**ОПИСАНИЕ НА ПРЕДЛОЖЕНИЕТО ЗА ЗАБОЛЯВАНЕ в съответствие с чл. 11, ал. 2 от Наредба № 16 от 30.07.2014 г. за условията и реда за регистриране на редките заболявания и за експертните центрове и референтните мрежи за редки заболявания. Издадена от Министъра на здравеопазването, обн., ДВ, бр. 67 от 12.08.2014 г.**

| **ИНФОРМАЦИЯ ЗА:** |
|---|
| **Наименование на заболяването** |
| Паркинсонизъм с алвеоларна хиповентилация и депресия |
| **Определение на заболяването** |
| Perry синдромът е рядко наследствено невродегенеративно заболяване, характеризиращо се с бързо прогресиращ паркинсонизъм с ранно начало, централна хиповентилация, загуба на тегло, безсъние и депресия. Perry синдромът се причинява от хетерозиготна мутация на DCTN1 гена на хромозома 2p13 и е с автозомно-доминантно унаследяване. |
| **Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)** |
| G23(предложение) |
| **Код на заболяването по Orpha code** |
| ORPHA178509 |
| **Епидемиологични данни за заболяването в Република България** |
| Неизвестна заболеваемост и болестност. Предполага се заболеваемост и болестност сходна на останалите страни в Европа. |
| **В т.ч. научни публикации от последните пет години и приложена библиографска справка** |
| 1. Milanov I, Kmetska K, Karakolev B, Nedialkov E. Prevalence of Parkinson's disease in Bulgaria. Neuroepidemiology. 2001;20(3):212-4.<br>2. Perry, T. L., Bratty, P. J. A., Hansen, S., Kennedy, J., Urquhart, N., Dolman, C. L. Hereditary mental depression and parkinsonism with taurine deficiency. Arch. Neurol. 32: 108-113, 1975.<br>3. Perry, T. L., Wright, J. M., Berry, K., Hansen, S., Perry, T. L., Jr. Dominantly inherited apathy, central hypoventilation, and parkinson's syndrome: clinical, biochemical, and neuropathologic studies of 2 new cases. Neurology 40: 1882-1887, 1990.<br>4. Purdy, A., Hahn, A., Barnett, H. J. M., Bratty, P., Ahmad, D., Lloyd, K. G., McGeer, E. G., Perry, T. L. Familial fatal parkinsonism with alveolar hypoventilation and mental depression. Ann. Neurol. 6: 523-531, 1979.<br>5. Roy, E. P., III, Riggs, J. E., Martin, J. D., Ringel, R. A., Gutmann, L. Familial parkinsonism, apathy, weight loss, and central hypoventilation: successful long-term management. Neurology 38: 637-639, 1988.<br>6. Lechevalier, B., Schupp, C., Fallet-Bianco, C., Viader, F., Eustache, F., Chapon, F., Morin, P. Syndrome Parkinsonien familial avec athymhormie et hypoventilation. Rev. Neurol. 148: 39-46, 1992.<br>7. Wider, C., Dachsel, J. C., Farrer, M. J., Dickson, D. W., Tsuboi, Y., Wszolek, Z. L. Elucidating the genetics and pathology of Perry syndrome. J. Neurol. Sci. 289: 149- |

154, 2010.
8. Newsway, V., Fish, M., Rohrer, J. D., Majounie, E., Williams, N., Hack, M., Warren, J. D., Morris, H. R. Perry syndrome due to the DCTN1 G71R mutation: a distinctive levodopa responsive disorder with behavioral syndrome, vertical gaze palsy, and respiratory failure. Mov. Disord. 25: 767-770, 2010.
9. Caroppo, P., Le Ber, I., Clot, F., Rivaud-Pechoux, S., Camuzat, A., De Septenville, A., Boutoleau-Bretonniere, C., Mourlon, V., Sauvee, M., Lebouvier, T., Bonnet, A.-M., Levy, R., Vercelletto, M., Brice, A. DCTN1 mutation analysis in families with progressive supranuclear palsy-like phenotypes. JAMA Neurol. 71: 208-215, 2014.

**Епидемиологични данни за заболяването в Европейския съюз**

<1 / 1 000 000. До момента са публикувани само 14 семейства в целия свят вкл. и в страни от Европейския съюз.

