитни плаки и акумулиране на тау-имунореактивни неврофибрилерни натрупвания и невронална загуба в специфични мозъчни региони, особено в субталамичното ядро и субстанция нигра.

Генетични изследвания и медико-генетично консултиране: Въпреки че множеството от случаите с ПСП са спорадични, има редки мутации в MAPT, които могат да доведат до сходен клиникопатологичен синдром. Прогресивната супрануклеарна парализа-1 (PSNP1) би могла да се дължи на хетерозиготна мутация на гена, кодиращ микротубулно-асоцииран тау протеин (MAPT) на хромозома 17 по АД тип на унаследяване. Други локуси за ПСП са картирани в хромозома 1q31 (PSNP2) и 11p12-P11 (PSNP3).

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Nath, U., Ben-Shlomo, Y., Thomson, R. G., Lees, A. J., Burn, D. J. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology 60: 910-916, 2003.
2. Tuite, P. J., Clark, H. B., Bergeron, C., Bower, M., St George-Hyslop, P., Mateva, V., Anderson, J., Knopman, D. S. Clinical and pathologic evidence of corticobasal degeneration and progressive supranuclear palsy in familial tauopathy. Arch. Neurol. 62: 1453-1457, 2005.
3. Piccini, P., de Yebenez, J., Lees, A. J., Ceravolo, R., Turjanski, N., Pramstaller, P., Brooks, D. J. Familial progressive supranuclear palsy: detection of subclinical cases using (18)F-dopa and (18)fluorodeoxyglucose positron emission tomography. Arch. Neurol. 58: 1846-1851, 2001.
4. de Yebenes, J. G., Sarasa, J. L., Daniel, S. E., Lees, A. J. Familial progressive supranuclear palsy: description of a pedigree and review of the literature. Brain 118: 1095-1103, 1995.
5. Rojo, A., Pernaute, R. S., Fontan, A., Ruiz, P. G., Honnorat, J., Lynch, T., Chin, S., Gonzalo, I., Rabano, A., Martinez, A., Daniel, S., Pramstaller, P., Morris, H., Wood, N., Lees, A., Tabernero, C., Nyggard, T., Jackson, A. C., Hanson, A., de Yebenes, J. G. Clinical genetics of familial progressive supranuclear palsy. Brain 122: 1233-1245, 1999.
6. Ros, R., Gomez Garre, P., Hirano, M., Tai, Y. F., Ampuero, I., Vidal, L., Rojo, A., Fontan, A., Vazquez, A., Fanjul, S., Hernandez, J., Cantarero, S., and 9 others. Genetic linkage of autosomal dominant progressive supranuclear palsy to 1q31.1. Ann. Neurol. 57: 634-641, 2005.
7. Melquist, S., Craig, D. W., Huentelman, M. J., Crook, R., Pearson, J. V., Baker, M., Zismann, V. L., Gass, J., Adamson, J., Szelinger, S., Corneveaux, J., Cannon, A., and 16 others. Identification of a novel risk locus for progressive supranuclear palsy by a pooled genomewide scan of 500,288 single-nucleotide polymorphisms. Am. J. Hum. Genet. 80: 769-778, 2007.

Алгоритми за лечение на заболяването

Алгоритми за лечение на заболяването: Съгласно Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на

деменция.
Терапевтичните подходи към заболяването, в това число консервативни и оперативни, техните предимства, рискове и очаквана ефективност: Все още няма терапия, която да излекува дефинитивно заболяването. Редица съобщения сочат, че пациентите с класически ПСП синдром нямат отговор на леводопа терапия. Amantadine може да подобри фрийзинг феномените и други антихолинергични лекарства, понякога подобряване на глас и нарушения на речта. Препоръчителен диетичен режим и физическа активност и др.:

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция, април 2015.
2. Nath, U., Ben-Shlomo, Y., Thomson, R. G., Lees, A. J., Burn, D. J. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology 60: 910-916, 2003.

Алгоритми за проследяване на заболяването

Алгоритми за проследяване на заболяването (Необходимостта от последващи болнични и извънболнични грижи; Необходимостта от консултации с други специалисти): Съгласно Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция.
Прогнозата на заболяването (Възможни усложнения; честота и тежест на усложненията и др): Поради чести падания пациентите постепенно стават зависими от инвалидна количка. Затрудненията в дишането и гълтането, както и инфекциите са основните причини за смърт, обикновено 4-8 години след появата на болестта.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция, април 2015.
2. Nath, U., Ben-Shlomo, Y., Thomson, R. G., Lees, A. J., Burn, D. J. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology 60: 910-916, 2003.

Алгоритми за рехабилитация на заболяването

Алгоритми за рехабилитация на заболяването: Съгласно Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция, април 2015.

Необходими дейности за профилактика на заболяването (ако такива са приложими)

Дейности за профилактика на заболяването: Не са известни факторите, които отключват тау-невродегенерацията.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция, април 2015.

Предложения за организация на медицинското обслужване на пациентите и за финансиране на съответните дейности, съобразени с действащата в страната нормативна уредба

Създаването на Национален експертен център „Редки невродегенеративни заболявания, протичащи с когнитивни, поведенчески и моторни нарушения" за диагностика, лечение и проследяване и рехабилитация включително и на пациенти с това заболявания под ръководството на чл.кор.проф.д-р Л. Трайков, дмн (национален експерт с най-голям опит и принос за диагностиката и лечението на тези заболявания).

Описание на опита с конкретни пациенти със съответното рядко заболяване (ако има такъв)

Опитът на кандидатстващия експертен център за диагноза и лечение на редки заболявания с атипичен паркинсонизъм, като Прогресивна супрануклеарна парализа, датира от 2001 година със създаването на център за диагноза и лечение на невродегенеративни заболявания, протичащи с деменция и допълнително на център за диагноза и лечение на Паркинсонова болест. От дълги години този център е реферирал център за заболявания, протичащи с атипичен паркинсонизъм, като Прогресивна супрануклеарна парализа, особено за комплексни, редки и наследствени случаи. През годините вследствие на натрупания опит и труд, както и значителен брой на пациенти с тези редки заболявания, реферирани към нашите два центъра, са осъществени няколко дисертации в областта: 1. Клинико-генетични корелации при невродегенеративни заболявания, протичащи с паркинсонизъм (защитена дисертация за доктор по медицина от д-р Радка Павлова, 2013 г., ръководител: чл.-кор. проф. Лъчезар Трайков), 2. Проучване на невропсихологичния профил при пациенти с Паркинсон плюс синдроми (защитена дисертация за доктор по медицина от д-р Силвия Скелина, 2016 г., ръководител: чл.-кор. проф. Лъчезар Трайков) и 3. Клинико-генетични проучвания при фронтотемпорална деменция и сродни заболявания (защитена дисертация за доктор по медицински науки от д-р Шима Мехрабиан, 2016 г.). Събрана е база данни за отделни пациенти с отделни групи редки заболявания, с атипичен паркинсонизъм, като Прогресивна супрануклеарна парализа с подробно фенотипизиране на всеки един случай, което дава възможност за добър мониторинг на пациентите, както и изследователски анализ върху характеристиката на отделните заболявания. Дейността на центъра по отношение на диагноза и лечение на редки заболявания с атипичен паркинсонизъм, като Прогресивна супрануклеарна парализа, обхваща всички диагностични дейности съобразно новите диагностични критерии на тези заболявания, включително допълнителни изследвания, които са нужни за диференциална диагноза на атипични/ранни/наследствени случаи, включващи изследвания за биомаркери, невроизобразяващи и генетични фактори. Центъра е член на European Multisystem Atrophy Study Group и Movement Disorder Society.

Публикации:

1. Petrova M, Pavlova R, Zhelev Y, Mehrabian S, Raycheva M, Traykov L. Investigation of neuropsychological characteristics of very mild and mild dementia with Lewy bodies. J Clin Exp Neuropsychol. 2015 Dec 17:1-7.

2. Petrova M, Mehrabian-Spasova S, Aarsland D, Raycheva M, Traykov L. Clinical and Neuropsychological Differences between Mild Parkinson's Disease Dementia and Dementia with Lewy Bodies. Dement Geriatr Cogn Dis Extra. 2015 May 29;5(2):212-20.

3. **Петрова М.**, Трайков Л., Райчева М., Григорова О., Чернинкова С., Желев Я., Мехрабиан Ш. Когнитивни нарушения при прогресивна супрануклеарна парализа. Българска Неврология, 2006, 6(2), 98-101.

4. Скелина С, Павлова Р, Петрова М, Мехрабиан Ш, Григорова О, Трайков Л. Проучване на профила на когнитивни нарушения при пациенти с прогресивна супрануклеарна офталмопареза. Българска неврология, бр. 2, 2015

5. Павлова Р, Мехрабиан Ш, Скелина С, Желев Я, Михова К, Кънева Р, Митев В, Йорданова А, Трайков Л. Характеристика на дегенеративния паркинсонов синдром в зависимост от Аполипопротеин Е генотипа. Неврология и психиатрия, 4, 30-33, 2014;

6. Скелина С, Павлова Р, Петрова М, Райчева М, Трайков Л. Невропсихологичен профил и тежест на когнитивните нарушения при атипичните паркинсонови синдроми. Българска неврология, бр. 2, 2015.

7. R. Pavlova, K. Mihova, S. Mehrabian, M. Petrova, S. Skelina, R. Kaneva, V. Mitev, L. Traykov. Novel LRRK2 6165C>G mutation in a patient with Parkinson's disease-dementia: a case report. In: JOINT CONGRESS OF EUROPEAN NEUROLOGY Istanbul, Turkey, May 31-June 3, 2014.

8. Pavlova R., K. Mihova, S. Mehrabian, M. Petrova, S. Skelina, R. Kaneva, A. Jordanova, V. Mitev, L. TraykovLRRK2 mutation c.4536+3A>G in a patient with multiple system atrophy: a case report. In: In: JOINT CONGRESS OF EUROPEAN NEUROLOGY Istanbul, Turkey, May 31-June 3, 2014.

Identification of a Novel Risk Locus for Progressive Supranuclear Palsy by a Pooled Genomewide Scan of 500,288 Single-Nucleotide Polymorphisms

Stacey Melquist,* David W. Craig,* Matthew J. Huentelman, Richard Crook, John V. Pearson, Matt Baker, Victoria L. Zismann, Jennifer Gass, Jennifer Adamson, Szabolcs Szelinger, Jason Corneveaux, Ashley Cannon, Keith D. Coon, Sarah Lincoln, Charles Adler, Paul Tuite, Donald B. Calne, Eileen H. Bigio, Ryan J. Uitti, Zbigniew K. Wszolek, Lawrence I. Golbe, Richard J. Caselli, Neill Graff-Radford, Irene Litvan, Matthew J. Farrer, Dennis W. Dickson, Mike Hutton, and Dietrich A. Stephan

To date, only the H1 *MAPT* haplotype has been consistently associated with risk of developing the neurodegenerative disease progressive supranuclear palsy (PSP). We hypothesized that additional genetic loci may be involved in conferring risk of PSP that could be identified through a pooling-based genomewide association study of >500,000 SNPs. Candidate SNPs with large differences in allelic frequency were identified by ranking all SNPs by their probe-intensity difference between cohorts. The *MAPT* H1 haplotype was strongly detected by this methodology, as was a second major locus on chromosome 11p12-p11 that showed evidence of association at allelic ($P < .001$), genotypic ($P < .001$), and haplotypic ($P < .001$) levels and was narrowed to a single haplotype block containing the DNA damage-binding protein 2 (*DDB2*) and lysosomal acid phosphatase 2 (*ACP2*) genes. Since DNA damage and lysosomal dysfunction have been implicated in aging and neurodegenerative processes, both genes are viable candidates for conferring risk of disease.

Progressive supranuclear palsy (PSP [MIM 601104]) is the second-most-common form of parkinsonism, with a population prevalence rate of 6–6.4 per 100,000.[1,2] Clinical features include vertical-gaze palsy and postural instability.[3,4] PSP is characterized neuropathologically by neuronal and glial inclusions composed of aggregated microtubule associated protein tau (MAPT) in the basal ganglia and brain stem.[5,6] Mutations in the *MAPT* (MIM 157140) gene have been identified in patients with a clinical presentation of PSP.[7–14] A recent report also described linkage to chromosome 1q31.1 in a family with autosomal dominant PSP.[15] However, only the *MAPT* locus has been consistently associated with increased risk for idiopathic PSP.[16–20] The *MAPT* locus exists as two major haplotype groups, termed "H1" and "H2"[16] in European populations, with the H2 haplotype defined by >100 SNPs that are inherited in strong linkage disequilibrium (LD) with each other, reflecting the total absence of H1-H2 recombination.[21] Inheritance of two copies of the H1 haplotype (H1/H1) is a major genetic risk factor for PSP.[16] A large collection of pathologically confirmed PSP samples was used recently to fine map PSP risk on H1 chromosomes in PSP cases and controls.[22,23] PSP risk was associated with an extended subhaplotype, and narrowing the region for PSP risk to a 22-kb region in intron 0 of *MAPT* was accomplished by examining younger patients with, presumably, a larger genetic component to their disease.[22,23] The most likely explanation of the association with the *MAPT* H1 haplotype and PSP is that variants in the H1 (and H2) haplotypes confer risk of (protect against) disease by altering expression at the locus, with the risky H1 haplotypes expressing higher levels of *MAPT*.[22–26]

Calculations of population-attributable risk suggest that only ~68% of the risk of PSP can be accounted for by the *MAPT* H1 haplotype, suggesting there may be additional risk genes involved in PSP. We hypothesized that additional genetic loci involved in conferring risk of PSP could be identified through genomewide association (GWA) methods. The cost of performing an association study that involved individual genotyping of thousands of SNPs for a series this size was prohibitive, so, instead, we used a pooled-DNA approach to identify additional risk factors. Whereas a pooling-based genomewide scan of thousands of SNPs has been proposed in principle, in large part, these studies have not been used for the discovery of genes pre-

From the Departments of Neuroscience (S.M.; R.C.; M.B.; J.G.; J.A.; A.C.; S.L.; M.J.F.; D.W.D.; M.H.) and Neurology (R.J.U.; Z.K.W.; N.G.-R.), Mayo Clinic College of Medicine, Jacksonville, FL; Neurogenomics Division, Translational Genomics Research Institute (TGen), Phoenix (D.W.C.; M.J.H.; J.V.P.; V.L.Z.; S.S.; J.C.; K.D.C.; D.A.S.); Department of Neurology, Mayo Clinic, Scottsdale, AZ (C.A.; R.J.C.); Department of Neurology, University of Minnesota, Minneapolis (P.T.); Pacific Parking's Research Centre, University of British Columbia, Vancouver (D.B.C.); Department of Neuropathy, Northwestern Feinberg School of Medicine, Chicago (E.H.B.); Department of Neurology, University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, New Brunswick, (L.G.B.); and Department of Neurology, University of Louisville School of Medicine, Louisville (I.L.)

Received September 4, 2006; accepted for publication January 12, 2007; electronically published March 8, 2007.

Address for correspondence and reprints: Dr. Mike Hutton, Department of Neuroscience, Mayo Clinic College of Medicine, 4500 San Pablo Road, Birdsall 2, Jacksonville, FL 32224. E-mail: hutton.michael@mayo.edu

* These two authors contributed equally to this work.

Am. J. Hum. Genet. 2007;80:769–778. 0002-9297/2007/8004-0018$15.00
DOI: 10.1086/513320

Table 1. Predicted Allelic Frequencies for the Top 1,000 SNPs

The table is available in its entirety in the online edition of *The American Journal of Human Genetics*.

disposing to complex diseases,[27,28] likely because of technical concerns or lack of technology and analysis tools.

The patients used in the initial pooling study, the "original" series, were largely derived from pathologically confirmed subjects collected by the PSP Society and sent to D.W.D. for brain autopsy. As described elsewhere, the patient samples in this brain bank were donated from the United States and Canada.[29] The patient series is similar to the one that we employed in previous studies to fine map the H1 genetic risk,[22] with 288 subjects with a primary pathological diagnosis of PSP used to create the pool of PSP-affected patients. A total of 344 age- and sex-matched cognitively normal control individuals were obtained through the Normal and Pathological Aging protocol at the Mayo Clinic (Scottsdale),[30,31] to create the pool of control individuals. All patient and control individuals were white from the United States and Canada, and institutional review board (IRB)–approved protocols were used in the collection of all samples.

Replicate pools of patients with PSP and control individuals were created as described elsewhere.[32] Samples were genotyped on 20 replicate Affymetrix 500K arrays and 20 Affymetrix 100K, in accordance with the Affymetrix protocols, whereby each of the five replicate pools was genotyped on two replicate arrays. This design therefore yielded probe-intensity data for both platforms on 10 replicate arrays per cohort. Data were analyzed using GenePool software (TGen Bioinformatics Research Unit).[32] In brief, probe-intensity data were directly read from cell-intensity (CEL) files, and relative allele signal (RAS) values were calculated for each quartet. These values yield independent measures of different hybridization events and are consequently treated as individual data points. We

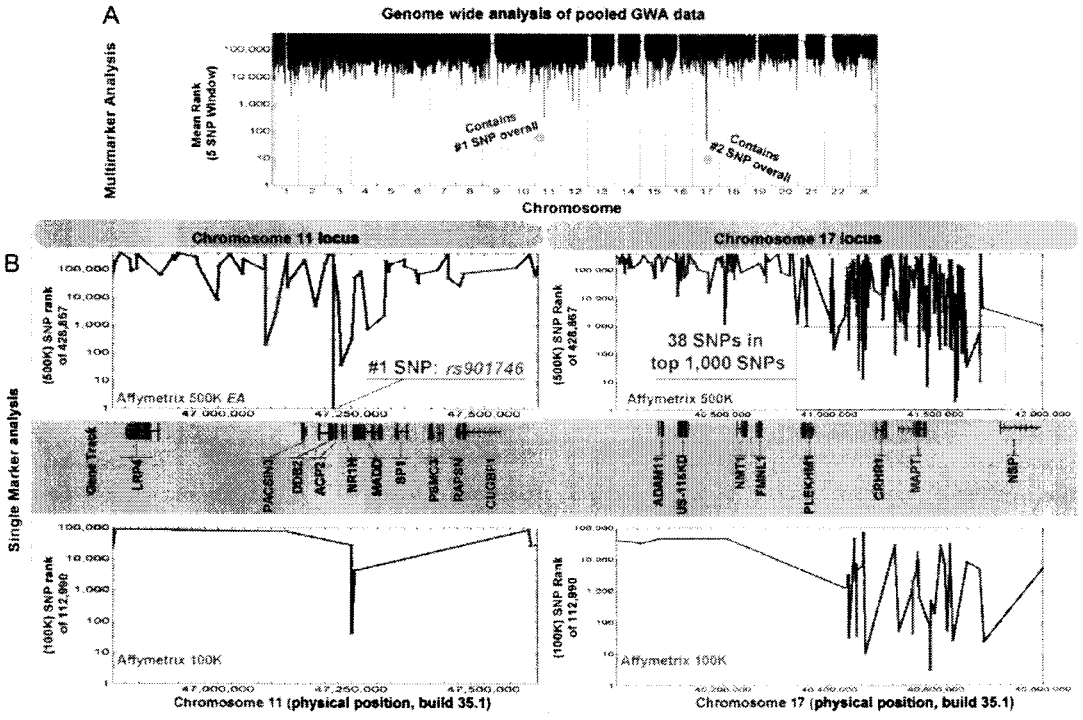

Figure 1. Two loci showing strong support for association by pooled analysis. *A*, Genomewide plot of the mean rank of five consecutive SNPs, calculated to identify clusters of high-ranking SNPs. The single best region was on chromosome 17, neighboring *MAPT*, and the second best region was on chromosome 11p12. Chromosome 11p12 also harbored the SNP that ranked #1 overall by single-marker statistics. *B*, Single-marker rank statistics for SNPs over the *MAPT* (*left*) and *DDB2/ACP2* (*right*) loci. SNPs deemed less reliable or showing high variability among replicates were removed, and the remaining SNPs were ranked in order from 1 (showing the greatest difference between cases and controls) to 428,867 (showing the least difference between cases and controls) with use of a silhouette-test statistic in GenePool software (TGen Bioinformatics Research Unit). Rank scores are plotted versus chromosomal position. Genes within the plotted chromosomal region are shown below. SNPs on the Affymetrix 500K platform are shown above, and SNPs on the Affymetrix 100K platform are shown below. EA = Early Access.

used a silhouette statistic to rank all genotyped SNPs,[43] because it avoids introducing unnecessary variance by averaging probe-intensity data from probes with different hybridization properties. Silhouette scores range from 1, where significant separation between data points has been achieved and cluster assignment can be made with confidence, to −1, where differences in allelic frequencies are less reliable. Poorly performing SNPs were identified by Affymetrix as unreliable in the transition to Mendel3 libraries or exhibited high variance between replicate arrays and were removed from the analysis; 428,867 SNPs remained. SNPs were ranked on the basis of silhouette score, whereby the SNP with the highest score was ranked 1 and the SNP with the lowest score was ranked 428,867, with use of Affymetrix's Mendel3 libraries for the Affymetrix 500K arrays and *Hin*dIII and *Xba*I libraries for the Affymetrix 100K arrays, then were sorted by chromosome and physical position. With this ranking, it is assumed that SNPs approaching a rank of 1 will have larger differences in allelic frequency. With each sample ranked by silhouette score, we calculated a sliding-window statistic of the mean rank for consecutively neighboring SNPs across a fixed window size. Window sizes from 2 to 31 were used.