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

1. Perry, T. L., Bratty, P. J. A., Hansen, S., Kennedy, J., Urquhart, N., Dolman, C. L. Hereditary mental depression and parkinsonism with taurine deficiency. Arch. Neurol. 32: 108-113, 1975.
2. Perry, T. L., Wright, J. M., Berry, K., Hansen, S., Perry, T. L., Jr. Dominantly inherited apathy, central hypoventilation, and parkinson's syndrome: clinical, biochemical, and neuropathologic studies of 2 new cases. Neurology 40: 1882-1887, 1990.
3. Purdy, A., Hahn, A., Barnett, H. J. M., Bratty, P., Ahmad, D., Lloyd, K. G., McGeer, E. G., Perry, T. L. Familial fatal parkinsonism with alveolar hypoventilation and mental depression. Ann. Neurol. 6: 523-531, 1979.
4. Roy, E. P., III, Riggs, J. E., Martin, J. D., Ringel, R. A., Gutmann, L. Familial parkinsonism, apathy, weight loss, and central hypoventilation: successful long-term management. Neurology 38: 637-639, 1988.
5. Lechevalier, B., Schupp, C., Fallet-Bianco, C., Viader, F., Eustache, F., Chapon, F., Morin, P. Syndrome Parkinsonien familial avec athymhormie et hypoventilation. Rev. Neurol. 148: 39-46, 1992.
6. Wider, C., Dachsel, J. C., Farrer, M. J., Dickson, D. W., Tsuboi, Y., Wszolek, Z. L. Elucidating the genetics and pathology of Perry syndrome. J. Neurol. Sci. 289: 149-154, 2010.
7. Newsway, V., Fish, M., Rohrer, J. D., Majounie, E., Williams, N., Hack, M., Warren, J. D., Morris, H. R. Perry syndrome due to the DCTN1 G71R mutation: a distinctive levodopa responsive disorder with behavioral syndrome, vertical gaze palsy, and respiratory failure. Mov. Disord. 25: 767-770, 2010.
8. Caroppo, P., Le Ber, I., Clot, F., Rivaud-Pechoux, S., Camuzat, A., De Septenville, A., Boutoleau-Bretonniere, C., Mourlon, V., Sauvee, M., Lebouvier, T., Bonnet, A.-M., Levy, R., Vercelletto, M., Brice, A. DCTN1 mutation analysis in families with progressive supranuclear palsy-like phenotypes. JAMA Neurol. 71: 208-215, 2014.

**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: Perry синдромът е със средна възраст на начало 48 години (в диапазона 35-61). Клинично се представя с паркинсонизъм (акинетично-ригиден и по-скоро симетричен), психиатрични нарушения (депресия, летаргия, отчужденост, апатия, промени в характера и нарушения в съня). Обичайната продължителност на Perry синдрома е 5 години с тежка загуба на тегло и централна хиповентилация в напредналите стадии на заболяването. В допълнение има съобщения за случаи със значими автономни нарушения, признаци наподобяващи фронтотемпорална деменция и прогресивна супрануклеарна пареза (забавеност на вертикални очни сакади надолу и мезенцефална атрофия).

Етиологията и патогенезата: Perry синдромът се причинява от мутации в екзон 2 на динактин DCTN1 гена, кодиращ p150glued, който представлява главната субединица на динактин протеиновия комплекс. Мутациите в този ген водят до промяна в афинитета за свързване на динактина към микротубулите, в резултат на което настъпва нарушение в този важен транспортен протеин. Нигралните клетки изглежда да са по-засегнати от дисфункцията на този протеин, което обяснява нарастващата локална клетъчна смъртност и отчетливата патология на Perry синдрома.

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


1. Perry, T. L., Bratty, P. J. A., Hansen, S., Kennedy, J., Urquhart, N., Dolman, C. L. Hereditary mental depression and parkinsonism with taurine deficiency. Arch. Neurol. 32: 108-113, 1975.
2. Caroppo, P., Le Ber, I., Clot, F., Rivaud-Pechoux, S., Camuzat, A., De Septenville, A., Boutoleau-Bretonniere, C., Mourlon, V., Sauvee, M., Lebouvier, T., Bonnet, A.-M., Levy, R., Vercelletto, M., Brice, A. DCTN1 mutation analysis in families with progressive supranuclear palsy-like phenotypes. JAMA Neurol. 71: 208-215, 2014.
3. Wider, C., Dachsel, J. C., Farrer, M. J., Dickson, D. W., Tsuboi, Y., Wszolek, Z. L. Elucidating the genetics and pathology of Perry syndrome. J. Neurol. Sci. 289: 149-154, 2010.
4. Newsway, V., Fish, M., Rohrer, J. D., Majounie, E., Williams, N., Hack, M., Warren, J. D., Morris, H. R. Perry syndrome due to the DCTN1 G71R mutation: a distinctive levodopa responsive disorder with behavioral syndrome, vertical gaze palsy, and respiratory failure. Mov. Disord. 25: 767-770, 2010.


**Алгоритми за диагностициране на заболяването**

Алгоритми за диагностициране на заболяването: Диагнозата се базира на клиничните данни за паркинсонизъм (съгласно Национален консенсус за диагностика и лечение на Паркинсоновата болест) с ранно начало в комбинация с депресия, загуба на тегло и хиповентилация, като синдрома се потвърждава от молекулно генетичното тестуване с установяване на мутация на DCTN1 ген.

Анамнезата: Perry синдромът е със средна възраст на начало 48 години (в диапазона 35-61). Клинично се представя с паркнсонизъм (акинетично-ригиден и по-скоро симетричен), психиатрични нарушения (депресия, летаргия, отчужденост, апатия, промени в характера и нарушения в съня). Обичайната продължителност на Perry синдрома е 5 години с тежка загуба на тегло и централна хиповентилация в напредналите стадии на заболяването. В допълнение има съобщения за случаи със значими автономни нарушения, признаци наподобяващи фронтотемпорална деменция и прогресивна супрануклеарна пареза (забавеност на вертикални очни сакади надолу и мезенцефална атрофия). Пациентите са често приковани към леглото или инвалидната

колична поради двигателните нарушения в напредналите стадии на заболяването.
Диференциалната диагноза на заболяването: други форми на фамилен паркинсонизъм с ранно начало (като асоциирани с мутации в PARK2, PINK1, PARK7 и LRRK2 гени), както и фронтотемпорална деменция.
Лабораторни, образни и хистологични изследвания: Perry и колеги (1975) установяват значимо намаление на таурина в плазмата и цереброспиналната течност при изследваните от тях пациенти. Таурина е предполагаем инхибитор на синаптичната трансмисия.
Патоанатомично изследване на Perry синдрома показва TDP43-свързана протеинопатия. Наблюдава се тежка невронална загуба в субстанция нигра и локус церулеус без телца на Lewy. Оцелелите неврони съдържат интрануклеарни и цитоплазмени TDP43-позитивни включвания, както и дистрофични неврити, аксонални сфероиди и глиални цитоплазмени включвания. Имунохистологията за MAPT и SNCA е негативна. Основната част от патологичните промени при Perry синдрома е свързана с палидонигрално засягане (което може да обясни паркинсонизма), при съхраняване на кората, хипокампа и моторните неврони (което съответства на липсата на деменция и двигателния неврон при голямата част от пациентите). Вероятна загуба на мозъчностволови неврони може да е в основата на централната хиповентилация.
Генетични изследвания и медико-генетично консултиране: Perry синдромът е с автозомно-доминантно унаследяване с пълна пенетрантност, като децата на пациенти със заболяването имат 50% шанс също да са носители на мутацията и да развият заболяването. Пресимптоматична диагноза може да бъде предложена на лицата с повишен риск. Пренатална диагноза е възможна в лабораториите, които предлагат пренатално тестуване на фамилии с установена DCTN1 мутация.