Since the *MAPT* H1 haplotype is associated with disease with a haplotypic odds ratio (OR) of ~3–4,[16,22,23,34] it served as an internal positive control for the study. For analysis, we used the 500K data to identify chromosomal regions of interest (i.e., those with small mean-rank scores). The 100K data were then used to confirm that a region identified in the 500K analysis contained SNPs with large allelic frequency differences. The SNP with the single best statistical rank on the 500K chip was *rs901746* on chromosome 11p12, and the second-best SNP was *rs17662235*, near *MAPT*. The top 1,000 SNPs, based on individual statistical rank, are given in table 1. Multimarker statistics also identified both chromosome 11p12 and chromosome 17q21 (*MAPT*) regions with sliding windows of multiple sizes. Although we recognize that this type of statistic is biased because of genomewide LD, it allowed us to identify clusters of high-ranking SNPs that neighbor one another, which reduced the possibility of technical errors influencing the results. Shown in figure 1*A*, the *MAPT* locus, labeled as having the #2 SNP overall, showed the greatest evidence of differences between case and control pools with use of the sliding-window analysis, largely because

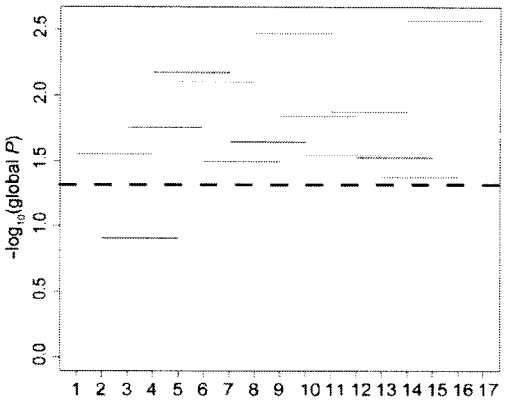

Figure 2. Haplotype sliding window–analysis results. The haplotype score–based method of Schaid et al.[46] was used to investigate evidence of association of haplotypes with case-control status. Only haplotypes with an estimated overall frequency of ≥5% were considered for these analyses. Reported *P* values are based on asymptotic assumptions but were verified by simulating *P* values derived from 1,000 permutations of case and control labels and were found to be consistent. Global *P* values for each 4-marker haplotype are denoted as lines at the $-\log_{10}P$. Only young pathologically confirmed PSP cases (death at age <76 years) were used for the analysis. All individuals in the control group were used in all analyses, since no single SNP showed significantly different allelic frequency distribution in controls when stratified by age. Global $P = .01$ is denoted by a dashed line. SNP numbers are as noted in table 3.

of 38 SNPs within the top 1,000 SNPs overall and a total of 75 SNPs in the region with a rank score of <10,000 (fig. 1*B* and table 1). Examination of the individual SNPs with high rank scores over this locus showed SNPs that were derived from a region covering the full extent of the *MAPT* H1 haplotype, spanning nearly 1 Mb (fig. 1*B*).[30] All of the 75 SNPs with genotype-frequency data in the database resembled *MAPT* H2 variants (which differentiate between H1 and H2 *MAPT* haplotypes) rather than H1 variants (which differentiate between H1 subhaplotypes); this is because, in white populations, the SNP minor-allele frequency was ~0.2, whereas the minor allele of the SNP was absent or rare in Asian populations and African populations.[36,37] In addition, two of the SNPs with low rank

Table 2. Association Analysis of *rs901746* in Original and Replication Series

		No. (%) of							
		Alleles		Genotypes			GG versus AG and AA		
Population	*n*	A	G	AA	AG	GG	OR	95% CI	*P*
Control combined	**735**	**1,011 (75)**	**335 (25)**	**377 (56)**	**257 (38)**	**39 (6)**	...	...	...
Control original	344	438 (78)	126 (22)	166 (58)	106 (37)	10 (4)	...	...	...
Control replication	391	573 (73)	209 (27)	211 (54)	151 (39)	29 (7)	...	...	...
PSP combined	**501**	**661 (68)**	**317 (32)**	**231 (47)**	**199(41)**	**59 (12)**	**2.2**	**1.5–3.4**	**.0001**
PSP original	288	374 (68)	178 (32)	131 (47)	112 (41)	33 (12)	4.0	1.9–8.3	.0001
PSP replication	213	287 (67)	139 (33)	100 (47)	87 (41)	26 (12)	1.7	1.0–3.0	.05

Table 3. Single-Marker Analysis of Tag SNPs in the Combined Series and in Both Young and Old Patient Populations

tagID[a] (SNP), and Allele	No. (%) of Alleles in Controls (n = 532)	All Cases (n = 448) No. (%) of Alleles	All Cases P	Young[b] Cases (n = 162) No. (%) of Alleles	Young[b] Cases P	Old[b] Cases (n = 182) No. (%) of Alleles	Old[b] Cases P
1 (*rs11039130*):			**.003**		**.02**		.25
C	600 (69)	614 (75)		224 (76)		245 (72)	
T	274 (31)	202 (25)		72 (24)		95 (28)	
2 (*rs4647709*):			.5		.57		.88
C	806 (91)	787 (90)		292 (90)		331 (91)	
T	78 (9)	85 (10)		32 (10)		31 (9)	
3 (*rs2291120*):			**.0004**		**.003**		**.006**
T	781 (92)	859 (87)		280 (86)		317 (87)	
C	67 (8)	115 (13)		44 (14)		47 (13)	
4 (*rs10742797*):			.81		.72		.98
A	591 (81)	572 (81)		212 (82)		243 (80)	
T	143 (19)	134 (19)		48 (18)		59 (20)	
5 (*rs1685404*):			.72		.97		.96
G	598 (68)	560 (67)		213 (68)		237 (68)	
C	282 (32)	274 (33)		101 (32)		111 (32)	
6 (*rs7395581*):			.03		**.02**		.07
A	378 (71)	437 (65)		157 (63)		180 (65)	
G	152 (29)	233 (35)		93 (37)		96 (35)	
7 (*rs11039138*):			**.01**		**.02**		.37
G	470 (56)	442 (62)		168 (64)		173 (59)	
A	372 (44)	268 (38)		94 (36)		121 (41)	
8 (*rs2957873*):			.22		.52		.28
A	728 (83)	679 (81)		257 (81)		281 (80)	
G	150 (17)	163 (19)		59 (19)		69 (20)	
9 (*rs4647736*):			**.03**		**.04**		.12
C	807 (91)	736 (88)		273 (88)		305 (89)	
T	75 (9)	98 (12)		39 (13)		39 (11)	
10 (*rs2013867*):			**.004**		**.006**		.02
T	657 (74)	549 (66)		206 (66)		236 (67)	
C	229 (26)	279 (34)		106 (34)		114 (33)	
11 (*rs901746*):			**<.0001**		**.003**		**.004**
A	659 (76)	570 (67)		204 (65)		242 (68)	
G	213 (24)	282 (33)		110 (35)		116 (32)	
12 (*rs1050244*):			.53		.89		.44
C	851 (97)	823 (96)		307 (97)		343 (96)	
T	29 (3)	33 (4)		11 (3)		15 (4)	
13 (*rs11039143*):			.87		.64		.52
T	830 (98)	782 (98)		293 (98)		319 (98)	
G	18 (2)	16 (2)		5 (2)		5 (2)	
14 (*rs7118396*):			.16		.27		.13
C	741 (86)	688 (84)		253 (84)		287 (83)	
T	117 (14)	132 (16)		49 (16)		59 (17)	
15 (*rs12577530*):			**.0009**		**.005**		**.04**
G	784 (88)	701 (82)		260 (82)		296 (84)	
C	106 (12)	149 (18)		58 (18)		58 (16)	
16 (*rs7114704*):			.01		.3		**.0006**
C	813 (93)	803 (96)		288 (95)		343 (98)	
T	61 (7)	35 (4)		16 (5)		7 (2)	
17 (*rs10501320*):			**<.0001**		**.003**		.16
G	609 (70)	641 (78)		230 (79)		255 (74)	
C	265 (30)	179 (22)		62 (21)		91 (26)	

NOTE.—Significant P values are shown in bold.

[a] Tag SNPs were chosen on the basis of the tagging algorithm in Haploview v3.32 software,[49] with the "Pairwise Tagging Only" option selected and the r^2 threshold set at .8.

[b] Subjects aged <76 years were classified as "young"; subjects aged ≥76 were classified as "old."

Table 4. SNP Discovery Results from Sequencing *DDB2* and *ACP2* in 18 Subjects with PSP

	Genotype at *DDB2* 5′→3′			Genotype at *ACP2* 3′→5′					
	Intron 8	Intron 9	3′ UTR	Intron 6		Exon 5	Intron 3		Exon 1
Sample	*rs326222*	***rs901746***	*rs1050244*	*rs11039146*	*rs2242261*	*rs10838677*[a]	ss68362654[b]	*rs4752973*	*rs2167079*[c]
1	GG	GG	CT	CT	AA	AG	AG	AG	AA
2	GG	GG	CC	CC	AA	GG	GG	AA	AA
3	GG	GG	CC	CC	CC	GG	GG	GG	AA
4	GG	GG	CC	CC	AC	GG	GG	AG	AA
5	GG	GG	CC	CC	AC	GG	GG	AG	AA
6	GG	GG	CC	CC	CC	GG	GG	GG	AA
7	GG	GG	CC	CC	AA	GG	GG	AA	AA
8	GG	GG	CT	CT	AA	AG	AG	AG	AA
9	AG	AG	CC	CC	AA	GG	GG	AA	AG
10	GG	GG	CC	CC	AC	GG	GG	AG	AA
11	GG	GG	CC	CC	AC	GG	GG	AG	AA
12	GG	GG	CC	CC	AC	GG	GG	AG	AA
13	AG	AG	CC	CC	AA	GG	GG	AA	AG
14	AG	AG	CC	CC	AA	GG	GG	AA	GG
15	AG	AG	CC	CC	AA	GG	GG	AA	AG
16	AG	AG	CC	CC	AA	GG	GG	AA	AG
17	AA	AA	CC	CC	AA	GG	GG	AA	GG
18	AA	AA	CC	CC	AA	GG	GG	AA	GG

[a] Encodes synonymous change L165L.
[b] No rs number; submitted to dbSNP.
[c] Encodes nonsynonymous change R29Q.

scores (*rs12150111* and *rs807072*) were identified definitively as *MAPT* H2 variants from prior *MAPT* genomic sequencing efforts.[22]

The chromosome 11p12 region that showed the highest rank SNP by single-marker statistics and multimarker sliding-window analysis was a novel locus and therefore was examined in greater detail (fig. 1*B*). The top overall ranked SNP, *rs901746*, a SNP in intron 9 of the DNA damage-binding protein 2 (*DDB2* [MIM 600811]) gene, was chosen for follow-up in the individual samples comprising the pooled DNA. A significant increase of 10% in the G allele frequency was seen in cases versus controls ($P = .0002$) (table 2). The SNP was then genotyped in a second U.S. series to confirm the association. This "replication" sample ($n = 161$) was made up of both pathologically confirmed ($n = 97$) and clinically defined PSP case individuals ($n = 64$), as described in Rademakers et al.[22] A total of 165 age- and sex-matched cognitively normal control individuals were obtained from the Normal and Pathological Aging Protocol at the Mayo Clinic (Scottsdale).[30,31] In addition, for the *rs901746* and *rs2167079* analysis, additional pathologically confirmed cases ($n = 41$) and clinically defined PSP case indivuals ($n = 22$) were genotyped, and 252 age- and sex-matched cognitively normal control individuals collected at Mayo Clinic Jacksonville were used as a second source of controls.[22] All case and control individuals in this set were white from the United States and Canada, and IRB-approved protocols were used in the collection of all samples.

When allele frequencies at *rs901746* were examined in the replication sample set, a 6% increase in the frequency of the G allele in subjects with PSP was observed; however, because of the smaller sample size, this allele frequency difference is borderline significant ($P = .05$). When genotype distributions were examined in both PSP case-control series, the frequencies were very similar, with an increase from 4% to 12% in the GG genotype in the original population and an increase from 7% to 12% in the replication set. The allelic frequency difference in both series is explained by an apparent doubling of the GG frequency in subjects with PSP compared with controls, suggesting that risk at this locus acts in a recessive manner. We explicitly tested dominant, recessive, and additive models at this locus, and the model that best fit the data was a recessive one ($P < .0001$). The OR for harboring an *rs901746* GG genotype versus all other genotypes in the original series was 3.7 (95% CI 1.2–3.9) and was 1.7 (95% CI 1.0–3.0) for the replication series. When these individuals in both of these series were combined and analyzed, the combined

Table 5. Association Analysis of *rs2167079* in the Combined Series

	No. (%) of Alleles		
SNP and Allele	All Controls ($n = 735$)	All Patients ($n = 501$)	*P*
rs901746:			**<.0001**
A	1,011 (75)	661 (68)	
G	335 (25)	317 (32)	
rs2167079:			**.002**
G	918 (73)	598 (67)	
A	332 (27)	292 (33)	

NOTE.—Results include the additional cases and controls used in the replication series.

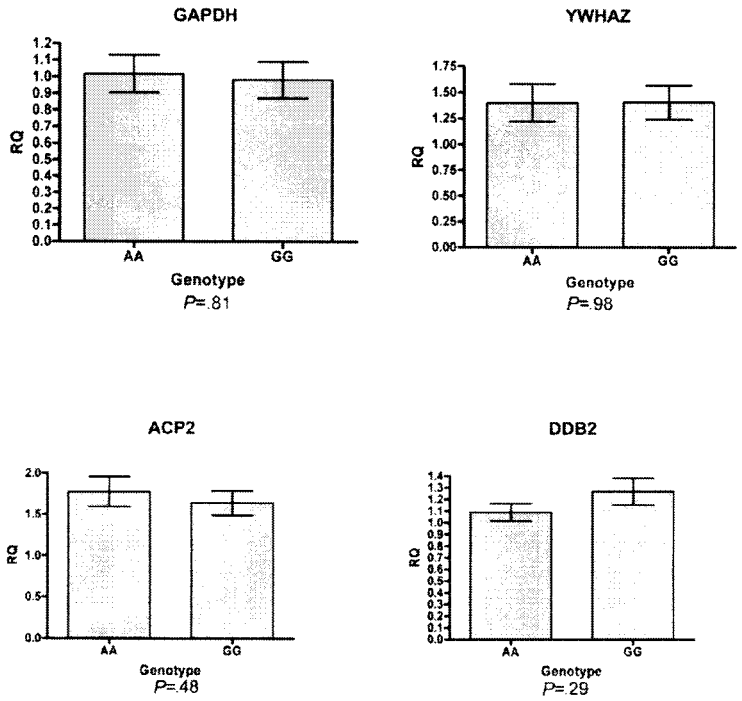

Figure 3. Relative mRNA expression with TATA-binding protein as an endogenous control. Plotted are relative levels of glyceraldehyde-3-phosphate dehydrogenase (GAPDH); tyrosine 3-monooxygenase/tryptophan 5-mono-oxygenase activation protein, zeta polypeptide (YWHAZ); ACP2 (assay Hs00155636_m1 [Applied Biosystems]); and DDB2 (assay Hs00172068_m1 [Applied Biosystems]) for 20 carriers of the *rs901746* AA (neutral) genotype and 20 carriers of the *rs901746* GG (risky) genotype. SE is denoted by the error bars. None of the comparisons between AA and GG carriers reach the level of statistical significance (*P* values noted below each graph). Similar results are seen when GAPDH or YWHAZ was used as the endogenous control (data not shown). RQ = relative quantity.

OR for the GG genotype compared with all other genotypes in the series was 2.2 (95% CI 1.4–3.4). To confirm that the *rs901746* association observed is not a control frequency artifact, we examined allele frequencies for *rs901746* in 250 cognitively normal controls recently published in a Parkinson disease (PD [MIM 168600]) GWA study.[38] We found that the frequency of the *rs901746* G allele in this independent control series was 0.27, consistent with our observed control frequencies (0.22 and 0.27).

The genomic context near *rs901746* was examined by downloading the CEPH-from-Utah SNP genotypes for 100 kb around *rs901746* from the HapMap genome browser and by examining the LD patterns and haplotype-block structure of the region with use of the Haploview software.[39] *rs901746* lies in the middle of a haplotype block encompassing at least two genes—the *DDB2* gene and the lysosomal acid phosphatase 2 (*ACP2* [MIM 171650]) gene—and can extend into the 3′ of another gene, nuclear receptor subfamily 1, group H, member 3 (*NR1H3* [MIM 602423]), depending on the type of haplotype-block definition used.[39] Variation in this 100-kb region could be fully described by 16 additional tag SNPs. These tag SNPs were genotyped in all PSP series, and both single and multimarker analysis was performed on the combined series (table 3). Single-marker analysis showed that nine tag SNPs showed significant allelic association. Of these, five tag SNP associations were highly significant (*P* values ≤.003), with *rs10501320* showing the greatest association after *rs901746* ($P < .0001$).

We examined the *DDB2/ACP2* tag SNP data set in different age groups in our combined series of cases and controls to see whether looking at younger cases might help further refine the associated region, as it had for the *MAPT* locus, where younger cases show a stronger association with the H1/H1 genotype.[22] Pathologically confirmed cases were divided into "young" and "old" groups on the basis of median age at death (75 years), and single-marker allelic association statistics were calculated using 2 × 2 contingency tables and were examined using χ^2 tests. On the whole, all of the SNPs that show significant association in the combined PSP case set also show significant association ($P < .05$) with the younger case subset, whereas there is less-significant association observed for the older cases.

To refine the disease-associated region, we performed haplotype-inference analysis in the young cases versus all controls, using a sliding-window approach.[40] As described elsewhere, this type of approach was key in refining the

associated region on the *MAPT* H1 haplotype.[22] However, as figure 2 displays, when data from all the tag SNPs were included in the analysis, there was no obvious resolution of the associated region when the young cases were considered separately. This may reflect the fact that the contribution to the overall signal of the association at this locus was not as great with the younger cases as had been seen with the *MAPT* locus; therefore, the sample size and/or the number of informative SNPs was inadequate to detect a smaller associated region.

Since a haplotype-inference approach was unsuccessful in narrowing the associated region, we decided to identify additional novel SNPs that may represent functional variant(s) accounting for increased risk of disease by sequencing a series of 18 subjects with PSP who had the various genotypes at *rs901746*, the majority of whom carried the risky GG genotype (n = 11 GG, n = 5 AG, and n = 2 AA) (table 4). Primers were designed to fully sequence coding exons of both *DDB2* and *ACP2*. Only one SNP, found 63 bp downstream of exon 3 in *ACP2*, was not already in the dbSNP database; however, this SNP appeared to be in near-complete LD with nearby *rs10838677* in exon 5 of *ACP2*, encoding a silent change (L165L). Interestingly, a number of SNPs identified through sequencing appeared to be in near-complete LD with *rs901746*, including *rs2167079*, a coding SNP in *ACP2* in which the minor allele changes the amino acid at position 29 from an arginine to a glutamine (R29Q). This converts the protein sequence to the mouse amino acid residue at the equivalent position. Interestingly, this position in ACP2 is predicted to encode the signal peptidase cleavage site,[41] suggesting that carriers of the minor allele encoding glutamine at position 29 may have altered cleavage of the signal peptide compared with those encoding arginine at that position. Since this SNP could affect function of the protein, we genotyped it through the combined series. Results from this analysis are shown in table 5. Overall, the LD between *rs901746* and *rs2167079* was high (cases r^2 = 0.97; controls r^2 = 0.94). As expected, significant allelic association was observed with *rs2167079* (P = .002); however, this was not any greater than the association observed with *rs901746*, suggesting that *rs2167079* is unlikely to fully explain the association at the *DDB2/ACP2* locus. We tested the R29Q variant for dominant, recessive, and additive models, and the additive model best fit the data (P < .0001).

In an alternative method for determining the gene responsible for disease risk at this locus, expression analysis was performed on the *DDB2* and *ACP2* genes. Analysis was performed, using real-time Taqman expression assays (Applied Biosystems), on mRNA extracted from the cerebella of 20 *rs901746* AA and 20 *rs901746* GG genotype carriers, to determine whether risk variants at the *DDB2/ACP2* locus have a direct effect on gene expression. Unfortunately, although DDB2 transcript levels are slightly increased in cases with a GG genotype, no significant differences were observed between the cases with AA and GG genotypes for either *DDB2* or *ACP2* mRNA levels (for *DDB2*, P = .29; for *ACP2*, P = .48) (fig. 3).

GWA studies are appealing because of their lack of bias, in that they represent a model-free approach for identification of new and novel genes that are involved in a disease process that may never be identified using other methodologies. However, even now, individually genotyping hundreds of individuals to perform a "traditional" GWA is not feasible for many rarer diseases, including PSP, because of the lack of available funding. Therefore, this type of pooled genomewide approach potentially represents a fast and economical initial solution to this problem. Pooling methods lack the analytical flexibility inherent in a traditional genomewide study because it is not possible to reanalyze the data with use of subgroups of cases or controls or to perform true haplotype-scanning analyses. However, there is still some uncertainty about how best to analyze the large amounts of individual genotype data used in GWA studies. An early GWA study of the PD showed problems in replication of results, potentially because of problems in study design.[42–47]

Although pooling methods clearly have limitations, the analysis procedures we used in the GenePool software (TGen Bioinformatics Research Unit) were developed using individual genotype data from samples that were also pooled, thereby allowing the algorithms to be adjusted until they predicted SNP ranks on the basis of what was known from the individual genotype data.[32] In the present analysis, we had prior knowledge that the *MAPT* H1 haplotype is associated with disease, so it could serve as a positive control for the genomewide analysis.

The identification of a new risk locus for PSP on chromosome 11 from the pooled genomewide approach was confirmed in a second U.S. PSP case-control series, with similar allele and genotype frequencies. Closer examination of this locus by dense SNP genotyping suggests that the association spans the entire haplotype block containing the *DDB2* and *ACP2* genes. Examination of potential functional variants yielded no definitive explanation for the observed association.