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


1. Национален консенсус за диагностика и лечение на Паркинсоновата болест, Двигателни заболявания, 2013, 10, 1.
2. Perry, T. L., Bratty, P. J. A., Hansen, S., Kennedy, J., Urquhart, N., Dolman, C. L. Hereditary mental depression and parkinsonism with taurine deficiency. Arch. Neurol. 32: 108-113, 1975.
3. Caroppo, P., Le Ber, I., Clot, F., Rivaud-Pechoux, S., Camuzat, A., De Septenville, A., Boutoleau-Bretonniere, C., Mourlon, V., Sauvee, M., Lebouvier, T., Bonnet, A.-M., Levy, R., Vercelletto, M., Brice, A. DCTN1 mutation analysis in families with progressive supranuclear palsy-like phenotypes. JAMA Neurol. 71: 208-215, 2014.
4. Wider, C., Dachsel, J. C., Farrer, M. J., Dickson, D. W., Tsuboi, Y., Wszolek, Z. L. Elucidating the genetics and pathology of Perry syndrome. J. Neurol. Sci. 289: 149-154, 2010.
5. Perry, T. L., Wright, J. M., Berry, K., Hansen, S., Perry, T. L., Jr. Dominantly inherited apathy, central hypoventilation, and parkinson's syndrome: clinical, biochemical, and neuropathologic studies of 2 new cases. Neurology 40: 1882-1887, 1990.
6. Farrer, M. J., Hulihan, M. M., Kachergus, J. M., Dachsel, J. C., Stoessl, A. J., Grantier, L. L., Calne, S., Calne, D. B., Lechevalier, B., Chapon, F., Tsuboi, Y., Yamada, T., and 10 others. DCTN1 mutations in Perry syndrome. Nature Genet. 41: 163-165, 2009.

**Алгоритми за лечение на заболяването**

Алгоритми за лечение на заболяването: Perry синдромът е нелечимо заболяване. Симптоматичното лечение изисква мултидисциплинарен екип. За лечение на паркинсонизма и някои немоторни симптоми може да се опита лечение в съответствие с Национален консенсус за диагностика и лечение на Паркинсоновата болест и 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: За лечение на паркинсонизма се използва обикновено леводопа терапия. Отговорът на леводопа терапията може да бъде отслабен, но големи дози (>2гр.) са показали ефективност при някои пациенти с Perry синдрома за намаление на симптомите. Пациентите с хиповентилация изискват вентилаторна подкрепа (инвазивна и неинвазивна) особено през нощта. Дихателната функция трябва да се следи непрекъснато. Психиатрично проследяване наред с приложението на антидепресанти са необходими за лечение на депресията и предотвратяване на самоубийство.

Препоръчителен диетичен режим и физическа активност и др.: Трябва да се проследява телесното тегло и при установяване на намаление на телесното тегло да се включи високо калорична диета.

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


1. Национален консенсус за диагностика и лечение на Паркинсоновата болест, Двигателни заболявания, 2013, 10, 1.
2. Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция, април 2015.
3. Roy, E. P., III, Riggs, J. E., Martin, J. D., Ringel, R. A., Gutmann, L. Familial parkinsonism, apathy, weight loss, and central hypoventilation: successful long-term management. Neurology 38: 637-639, 1988.
4. Wider, C., Dachsel, J. C., Farrer, M. J., Dickson, D. W., Tsuboi, Y., Wszolek, Z. L. Elucidating the genetics and pathology of Perry syndrome. J. Neurol. Sci. 289: 149-154, 2010.


**Алгоритми за проследяване на заболяването**

Алгоритми за проследяване на заболяването:

Прогнозата на заболяването: Обичайната продължителност на Perry синдрома е 5 години с тежка загуба на тегло и централна хиповентилация в напредналите стадии на заболяването. Пациентите са често приковани към леглото или инвалидната количка поради двигателните нарушения в напредналите стадии на заболяването. Смъртта се дължи на дихателна недостатъчност или самоубийство, като при някой случаи смъртта настъпва внезапно и необяснимо. Вентилационното подпомагане може да удължи продължителността и качеството на живот.

Необходимостта от последващи болнични и извънболнични грижи: Roy и колеги (1988) описват пациент, който след множество епизоди на респираторен арест е третиран с агресивно пулмонално обгрижване, трахиостомия и интермитентна механична вентилация в домашни условия, които в съчетание с Л-Допа терапия са подобрили значително състоянието.

Необходимостта от консултации с други специалисти: пулмолог, психиатър

Възможни усложнения: тежка загуба на тегло, централна хиповентилация, обездвижване с приковаване към леглото или инвалидната количка, усложнения свързани с обездвижването.
Честота и тежест на усложненията и др:.