Both *ACP2* and *DDB2* are reasonable candidate genes that highlight previously implicated pathways for neurodegenerative disease. There are many lines of evidence suggesting a role for lysosomes and autophagic processes in neurodegeneration. Autophagy has been implicated in the clearance of protein aggregates, a common feature of many neurodegenerative disorders.[48,49] Interestingly, patients with lysosomal-storage disorders often exhibit neurological phenotypes with pathology similar to that seen in PSP.[50–52] Two lines of evidence implicate *ACP2* in neurodegeneration. First, it has been reported that, in brains of subjects with Alzheimer disease (AD [MIM 104300]), microglia surrounding the amyloid plaques stain strongly for ACP2.[53] In addition, cerebrospinal fluid from half of the examined subjects with AD showed evidence of ACP2 activity, whereas patients not affected with AD showed no activity.[53] These results leave open the question of whether

ACP2 in AD is just a secondary marker of neurodegeneration or perhaps plays a more active role in the neurodegenerative process. Second, knockouts and mutations of *Acp2* in mice have neurological phenotypes.[54,55] Neuropathology of $Acp2^{-/-}$ tissue showed increased lysosomal staining (as detected by lamp-1 and cathepsin D immunoreactivity), primarily in glial cells. Interestingly, ~7% of these $Acp2^{-/-}$ mice presented with generalized seizures after age 8 wk, and it has been suggested that this phenotype may be correlated with the defective lysosomal storage observed in glial cells.[54] The observation that loss of Acp2 causes deficits in glial lysosomal storage in the $Acp2^{-/-}$ mice may also be significant, given that, in PSP, there is abundant MAPT-inclusion pathology within glia (astrocytes and olgodendroglia), as well as in neurons.[56]

Mutations in the *DDB2* gene are responsible for xeroderma pigmentosum (XP) complementation group E (XPE [MIM 278740]). Interestingly, some mutations in the nucleotide excision–repair pathway that cause the diseases XP and Cockayne syndrome (MIM 216400) present with neurological phenotypes; however, XPE does not seem to be one of them.[57,58] DDB2 forms a ubiquitin E3-ligase complex, with DNA damage-binding protein 1 (DDB1 [MIM 600045]) and Cullin 4a (CUL4A [MIM 603137]), that binds damaged DNA. Both histone H2A (H2AA [MIM 603137]) and XP complementation group C (XPC [MIM 278720]) proteins have been implicated as substrates for the DDB1/DDB2/CUL4A complex upon activation.[59,60] Ubiquitination of histone H2A may change local chromatin configuration at the damage site, thereby allowing access to other DNA-repair proteins farther down the pathway.[60] The accumulation of damaged DNA in aging brain suggests that DNA-repair capacity is reduced as we age and appears to be selective to genes important in learning and memory. Interestingly, there is evidence of brain-specific alternatively spliced forms of *DDB2* that splice out either exons 4–7 or exons 4 and 6 alone.[61] The proteins encoded by these alternatively spliced transcripts act as dominant negative inhibitors of DNA repair, when tested in an in vitro system.[61] It will be interesting to tease apart which gene or genes at this locus are involved in conferring risk of PSP, but functional studies, rather than genetic ones, will probably be required to address these issues.

Given the size of the association seen at the *DDB2/ACP2* locus, the fact that the described PSP series represents the largest collection of PSP-affected subjects worldwide, and the fact that our U.S. replication series is underpowered to detect changes with an OR <2.0, we may be at the limit of what can be consistently detected and confirmed using the case-control populations available. Six additional weaker loci were identified in the genomewide screen that still need to be analyzed in detail, and it will be interesting to examine this potential power issue in closer detail. This genomewide analysis has identified a novel second locus implicated in PSP risk, accelerating research and the hope of identifying effective therapeutics for this devastating disease.

Acknowledgments

We are grateful to the patients and their families for their cooperation in this project. We also thank the Society for Progressive Supranuclear Palsy brain bank for providing samples. We thank John Gonzalez and Monica Castanedes-Casey in the Neuropathology Laboratory at Mayo Clinic Jacksonville for technical assistance. This research was funded by National Institutes of Aging grant PO1 AG 17216 (to M.H., D.W.D., and M.J.F.); the Mayo Foundation, USA; The Society for Progressive Supranuclear Palsy; and a Robert and Clarice Smith Fellowship. S.M. was funded by the National Research Service Award postdoctoral fellowship AG24030. Funding was also provided by a foundation grant from the Stardust Foundation (to D.W.C.) and the National Institutes of Health Neuroscience Blueprint grant 1U24NS043571 (to D.A.S.).

Web Resources

The URLs for data presented herein are as follows:

dbSNP, http://www.ncbi.nlm.nih.gov/SNP/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PSP, *MAPT*, *DDB2*, PD, *ACP2*, *NR1H3*, AD, XPE, Cockayne syndrome, DDB1, CUL4A, H2AA, and XPC)
TGen Bioinformatics Research Unit, http://bioinformatics.tgen.org/ (for the GenePool source code)

References

1. Steele JC, Richardson JC, Olszewski J (1964) Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch Neurol 10:333–359
2. Litvan I (2004) Update on progressive supranuclear palsy. Curr Neurol Neurosci Rep 4:296–302
3. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, et al (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP International Workshop. Neurology 47:1–9
4. Litvan I, Agid Y, Jankovic J, Goetz C, Brandel JP, Lai EC, Wenning G, D'Olhaberriague L, Verny M, Chaudhuri KR, et al (1996) Accuracy of clinical criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). Neurology 46:922–930
5. Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, McKee A, Tabaton M, Litvan I (1994) Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 44: 2015–2019
6. Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, McKee A, Dickson D, Bancher C, Tabaton M, et al (1996) Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol 55:97–105
7. Rojo A, Pernaute RS, Fontan A, Ruiz PG, Honnorat J, Lynch T, Chin S, Gonzalo I, Rabano A, Martinez A, et al (1999) Clinical genetics of familial progressive supranuclear palsy. Brain 122:1233–1245 (erratum 123:419)
8. Ros R, Thobois S, Streichenberger N, Kopp N, Sanchez MP, Perez M, Hoenicka J, Avila J, Honnorat J, de Yebenes JG (2005)

A new mutation of the τ gene, G303V, in early-onset familial progressive supranuclear palsy. Arch Neurol 62:1444–1450
9. Spillantini MG, Goedert M (2000) *Tau* mutations in familial frontotemporal dementia. Brain 123:857–859
10. Stanford PM, Halliday GM, Brooks WS, Kwok JB, Storey CE, Creasey H, Morris JG, Fulham MJ, Schofield PR (2000) Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the *tau* gene: expansion of the disease phenotype caused by *tau* gene mutations. Brain 123:880–893
11. Wszolek ZK, Tsuboi Y, Uitti RJ, Reed L, Hutton ML, Dickson DW (2001) Progressive supranuclear palsy as a disease phenotype caused by the S305S tau gene mutation. Brain 124: 1666–1670
12. Pastor P, Pastor E, Carnero C, Vela R, Garcia T, Amer G, Tolosa E, Oliva R (2001) Familial atypical progressive supranuclear palsy associated with homozigosity for the delN296 mutation in the tau gene. Ann Neurol 49:263–267
13. Oliva R, Pastor P (2004) Tau gene delN296 mutation, Parkinson's disease, and atypical supranuclear palsy. Ann Neurol 55:448–449
14. Rossi G, Gasparoli E, Pasquali C, Di Fede G, Testa D, Albanese A, Bracco F, Tagliavini F (2004) Progressive supranuclear palsy and Parkinson's disease in a family with a new mutation in the tau gene. Ann Neurol 55:448
15. Ros R, Gomez Garre P, Hirano M, Tai YF, Ampuero I, Vidal L, Rojo A, Fontan A, Vazquez A, Fanjul S, et al (2005) Genetic linkage of autosomal dominant progressive supranuclear palsy to 1q31.1. Ann Neurol 57:634–641
16. Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, Hardy J, Lynch T, Bigio E, Hutton M (1999) Association of an extended haplotype in the *tau* gene with progressive supranuclear palsy. Hum Mol Genet 8:711–715
17. Conrad C, Andreadis A, Trojanowski JQ, Dickson DW, Kang D, Chen X, Wiederholt W, Hansen L, Masliah E, Thal LJ, et al (1997) Genetic evidence for the involvement of τ in progressive supranuclear palsy. Ann Neurol 41:277–281
18. Higgins JJ, Golbe LI, De Biase A, Jankovic J, Factor SA, Adler RL (2000) An extended 5′-*tau* susceptibility haplotype in progressive supranuclear palsy. Neurology 55:1364–1367
19. Morris HR, Janssen JC, Bandmann O, Daniel SE, Rossor MN, Lees AJ, Wood NW (1999) The tau gene A0 polymorphism in progressive supranuclear palsy and related neurodegenerative diseases. J Neurol Neurosurg Psychiatry 66:665–667
20. Oliva R, Tolosa E, Ezquerra M, Molinuevo JL, Valldeoriola F, Burguera J, Calopa M, Villa M, Ballesta F (1998) Significant changes in the tau A0 and A3 alleles in progressive supranuclear palsy and improved genotyping by silver detection. Arch Neurol 55:1122–1124
21. Cruts M, Rademakers R, Gijselinck I, van der Zee J, Dermaut B, de Pooter T, de Rijk P, Del-Favero J, van Broeckhoven C (2005) Genomic architecture of human 17q21 linked to frontotemporal dementia uncovers a highly homologous family of low-copy repeats in the tau region. Hum Mol Genet 14: 1753–1762
22. Rademakers R, Melquist S, Cruts M, Theuns J, Del-Favero J, Poorkaj P, Baker M, Sleegers K, Crook R, De Pooter T, et al (2005) High-density SNP haplotyping suggests altered regulation of tau gene expression in progressive supranuclear palsy. Hum Mol Genet 14:3281–3292
23. Pittman AM, Myers AJ, Abou-Sleiman P, Fung HC, Kaleem M, Marlowe L, Duckworth J, Leung D, Williams D, Kilford L, et al (2005) Linkage disequilibrium fine mapping and haplotype association analysis of the *tau* gene in progressive supranuclear palsy and corticobasal degeneration. J Med Genet 42: 837–846
24. Kwok JB, Teber ET, Loy C, Hallupp M, Nicholson G, Mellick GD, Buchanan DD, Silburn PA, Schofield PR (2004) Tau haplotypes regulate transcription and are associated with Parkinson's disease. Ann Neurol 55:329–334
25. Caffrey TM, Joachim C, Paracchini S, Esiri MM, Wade-Martins R (2006) Haplotype-specific expression of exon 10 at the human *MAPT* locus. Hum Mol Genet 15:3529–3537
26. Myers AJ, Pittman AM, Zhao AS, Rohrer K, Kaleem M, Marlowe L, Lees A, Leung D, McKeith IG, Perry RH, et al (2006) The *MAPT* H1c risk haplotype is associated with increased expression of tau and especially of 4 repeat containing transcripts. Neurobiol Dis (electronically published ahead of print December 14, 2006; accessed February 7, 2007)
27. Bansal A, van den Boom D, Kammerer S, Honisch C, Adam G, Cantor CR, Kleyn P, Braun A (2002) Association testing by DNA pooling: an effective initial screen. Proc Natl Acad Sci USA 99:16871–16874
28. Meaburn E, Butcher LM, Schalkwyk LC, Plomin R (2006) Genotyping pooled DNA using 100K SNP microarrays: a step towards genomewide association scans. Nucleic Acids Res 34: e28
29. Josephs KA, Dickson DW (2003) Diagnostic accuracy of progressive supranuclear palsy in the Society for Progressive Supranuclear Palsy brain bank. Mov Disord 18:1018–1026
30. Caselli RJ, Osborne D, Reiman EM, Hentz JG, Barbieri CJ, Saunders AM, Hardy J, Graff-Radford NR, Hall GR, Alexander GE (2001) Preclinical cognitive decline in late middle-aged asymptomatic apolipoprotein E-e4/4 homozygotes: a replication study. J Neurol Sci 189:93–98
31. Caselli RJ, Hentz JG, Osborne D, Graff-Radford NR, Barbieri CJ, Alexander GE, Hall GR, Reiman EM, Hardy J, Saunders AM (2002) Apolipoprotein E and intellectual achievement. J Am Geriatr Soc 50:49–54
32. Pearson JV, Huentelman MJ, Halperin RF, Tembe WD, Melquist S, Homer N, Brun M, Szelinger S, Coon KD, Zismann VL, et al (2007) Identification of the genetic basis for complex disorders by use of pooling-based genomewide single-nucleotide–polymorphism association studies. Am J Hum Genet 80: 126–139
33. Lovmar L, Ahlford A, Jonsson M, Syvanen AC (2005) Silhouette scores for assessment of SNP genotype clusters. BMC Genomics 6:35
34. Pittman AM, Myers AJ, Duckworth J, Bryden L, Hanson M, Abou-Sleiman P, Wood NW, Hardy J, Lees A, de Silva R (2004) The structure of the tau haplotype in controls and in progressive supranuclear palsy. Hum Mol Genet 13:1267–1274
35. Craig DW, Huentelman MJ, Hu-Lince D, Zismann VL, Kruer MC, Lee AM, Puffenberger EG, Pearson JM, Stephan DA (2005) Identification of disease causing loci using an array-based genotyping approach on pooled DNA. BMC Genomics 6:138
36. Stefansson H, Helgason A, Thorleifsson G, Steinthorsdottir V, Masson G, Barnard J, Baker A, Jonasdottir A, Ingason A, Gudnadottir VG, et al (2005) A common inversion under selection in Europeans. Nat Genet 37:129–137
37. Evans W, Fung HC, Steele J, Eerola J, Tienari P, Pittman A, Silva R, Myers A, Vrieze FW, Singleton A, et al (2004) The tau H2 haplotype is almost exclusively Caucasian in origin. Neurosci Lett 369:183–185
38. Fung HC, Scholz S, Matarin M, Simon-Sanchez J, Hernandez

D, Britton A, Gibbs JR, Langefeld C, Stiegert ML, Schymick J, et al (2006) Genome-wide genotyping in Parkinson's disease and neurologically normal controls: first stage analysis and public release of data. Lancet Neurol 5:911–916
39. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265
40. Schaid DJ, Rowland CM, Tines DE, Jacobson RM, Poland GA (2002) Score tests for association between traits and haplotypes when linkage phase is ambiguous. Am J Hum Genet 70:425–434
41. Pohlmann R, Krentler C, Schmidt B, Schroder W, Lorkowski G, Culley J, Mersmann G, Geier C, Waheed A, Gottschalk S, et al (1988) Human lysosomal acid phosphatase: cloning, expression and chromosomal assignment. EMBO J 7:2343–2350
42. Maraganore DM, de Andrade M, Lesnick TG, Strain KJ, Farrer MJ, Rocca WA, Pant PV, Frazer KA, Cox DR, Ballinger DG (2005) High-resolution whole-genome association study of Parkinson disease. Am J Hum Genet 77:685–693
43. Clarimon J, Scholz S, Fung H-C, Hardy J, Eerola J, Hellstrom O, Chen C-M, Wu Y-R, Ticnari PJ, Singleton A (2006) Conflicting results regarding the semaphorin gene (*SEMA5A*) and the risk for Parkinson disease. Am J Hum Genet 78:1082–1084 (author reply 78:1092–1094)
44. Farrer MJ, Haugarvoll K, Ross OA, Stone JT, Milkovic NM, Cobb SA, Whittle AJ, Lincoln SJ, Hulihan MM, Heckman MG, et al (2006) Genomewide association, Parkinson disease, and *PARK10*. Am J Hum Genet 78:1084–1088 (author reply 78: 1092–1094)
45. Goris A, Williams-Gray CH, Foltynie T, Compston DAS, Barker RA, Sawcer SJ (2006) No evidence for association with Parkinson disease for 13 single-nucleotide polymorphisms identified by whole-genome association screening. Am J Hum Genet 78:1088–1090 (author reply 78:1092–1094)
46. Li Y, Rowland C, Schrodi S, Laird W, Tacey K, Ross D, Leong D, Catanese J, Sninsky J, Grupe A (2006) A case-control association study of the 12 single-nucleotide polymorphisms implicated in Parkinson disease by a recent genome scan. Am J Hum Genet 78:1090–1092 (author reply 1092–1094)
47. Myers DR (2006) Considerations for genomewide association studies in Parkinson disease. Am J Hum Genet 78:1081–1082
48. Webb JL, Ravikumar B, Atkins J, Skepper JN, Rubinsztein DC (2003) α-Synuclein is degraded by both autophagy and the proteasome. J Biol Chem 278:25009–25013
49. Qin ZH, Wang Y, Kegel KB, Kazantsev A, Apostol BL, Thompson LM, Yoder J, Aronin N, DiFiglia M (2003) Autophagy regulates the processing of amino terminal huntingtin fragments. Hum Mol Genet 12:3231–3244
50. Auer IA, Schmidt ML, Lee VM, Curry B, Suzuki K, Shin RW, Pentchev PG, Carstea ED, Trojanowski JQ (1995) Paired helical filament tau (PHFtau) in Niemann-Pick type C disease is similar to PHFtau in Alzheimer's disease. Acta Neuropathol (Berl) 90:547–551
51. Love S, Bridges LR, Case CP (1995) Neurofibrillary tangles in Niemann-Pick disease type C. Brain 118:119–129
52. Suzuki K, Parker CC, Pentchev PG, Katz D, Ghetti B, D'Agostino AN, Carstea ED (1995) Neurofibrillary tangles in Niemann-Pick disease type C. Acta Neuropathol (Berl) 89:227–238
53. Omar R, Pappolla M, Argani I, Davis K (1993) Acid phosphatase activity in senile plaques and cerebrospinal fluid of patients with Alzheimer's disease. Arch Pathol Lab Med 117: 166–169
54. Saftig P, Hartmann D, Lullmann-Rauch R, Wolff J, Evers M, Koster A, Hetman M, von Figura K, Peters C (1997) Mice deficient in lysosomal acid phosphatase develop lysosomal storage in the kidney and central nervous system. J Biol Chem 272:18628–18635
55. Mannan AU, Roussa E, Kraus C, Rickmann M, Maenner J, Nayernia K, Krieglstein K, Reis A, Engel W (2004) Mutation in the gene encoding lysosomal acid phosphatase (Acp2) causes cerebellum and skin malformation in mouse. Neurogenetics 5:229–238
56. Ishizawa K, Dickson DW (2001) Microglial activation parallels system degeneration in progressive supranuclear palsy and corticobasal degeneration. J Neuropathol Exp Neurol 60:647–657
57. Cleaver JE (2005) Cancer in xeroderma pigmentosum and related disorders of DNA repair. Nat Rev Cancer 5:564–573
58. Robbins JH, Brumback RA, Moshell AN (1993) Clinically asymptomatic xeroderma pigmentosum neurological disease in an adult: evidence for a neurodegeneration in later life caused by defective DNA repair. Eur Neurol 33:188–190
59. Sugasawa K, Okuda Y, Saijo M, Nishi R, Matsuda N, Chu G, Mori T, Iwai S, Tanaka K, Tanaka K, et al (2005) UV-induced ubiquitylation of XPC protein mediated by UV-DDB-ubiquitin ligase complex. Cell 121:387–400
60. Kapetanaki MG, Guerrero-Santoro J, Bisi DC, Hsieh CL, Rapic-Otrin V, Levine AS (2006) The DDB1-CUL4ADDB2 ubiquitin ligase is deficient in xeroderma pigmentosum group E and targets histone H2A at UV-damaged DNA sites. Proc Natl Acad Sci USA 103:2588–2593
61. Inoki T, Yamagami S, Inoki Y, Tsuru T, Hamamoto T, Kagawa Y, Mori T, Endo H (2004) Human DDB2 splicing variants are dominant negative inhibitors of UV-damaged DNA repair. Biochem Biophys Res Commun 314:1036–1043

OBSERVATION

Clinical and Pathologic Evidence of Corticobasal Degeneration and Progressive Supranuclear Palsy in Familial Tauopathy

Paul J. Tuite, MD; H. Brent Clark, MD, PhD; Catherine Bergeron, MD; Matthew Bower, MS, CGC; Peter St George-Hyslop, PhD; Vesselina Mateva, MD; John Anderson, MD; David S. Knopman, MD

Background: Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are neurodegenerative tauopathies. Sporadic and familial cases of PSP and CBD have been noted, but both have not been reported in a single family.

Objective: To describe the clinical, oculomotor, balance, functional imaging, histopathologic, and genetic studies in a family with CBD and PSP.

Design: A report of the clinical and pathological features in a familial tauopathy.

Setting: University of Minnesota.

Patients: We evaluated 2 siblings and clinically assessed 20 additional family members.

Main Outcome Measures: Demonstration of salient features in deceased and living family members.

Results: Histopathologically confirmed CBD in one sibling and PSP in another deceased sibling were demonstrated; both had clinical features of corticobasal syndrome. In addition, 3 siblings had probable PSP by clinical criteria. Genetic studies of 4 affected family members demonstrated the H1/H1 haplotype but did not reveal pathogenic *tau* mutations. The family history revealed consanguinity.

Conclusions: This is the first report, to our knowledge, of CBD and PSP in 2 individuals in a single family who presented with corticobasal syndrome and had other affected siblings with clinical PSP. Despite clinical and pathologic heterogeneity, a unifying genetic etiology appears likely in this familial tauopathy.

Arch Neurol. 2005;62:1453-1457

Author Affiliations:
Departments of Neurology (Drs Tuite, Clark, and Mateva), Otolaryngology (Dr Anderson), and Laboratory Medicine and Pathology (Dr Clark) and Institute of Human Genetics (Mr Bower), University of Minnesota, Minneapolis; Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario (Drs Bergeron and St George-Hyslop); and Department of Neurology, Mayo Clinic, Rochester, Minn (Dr Knopman).

CORTICOBASAL DEGENERATION (CBD) and progressive supranuclear palsy (PSP) are considered separate diseases with distinct diagnostic criteria.[1] Previously, CBD and PSP have not been reported in the same family. Both conditions exhibit phenotypic variability, even in different members of the same family.[2-5] Although clinically CBD and PSP may overlap, histopathologic features usually allow for a separation of the conditions.[6,7]

Genetic studies have not resolved the issue of pathogenesis of these 2 tauopathies. Several pedigrees have reported autosomal dominant transmission in PSP along with reduced penetrance and variable expressivity.[5] Presumed autosomal recessive inheritance has also been reported in families with PSP.[8] Rarely, pathogenic *tau* mutations have been described in familial PSP pedigrees, whereas most do not have *tau* mutations.[8,9]

Conrad et al[10] provided the first evidence of an association between the *A0* allele of the *tau* gene and sporadic PSP. The *A0* allele was later shown to segregate with a tau haplotype, designated H1.[11] Case-control studies have demonstrated a significant association between the H1 haplotype and both PSP and CBD.[11,12] The exact mechanism by which the H1 haplotype confers an increased risk for these conditions is not known, and postmortem studies suggest that the tau protein appears to undergo distinct processing in each of these 2 conditions.[13] Therefore, additional genetic or environmental factors may interact to dictate the exact pathologic findings.

METHODS

We evaluated clinical features, laboratory findings, and *tau* pathologic features of 2 siblings (patients VI:1 and VI:4) and clinically assessed 20 additional family members. The study

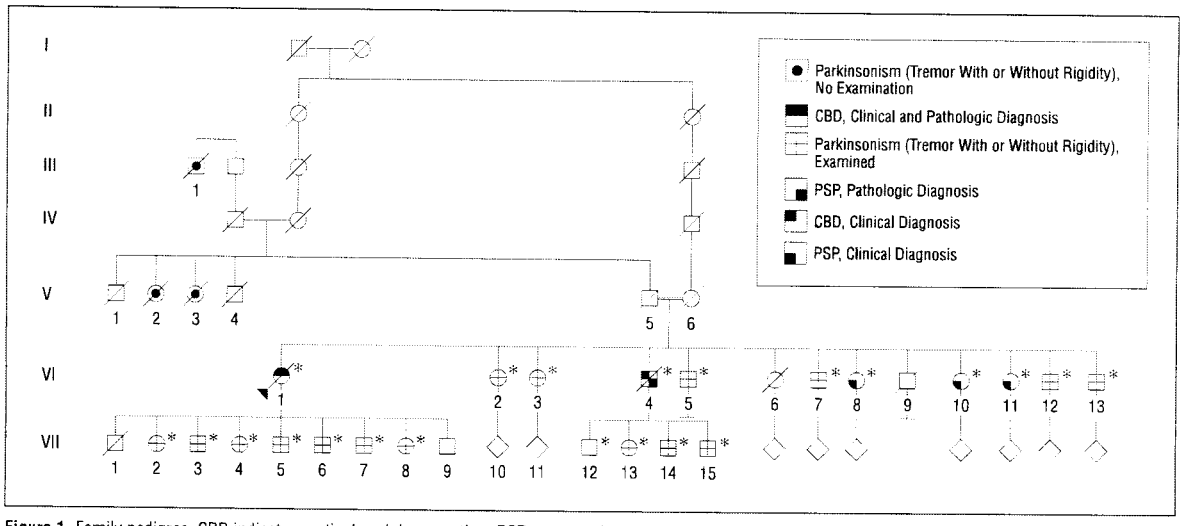

Figure 1. Family pedigree. CBD indicates corticobasal degeneration; PSP, progressive supranuclear palsy. Asterisk indicates patient was examined.

Table 1. Clinical Histories of 2 Sibling Probands With Tauopathy[18]

Finding	Patient 1 (VI:1)	Patient 2 (VI:4)
Clinical diagnosis	Corticobasal syndrome	Corticobasal syndrome
Sex	Female	Male
Age at symptom onset, y	57	63
Duration of illness, y	8	4
Initial symptom	Right leg clumsiness	Left hand clumsiness
Asymmetry	Yes	Yes
Rigidity or bradykinesia*	Yes	Yes
Dystonia*	Yes, right arm	Yes, left arm
Action tremor*	Yes	Yes
Myoclonus*	Yes	Possibly
Alien limb*	Yes	Possibly
Ideomotor apraxia*	Yes	Yes
Aphasia	Possibly	Possibly
Blepharospasm	Yes	Yes
Ophthalmoparesis	Yes	Yes
Apraxia of eyelids	Yes	Yes
Dysarthria	Yes	Yes
Pseudobulbar	Yes	No
Grasp reflexes	Yes	Unknown
UMN signs	Yes	Possibly
Quadriparesis	Yes	Yes
Response to dopamine	None	None
MRI white matter changes	Yes	Yes

Abbreviations: MRI, magnetic resonance imaging; UMN, upper motor neuron signs.
*Major diagnostic features of corticobasal syndrome.

was approved by the institutional review board at the University of Minnesota.

Two living siblings (patients VI:8 and VI:10, **Figure 1**) underwent brain magnetic resonance imaging (MRI) studies, genetic evaluations, and balance testing. Postural stability was evaluated using the Equitest protocol.[14] Patient VI:8 also underwent ocular motor testing and fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning.[15] Horizontal and vertical components of eye movements were recorded using the magnetic search coil technique.[16] A third sibling has recently presented with similar clinical findings (VI:11).

Genetic testing for *tau* mutations was conducted on paraffin-embedded brain tissue samples from the deceased patients (VI:1 and VI:4) and genomic DNA from patients VI:8 and VI:10 using polymerase chain reaction methods.[17] Exons 9, 10, 11, 12, and 13 of the *tau* gene were amplified using primers complementary to intronic sequences and sequenced using internal primers. The dinucleotide repeat in the intron downstream of *tau* exon 9 was also analyzed, as described elsewhere.[19]

PATIENTS

Relevant family history is illustrated in Figure 1. Patient VI:1 developed symptoms at 58 years of age, with right arm dystonic posturing. Ideomotor apraxia, generalized rigidity, supranuclear ophthalmoparesis, and blepharospasm were noted in subsequent examinations, and ultimately the patient became quadriparetic. After 8 years of symptoms, the patient died.

Patient VI:4 presented at 63 years of age with dystonia of his left arm. Blepharospasm with apraxia of eyelid opening was noted, as were generalized rigidity, ideomotor apraxia, and vertical ophthalmoparesis. The patient died less than 4 years after the onset of symptoms.

Table 1 and **Table 2** summarize the clinical and pathologic findings of these patients. Clinically, both patients had features of CBD and symptoms that precluded a diagnosis of PSP by traditional criteria. Neuropathologically, patient VI:1, who had a longer course of illness, had features more consistent with CBD[19] (**Figure 2**A and B). The neuropathologic findings in patient VI:4 were more consistent with the changes seen in PSP[20] (Figure 2C and D). For both patients, the *A0/A0* genotype at the intragenic microsatellite marker of the *tau* gene was observed, but no pathogenic mutations were found in the sequenced regions of the *tau* gene.

OTHER FAMILY MEMBERS

As shown in Figure 1, 20 family members were examined in 1999 after the death of the second sibling. Of the 20 evaluated, 19 had subtle tremor with or without rigidity. In 2001 and 2002, patients VI:8 and VI:10 presented, and in 2004, patients VI:2 and VI:11 were again evaluated.

AFFECTED SIBLINGS

Case 1 (Patient VI:8)

Patient VI:8 was a 64-year-old right-handed woman with a 2-year history of bradykinesia, 2 unexplained falls when going up or down stairs, micrographia, neck stiffness, and depression. Her symptoms were "mild" and did not affect activities of daily living.

Her Mini-Mental State Examination (MMSE) score was 28 of 30. A cranial nerve examination showed slowed saccades, more marked vertically than horizontally, hypomimia, and hypophonia. A motor examination revealed mild rigidity in her neck and all extremities and a mild bilateral postural tremor of the upper extremities. Reflexes were hyperreflexic but symmetric in the upper extremities with unsustained ankle clonus. Extensor toe signs were absent. Postural stability was normal, and there was reduced right arm swing on ambulation.

An MRI study demonstrated periventricular white matter and basal ganglia T2-weighted signal changes consistent with small-vessel ischemic disease. An FDG PET scan demonstrated decreased glucose metabolism in the posterior frontal and parietal regions bilaterally, extending to the frontal operculum inferiorly.

Oculomotor testing showed hypometric saccades followed by a "staircase pattern" as the eye moved toward the target and an abnormal frequency of horizontal micro–square wave jerks, consistent with PSP. Quantitative posturography results were normal. Genetic testing revealed no pathogenic *tau* mutations and an *A0/A0* genotype at the intragenic microsatellite marker. Three years after presentation, she has increasing postural instability and saccadic impairment (more marked vertically) but no evidence of apraxia, an alien limb, or marked asymmetric parkinsonian signs.

Case 2 (Patient VI:10)

Patient VI:10 was a 59-year-old right-handed woman who presented for an evaluation because of concern about developing the familial tauopathy. She reported a 2-year history of slight difficulty walking and denied other characteristic symptoms. She had subtle cognitive and motor difficulties after a myocardial infarction and cardiac arrest (in 1986), which were stable until her recent symptoms developed.

Her MMSE score was 29 of 30. A cranial nerve examination demonstrated hypomimia and saccadic pursuit. A motor examination showed rigidity in the neck, arms, and legs and bilateral slowness of fine finger movements and foot tapping. An upper extremity postural tremor was noted bilaterally and was more prominent on the left side. She had normal postural stability and gait. A brain MRI study showed mild white matter hyperintensities and mild generalized cerebral atrophy, possibly greater in the frontal lobes. The results of the genetic testing were identical to those of patient 1. One year after presentation, she was noted to have increasing gait instability and impaired vertical saccades without profound asymmetric parkinsonism, alien limb, or apraxia.

Case 3 (Patient VI:11)

Patient VI:11 was a 61-year-old right-handed woman who requested an evaluation in 2004 because of concerns about the familial condition. Two years before consultation she had developed unsteadiness of gait, experienced several unexplained falls, developed slowness on the right more than the left side of her body, and noted softening of her voice.

When evaluated in 1999, she had a head tilt, mild rigidity of her limbs, and reduced arm swing. At her 2004 examination, her MMSE score was 27 of 30. She had saccadic pursuit movements with slowing of vertical saccades. Neck and appendicular rigidity was noted, with slightly greater rigidity and bradykinesia of her right than left arm. She had a subtle postural tremor and impaired postural reflexes. Imaging studies have not been performed.

Table 2. Neuropathologic Findings in 2 Probands With Tauopathy

Finding	Patient 1 (VI:1)	Patient 2 (VI:4)
Pathologic diagnosis	Corticobasal degeneration	Progressive supranuclear palsy
Neuronal loss and gliosis		
Frontal lobe	Moderate	Focally mild
Parietal lobe	Focally moderate	No
Putamen	Moderate	Mild
Globus pallidus	Moderate	Mild to moderate
Subthalamic nucleus	Mild	Mild
Substantia nigra	Severe	Severe
Cerebral white matter rarefaction	Yes	No
Cytologic pathologic findings		
Tufted astrocytes	No	Yes
Coiled bodies	Yes	Yes
Astrocytic plaques	Yes	No
Ballooned neurons*	Yes	No
Neuronal neurofibrillary tangles (corticobasal bodies)	SN	SN, GP, LC, RN, PAG, ION, STN, OMN

Abbreviations: GP, globus pallidus; ION, inferior olivary nucleus; LC, locus coeruleus; OMN, oculomotor nucleus; PAG, periaqueductal gray matter; RN, red nucleus; SN, substantia nigra; STN, subthalamic nucleus.
*Ballooned neurons were immunohistochemically positive for phosphorylated neurofilaments.

ADDITIONAL SIBLINGS AND FAMILY HISTORY

After the death of patient VI:4, in 1999, all surviving members of this sibship were examined, and DNA samples were collected. All 6 siblings had subtle parkinsonian features. Subsequently, 1 has been diagnosed elsewhere as having parkinsonism (VI:5), 1 continues to have mild parkinsonian findings (VI:2), and 2 have reportedly developed parkinsonism but have not yet been evaluated (VI:3 and VI:13).

Two family members in generation V (V:2 and V:3) were reported to have parkinsonism with similar features to patients VI:1 and VI:4, but no formal clinical or pathologic data were collected. An additional family member (III:1) was also reported to have parkinsonism. A review of marriage and birth records confirmed that patients V:5 and V:6 were consanguineous (third cousins). Evidence for additional loops of consanguinity in this family may exist, but these relationships have not been confirmed.

COMMENT

This family presents an opportunity to characterize factors that underlie PSP and CBD. The possibility of an environmental etiology seems unlikely in light of the preponderance of parkinsonian features in multiple

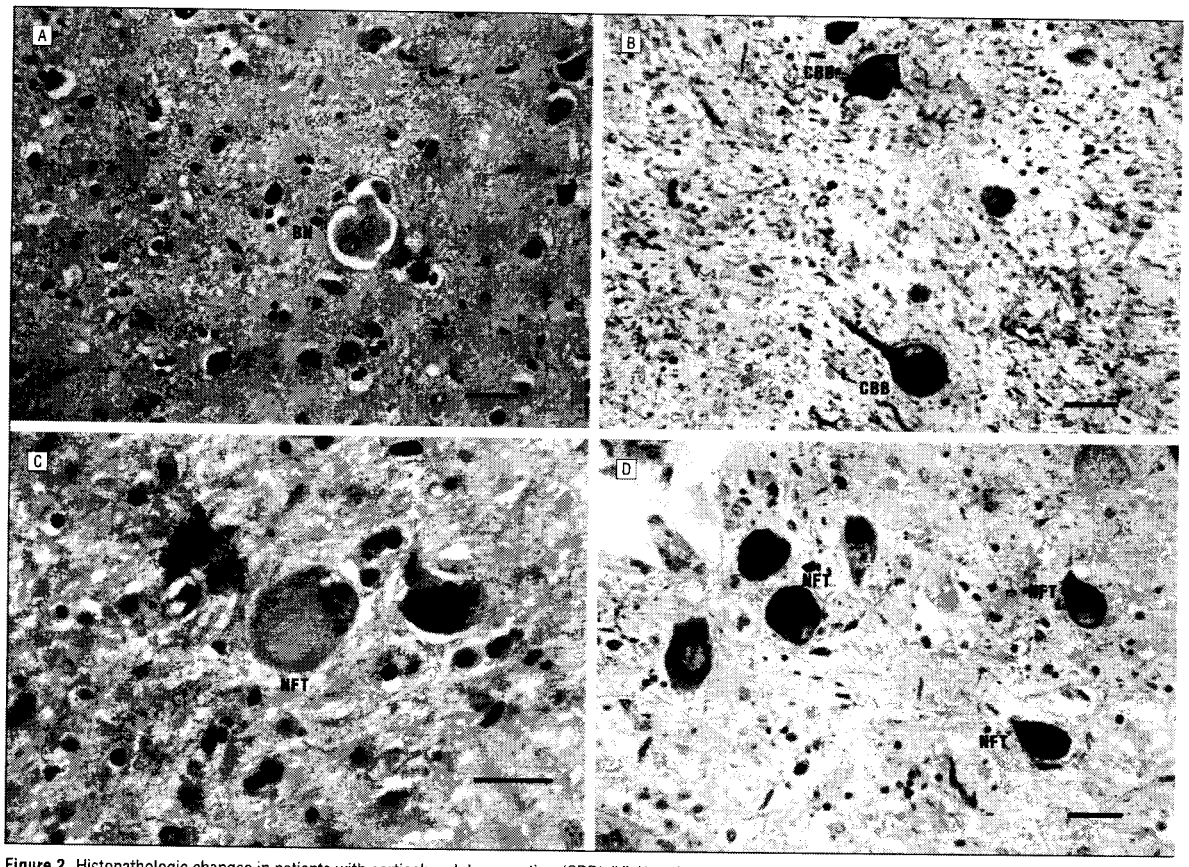

Figure 2. Histopathologic changes in patients with corticobasal degeneration (CBD) (VI:1) and progressive supranuclear palsy (PSP) (VI:4). A, Ballooned neuron (BN) in frontal cortex (hematoxylin-eosin, original magnification ×200). B, Glial plaque in cerebral cortex (*tau* immunohistochemistry with hematoxylin, original magnification ×200). C, Neurofibrillary tangle (NFT) in globus pallidus (*tau* immunohistochemistry with hematoxylin, original magnification ×300). D, Tufted astrocyte in striatum (*tau* immunohistochemistry with hematoxylin, original magnification ×200). CBB indicates corticobasal body. Scale bars=50 μm.

generations. Meanwhile, several factors complicate the search for a genetic basis. First, the segregation of the disease phenotype does not fit with classic inheritance patterns; this family may not have a single mendelian explanation. A somewhat analogous story relates to the parkin gene associated with familial parkinsonism, which has a clear manner of transmission.[21] Determining the mode of inheritance is further complicated by the uncertainty of clinical status for those with mild parkinsonism. Although some individuals have developed PSP, 1 individual has not experienced disease progression. It is also possible that this is not a single pathologic process; there may be 2 separate but related processes in this family. Nonetheless, despite differing clinical (corticobasal syndrome and PSP) and pathologic (CBD and PSP) features, a primary genetic basis remains the focus of research. To address this, the ongoing work is evaluating the *tau* locus, sequencing genes associated with familial parkinsonism, ascertaining a dosage effect of *tau*, and performing additional pathologic studies. Further characterization of this family may provide insights into the pathogeneses of sporadic CBD and PSP. Even if genetic markers remain out of reach, it is hoped that additional longitudinal studies with neuropsychological measures, brain MRI morphometry, and fluorodeoxyglucose positron emission tomography may prove useful as a means to predict risk of disease and allow for monitoring of disease progression.

Accepted for Publication: December 7, 2004.
Correspondence: Paul J. Tuite, MD, Department of Neurology, University of Minnesota School of Medicine, 12-100 Phillips Wangensteen Building, MMC 295, 420 Delaware St SE, Minneapolis, MN 55455-0323 (tuite002@umn.edu).
Author Contributions: *Study concept and design:* Tuite and Anderson. *Acquisition of data:* Tuite, Clark, Bergeron, Bower, St George-Hyslop, Mateva, Anderson, and Knopman. *Analysis and interpretation of data:* Tuite, Clark, Bergeron, St George-Hyslop, Mateva, and Anderson. *Drafting of the manuscript:* Tuite, Clark, Bower, Mateva, and Anderson. *Critical revision of the manuscript for important intellectual content:* Tuite, Clark, Bergeron, Bower, St George-Hyslop, Anderson, and Knopman. *Statistical analysis:* Anderson. *Obtained funding:* Tuite. *Administrative, technical, and material support:* Tuite, Bergeron, Anderson, and Knopman. *Study supervision:* Tuite, St George-Hyslop, Anderson, and Knopman.
Acknowledgment: We thank Vickie Matthias-Hagen, MS, CGC, and Raabeaa Malik, BA, for their help in collect-

ing DNA samples and pertinent history from family members, and Pat Bulgerin and Lisa Brauer, PhD, for their editorial assistance.

REFERENCES

1. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*. 1996;47:1-9.
2. Brown J, Lantos P, Stratton M, Roques P, Rossor M. Familial progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry*. 1993;56:473-476.
3. de Yebenes JG, Sarasa JL, Daniel SE, Lees AJ. Familial progressive supranuclear palsy: description of a pedigree and review of the literature. *Brain*. 1995;118:1095-1103.
4. Gallien P, Verin M, Rancurel G, De Marco O, Eden G. First familial cases of corticobasal degeneration [abstract]. *Neurology*. 1998;50(suppl 4):A428.
5. Rojo A, Pernaute RS, Fontan A, et al. Clinical genetics of familial progressive supranuclear palsy. *Brain*. 1999;122:1233-1245.
6. Hattori M, Hashizume Y, Yoshida M, et al. Distribution of astrocytic plaques in the corticobasal degeneration brain and comparison with tuft-shaped astrocytes in the progressive supranuclear palsy brain. *Acta Neuropathol (Berl)*. 2003;106:143-149.
7. Jellinger KA. The neuropathologic diagnosis of secondary parkinsonian syndromes. *Adv Neurol*. 1996;69:293-303.
8. Pastor P, Pastor E, Carnero C, et al. Familial atypical progressive supranuclear palsy associated with homozigosity for the delN296 mutation in the tau gene. *Ann Neurol*. 2001;49:263-267.
9. Poorkaj P, Muma NA, Zhukareva V, et al. An R5L tau mutation in a subject with a progressive supranuclear palsy phenotype. *Ann Neurol*. 2002;52:511-516.
10. Conrad C, Andreadis A, Trojanowski JQ, et al. Genetic evidence for the involvement of tau in progressive supranuclear palsy. *Ann Neurol*. 1997;41:277-281.
11. Baker M, Litvan I, Houlden H, et al. Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet*. 1999;8:711-715.
12. Houlden H, Baker M, Morris HR, et al. Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. *Neurology*. 2001;56:1702-1706.
13. Arai T, Ikeda K, Akiyama H, et al. Different immunoreactivities of the microtubule-binding region of tau and its molecular basis in brains from patients with Alzheimer's disease, Pick's disease, progressive supranuclear palsy and corticobasal degeneration. *Acta Neuropathol (Berl)*. 2003;105:489-498.
14. Nasher L. Computerized dynamic posturography. In: Jacobson G, Newman C, Kartush J, eds. *Handbook of Balance Function Testing*. Chicago, Ill: Mosby-Year Book; 1993:280-307.
15. Jendroska K, Rossor MN, Mathias CJ, Daniel SE. Morphological overlap between corticobasal degeneration and Pick's disease: a clinicopathological report. *Mov Disord*. 1995;10:111-114.
16. Robinson DA. A method of measuring eye movement using a scleral search coil in a magnetic field. *IEEE Trans Biomed Eng*. 1963;10:137-145.
17. Wright D, Manos M. *PCR Protocol*. San Diego, Calif: Academic Press; 1990.
18. Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Ann Neurol*. 2003;54(suppl 5):S15-S19.
19. Dickson DW, Bergeron C, Chin SS, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. *J Neuropathol Exp Neurol*. 2002;61:935-946.
20. Litvan I, Hauw JJ, Bartko JJ, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. *J Neuropathol Exp Neurol*. 1996;55:97-105.
21. Farrer M, Chan P, Chen R, et al. Lewy bodies and parkinsonism in families with parkin mutations. *Ann Neurol*. 2001;50:293-300.

ORIGINAL CONTRIBUTION

Familial Progressive Supranuclear Palsy

Detection of Subclinical Cases Using ^{18}F-Dopa and ^{18}Fluorodeoxyglucose Positron Emission Tomography

Paola Piccini, MD; Justo de Yebenez, MD; Andrew J. Lees, MD; Roberto Ceravolo, MD; Nora Turjanski, MD; Peter Pramstaller, MD; David J. Brooks, MD

Background: Progressive supranuclear palsy (PSP) is generally considered to be a sporadic disease; however, occasional cases of familial PSP have been described. The rarity of reports of familial PSP may be attributed in part to an inability to detect subclinical disease in affected relatives who subsequently die before symptoms clinically develop.

Objective: To study regional cerebral dopaminergic function and glucose metabolism in members of 2 large kindreds with familial PSP to identify subclinical cases.

Methods: Three clinically affected members from the 2 PSP kindreds were scanned with both ^{18}F-dopa and ^{18}fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET). Fifteen asymptomatic first-degree relatives were scanned with ^{18}F-dopa PET; 10 of them also underwent a second PET study with ^{18}FDG.