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


1. Roy, E. P., III, Riggs, J. E., Martin, J. D., Ringel, R. A., Gutmann, L. Familial parkinsonism, apathy, weight loss, and central hypoventilation: successful long-term management. Neurology 38: 637-639, 1988.
2. Lechevalier, B., Schupp, C., Fallet-Bianco, C., Viader, F., Eustache, F., Chapon, F., Morin, P. Syndrome Parkinsonien familial avec athymhormie et hypoventilation. Rev. Neurol. 148: 39-46, 1992.
3. Tsuboi, Y., Wszolek, Z. K., Kusuhara, T., Doh-ura, K., Yamada, T. Japanese family with parkinsonism, depression, weight loss, and central hypoventilation. Neurology 58: 1025-1030, 2002.


**Алгоритми за рехабилитация на заболяването**

Алгоритми за рехабилитация на заболяването: За рехабилитация на паркинсонизма и някои немоторни симптоми може да се опита лечение в съответствие с Национален консенсус за диагностика и лечение на Паркинсоновата болест и 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 диагностика и лечение на Паркинсоновата болест, Двигателни заболявания, 2013, 10, 1.
2. 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:
Първична, вторична и третична превенция: Perry синдромът е с автозомно-доминантно унаследяване с пълна пенетрантност, като децата на пациенти със заболяването имат 50% шанс също да са носители на мутацията и да развият заболяването.
Пресимптоматична диагноза може да бъде предложена на лицата с повишен риск.
Пренатална диагноза е възможна в лабораториите, които предлагат пренатално тестуване на фамилии с установена DCTN1 мутация.

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


1. Farrer, M. J., Hulihan, M. M., Kachergus, J. M., Dachsel, J. C., Stoessl, A. J., Grantier, L. L., Calne, S., Calne, D. B., Lechevalier, B., Chapon, F., Tsuboi, Y., Yamada, T., and 10 others. DCTN1 mutations in Perry syndrome. Nature Genet. 41: 163-165, 2009.


**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 под ръководството на чл. кор. проф.Трайков за диагноза и лечение на редки заболявания, протичащи с паркинсонизъм с и без когнитивни нарушения, 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 паркинсонизъм с и без когнитивни нарушения, 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 центъра са осъществени няколко дисертации в областта: 1. Когнитивни нарушения при Паркинсонова болест (защитена дисертация за доктор по медицина от д-р Мария Петрова, 2010 г., ръководител: чл.-кор. проф. Лъчезар Трайков), 2. Лонгитудинално проследяване на когнитивните нарушения при Паркинсонова болест (защитена дисертация за доктор по медицина от д-р Явор Желев, 2012 г., ръководител: чл.-кор. проф. Лъчезар Трайков) и 3. 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). Събрана е база данни за отделни пациенти с отделни групи редки заболявания, протичащи с паркинсонизъм с и без когнитивен дефицит 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, протичащи с моторни и когнитивни нарушения, 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.

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Original Investigation

# *DCTN1* Mutation Analysis in Families With Progressive Supranuclear Palsy–Like Phenotypes

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**IMPORTANCE** Progressive supranuclear palsy (PSP) is usually sporadic, but few pedigrees with familial clustering of PSP-like phenotypes have been described. Occasionally, *MAPT*, *C9ORF72*, and *TARDBP* mutations have been identified.

**OBJECTIVE** To analyze the *DCTN1* gene in 19 families with a clinical phenotype of PSP (PSP-like phenotype).

**DESIGN, SETTING, AND PARTICIPANTS** Sequencing of the *DCTN1* gene in familial forms of PSP at a referral center among 21 patients with familial PSP-like phenotypes. In addition, 8 patients and relatives from a family carrying a *DCTN1* mutation were evaluated.

**MAIN OUTCOMES AND MEASURES** Identification of the *DCTN1* mutation and clinical description of *DCTN1* mutation carriers.

**RESULTS** We identified a *DCTN1* mutation in a large family characterized by high intrafamilial clinical phenotype variability. Two patients had PSP-like phenotypes with dystonia, vertical gaze slowness, dysexecutive syndrome, predominant axial rigidity, and midbrain atrophy on brain magnetic resonance imaging. The other patients manifested Perry syndrome, isolated parkinsonism, or a predominant behavioral variant of frontotemporal dementia.

**CONCLUSIONS AND RELEVANCE** Mutations of the *DCTN1* gene have been previously associated with amyotrophic lateral sclerosis and with Perry syndrome, a rare autosomal dominant disorder characterized by weight loss, parkinsonism, central hypoventilation, and psychiatric disturbances. Our study demonstrates that *DCTN1* mutations should be searched for in patients with clinical PSP-like phenotypes and a behavioral variant of frontotemporal dementia, especially when a familial history of dementia, psychiatric disturbances, associated parkinsonism, or an autosomal dominant disorder is present.

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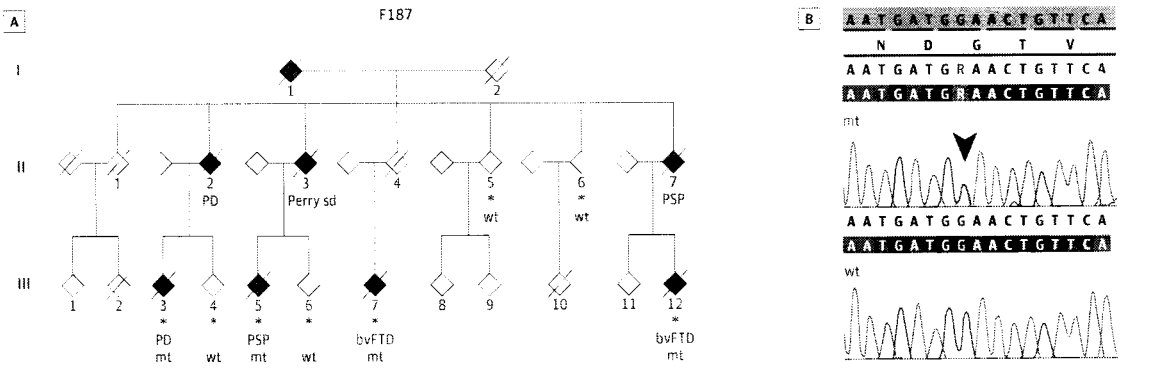
Progressive supranuclear palsy (PSP) is a neurodegenerative disorder clinically characterized by the presence of an akinetic-rigid parkinsonian syndrome associated with postural instability, frontal lobe dysfunction, and vertical supranuclear gaze palsy.[1] The National Institute of Neurological Disorders-Society for Progressive Supranuclear Palsy clinical diagnostic criteria rely on (1) age at onset older than 40 years and (2) the presence of a gradually progressive disorder, combined with (3) slow vertical saccades or supranuclear gaze palsy and (4) early postural instability and falls during the first year of the disease.[1] Modified clinical diagnostic criteria have been recently proposed (Neuroprotection and Natural History in Parkinson Plus Syndromes criteria) that allow an age at onset older than 30 years, postural instability or falls within 3 years from disease onset, and a disease duration ranging from 1 to 8 years.[2] Five distinct clinical phenotypes have been described according to the predominant symptoms.[3] Pathological diagnosis is based on the presence of neuropil threads, neurofibrillary tangles, and tau-positive astrocytes.[4] Progressive supranuclear palsy is usually sporadic; a familial aggregation of Parkinson disease and other neurodegenerative disorders, such as tremor, dementia, and parkinsonism remain controversial, having been observed in only one recent PSP case-control study.[5] Few pedigrees with familial clustering of PSP-like phenotypes have been described.[5-7] The genetic cause is unknown in most familial cases. Mutations in

Figure 1. Family Pedigree and *DCTN1* Mutation




A, Solid symbols indicate affected members; open symbols, unaffected individuals. Individuals are represented by diamonds for confidentiality. An asterisk indicates DNA availability; bvFTD, behavioral variant of frontotemporal dementia; mt, mutation; PD, Parkinson disease; Perry sd, Perry syndrome; PSP, progressive supranuclear palsy; slash, deceased; and wt, wild type. B, Chromatograms of coding exon 2 of the *DCTN1* gene. The c.212G>A (p.Gly71Glu) mutation is shown by the arrowhead, and the corresponding normal sequence is shown below.

the *MAPT* (Online Mendelian Inheritance in Man [OMIM] 157140)[5,8,9] gene have been identified in a few families, and *TARDBP* (OMIM 605078)[10] and *C9ORF72* (OMIM 614260)[11,12] mutations are extremely rare in patients with PSP. A locus has been mapped on chromosome 1, but the disease-causing gene has not been identified.[13] In this study, we analyzed the *DCTN1* (OMIM 601143) gene in 19 families with a clinical phenotype of PSP (PSP-like phenotype).