Results: All 3 clinically affected PSP patients showed a significant reduction in caudate and putamen ^{18}F-dopa uptake along with a significant reduction in striatal, lateral, and medial premotor area and dorsal prefrontal cortex glucose metabolism. In 4 of the 15 asymptomatic relatives, caudate and putamen ^{18}F-dopa uptake was 2.5 SDs lower than the normal mean. These 4 subjects and a fifth asymptomatic relative with normal ^{18}F-dopa uptake showed a significant reduction of cortical and striatal glucose metabolism in a pattern similar to that of their affected relatives.

Conclusion: ^{18}F-dopa and ^{18}FDG PET allowed us to identify 5 cases with subclinical metabolic dysfunction among 15 subjects (33%) at risk for PSP, suggesting that this approach is useful for characterizing the pattern of aggregation in PSP kindreds.

Arch Neurol. 2001;58:1846-1851

From the Medical Research Council Clinical Sciences Centre, Imperial College School of Medicine, Hammersmith Hospital, London, England (Drs Piccini, Ceravolo, Turjanski, and Brooks); Department of Neurology, Fundacion Jimenez Diaz, Universidad Autonoma de Madrid, Madrid, Spain (Dr de Yebenez); Institute of Neurology, Queen Square, London (Drs Lees and Brooks); and the Department of Neurology, Regional General Hospital, Bolzano, Italy (Dr Pramstaller).

PROGRESSIVE supranuclear palsy (PSP) is a late-onset neurodegenerative disease characterized by supranuclear vertical gaze palsy, postural instability, rigidity, bulbar dysfunction, and dementia with the variable presence of pyramidal and cerebellar signs.[1,2] It is usually considered a sporadic disorder, even though a few familial, pathologically proven PSP cases have been reported.[3] In a recent article concerning PSP kindreds from Europe and North America, 12 probands with 22 secondary cases with typical clinical PSP features have been described.[4] Thus, the apparent rarity of familial PSP may reflect the difficulty in recognizing PSP cases in epidemiological surveys. In particular, atypical presentations of PSP cases may hinder accurate phenotypic assignment, and mortality owing to other diseases may be responsible for a censoring effect with subclinically affected relatives dying before symptoms develop.

Positron emission tomography (PET) has proven to be a reliable method for detecting in vivo subclinical dysfunction in degenerative diseases. ^{18}F-dopa PET studies have shown that 25% of asymptomatic adult relatives of patients with familial Parkinson disease (PD) and 55% of elderly asymptomatic co-twins of PD patients show subclinical dopaminergic nigrostriatal dysfunction[5,6]; ^{11}C-raclopride PET revealed that 50% of asymptomatic adult carriers of the Huntington disease *IT15* gene had significant reductions in striatal dopamine D_2 receptor binding.[7]

In this study we used ^{18}F-dopa and ^{18}fluorodeoxyglucose (^{18}FDG) PET to investigate regional cerebral dopaminergic function and glucose metabolism in clinically affected patients and their asymptomatic relatives from 2 kindreds with familial PSP. Our aim was to determine the prevalence of subclinical cases with disease.

SUBJECTS AND METHODS

We studied 2 unrelated kindreds in which PSP was present across several generations. The members of these families were referred to our PET Centre from the Movement Disorder Clinics at the National Hospital for Neurology, Queen Square, London, England (kindred 1) and from the Fundacion Jimenez Diaz, Avenida de los Reyes Catolicos, Ciudad Universitaria, Madrid, Spain (kindred 2). One of the 2 original probands (kindred 2) had died by the time of this study, and postmortem analysis showed typical PSP neurofibrillary tangle disease. In the antecedent relatives, the diagnosis of PSP was based on review of hospital records.

The diagnosis of possible or probable PSP was made according to the National Institute of Neurological Disorders and Stroke PSP society criteria.[8] Three affected subjects (2 from kindred 1; 1 from kindred 2) had an akinetic-rigid syndrome poorly responsive to levodopa with onset at age 53, 60, and 70 years, respectively; 2 had a supranuclear down-gaze palsy, whereas the third had slowing of vertical saccades and prominent postural instability. All 3 PSP subjects had axial rigidity, and 2 had a pseudobulbar palsy. Two of the 3 patients had mild to moderate cognitive impairment of frontal type. (For more clinical details see reference 4.) To establish the pattern of dopaminergic and metabolic dysfunction in these families, we studied the 3 clinically affected members with ^{18}F-dopa and ^{18}FDG PET (**Table**).

All asymptomatic first-degree adult relatives aged 40 years or older were asked to participate in the study. Fifteen subjects agreed to undergo PET scanning with both ^{18}F-dopa and ^{18}FDG. All 15 relatives underwent ^{18}F-dopa PET, and 10 of them also underwent ^{18}FDG PET. Of the other 5 that did not have ^{18}FDG, 3 could not be rescanned for technical reasons, and 2 subjects refused to have a second scan because they experienced claustrophobia during the first scan.

The 15 asymptomatic relatives had no history of neurological illness and had not taken drugs known to affect the dopaminergic system. At the time of scanning, all underwent a full neurological examination. Fourteen subjects had no signs or symptoms of neurological disease, while 1 subject, aged 68 years (kindred 2, III.3), had an isolated postural hand tremor. The characteristics of these 15 subjects are detailed in Table 1B.

SCANNING PROTOCOLS

Permission for these studies was obtained from the Ethics Committee of the Hammersmith Hospitals Trust, London. Approval to administer radio-labeled ligands was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom. Written consent was obtained from all subjects after a full explanation of the procedure.

The PET studies were performed using a camera at the Medical Research Council, Cyclotron Building, Hammersmith Hospital, London (ECAT 953B; CTI Inc, Knoxville, Tenn). This camera acquired data simultaneously from 31 consecutive transaxial planes (slice separation, 3.4 mm with an average in-plane resolution of 6 mm full width at half maximum). Scanning was performed with the orbitomeatal line parallel to the detector rings. A 10-minute transmission scan, using a retractable ^{68}Ga/^{68}Ge ring source, was performed prior to the acquisition of the emission data to correct for tissue attenuation.

^{18}F-Dopa Scans

Prior to ^{18}F-dopa injection, subjects were given oral carbidopa, 100 mg, 1 hour before and 50 mg 5 minutes before the study to block peripheral aromatic amino acid decarboxylase. A mean dose of 4.4 mCi (163 MBq) of ^{18}F-dopa was infused into each subject intravenously over 30 seconds, and the dynamic emission data were acquired in 3-dimensional (D) mode as 25 time-frames over 95 minutes.

^{18}FDG Scans

A mean dose of 4.7 mCi (174 MBq) of ^{18}FDG was administered to each subject by intravenous infusion over 30

Continued on next page

RESULTS

CLINICALLY AFFECTED RELATIVES

^{18}F-Dopa

Mean ^{18}F-dopa caudate and putamen K_i values (0.0051 ± 0.0011 min^{-1} and 0.0049 ± 0.008 min^{-1}) were significantly reduced ($P<.001$) in the 3 PSP relatives compared with normal subjects (0.0104 ± 0.0010 min^{-1} and 0.0102 ± 0.009 min^{-1}) (**Figure 1**).

^{18}Fluorodeoxyglucose

The SPM analysis revealed areas of significantly reduced ^{18}FDG uptake in bilateral lateral and medial premotor areas (areas 6 and 8) (x, y, z=−24, −8, 56; z score, 5.31; and x, y, z=2, −2, 58; z score, 4.50), bilateral dorsal prefrontal cortex (area 10) (x, y, z=−30, −58, 8; z score, 6.12; and x, y, z=50, −48, 12; z score, 5.80), right thalamus (x, y, z=−4, 20, 8; z score, 4.86), and bilateral striatum (x, y, z=−12, −6, 4; z score, 6.46; and x, y, z=8, −10, 4; z score, 6.32) (**Figure 2**) in the PSP patients compared with controls. Increases in ^{18}FDG uptake were not found in any location.

ASYMPTOMATIC MEMBERS

^{18}F-Dopa

Four of the 15 asymptomatic relatives had ^{18}F-dopa caudate and putamen uptake values that were 2.5 SDs lower than the normal mean (Figure 1). One subject was from kindred 1, and 3 subjects were from kindred 2 (**Figure 3**).

^{18}Fluorodeoxyglucose

The comparison of individual scans for each asymptomatic relative vs the control group identified 5 subjects with areas of significantly decreased regional glucose uptake.

seconds, and the data were acquired in 3-dimensional mode as 24 time-frames over 60 minutes. In those subjects who underwent both scans, the interval between PET studies was 2 to 7 days. ^{18}F-dopa data were compared with those obtained from a group of 19 age-matched control subjects (mean ± SD, 64 ± 12.1 years) and ^{18}FDG data with those of 8 control subjects (60 ± 14.5 years) scanned using the same camera with the same protocols.

Data Analysis

^{18}F-dopa. The analysis was performed using in-house software written in Interactive Data Language (Research System Inc, Boulder, Colo) on SUN Sparc workstations (SUN Microsystems Inc, Palo Alto, Calif). Region-of-interest (ROI) placement was defined with a standard template. We used standardized regions: a 10-mm diameter circle ROI to sample head of caudate and 10 × 24-mm elliptical ROI to sample dorsal putamen aligned along the long axis. These regions were placed manually by visual inspection on 3 contiguous planes encompassing the striatum. Mean counts per pixel were measured for left and right caudate and putamen in the last 14 time-frames corresponding to the period 25 to 95 minutes after injection. ^{18}F-dopa influx rate constants (K_i) were then calculated for the left and right caudate and putamen using multiple-time graphical analysis with a nonspecific occipital tissue input function.[9] Two circular regions of 32-mm diameter were placed on the occipital lobes in the same planes as those used to sample striatal regions and averaged to provide the tissue input function. Comparisons of group means were made using unpaired *t* tests. Individual putamen and caudate K_i values were considered abnormal if they were more than 2.5 SDs lower than the normal group means.

^{18}Fluorodeoxyglucose. The analysis was performed by applying statistical parametric mapping (SPM) to integrated images of ^{18}FDG activity spanning the last 20 minutes of the dynamic scan to identify areas of significant altered regional cerebral glucose metabolism in the PSP patients and the asymptomatic relatives compared with the control group. The validation of voxel-by-voxel statistical techniques to localize significantly altered ^{18}FDG uptake data has been recently reported.[10,11] The SPM analysis showed the same findings whether rCMRGlu (glucose regional cerebral metabolic rate) or ^{18}FDG uptake datasets were used.[10] We have chosen to use SPM and ^{18}FDG uptake data to avoid the invasive arterial cannulation required to calculate rCMRGlu.

Integral ^{18}FDG images for each subject were transformed into standard stereotactic space.[12] The template used in this study was an ^{18}FDG average image of 8 ^{18}FDG PET scans of healthy subjects normalized to the standard SPM 95 flow template.[10] The images were then smoothed using a Gaussian kernel (20 × 20 × 12-mm full width at half maximum) to remove high-frequency noise from the images. The variance in global cerebral metabolic rate for glucose across all subjects was removed using analysis of covariance; between-group comparisons were then performed with a *t* statistic on a voxel-by-voxel basis.[13] The first comparison aimed to identify differences in regional ^{18}FDG uptake between the 3 PSP patients and the group of 8 normal controls to establish the pattern of metabolic abnormalities in the clinically affected subjects; for this comparison, significance was accepted if voxels survived an uncorrected threshold of $P<.001$. In phantom experiments, this value of significance has been shown to be sufficiently conservative to protect against false-positive results.[14]

As most asymptomatic relatives would be expected to have normal ^{18}FDG uptake, a group analysis could mask those few subjects with significant abnormalities. We therefore compared individual scans for each asymptomatic subject against the group of 8 normal controls with the objective of finding a pattern of ^{18}FDG uptake abnormalities in those with subclinical disease similar to the affected relatives. For this comparison significance was accepted if voxels survived at a corrected threshold of $P<.01$. In this way we were able to identify 5 subjects who had at least 1 area of abnormal ^{18}FDG uptake in the same region as those of the affected relatives. We then compared these 5 subjects as a group against the group of 8 normal controls.

Four of them were also subjects with reduced striatal ^{18}F-dopa K_i values. In these 4 subjects, we found cortical and subcortical reductions of ^{18}FDG uptake similar to those found in their affected relatives. A fifth asymptomatic relative, with normal striatal ^{18}F-dopa uptake, showed a reduction of ^{18}FDG uptake in the lateral premotor cortex and dorsal prefrontal cortex (x, y, z = 40, −22, 50, maximal *z* score, 3.17; and x, y, z = −46, −54, 8, maximal *z* score, 3.84, respectively).

The voxel-by-voxel analysis applied to these 5 asymptomatic members as a group showed significant decreases in ^{18}FDG uptake in bilateral lateral and medial premotor areas (x, y, z = −30, −14, 56; *z* score, 5.31; and x, y, z = 10, −6, 52; *z* score, 4.24), right dorsal prefrontal cortex (x ,y, z = −46, −54, 8; *z* score, 5.42) and bilateral striatum (x, y, z = −6, −16, 8; *z* score, 4.7; and x, y, z = 20, −12, 8; *z* score, 4.15) compared with controls (Figure 2).

Figure 3 shows the genealogical trees for kindred 1 and kindred 2. The members scanned with ^{18}FDG and/or ^{18}F-dopa and those asymptomatic subjects with abnormal scans are also indicated.

COMMENT

In our familial PSP patients, striatal ^{18}F-dopa uptake was significantly reduced bilaterally, with putamen and caudate being similarly affected. Such a uniform reduction of dopamine storage throughout the striatum has also been reported for sporadic idiopathic PSP patients[15-18] and suggests that the substantia nigra in PSP patients is globally involved. Glucose metabolism was also reduced in the striatum of our patients, in agreement with findings reported for sporadic PSP patients[19-21] and in contrast to findings for patients with PD in which striatal ^{18}FDG uptake is preserved.[19] The reduction in premotor, prefrontal, and thalamic glucose metabolism that we have found in our familial PSP members is also typical of patients with sporadic PSP,[19-22] although other areas, such as pa-

Characteristics of the Clinically Affected Members and of the Asymptomatic Members Studied With ^{18}F-Dopa and ^{18}FDG PET*

Subject	Kindred	Sex	Age, y	Duration, y	PET Studies Performed	
					^{18}F-Dopa	^{18}FDG
Clinically affected relatives						
III.1	1	F	75	5	Yes	Yes
III.6	1	M	63	4	Yes	Yes
III.11	2	F	58	5	Yes	Yes
Asymptomatic relatives						
III.3	1	M	71		Yes	Yes
IV.1	1	M	51		Yes	No
IV.2	1	M	46		Yes	No
IV.3	1	M	41		Yes	Yes
IV.7	1	M	41		Yes	No
IV.8	1	M	40		Yes	No
			48.3 ± 11.8†		6‡	2‡
III.2	2	F	69		Yes	Yes
III.3	2	M	68		Yes	Yes
III.4	2	F	67		Yes	Yes
III.5	2	F	62		Yes	Yes
III.15	2	F	53		Yes	No
III.16	2	F	50		Yes	Yes
III.21	2	M	70		Yes	Yes
III.23	2	F	66		Yes	Yes
III.26	2	M	57		Yes	Yes
			62.4 ± 7.4†		9‡	8‡
Total			**55.4 ± 13.2†**		**15‡**	**10‡**

*^{18}FDG indicates ^{18}fluorodeoxyglucose; PET, positron emission tomography.
†Mean ± SD for kindred.
‡No. of studies performed or number. of subjects studied.

rietal cortex and cerebellum, have also been reported to be involved in this condition.[23]

Four of 15 asymptomatic relatives (27%) showed reductions in striatal ^{18}F-dopa and ^{18}FDG uptake bilaterally. These 4 subjects also had decreased ^{18}FDG uptake in a pattern similar to that of their clinically affected relatives; cortical glucose metabolism was reduced in lateral and medial premotor areas and right dorsal prefrontal cortex, while left dorsal prefrontal cortex and thalamus were spared. In addition to these 4 relatives, we identified a fifth asymptomatic subject with normal striatal ^{18}FDG and ^{18}F-dopa uptake who had reduced glucose metabolism in the premotor cortex bilaterally and the right dorsal prefrontal cortex. If we include this last subject, the percentage of asymptomatic adult relatives with abnormal PET findings increases to 33%.

Since the pattern of cerebral glucose hypometabolism and reduction of ^{18}F-dopa uptake in the clinically asymptomatic relatives is similar to that observed in the cases with established disease, we assume that these 5 among the 15 subjects at risk for PSP indeed have subclinical disease. In support of this assumption, 1 of the relatives with abnormal ^{18}F-dopa and ^{18}FDG scans developed clinical PSP 2 years after scanning at age 59 years (kindred 2, III.26). When we arbitrarily divided the asymptomatic relatives who underwent PET scanning into groups older and younger than age 50 years, we observed that none of the 4 subjects younger than 50 years had subclinical abnormalities, while the percentage of subclinical abnormalities among the 11 subjects who were aged 50 years or older rose to 45%. Since the mean age of onset of the disease in the two families is 61 years, this additional finding implies that the duration of the subclinical phase of PSP, at least in these families, is only a few years.

The reduced ^{18}FDG uptake in the frontal cortex of some asymptomatic relatives suggests that frontal cortex hypometabolism constitutes an early disease marker. In agreement with this hypothesis, a previous ^{18}FDG PET/neuropsychological study conducted in a cohort of 41 PSP patients in different stages of the disease reported that, although frontal glucose uptake decreases with disease duration, frontal hypometabolism is already present in the very early stage of the disease and precedes the onset of overt frontal lobe deficits.[22]

In 1 of our asymptomatic subjects, ^{18}FDG uptake was found only to be reduced in cortical areas with sparing of subcortical structures. In early reports of PSP, the cortex was thought to be spared,[24] and this led to the concept of a "subcortical dementia" supposedly owing to an impairment of afferent stimulating systems, maybe reticular or thalamic in origin.[24,25] Subsequent postmortem studies have consistently reported neurofibrillary tangles in frontal cortex,[26-29] suggesting that at least some of the intellectual deficits in PSP are owing to lesions in the cortex itself.[29] The finding in 1 of our asymptomatic subjects of cortical hypometabolism in a pattern similar to that of his affected relatives but without subcortical involvement supports the idea that some of the dysfunction in PSP is cortical in origin and can occur very early.

The presence of subclinical cases detected with ^{18}F-dopa and ^{18}FDG PET in asymptomatic members of PSP families suggests that the familial aggregation for this disease is greater than that ascertained on the basis of clini-

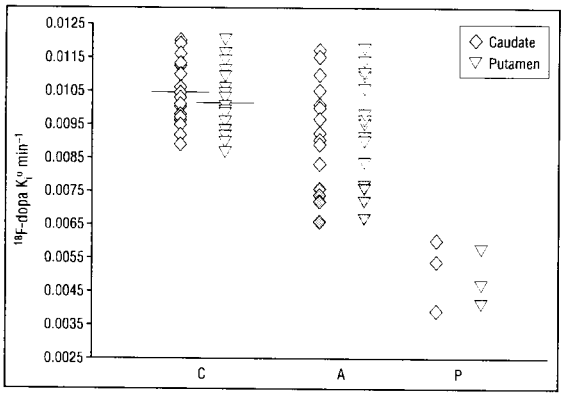

Figure 1. Caudate and putamen ^{18}F-dopa K_i values (min^{-1}) in 19 controls (C), in 15 asymptomatic members of the 2 families (A), and 3 clinically affected members (P). Symbols filled in dark gray indicate the asymptomatic relatives in that caudate and putamen ^{18}F-dopa uptake is 2.5 SDs lower than the mean caudate and putamen uptake values for the controls.

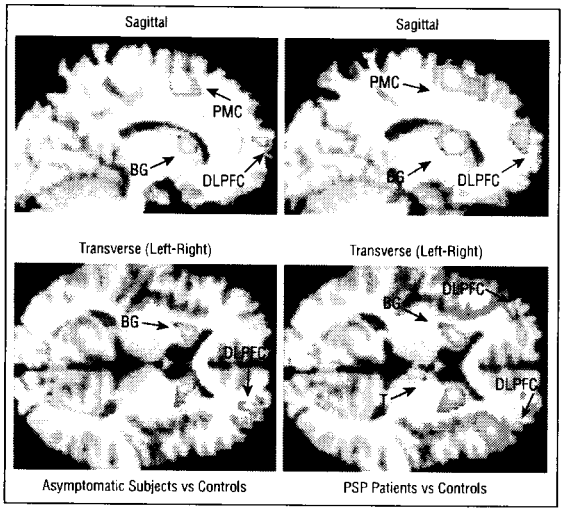

Figure 2. Areas of decreased ^{18}fluorodeoxyglucose (^{18}FDG) uptake in 3 clinically affected members compared with 8 controls (right) ($P<.001$) and in 5 asymptomatic members compared with 8 controls (left) ($P<.001$). Regions of decreased ^{18}FDG uptake have been superimposed on a normalized T1-weighted magnetic resonance imaging scan. PMC indicates premotor cortex; DPFC, dorsal prefrontal cortex; BG, basal ganglia; and T, thalamus.

cal surveys alone, indicating that PSP could have a greater hereditary component than previously realized. Factors that may explain the difficulty in recognition of familial cases of PSP on the basis of clinical findings include the late onset of the condition and the presence of occasional atypical cases given the variation in clinical phenotype. The typical syndrome is characterized by a variable combination of supranuclear ophthalmoplegia, axial dystonia, akinesia, pseudobulbar palsy, and mild dementia.[30,31] However, PSP can present with atypical clinical pictures, including a pure akinetic syndrome and pure dementia.[30,32,33] Recently, an elderly patient with pathologically confirmed PSP has been described who had a pure psychiatric syndrome without neurological signs.[34]

The prevalence of PSP in the United States[35] is reported to be 77 times lower than the prevalence of PD,[36]

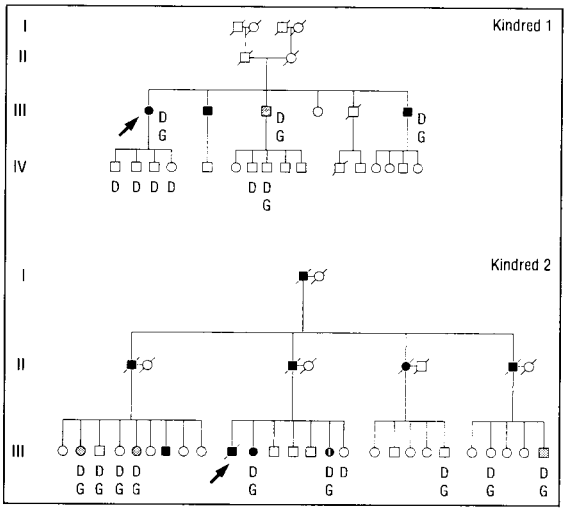

Figure 3. Genealogical trees for kindreds 1 and 2. D indicates which subjects have been scanned with ^{18}F-dopa and G with ^{18}fluorodeoxyglucose.

while, in contrast, the incidence of PSP[37] has been reported to be only 12 times lower than that of PD.[36] Although the median survival time from symptom onset is shorter in PSP[37] than in treated PD patients,[38] survival differences cannot explain the discordance in incidence and prevalence rates reported for PSP.[31] With current clinical diagnostic tools, PSP patients are diagnosed late in their disease course, and many PSP patients die with other diagnoses,[39,40] so it is likely that clinical prevalence estimates have been grossly underestimated.[31]

There have been a few previous reports of familial cases with pathologically confirmed PSP. To date, familial clustering of PSP has been reported in a total of 20 kindreds.[4] The pattern of inheritance in these reports was variable but generally suggestive of dominant transmission. Higgins et al[41] suggest that PSP can also be inherited as an autosomal recessive disorder linked to the *TAU* gene, but these data have not been confirmed. Other familial PSP clusters need to be recognized and included in a wider genetic search.