## Methods

### Patients and Families

This study was approved by the ethics committee of Assistance Publique-Hôpitaux de Paris, Paris, France. All participants signed an informed consent form for genetic studies. During the past several years, we evaluated 21 families with PSP-like phenotypes. A PSP phenotype was clinically diagnosed using National Institute of Neurological Disorders-Society for Progressive Supranuclear Palsy international diagnostic criteria.[1] The diagnosis of PSP was confirmed by pathological examination in 2 families. A positive family history was defined by at least 1 first- or second-degree relative manifesting a clinical phenotype of PSP. We recorded familial histories of related disorders, including Parkinson disease, frontotemporal dementia (FTD), and corticobasal degeneration syndrome, diagnosed according to international criteria. Clinical data and biological samples were collected for all the patients. The genealogy of the families was reconstructed, and clinical data and biological samples of relatives were collected whenever possible.

### Molecular Analysis

Blood genomic DNA was extracted from peripheral white blood cells using standard methods. Point mutations, as well as gene deletions and duplications, were previously searched for in the main genes responsible for FTD (*C9ORF72*, *PGRN*, *MAPT*, *VCP*, and *TARDBP*) and for Parkinson disease (*SNCA*, *LRRK2*, *parkin*, *ATP13A2*, and *FBXO7*) by direct sequencing or repeat-primed polymerase chain reaction (for *C9ORF72*). *MAPT* and *C9ORF72* mutations were identified in one family each (7%, respectively).[8,11]

No mutations were found in the 19 remaining families. The 32 exons and exon-intron junctions of the *DCTN1* gene were then amplified by polymerase chain reaction, as previously described.[14] The purified amplified fragments were sequenced on an automated system with a cycle kit (ABI 3730, Big Dye 3.1; Applied Biosystems). The sequencing data were analyzed using available software (SeqScape 2.5; Applied Biosystems).

## Results

We identified a point mutation in exon 2 of the *DCTN1* gene in a large French family. Our findings enlarge the genetic causes of familial PSP and the phenotypic spectrum associated with *DCTN1* mutations.

### Molecular Analysis

In the patient (III-5) of one family (F187), we identified a heterozygous missense mutation, c.212G>A, p.Gly71Glu (NM_004082.4), in exon 2 of the *DCTN1* gene. These results are shown in **Figure 1**.

Two patients (III-5 and II-7) of family F187 manifested a PSP-like phenotype at disease onset. Other patients had clinical diagnoses of Perry syndrome (II-3), Parkinson disease (III-3 and II-2), and behavioral variant of FTD (bvFTD) (III-7 and III-12). Two patients (III-5 and III-12) were independently referred to us by their neurologist, and genealogical extension of the family allowed us to link the 2 patients to the same pedigree.

The mutation segregated with the disease: patients III-3, III-7, and III-12 carried the mutation, whereas 4 asymptomatic relatives older than 60 years (II-5, II-6, III-4, and III-6) did