In conclusion, we have used ^{18}F-dopa and ^{18}FDG PET to assess clinically affected and asymptomatic adult members of 2 kindreds with familial PSP. Cortical and subcortical glucose and dopaminergic metabolic abnormalities with a pattern similar to that of their clinically affected relatives were found in 33% of asymptomatic adult members, suggesting that these subjects have subclinical PSP. The possibility of detecting subclinical cases and atypical phenotypes by using ^{18}F-dopa and ^{18}FDG PET could therefore improve the diagnostic recognition of PSP cases and be a valuable aid in finding a gene or genes responsible for this disease.

Accepted for publication April 3, 2001.

Corresponding author and reprints: Paola Piccini, MRC Clinical Science Center, Cyclotron Unit, Hammersmith Hospital, DuCane Road, W12 ONN London, England (e-mail: paola.piccini@csc.mrc.ac.uk).

REFERENCES

1. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. *Arch Neurol.* 1964;10:333-359.
2. Steele JC. Progressive supranuclear palsy. *Brain.* 1972;95:693-704.
3. De Yebenes JG, Sarasa JL, Daniel SE, Lees AJ. Familial progressive supranuclear palsy: description of a pedigree and review of the literature. *Brain.* 1995; 118:1095-1103.
4. Rojo A, Pernaute RS, Fontan A, et al. Clinical genetics of familial progressive supranuclear palsy. *Brain.* 1999;122:1233-1245.
5. Piccini P, Morrish PK, Turjanski N, et al. Dopaminergic function in familial Parkinson's disease: a clinical and ^{18}F-dopa positron emission tomography study. *Ann Neurol.* 1997;41:222-229.
6. Piccini P, Burn DJ, Ceravolo R, Maraganore D, Marsden CD, Brooks DJ. The role of inheritance in Parkinson's disease: evidence from a longitudinal study of dopaminergic function in twins. *Ann Neurol.* 1999;45:577-582.
7. Weeks RA, Piccini P, Harding AE, Brooks DJ. Striatal D1 and D2 dopamine receptor loss in asymptomatic mutation carriers of Huntington's disease. *Ann Neurol.* 1996;40:49-54.
8. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP International Workshop. *Neurology.* 1996;47:1-9.
9. Brooks DJ, Salmon EP, Mathias CJ, et al. The relationship between locomotor disability, autonomic dysfunction, and the integrity of the striatal dopaminergic system in patients with multiple system atrophy, pure autonomic failure and Parkinson's disease, studied with PET. *Brain.* 1990;113:1539-1552.
10. Signorini M, Paulesu E, Friston K, et al. Rapid assessment of regional cerebral metabolic abnormalities in single subjects with quantitative and nonquantitative [18F]FDG PET: a clinical validation of statistical parametric mapping. *Neuroimage.* 1999;9:63-80.
11. Kennedy AM, Frackowiack RSJ, Newman SK, et al. Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. *Neurosci Lett.* 1995;186:17-20.
12. Talairach J, Tournoux P. *Coplanar Stereotaxic Atlas of the Human Brain.* New York, NY: Georg Thieme; 1988.
13. Friston KJ, Holmes AP, Worsley KJ, Poline J-B, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp.* 1995;2:189-210.
14. Bailey DL, Jones T, Friston KJ, Colebatch JG, Frackowiack RSJ. Physical validation of statistical parametric mapping [abstract]. *J Cereb Blood Flow Metab.* 1991; 11(suppl 2):S150.
15. Ilgin N, Zubjeta J, Reich SG, Dannals RF, Ravert HT, Frost JJ. PET imaging of the dopamine transporter in progressive supranuclear palsy and Parkinson's disease. *Neurology.* 1999;52:1221-1226.
16. Brooks DJ, Ibanez V, Sawle GV, et al. Differing pattern of striatal ^{18}F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Ann Neurol.* 1990;28:547-555.
17. Bhatt MH, Snow BJ, Martin WRW, Peppard R, Calne DB. Positron emission tomography in progressive supranuclear palsy. *Arch Neurol.* 1991;48:389-391.
18. Burn DJ, Sawle CV, Brooks DJ. Differential diagnosis of Parkinson's disease, multiple system atrophy, and Steele-Richardson-Olszewski syndrome: discriminant analysis of striatal ^{18}F-dopa PET data. *J Neurol Neurosurg Psychiatry.* 1994; 57:278-284.
19. Goffinet AM, De Volder AG, Gillian C, et al. Positron tomography demonstrates frontal lobe hypometabolism in progressive supranuclear palsy. *Ann Neurol.* 1989; 25:131-139.
20. Krabe H, Grond M, Huber M, Herholz K, Kessler J, Heiss WD. Subcortical damage and cortical dysfunction in progressive supranuclear palsy demonstrated by positron emission tomography. *J Neurol.* 1992;239:98-102.
21. Nagahama Y, Fukuyama H, Turjanski N, et al. Cerebral glucose metabolism in corticobasal degeneration: comparison with progressive supranuclear palsy and normal controls. *Mov Disord.* 1997;12:691-696.
22. Blin J, Baron JC, Dubois B, et al. Positron emission tomography study in progressive supranuclear palsy: brain hypometabolic pattern and clinicometabolic correlations. *Arch Neurol.* 1990;47:747-752.
23. Santens P, DeReuck J, Crevits L, et al. Cerebral oxygen metabolism in patients with progressive supranuclear palsy: a positron emission tomography study. *Eur Neurol.* 1997;37:18-22.
24. Albert ML, Feldman RG, Willis AL. The "subcortical dementia" of progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry.* 1974;37:121-130.
25. Agid Y, Ruberg M, Dubois B, Pillon B. Anatomoclinical and biochemical concepts of subcortical dementia. In: Stahl SM, Iversen SD, Goodman EC, eds. *Cognitive Neurochemistry.* Oxford, England: Oxford University Press; 1987:248-271.
26. Braak H, Jellinger K, Braak E, Bohl J. Allocortical neurofibrillary changes in progressive supranuclear palsy. *Acta Neuropathol (Berl).* 1992;84:478-483.
27. Jellinger KA, Bancher C. Neuropathology. In: Litvan I, Agid Y, eds. *Progressive Supranuclear Palsy: Clinical and Research Approaches.* New York, NY: Oxford University Press; 1992:44-88.
28. Hanihara T, Amano N, Takahashi T, Nagatomo H, Yagashita S. Distribution of tangles and threads in the cerebral cortex in progressive supranuclear palsy. *Neuropathol Appl Neurobiol.* 1995;21:319-326.
29. Verny M, Duyckaerts C, Agid Y, Hauw JJ. The significance of cortical pathology in progressive supranuclear palsy: clinico-pathological data in 10 cases. *Brain.* 1996;119:1123-1136.
30. Daniel SE, De Bruin VMS, Lees AJ. The clinical and pathological spectrum of Steel-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Brain.* 1995; 118:759-770.
31. Litvan I, Hutton M. Clinical and genetic aspects of progressive supranuclear palsy. *J Geriatric Psychiatr Neurol.* 1998;11:107-114.
32. Dubas F, Gray F, Escourolle R, Steele-Richardson-Olszewski disease without ophthalmoplegia: 6 clinical-anatomic cases. *Rev Neurol Paris.* 1983;139:407-416.
33. Davis PH, Bergeron C, McLachlan DR. Atypical presentation of progressive supranuclear palsy. *Ann Neurol.* 1985;17:337-343.
34. Niizato K, Kuroki N, Arai T, Kase K, Iritani S, Ikeda K. An elderly patient with progressive supranuclear palsy without neurological signs. *No To Shinkei.* 1997; 49:829-833.
35. Golbe LI, Davis PH, Schoenberg BS, Duvoisin RC. Prevalence and natural history of progressive supranuclear palsy. *Neurology.* 1988;38:1031-1034.
36. Mayeux R, Marder K, Kote LJ, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. *Am J Epidemiol.* 1995;142:820-827.
37. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence of progressive supranuclear palsy and multiple system atrophy in Olmstead County, Minnesota, 1976 to 1990. *Neurology.* 1997;49:1284-1288.
38. Parkinson Study group. Mortality in DATATOP: a multicenter trial in early Parkinson's disease. *Ann Neurol.* 1998;43:318-325.
39. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992;55:181-184.
40. Litvan I, Mangone CA, McKee A, et al. Natural history of progressive supranuclear palsy and clinical predictors of survival: a clinico-pathological study. *J Neurol Neurosurg Psychiatry.* 1996;60:615-620.
41. Higgins JJ, Litvan I, Pho LT, Li W, Nee LE. Progressive supranuclear palsy is in linkage disequilibrium with the tau and not the alpha-synuclein gene. *Neurology.* 1998;50:270-273.

Brain (1999), **122**, 1233–1245

Clinical genetics of familial progressive supranuclear palsy

A. Rojo,[1] R. S. Pernaute,[1] A. Fontán,[1] P. G. Ruíz,[1] J. Honnorat,[4] T. Lynch,[5] S. Chin,[5] I. Gonzalo,[2] A. Rábano,[2] A. Martínez,[2] S. Daniel,[6] P. Pramsteller,[8] H. Morris,[7] N. Wood,[7] A. Lees,[6,7] C. Tabernero,[3] T. Nyggard,[5] A. C. Jackson,[9] A. Hanson[9] and J. G. de Yébenes[1,2]

[1]*Department of Neurology, Fundación Jiménez Díaz, Universidad Autónoma de Madrid,* [2]*Banco de Tejidos para Investigaciones Neurológicas, Madrid,* [3]*Departamento de Neurología, Hospital del Insalud de Segovia, Spain,* [4]*Neurologie B, Hôpital Neurologique, Lyon, France,* [5]*Departments of Neurology and Pathology, Medical College of Physicians and Surgeons, Columbia University, New York, USA,* [6]*Parkinson's Disease Society Brain Research Centre,* [7]*National Hospital for Neurology and Neurosurgery, London, UK,* [8]*Department of Neurology, University of Insbruck, Austria and* [9]*Department of Neurology, Kingston General Hospital, Ontario, Canada*

Correspondence to: Justo García de Yébenes MD, Servicio de Neurología, Fundación Jiménez Díaz Avda de Reyes Católicos 2, Madrid 28040, Spain
E-mail: jgyebenes@fjd.es

Summary

Recent studies have shown that progressive supranuclear palsy (PSP) could be inherited, but the pattern of inheritance and the spectrum of the clinical findings in relatives are unknown. We here report 12 pedigrees, confirmed by pathology in four probands, with familial PSP. Pathological diagnosis was confirmed according to recently reported internationally agreed criteria. The spectrum of the clinical phenotypes in these families was variable including 34 typical cases of PSP (12 probands plus 22 secondary cases), three patients with postural tremor, three with dementia, one with parkinsonism, two with tremor, dystonia, gaze palsy and tics, and one with gait disturbance. The presence of affected members in at least two generations in eight of the families and the absence of consanguinity suggests autosomal dominant transmission with incomplete penetrance. We conclude that hereditary PSP is more frequent than previously thought and that the scarcity of familial cases may be related to a lack of recognition of the variable phenotypic expression of the disease.

Keywords: progressive supranuclear palsy; Steele–Richardson–Olzsewski syndrome; genetics; akinetic rigid syndrome; dementia

Abbreviation: PSP = progressive supranuclear palsy

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disease clinically characterized by a variable combination of akinesia, supranuclear gaze palsy, rigidity, axial dystonia, gait disturbance and frontolimbic dementia. Pathological abnormalities include neuronal loss, gliosis and the presence of neurofibrillary tangles and neuropil threads, mainly in basal ganglia, diencephalon, brainstem and frontal and temporal lobes (Steele *et al.*, 1964). Atypical cases with characteristic pathological findings but an incomplete clinical syndrome have been previously described (Hauw *et al.*, 1994; Collins *et al.*, 1995; Daniel *et al.*, 1995; Litvan *et al.*, 1996*a*; Verny *et al.*, 1996).

The cause is unknown but toxic and infectious aetiologies have been considered, based upon the pathological similarities with post-encephalitic parkinsonism, metal poisoning and with the Parkinson–dementia complex of Guam (Jellinger, 1971; Steele, 1972, 1975; Jankovic, 1984; Kristensen, 1985; Jendroska *et al.*, 1994; Lilienfeld *et al.*,1994). Because of the coexistence of cerebrovascular disease in some cases a vascular mechanism has also been postulated (Dubinsky and Jancovic, 1987; Winikates and Jankovic, 1994). PSP is still considered a sporadic disorder, despite a small number of recent reports suggesting familial clustering (David *et al.*, 1968; Mata *et al.*, 1983; Ohara *et al.*, 1992; Brown *et al.*,

1993; Gazely and Maguire, 1994; Tetrud *et al.*, 1994; de Yébenes *et al.*, 1995; Golbe *et al.*, 1995; Lanotte *et al.*,1996; Tetrud *et al.*, 1996). In view of the few families reported it is not possible to decide whether familial and sporadic PSP are the same disease.

In this study we investigated our cases of PSP in order to describe familial aggregation, clinical phenotypes and pattern of inheritance.

Methods

A retrospective study of all patients with familial PSP seen by or referred to one of us (J.G.Y.) during the period 1991–97 was carried out. The index cases were seen at the Movement Disorders Clinic, Department of Neurology, Fundación Jiménez Díaz (five cases), the Institute of Neurology, Queen Square, London (two cases), Hospital General de Segovia (one case), Hôpital Neurologique, Lyon (one case), Columbia University, New York (two cases) and Kingston General Hospital, Ontario (one case). Review of medical records, professional or domestic videos, photographs, samples of hand writing, telephone calls and visits to the homes of the patients and relatives were undertaken by members of the research team when needed in order to evaluate secondary cases.

The diagnosis of PSP in a proband required either (i) pathology proven diagnosis according to international criteria (Hauw *et al.*, 1994; Litvan *et al.*, 1996*a*), (ii) the presence of the international clinical research criteria for the diagnosis of PSP (Litvan *et al.*, 1996*b*) or (iii) in some cases, analysed retrospectively, with insufficient details in the available history to fulfil the international clinical research criteria, the diagnosis of PSP was accepted if the patients had at least five out of the seven most common clinical symptoms of the disease (bradykinesia, gait disturbance, supranuclear gaze palsy, dysphagia, dysarthria, axial dystonia or disabling mental changes with frontosubcortical characteristics) as described in a recent clinicopathological series (Daniel *et al.*, 1995). The presence of these signs was determined clinically. Supranuclear gaze palsy was defined by saccades smaller than 15° in the vertical or horizontal plane. Whenever possible, in patients seen at Fundación Jiménez Díaz, supranuclear gaze palsy was confirmed by oculonystamographic analysis. Abnormal findings were defined by latency, velocity or accuracy of saccadic movements more than 2 SD away from the mean for that age group.

When the available information was insufficient to make a reliable diagnosis of PSP, but it was suggested by the relatives describing the phenotype as 'similar' or 'the same' as the proband, the individual was diagnosed as 'likely PSP'. We respected the initial diagnosis of other neurological disorders including parkinsonism, dementia, etc. when there was not additional clinical information that allowed for reclassification.

We obtained information on all available or deceased first and second degree relatives (parents, brothers, sisters, uncles, cousins) of the probands when possible. Children of probands were excluded since they were too young to clinically express PSP.

Results

Description of the families

A brief description of the pedigrees is presented in Table 1 and Fig. 1 (relationship, age of onset, years of evolution, medical history and clinical diagnosis). Detailed clinical phenotypes and response to L-dopa therapy are described in Table 2.

Family 1

Proband, individual 1.III.12. This was a 57-year-old female who presented progressive difficulty in doing up buttons and turning in bed. She had a long history of smoking and hypercholesterolaemia. At the age of 60 her neurological examination revealed moderate axial and limb rigidity, and dystonia in the left arm. She was diagnosed as having Parkinson's disease and treated with L-dopa, which improved her symptoms but induced akathisia and orolingual dyskinesias. She was then seen by one of us (J.G.Y.) at age 65. She complained of slowness, gait disturbance, speech problems with hypophonia and progressive dysphagia. A bruit was heard over the left carotid artery. Mental status and cranial nerves were normal with the exception of limitation of downgaze. She had dystonic posturing of the neck (anterocollis) and dystonic up-going toes. She showed severe, generalized akinesia and postural instability with a tendency to fall backwards. MRI of the brain was normal. She became unresponsive to L-dopa and pergolide and died at the age of 67.

The macroscopic examination of the brain revealed a pale substantia nigra. Light microscopy examination showed neuronal loss, gliosis and a high density of neurofibrillary tangles in the globus pallidus, putamen, subthalamic nucleus, substantia nigra and the inferior olivary nucleus. There were a moderate number of tangles in the neocortex (predominantly in anterior frontal and parietal regions), hippocampus, amygdala, nucleus basalis of Meynert and locus coeruleus. Tangles were also identified in both colliculi, peri-aqueductal region, red nucleus, dentate nucleus and oculomotor complex.

Individual 1.III.3. This was the first cousin of the proband, with a history of diabetes. His neurological disorder began with a progressive slowness of the left arm and leg when he was 68 years old. He was thought to have Parkinson's disease and received treatment with L-dopa with improvement of his symptoms. At the age of 73 he was evaluated by one of us (J.G.Y.) and the neurological examination revealed slowness, clumsiness, severe dysphagia and diplopia. His physical examination revealed a bruit over the left internal carotid artery. Formal neuropsychological testing revealed bradyphrenia and abnormalities of executive memory and

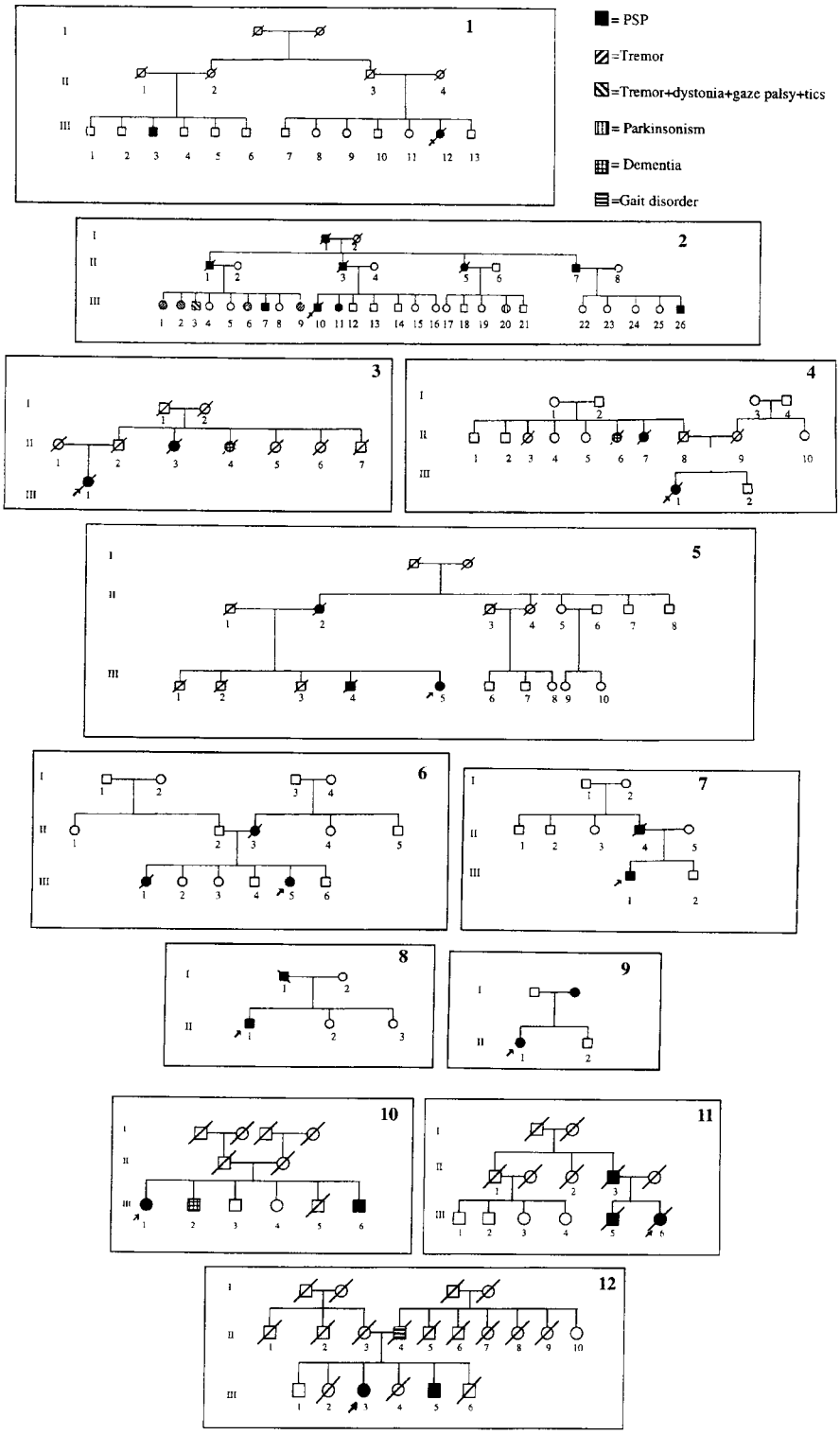

Fig. 1 Familial trees of families 1–12. Arrows point to probands.

Table 1 *Epidemiological data*

Family	Number		Sex	Age at onset (years)	Actual age (years)	Age at death	Actual diagnosis
1	III.12	Proband*	F	57	–	67	PSP
	III.3	Cousin	M	68	73	–	PSP
2	III.10	Proband*	M	53	–	59	PSP
	I.1	Grandfather	M	NA	–	NA	Likely PSP
	II.1	Uncle	M	NA	–	81	PSP
	II.3	Father	M	62	–	71	Likely PSP
	II.5	Aunt	F	70	–	84	PSP
	II.7	Uncle	M	NA	–	77	PSP
	III.1	Cousin	F	NA	73	–	Tremor
	III.2	Cousin	F	NA	72	–	Dystonia, tremor, gaze palsy, tics
	III.3	Cousin	M	NA	71	–	Dystonia, tremor, gaze palsy, tics
	III.6	Cousin	F	NA	63	–	Tremor
	III.7	Cousin	M	NA	60	–	Likely PSP
	III.9	Cousin	F	NA	52	–	Tremor
	III.11	Sister	F	53	59	–	PSP
	III.20	Cousin	F	63	71	–	Parkinsonism
	III.26	Cousin	M	59	NA	–	Likely PSP
3	III.1	Proband*	F	60	–	72	PSP
	II.3	Aunt	F	70	–	86	Likely PSP
	II.4	Aunt	F	70	–	74	Dementia
4	III.1	Proband*	F	62	–	71	PSP
	II.6	Aunt	F	91	–	96	Dementia
	II.7	Aunt	F	73	–	78	Likely PSP
5	III.5	Proband	F	75	86	–	PSP
	III.4	Brother	M	75	–	86	PSP
	II.2	Mother	F	73	–	83	Likely PSP
6	III.5	Proband	F	37	41	–	PSP
	II.3	Mother	F	41	–	45	PSP
	III.1	Sister	F	37	–	41	Likely PSP
7	III.1	Proband	M	55	59	–	PSP
	II.4	Father	M	70	–	83	PSP
8	II.1	Proband	M	49	68	–	PSP
	I.1	Father	M	NA	–	80	Likely PSP
9	II.1	Proband	F	67	69	–	PSP
	I.2	Mother	F	75	–	83	Likely PSP
10	III.1	Proband	F	70	77	–	PSP
	III.2	Brother	M	70	76	–	Dementia
	III.6	Brother	M	60	64	–	PSP
11	III.6	Proband	F	43	–	48	PSP
	II.3	Father	M	40	–	47	Likely PSP
	III.5	Brother	M	48	–	53	PSP
12	III.3	Proband	F	71	72	–	Likely PSP
	III.5	Brother	M	63	68	–	PSP
	II.4	Father	M	NA	–	49	Gait disorder

M = male; F = female; NA = not available; PSP = progressive supranuclear palsy. *Pathological confirmation.

learning suggestive of abnormal frontal function. He had limitation of voluntary eye movements in all directions, limb rigidity, hypokinesia and gait disturbance which was greater when turning. The retropulsion test was negative but he had bilateral Babinski signs. The patient was thought to have PSP. He informed us that two of his brothers had diplopia, but they have not been examined yet.

Family 2

Clinical data from the proband and other family relatives (individuals 2.III.10, 2.I.1, 2.II.1, 2.II.3, 2.II.5) have been reported elsewhere (de Yébenes *et al.*, 1995). More recently we have personally examined 25 additional family members. The most important new findings are described below.

Individual 2.II.7. He died at the age of 77. His relatives said that he had 'the same' neurological syndrome as his brothers. He had parkinsonism, proven by pictures, and micrographia as shown by samples of his handwriting.

Individual 2.III.1. The 73-year-old female was a cousin of the proband, who suffered from postural hand and head

Table 2 *Clinical features*

No.	Akinesia	Gait	Gaze	Dysp.	Dysa.	Axial dystonia	Dementia	Other	Response to L-dopa	Initial diagnosis	Actual diagnosis
Family 1											
II.12	+	+	+	+	+	+	–	6	+	Parkinsonism	PSP*
III.3	+	–	+	+	+	–	+	.	+	Parkinsonism	PSP
Family 2											
III.10	+	+	+	+	+	+	+	.	+	PSP	PSP*
I.1	+	+	+	–	–	–	–	.	NA	NA	Likely PSP
II.3	–	+	+	+	–	–	–	.	NA	NA	Likely PSP
II.1	+	+	+	+	–	–	+	.	NA	NA	PSP
II.5	+	+	+	+	+	–	+	.	NA	NA	PSP
II.7	+	+	–	–	–	–	–	.	NA	NA	PSP
III.1	+	–	–	–	–	–	–	1	NA	Tremor	Tremor
III.2	–	–	+	–	–	–	–	1, 2, 3	NA	Dystonia	Dystonia, tremor gaze palsy, tics
III.3	–	–	+	–	–	–	–	1, 2, 3	NA	Tremor, dystonia	Dystonia, tremor gaze palsy, tics
III.6	–	–	–	–	–	–	–	1, 4	NA	Tremor	Tremor
III.7	+	+	+	–	–	–	–	1	NA	Tremor	Likely PSP
III.9	–	–	–	–	–	–	–	1	NA	Tremor	Tremor
III.11	+	+	+	+	–	–	–	6	+	Parkinsonism	PSP
III.20	+	+	–	+	–	–	–	1	NA	NA	PK
III.26	+	–	+	–	+	–	–	1	NA	NA	Likely PSP
Family 3											
III.1	+	+	+	+	+	–	+	2, 5, 6	+	Binswanger	PSP*
II.3	+	+	–	–	+	–	–	1	NA	Parkinsonism	Likely PSP
II.4	–	+	–	–	–	–	+	.	NA	Dementia	Dementia
Family 4											
III.1	+	+	+	–	+	–	–	.	–	Parkinsonism	PSP*
II.6	–	+	–	–	–	–	+	.	NA	Dementia	Dementia
II.7	+	+	–	+	+	–	–	.	NA	Parkinsonism	Likely PSP
Family 5											
III.5	+	+	+	–	+	+	+	6, 7	NA	PSP	PSP
III.4	+	+	+	+	+	–	+	2	–	PSP	PSP
II.2	+	+	–	+	–	–	–	.	NA	NA	Likely PSP
Family 6											
III.5	+	+	+	+	+	+	+	5, 6	–	PSP	PSP
II.3	+	+	+	+	+	–	–	1	NA	Parkinsonism	PSP
III.1	+	+	+	–	+	–	–	5	–	Parkinsonism	Likely PSP
Family 7											
III.1	+	+	+	+	–	+	+	5	NA	PSP	PSP
II.4	+	+	+	+	–	+	+	1, 5	–	Parkinsonism	PSP
Family 8											
II.1	+	+	+	+	+	+	+	1	+	Parkinsonism	PSP
I.1	+	+	–	+	–	–	+	.	NA	Dementia	Likely PSP
Family 9											
II.1	+	+	+	–	+	+	–	6	NA	PSP	PSP
I.2	–	+	–	+	+	–	+	1	+	Parkinsonism	Likely PSP
III.1	+	+	+	+	+	+	–	5, 6	–	PSP	PSP
Family 10											
I III.2	–	–	–	–	–	–	+	.	NA	Dementia	Dementia
III.6	+	+	+	–	+	–	–	2	–	Gait disorder	PSP
Family 11											
III.6	+	+	+	+	+	–	–	.	NA	PSP	PSP
II.3	–	+	+	–	–	–	–	.	NA	CJD	Likely PSP
III.5	+	+	+	+	+	–	–	.	NA	PSP	PSP
Family 12											
III.3	+	+	+	–	–	–	–	.	–	NA	Likely PSP
III.5	+	+	+	+	+	+	+	1, 6	–	Neurodeg. dis.	PSP
II.4	–	+	–	–	–	–	–	.	NA	NA	Gait disorder

Gait = gait disturbance; gaze = supranuclear gaze palsy; dysp. = dysphagia; dysa. = dysarthria; + = present; – = absent; 1 = tremor; 2 = cranial dystonia; 3 = tics; 4 = orofacial dyskinesia; 5 = apraxia of eyelid opening; 6 = limb dystonia; 7 = myoclonic jerks; PSP = progressive supranuclear palsy; CJD: Creutzfeldt–Jacob disease; neurodeg. dis. = neorodegenerative disease; NA = not available. *Pathological confirmation.

tremor, compatible with essential tremor and mild bradykinesia. At present she is considered not to have PSP.

Individual 2.III.2. The 72-year-old female had cranial dystonia (blepharospasm and dystonia in the lower half of the face), postural tremor, facial tics and vertical supranuclear gaze palsy. Her neuropsychological examination was normal.

Individual 2.III.3. The 71-year-old male had blepharospasm and oromandibular dystonia, facial and phonic tics, vertical upward gaze palsy, predominantly axial rigidity and postural tremor in the right arm. His oculonystagmographic examination revealed slow vertical saccades, with a marked decrease in range and precision, both with predictable and random stimuli, and breakdown of optokinetic nystagmus in the vertical plane. His neuropsychological testing was normal.

Individual 2.III.6. The 63-year-old female had orofacial dyskinesia, increased blink rate, postural tremor in the left arm, and axial and right arm rigidity. Her mental status and gaze were normal.

Individual 2.III.7. The 60-year-old male had bruxism, akinesia and rigidity predominantly in the left arm and leg and postural tremor in the arms. He also had exophoria and failure of convergence. His mental status was normal.

Individual 2.III.9. The 52-year-old female had postural tremor for several years in the upper limbs and a diminished left arm swing. Neuropsychological testing and oculonystagmographic analysis were normal.

Individual 2.III.11. This was a sister of the proband who was diagnosed as having Parkinson's disease at age 53 when she required medical attention for a slowly progressive akinetic rigid syndrome without tremor. She was treated with small doses of L-dopa and her symptoms improved greatly, although she developed visual hallucinations. At the age of 57 she developed typical wearing off fluctuations and at age 59 she complained of swallowing problems which were accompanied by severe weight loss. On examination she had generalized slowness, difficulty in convergence, anterocollis and limb dystonia in the four extremities, a persistent glabellar tap reflex, brisk sustained palmomental responses, hyperreflexia and extensor plantar reflexes. She developed increasing gait difficulty with frequent freezing.

Individual 2.III.20. This patient complained of head tremor at age 63 and progressive slowness and tremor in her right arm. At age 71 she is still active, but with moderate right side akinesia and rigidity, mild walking difficulty, dysphagia and urinary incontinence.

Individual 2.III.26. At age 59 he complained of tremor at rest in the right hand, hypophonia and excessive sweating. During the following year he developed an akinetic syndrome with gait disturbance, hypomimia, generalized rigidity, dystonia in the lower face and supranuclear gaze palsy with slowing of horizontal and vertical saccades in the oculonystagmographic study. Cognitive testing was normal.

Family 3

Proband, individual 3.III.1. This 72-year-old female developed a lack of initiative, lack of social interest and apathy at age 60. One year later she had speech abnormalities and gait disturbance with frequent falls. She had hypertension and a history of smoking. Her neurological examination at age 64 revealed hypomimia, bradykinesia, hyperreflexia and gait disturbance and she was diagnosed as having Binswanger's disease. Her symptoms worsened slowly over the following years, her walking became progressively worse and she developed limitation of downgaze. Two years later she complained of dysphagia and urinary incontinence. At age 69 she was treated with L-dopa, which produced a mild, transient improvement, and with dopamine agonists, without improvement. She was examined at age 70 when there was evidence of frontal lobe dysfunction, severe dysarthria and dysphagia, facial dystonia and apraxia of eyelid opening. The oculomotor examination revealed limitation of downgaze, difficulty in convergence and slowing of horizontal and vertical saccades. Her neurological examination revealed rigidity and akinesia predominantly in her left limbs, retrocollis and left lower limb dystonia. Her stretch reflexes were exaggerated and she had left foot dystonia. Investigation of her regional cerebral blood flow by HMPAO-SPECT (single photon emission tomography) revealed a deficit of perfusion in the frontal region. A cerebral MRI showed midbrain and subcortical atrophy which was more severe in frontal region. During the ensuing months she became wheelchair bound, unable to read because of complete vertical and horizontal gaze palsy and she developed severe dysphagia and oromandibular dystonia but she declined gastrostomy. She died of pneumonia at age 72. Macroscopic examination of the brain was normal except for pallidal atrophy with brownish discoloration and loss of pigment in the substantia nigra. Light microscopy revealed neuronal loss, gliosis and high density of neurofibrillary tangles and neuropilic threads with positive immunoreactivity to tau and PHF-1 (paired helical filaments) in globus pallidus, subthalamic nucleus, substantia nigra, peri-aqueductal region and oculomotor complex. There was a moderate number of tangles in caudate, putamen, locus coeruleus, pontine nuclei, inferior olive, nucleus ambiguus, raphe nuclei and dentate nucleus.

Individual 3.II.3. This was the proband's aunt on whom we only have retrospective information from relatives. Photographs of the patient taken during her youth and early adult life did not reveal any neurological disease. She developed a parkinsonian syndrome around age 70 with tremor in her hands, early gait disturbance with frequent falls

and speech difficulties. She developed progressive and severe deterioration of her gait and speech and became bedridden and virtually mute for the last few years before her death at age 86.

Individual 3.II.4. This was the proband's aunt on whom we only have reports from relatives. In the last years of her life she developed dementia with frequent hallucinations and severe gait disturbance and she died at age 74.

Family 4

Proband, individual 4.III.1. This was a 62-year-old woman with a history of hypertension, diabetes and smoking who developed progressive gait disturbance and speech difficulty. One year later her neurological examination revealed dysarthria with orolingual apraxia, and persistent glabellar tap and palmomental reflexes. Her mental status was normal. She had ocular dysmetria, slowing of saccades and breakdown of vertical opticokinetic nystagmus. Standing and tandem walking were difficult. She was treated with L-dopa without improvement and at age 65 she lost vertical gaze (up and down) with abolition of vertical optokinetic nystagmus. She had axial and limb rigidity, facial dystonia, bradykinesia and loss of balance and gait difficulty. A cerebral MRI revealed corticosubcortical and brainstem atrophy, mostly in the mesencephalic tegmentum. She died at age 71 and had a post-mortem examination. Light microscopy revealed neuronal loss, gliosis and presence of neurofibrillary tangles and neuropil threads in neurons and glia in globus pallidus (more severe in the medial segment), frontal cortex, subthalamic nucleus, substantia nigra, red nucleus, oculomotor complex, locus coeruleus, dentate and inferior olivary nucleus. Tangles were also identified in Meynert's nucleus, hippocampus, subiculum and pons.

Individual 4.II.6. This was the proband's aunt for whom we only have reports from relatives. In the last years of her life she had a neurological syndrome characterized by dementia, gait disturbance and severe weight loss. She died aged 96 years.

Individual 4.II.7. This was the proband's aunt and a sister of 4.II.6 for whom we only have reports from relatives. She was said to have Parkinson's disease in her seventies. She moved slowly, had no tremor, had frequent falls backwards, developed severe dysphagia and dysarthria and died at age 78.

Family 5

Proband, individual 5.III.5. This 75-year-old female had a progressive syndrome characterized by slowness, clumsiness and dementia. Her neurological examination at age 83 revealed facial dystonia, dysarthria, rigid-akinetic syndrome and gait disturbance. A cerebral MRI revealed corticosubcortical atrophy. During a visit to her home when she was 85 years old, a neurological examination revealed disorientation, abnormalities of memory, limitation of vertical gaze, generalized rigidity (predominantly axial), retrocollis, facial and upper limb dystonia. She was unable to walk and she had a spontaneous tendency to fall backwards. Occasionally she had myoclonic jerks in the arms. She is still alive at age 86.

Individual 5.III.4. This was the proband's brother and his neurological disorder began at age 75 with an akinetic rigid syndrome, dementia, dysphagia, dystonia (antero- and retrocollis) and blepharospasm. His neurological examination 10 years later revealed hypokinesia, upgaze abolition, reduction of the verbal fluency and axial and limb rigidity. A cerebral MRI revealed corticosubcortical and brainstem atrophy. He was unable to walk, developed severe dysphagia and he lost 12–15 kg. He died at the age of 86. During the last few months of his life he took L-dopa without apparent improvement.

Individual 5.II.2. This was the mother of the previous patients for whom we only have information from relatives. For several years she had a neurological syndrome similar to that suffered by her children before dying aged 83.

Family 6

Proband, individual 6.III.5. At age 37 she developed generalized slowness, gait disturbance with frequent falls and micrographia. Her neurological examination 1 year later revealed dysarthria, difficulty in convergence, abolition of upgaze and apraxia of eyelid opening. Stretch reflexes were exaggerated, the left plantar response was extensor and she had axial rigidity and right arm dystonia. She was treated for 3 months with L-dopa without improvement and in the following years she developed axial dystonia, vertical gaze palsy and slow horizontal saccades. Her dysphagia became so severe that she lost weight and required percutaneous gastrostomy. She became virtually mute only being able to express affirmation or negation with slow movements of her hand. Cognitive evaluation was difficult but she was suspected by her physicians to have frontal lobe dementia. She is now 41 years old.

Individual 6.II.3. This was the proband's mother whose neurological disorder began at age 41 with tremor in the left arm and progressive slowness. She was diagnosed with Parkinson's disease 2 years later. When she was 44 years old she had hypophonia, dysphagia and gait disturbance with frequent falls. Neurological examination revealed rigidity, exaggerated stretch reflex, left extensor plantar response and micrographia. A right thalamotomy was performed without improvement. One year later her left arm was fixed in flexion and pronation, she had severe generalized bradykinesia and extensor plantar responses. A few months later there was evidence of voluntary upgaze paralysis and she died at age 45.

Individual 6.III.1. This was the proband's sister who developed a progressive akinetic syndrome when she was 37 years old. Two years later she had a gait disturbance with frequent falls and micrographia and neurological examination revealed hypophonia, a reduced range of vertical gaze movements, difficulty for ocular convergence, apraxia of eyelid opening, exaggerated stretch reflexes and axial rigidity. She was treated with bromocriptine without improvement and died aged 41.

Family 7

Proband, individual 7.III.1. A 55-year-old male presented with loss of memory and progressive gait disturbance, frequent backwards falls and dysphagia, and neurological examination 3 years later revealed downgaze limitation. He is now 59 years old and has an akinetic rigid syndrome with severe gait disturbance, retrocollis, apraxia of eyelid opening and downgaze limitation with occasional diplopia.

Individual 7.II.4. This was the proband's father who, during the last 13 years of his life, had an akinetic rigid syndrome with postural tremor in the left arm, dementia with apathy, gait disturbance, dysphagia and significant weight loss. Neurological examination revealed retrocollis, apraxia of eyelid opening and micrographia. He was treated with L-dopa without improvement. Later he lost vertical downgaze and developed diplopia. He died at age 83.

Family 8

Proband, individual 8.II.1. This was a 49-year-old male who developed bradykinesia in his left arm. He was diagnosed with Parkinson's disease and was treated with L-dopa and bromocriptine with clear improvement for many years. When we saw him for the first time at age 63 he was hallucinating and examination revealed hypokinesia, bilateral rest and postural tremor, somnolence and fatigue. Two years later he had frequent falls, dysarthria and memory loss and at age 66 the akinetic syndrome had progressed and he had horizontal gaze limitation, difficulties in convergence and 'frontal dementia'. After 15 years of L-dopa therapy his akinesia was still improved but now at age 68 he has dysphagia, facial dystonia, retrocollis, supranuclear gaze palsy affecting all directions and gait disturbance.

Individual 8.I.1. This was the proband's father on whom we only have reports from relatives. He had an akinetic rigid syndrome without tremor with frequent falls and dementia. During the last years of his life he had dysphagia with weight loss and he died at age 80.

Family 9

Proband, individual 9.II.1. At the age of 67 this woman had a predominantly right-sided akinetic rigid syndrome. Two years later she developed dysarthria, palilalia, facial dystonia and axial and right arm dystonia. Vertical ocular movements were abolished and horizontal ones were slow. She developed urinary incontinence and loss of balance with frequent backwards falls.

Individual 9.I.2. This was the proband's mother who, at age 75, developed loss of balance, gait disturbance, postural tremor, dementia, dysarthria and severe dysphagia with weight loss. She received treatment with L-dopa with clear improvement, but she had hallucinations. She died at age 83.

Family 10

Proband, individual 10.III.1. At the age of 70 this lady developed unexplained falls. Her balance progressively deteriorated with frequent falls and she also had micrographia and general slowness of movement. By the time we examined her 7 years after symptom onset, she was unable to stand unaided but was able to walk with the aid of two people, with a tendency to fall backwards. Her neck was fixed in an anteroverted position and she had a complete vertical supranuclear palsy with slow and hypometric lateral saccades, blepharospasm and apraxia of eye lid opening. She had a low pitched dysarthria and mild symmetrical distal bradykinesia and rigidity. There was intermittent dystonic posturing of the right leg with extension at the knee and plantar flexion at the ankle.

Individual 10.III.2. At the age of 70 this man developed nocturnal restlessness and was frequently found by his wife wandering around the house. He developed urinary frequency and mild short-term and remote memory loss. At the age of 76 he was unable to answer any questions or follow commands but he had dressing apraxia and required assistance for feeding. He walked unaided with steady balance as he turned and his eye movements were normal. Although he could not be formally examined there was no obvious bradykinesia, but there was mild symmetrical cogwheel rigidity, together with mild axial rigidity and turning and sitting *en bloc*. There were small amplitude irregular, stimulus sensitive finger movements indicating cortical myoclonus. He developed marked bradykinesia and rigidity following a depot injection of anti-psychotic medication.

Individual 10.III.6. At the age of 60 this man developed difficulty walking with unsteadiness and backwards falls while pushing a wheelbarrow. Over the following year he noted that he had difficulty in starting to walk with his feet 'glued to the floor' and had difficulty in turning, particularly in confined spaces, although he walked with normal step size. He also developed mild micrographia. At this time he had no bulbar symptoms and examination of his extraocular movements was normal. His cranial MRI showed no vascular changes and the diagnosis was of a frontal gait disorder. Four years after symptom onset he developed mild dysarthria

and difficulty with reading. Examination showed that he had developed mild slowing of vertical saccadic eye movements and blepharospasm.

Family 11

Proband, individual 11.III.6. At the age of 43 this lady developed a lack of interest in day-to-day events and chronic insomnia. She had slowing of her speech, difficulty in shifting her gaze and she became obsessional about performing particular tasks. Two years after symptom onset she had impairment of postural reflexes and a complete absence of vertical saccadic eye movements to command but well preserved smooth pursuit eye movements. The mini-mental test score was 30/30 but there was impaired verbal fluency. Over the next few years she developed increasingly severe dysarthria and dysphagia and died of a respiratory infection 5 years after symptom onset.

Individual 11.II.3. In his forties this man developed 'problems with his eyes', gait unsteadiness and frequent falls, some of them quite serious. He also found it hard to judge distances and frequently bumped into people, and he is recalled by his family as having had staring eyes. He deteriorated quite rapidly, was transferred to a nursing home and then to a hospital where he died in 1954 at the age of 47 years. The death certificate diagnosis was of Creutzfeldt–Jacob disease but no pathological report has been ever found. Both his children are now dead and we have never obtained medical records or the post-mortem details on him. However, from accounts given by his daughter and members of the broader family that this patient had the same staring eyes and other neurological features observed in his children we feel that there is sufficient grounds to be suspicious of PSP.

Individual 11.III.5. He was a professor of economic geography who, in his forties, was noted by his work colleagues to become obsessive and worried about small details. At the age of 48 he developed difficulty in focusing and then in reading and started to have frequent falls and memory loss, particularly for recent events. When seen by a neurologist in 1989 he had symmetric akinetic–rigid syndrome with severe supranuclear downgaze palsy, slurring of speech, marked hypomimia, diffuse pyramidal signs, a brisk jaw jerk and bilateral grasp reflexes. At the age of 52 he had a severe supranuclear gaze palsy and was profoundly bradykinetic and dysarthric with marked postural instability. There were no sensory or cerebellar signs and he scored 25/30 on the Mini-Mental State Examination. All laboratory tests were normal and L-dopa was tried without benefit. He became mute and increasingly immobile and died at the age of 53.

Family 12

Proband, individual 12.III.3. This right-handed woman started to fall at 71 and she also complained of unsteady gait and had difficulty looking down, particularly when going down stairs or eating. Anti-parkinsonian therapy was initiated but with no benefit. On examination she had a 'dystonic, pseudobulbar' face, markedly impaired vertical gaze (supranuclear), impaired vertical pursuit, hypometric saccades and square wave jerks. On motor examination there was bradykinesia, tone was normal and there was no cogwheeling. Stretch reflexes were exaggerated but the plantar responses were down going. Her gait was narrow-based and unsteady with unpredictable falls and there was limited arm-swing and she turned en bloc. She is still alive.

Individual 12.III.5. This man began having symptoms at the age of 63 with personality changes and increasing irritability. He subsequently developed dysarthria followed by falls and an unsteady gait. One year later a 'wide-eyed' stare was evident and he later developed coarse rhythmical activity and posturing in his right hand. The family noted rigidity and dysphagia as well as cognitive changes (poor memory and judgement) but he did not benefit from L-dopa. On examination he had typical PSP facies and there was also hypophonia and fluctuating dysarthria. He had impaired vertical gaze and pursuit with a normal oculocephalic reflex. There was left facial weakness. On motor examination there was bradykinesia, axial dystonia and dystonic posturing of his right hand. There was also a coarse, intermittent tremor of his right hand and gegenhalten was present in the legs. He had a persistent glabellar tap and grasp reflex, rapid alternating movements were severely impaired, there was axial dystonia and his gait was unsteady. He is still alive.

Individual 12.II.4. This man died at the age of 49 years from liver disease. He had gait problems with frequent falls.

Clinical genetics

In these families we have found 22 secondary PSP cases among 133 first and second degree relatives from whom there was available information. All the patients with 'likely PSP' (n = 12) had supranuclear gaze palsy and/or frequent falls or gait disturbance early in the course of the disease. Other individual members of these families presented with other neurological disorders including isolated tremor (n = 3), dementia (n = 3), parkinsonism (n = 1), gait disturbance (n = 1), and tremor, dystonia, gaze palsy and tics (n = 2).

In these families we found 34 individuals with clinical or pathological criteria of PSP (12 probands and 22 familial cases). Seventeen were male and 17 female and the mean age at onset of symptoms was 59.9 ± 12.4 years (n = 28). In 17 of these patients there was information available about vascular risk factors: five (29.41 %) were heavy smokers, two had high blood pressure (11.76 %) and two diabetes (11.76%). The duration of the disease from clinical onset to death was 8.81 ± 3.76 years (n = 16). Bradykinesia was the presenting feature in 15 patients, gait disturbance in five

Table 3 *Clinical features in 34 individuals with PSP*

	n	%
Bradykinesia	31	91
Gait disturbance	32	94
Supranuclear gaze palsy	29	85
Dysphagia	22	65
Dysarthria	21	62
Axial dystonia	12	35
Dementia	14	41
Tremor	8	23
Apraxia of eyelid opening	6	18
Blepharospasm	2	6
Limb dystonia	8	23
Myoclonic jerks	1	3
Response to L-dopa	7	44*

*Percentage of 16 patients who received L-dopa.

and change in personality in three. In nine patients it was not possible to determine the initial clinical symptom.

The frequency of the different clinical symptoms is summarized in Table 3. Gait disturbance was the most frequent alteration during the progression of disease (94% of the patients). Seven out of 16 patients treated with L-dopa improved initially (three out of the four cases confirmed by pathology) and in three of them this response was sustained for more than 3 years. In one patient, L-dopa therapy was thought to be of marginal efficacy, but its discontinuation because of paralytic ileus produced a malignant catatonic syndrome that caused his death in spite of intravenous administration of lisuride.

In order to evaluate if there were any differences between familial and sporadic PSP we compared clinical features of the five probands from the families seen in Fundación Jiménez Díaz with the last five cases of sporadic PSP seen by us in the same hospital (Table 4). We did not find clinical differences between familial and sporadic PSP in terms of age at onset and initial clinical findings. Patients with familial PSP more frequently had dystonia which may have reflected the more prolonged follow-up.

Discussion

This study presents a set of clinical data and clinical genetics of familial PSP. In 12 families from Europe and North America we found 22 secondary cases compatible with PSP in addition to the 12 probands, all with typical clinical features. Four of the probands had neuropathological confirmation of the diagnosis of PSP. In these families there were relatives with other neurological disorders including tremor (three patients), adult onset focal dystonia, tremor, gaze palsy and tics (two patients), dementia (three patients), parkinsonism (one patient) and gait disorder (one patient). Most of these disorders are frequent in the general population and, therefore, it is not possible to conclude whether these disorders appeared in these families by chance or as oligosymptomatic manifestation of PSP.

The recognition of familial cases of PSP requires (i) intensive investigation of the families including field trips and home visits of apparently healthy family relatives and (ii) long-term care and follow-up of the proband and relatives by specialized neurologists. These methods of evaluation and long-term follow-up are not common in our health care systems. For example, patient I.III.12 was thought to be a sporadic case of PSP during her lifetime, although an intensive search for other cases in the family was performed. However, 4 years after the proband's death a secondary case appeared in her family. Patient 2.III.10 was thought to have sporadic PSP during his lifetime. He had a sister who at first was considered to have idiopathic, L-dopa responsive, Parkinson's disease but 1 year after the proband's death, his sister developed severe dysphagia, weight loss and opthalmoplegia. Four years later a first cousin developed akinesia, apathy, cranial dystonia and gaze palsy. After interviewing around 30 family relatives we concluded that five deceased ancestors considered, during their lives, to have 'parkinsonism', 'dementia', 'senility' or 'cerebrovascular disease' in fact had PSP. Patient 7.III.1 was thought to have idiopathic Parkinson's disease. His attending neurologist was not told that the patient's father died of 'parkinsonism'. Interviews with the patient's mother and brother, in addition to a review of the records and family pictures, provided convincing evidence of PSP.

The pattern of inheritance is compatible with autosomal dominance with reduced penetrance. Lack of evidence for vertical transmission in three or more generations, except in one family, could be related to insufficient information about grandparents of elderly patients, most of them with some kind of cognitive impairment. There are, however, other explanations. The disease was only described 3 decades ago (Steele *et al.*, 1964) and people lose contacts with their place of origin because of the strong migratory movements that have taken place in many parts of the world, and the increased life expectancy of around 25 years that has occurred during this century. Since the prevalence of PSP is age related (Daniel *et al.*, 1995) the chances of developing the disease in gene carriers is now much greater than at the beginning of the century.

The proportion of affected individuals in different generations increases with age. The number of secondary cases in the generation of the probands (6 out of 37 siblings and 3 out of 34 cousins, i.e. 9 out of 71) was smaller than the number of secondary cases in the previous generation (7 out of 24 parents and 5 out of 37 uncles and aunts, i.e. 12 out of 61) (Table 3). This is not surprising since the mean age of the siblings is 53 years and the age adjusted annual incidence of PSP increases from 1.4 at age 50 to 14.2 per 100 000 inhabitants at an age higher than 80 years (Bower *et al.*, 1997). Therefore, it is likely that some living relatives will develop the disease in the future.

The diagnosis of PSP is difficult in patients with atypical clinical phenotypes. Confirmed cases of PSP by autopsy have been diagnosed in life as Parkinson's disease, corticobasal

Table 4 *Clinical features in sporadic and familial PSP*

	Sporadic (n = 5)	Familial (n = 5)
Age of onset*	59.2 ± 6.8	60.2 ± 6.2
Smoking	2	4
High blood pressure	2	1
Other	1 diabetes mellitus	1 high cholesterol levels
Presenting feature	4 gait disorder, 1 cognitive changes	3 bradykynesia, 1 gait disorder, 1 cognitive changes
Bradykinesia	5	5
Gait disturbance	5	5
Supranuclear gaze palsy	5	5
Dysphagia	3	4
Dysarthria	4	5
Axial dystonia	1	5
Dementia	4	3
Tremor	1	1
Apraxia of eyelid opening	1	1
Blepharospasm	1	0
Limb dystonia	0	3

*Mean ± SE.

degeneration, multisystemic atrophy or Alzheimer's disease (Jackson *et al.*, 1983; Boller *et al.*, 1989; Rajput *et al.*, 1991; Hughes *et al.*, 1992). The pathology of PSP is characterized by a variable combination of neuronal loss, gliosis and neurofibrillary tangles in many brain areas including the cerebral cortex, basal ganglia and the brainstem (Hauw *et al.*, 1994; Daniel *et al.*, 1995). Although typical cases are characterized by akinesia, supranuclear gaze palsy, rigidity, axial dystonia, gait disturbance and dementia, there are patients with atypical symptoms and typical pathology (Daniel *et al.*, 1995). In some of these patients the diagnosis of PSP could be easily missed.

Improvement with L-dopa is considered typical of Parkinson's disease and rare in PSP to the point that lack of response is considered support criteria for the diagnosis of PSP (Jellinger, 1995). However, 35–50% of the patients improve their bradykinesia or rigidity with L-dopa (Nieforth and Golbe 1993; Litvan *et al.*, 1997). In the present study we found that 7 out of 16, 44% of the treated patients, improved with this treatment. Furthermore, three out of the four cases confirmed by pathology responded to L-dopa. In most of the patients the response was modest and transient, but in three individuals (I.III.3, 2.II.11 and 8.II.1) the benefit was maintained for several years. These patients were considered to have Parkinson's disease before they developed the complete typical syndrome of PSP. The possibility that some of these patients had Lewy body pathology cannot be ruled out in spite of the lack of Lewy bodies in the three patients with pathological confirmation of PSP and response to L-dopa. Unfortunately, we could not obtain post-mortem evaluation of some of the relatives of the probands with atypical clinical findings but [^{18}F]dopa and deoxyglucose-PET scans have revealed abnormal data compatible with PSP in members of these families with atypical phenotypes or who are clinically asymptomatic (Piccini *et al.*, 1998).

Genetic risk factors for PSP are uncertain. In a case-control study by means of questionnaires answered by 50 patients it was found that parkinsonism (odds ratio 5.0) and dementia (odds ratio 3.6) were more common among first degree relatives of PSP patients (Davis *et al.*, 1988) but, due to the small size of the cohort, the difference was not significant. Recent reports of familial PSP have raised the possibility of a genetic factor in the cause of this disease (David *et al.*, 1968; Mata *et al.*, 1983; Ohara *et al.*, 1992; Brown *et al.*, 1993; Gazely and Maguire, 1994; Tetrud *et al.*, 1994; de Yébenes *et al.*, 1995; Golbe *et al.*, 1995; Lanotte *et al.*, 1996; Tetrud *et al.*, 1996). The pattern of inheritance in these previous reports was variable. Four of these families had affected members in two or more generations, suggesting autosomal dominant transmission, while five families had affected individuals in the same generation and consanguinity was observed in one. So far, familial clustering PSP has been reported in 20 families including those in the present study. There is evidence for vertical transmission in 10 families, consanguinity in one and horizontal aggregation in 13 families. Considering the difficulties in the diagnosis it is likely that the number of familial aggregates of PSP is greater than previously thought, suggesting that PSP could be a hereditary disorder, at least in some families.

Recent reports (Conrad *et al.*, 1997; Lazzarini *et al.*, 1997) have described a higher prevalence of the A_0 polymorphism of the gene for tau in patients with sporadic PSP than in the general population. Higgins and colleagues (Higgins *et al.*, 1998) confirmed these data and suggested that familial PSP could be inherited as an autosomal recessive disorder linked to the tau gene. These observations are interesting since the pathological lesions found in the brain of patients with PSP are tau containing neurofibrillary tangles. The significance of this finding, however, is very difficult to interpret since homozygosity for the A_0 polymorphism occurs in around 55% of the population while the prevalence of PSP, even in aged individuals, is only 70 out of 100 000 inhabitants.

Furthermore, no linkage has been found (J. Hoenicka, M. Pérez, J. Pérez-Tur, A. Barabash, M. Godoy, R. Astarloa, J. Avila, T. Nyggard, J. G. de Yébenes, unpublished results) in the region 17q 21–22 where the gene for tau is localized, during a genomic search performed in families 2 and 7 of this study. In addition, we found that the polymorphism A_0 has a similar distribution in affected and non-affected members of families 2 and 6 of this study (Hoenicka *et al.*, manuscript in preparation), and no evidence of linkage was found between the PSP phenotype and the gene for tau after analysing the data for both a pattern of autosomal dominant and recessive inheritance in these families.

It is very important that the familial character of PSP is recognized in order to look for additional families that could be included in a genetic search. Finding a gene responsible for PSP could be a great step forward towards finding a valuable treatment for this disease.

Acknowledgements

This study was supported in part by grants from the PSP Society and Comunidad Autónoma de Madrid. Dra Rojo is supported by a grant from the Fondo de Investigaciones Sanitarias (BAE 98/5039).

References

Boller F, López OL, Moossy J. Diagnosis of dementia: clinicopathologic correlations [see comments]. Neurology 1989; 39: 76–9. Comment in: Neurology 1989; 39: 1559–60.

Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota, 1976 to 1990. Neurology 1997; 49: 1284–8.

Brown J, Lantos P, Stratton M, Roques P, Rossor M. Familial progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 1993; 56: 473–6.

Collins SJ, Ahlskog JE, Parisi JE, Maraganore DM. Progressive supranuclear palsy: neuropathologically based diagnostic clinical criteria [see comments]. J Neurol Neurosurg Psychiatry 1995; 58: 167–73. Comment in: J Neurol Neurosurg Psychiatry 1995; 59: 106. Comment in: J Neurol Neurosurg Psychiatry 1995; 59: 343.

Conrad C, Andreadis A, Trojanowski JQ, Dikson DW, Kang D, Chen X, et al. Genetic evidence for the involvement of tau in progressive supranuclear palsy. Ann Neurol 1997; 41: 277–81.

Daniel SE, de Bruin VM, Lees AJ. The clinical and pathological spectrum of Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy): a reappraisal. [Review]. Brain 1995; 118: 759–70.

David NJ, Mackey EA, Smith JL. Further observations in progressive supranuclear palsy. Neurology 1968; 18: 349–56.

Davis PH, Golbe LI, Duvoisin RC, Schoenberg BS. Risk factors for progressive supranuclear palsy [see comments]. Neurology 1988; 38: 1546–52. Comment in: Neurology 1990; 40: 1637.

de Yébenes JG, Sarasa JL, Daniel SE, Lees AJ. Familial progressive supranuclear palsy. Description of a pedigree and review of the literature. [Review]. Brain 1995; 118: 1095–103.

Dubinsky RM, Jankovic J. Progressive supranuclear palsy and a multi-infarct state. Neurology 1987; 37: 570–6.

Gazely S, Maguire J. Familial progressive supranuclear palsy [abstract]. Brain Pathol 1994; 4: 534.

Golbe LI, Dickson DW. Familial autopsy-proven progressive supranuclear palsy [abstract]. Neurology 1995; 45 (4 Suppl): A255.

Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewsky syndrome (progressive supranuclear palsy) [Review]. Neurology 1994; 44: 2015–9.

Higgins JJ, Litvan I, Pho LT, Li W, Nee LE. Progressive supranuclear gaze palsy is in linkage disequibrium with the tau and not the α-synuclein gene. Neurology 1998; 50: 270–3.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases [see comments]. J Neurol Neurosurg Psychiatry1992; 55: 181–4. Comment in: J Neurol Neurosurg Psychiatry 1993; 56: 938–9.

Jackson JA, Jankovic J, Ford J. Progressive supranuclear palsy: clinical features and response to treatment in 16 patients. Ann Neurol 1983; 13: 273–8.

Jankovic J. Progressive supranuclear palsy: clinical and pharmacologic update. [Review]. Neurol Clin 1984; 2: 473–86.

Jellinger K. Progressive supranuclear palsy: (subcortical argyrophilic dystrophy). Acta Neuropathol (Berl) 1971; 19: 347–52.

Jellinger KA. Neurodegenerative disorders with extrapyramidal features – a neuropathological overview. [Review]. J Neural Transm 1995; Suppl 46: 33–57.

Jendroska K, Hoffmann O, Schelosky L, Lees AJ, Poewe, Daniel SE. Absence of disease related prion protein in neurodegenerative disorders presenting with Parkinson's syndrome. J Neurol Neurosurg Psychiatry 1994; 57: 1249–51.

Kristensen MO. Progressive supranuclear palsy: 20 years later. Acta Neurol Scand 1985; 71: 177–89.

Lanotte L, Barroche G, Taillandier L, Lacour JC. Familial progressive supranuclear palsy [abstract]. Mov Disord 1996; 11 Suppl 1: 126.

Lazzarini AM, Golbe LI, Dickson DW, Duvoisin RC, Johnson WC. Tau intronic polymorphism in Parkinson's disease and progressive supranuclear palsy [abstract]. Neurology 1997; 48 (3 Suppl): A427.

Lilienfeld DE, Perl DP, Olanow W. Guam neurodegeneration. In: Calne DB editor Neurodegenerative diseases. Philadelphia: W.B. Saunders; 1994. p. 895–908.

Litvan I, Hauw J-J, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders [see comments]. J Neuropathol Exp Neurol 1996a; 55: 97–105. Comment in: J Neuropathol Exp Neurol 1996; 55: 1278–9.

Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP International Workshop. [Review]. Neurology 1996b; 47: 1–9.

Litvan I, Campbell G, Mangone CA, Verny M, McKnee A, Chaudhuri KR, et al. Which clinical features differentiate progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) from related disorders? Brain 1997; 120: 65–74.

Mata M, Dorovini-Zis K, Wilson M, Young AB. New form of familial Parkinson-dementia syndrome: clinical and pathologic findings. Neurology 1983; 33: 1439–43.

Nieforth KA, Golbe LI. Retrospective study of drug response in 87 patients with progressive supranuclear palsy. Clin Neuropharmacol 1993; 16: 338–46.

Ohara S, Kondo K, Morita H, Maruyama K, Ikeda S, Yanagisawa N. Progressive supranuclear palsy-like syndrome in two siblings of a consanguineous marriage. Neurology 1992; 42: 1009–14.

Piccini PP, Lees AJ, de Yebenes JG, Pramstaller PP, Turjanski N, Brooks DJ. 18F-dopa and 18FDG studies in 3 kindreds with familial progressive supranuclear palsy [abstract]. Neurology 1998; 50 Suppl 4: A429.

Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism – a prospective study. Can J Neurol Sci 1991; 18: 275–8.

Steele JC. Progressive supranuclear palsy. Brain 1972; 95: 693–704

Steele JC. Progressive supranuclear palsy. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology, Vol. 22. Amsterdam: North-Holland; 1975. p. 217–29.

Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch Neurol 1964; 10: 333–59.

Tetrud JW, Golbe LI, Farmer PM, Forno LS. Autopsy-proven progressive supranuclear palsy in two siblings [abstract]. Mov Disord 1994; 9 Suppl 1: 30.

Tetrud JW, Golbe LI, Forno LS, Farmer PM. Autopsy-proven progressive supranuclear palsy in two siblings. Neurology 1996; 46: 931–4.

Verny M, Jellinger KA, Hauw JJ, Bancher C, Litvan I, Agid Y. Progressive supranuclear palsy. A clinicopathological study of 21 cases. Acta Neuropathol (Berl) 1996; 91: 427–31.

Winikates J, Jankovic J. Vascular progressive supranuclear palsy. J Neural Transm 1994; Suppl 42: 189–201.

Received October 15, 1998. Revised February 1, 1999.
Accepted February 5, 1999