Table 1. Demographic and Clinical Variables of Affected Participants

| Variable | I-1 | II-2 | II-3 | II-7 | III-3 | III-5 | III-7 | III-12 |
|---|---|---|---|---|---|---|---|---|
| Age at onset, y | 50 | NA | NA | 49 | 46 | 59 | 40 | 39 |
| Duration of disease, y | 4 | 4 | NA | 3 | 5 | 5 | 14 | 4 |
| Age at death, y | 54 | 50 | 47 | 52 | 51 | 64 | 54 | 43 |
| Clinical diagnosis | PD | PD | PD or Perry syndrome | PSP | PD | PSP | bvFTD | bvFTD |
| Symptoms at onset | Parkinsonism | Parkinsonism | Parkinsonism | Depression, anxiety | Parkinsonism | Apathy | Gait imbalance, falls | Depression, apathy, eating conduct disorders |
| Parkinsonism | + | + | + | + | + | + | + | + |
| Rigidity | NA | + | + | + | + | + | NA | + |
| Akinesia | NA | + | + | + | + | + | NA | + |
| Tremor | NA | NA | + | – | – | – | – | + |
| Levodopa or dopamine agonist response, adverse effects | NA | NA | NA | NA | + | NA | NA | Levodopa-induced dyskinesia, hallucinations |
| Dystonia | – | – | – | + | – | + | – | – |
| Oculomotor disorders | NA | NA | NA | + PSP-like | NA | + PSP-like | NA | – |
| Frontal signs | NA | NA | NA | + | + | + | + | + |
| Disinhibition | | | | + | – | – | + | – |
| Apathy or inertia | | | | + | + | + | – | + |
| Hyperorality | | | | – | – | – | + | + |
| Archaic reflexes | | | | + | NA | + | NA | + |
| Dysexecutive syndrome | | | | NA | NA | + | NA | + |
| Psychiatric symptoms | NA | NA | + | + Anxiety, obsessions | – | – | + Depression, suicidal ideation | + Depression, anxiety |
| Weight loss | NA | NA | NA | NA | – | – | – | + |
| Hypoventilation | NA | NA | + | + | – | NA | + | – |
| Cause of death | NA | NA | Respiratory arrest | Respiratory arrest | Unknown | Unknown | Respiratory arrest | Acute alcoholism |
| Brain magnetic resonance imaging/ single-photon emission computed tomography | NA | NA | NA | Normal | NA | Frontotemporal and midbrain atrophy /prefrontal superior hypoperfusion | Normal | Moderate frontal atrophy/bilateral frontal hypoperfusion |

Abbreviations: bvFTD, behavioral variant of frontotemporal dementia; NA, not available; PD, Parkinson disease; PSP, progressive supranuclear palsy; +, present; –, absent.

not carry the mutation. The DNA of patients II-2, II-3, and II-7, who were obligate carriers, was unavailable.

The c.212G>A, p.Gly71Glu mutation has been previously identified in an apparently unrelated French family with a phenotype of Perry syndrome.[14,15] The glycine at codon 212 is conserved among multiple species. This mutation is located in the cytoskeleton-associated protein, glycine-rich domain, which contains the most conserved GKNDG motif (Gly-Lys-Asn-Asp-Gly). In silico analysis of missense substitutions pathogenicity revealed that p.Gly71Glu was classified as pathogenic using the following 4 algorithms: (1) PolyPhen-2 (Polymorphism Phenotyping version 2) software (http://genetics.bwh.harvard.edu/pph2), (2) Align GVGD (http://agvgd.iarc.fr/), (3) SIFT (Sorting Intolerant From Tolerant) (http://sift.jcvi.org), and (4) Mutation Taster (http://www.mutationtaster.org). It was not detected in 949 control subjects from another study[11] and was not present in 6503 individuals from an available database (Exome Variant Server [http://evs.gs.washington.edu/EVS/]), supporting its pathogenicity.

## Clinical Features

Detailed clinical features were available for 8 patients of the family (**Table 1**). Four patients (III-3, III-5, III-7, and III-12) were examined and followed up by one of us (C.B.B., M.S., T.L., A.-M.B., R.L., or M.V.). Clinical data of deceased patients (I-1, II-2, II-3, and II-7) were collected from their medical records and by interview with their relatives.

In 6 patients, the mean (SD) age at onset was 47 (7) years (age range, 39-59 years). The first symptom was parkinsonism in 4 of 8 patients. Parkinsonism was predominantly of rigid-akinetic type; asymmetric tremor was present in one patient. Beneficial effect of levodopa was variable and often mild. It was often not well tolerated, rapidly causing levodopa-induced delirium, dyskinesias, and hallucinations. Initial depression and behavioral disorders (each in 2 of 8 patients) were less frequent. None of the patients developed clinical symptoms of amyotrophic lateral sclerosis (ALS). Among 8 patients, the mean (SD) age at death was 52 (6) years (age range, 43-64 years). Among 7 patients, the mean

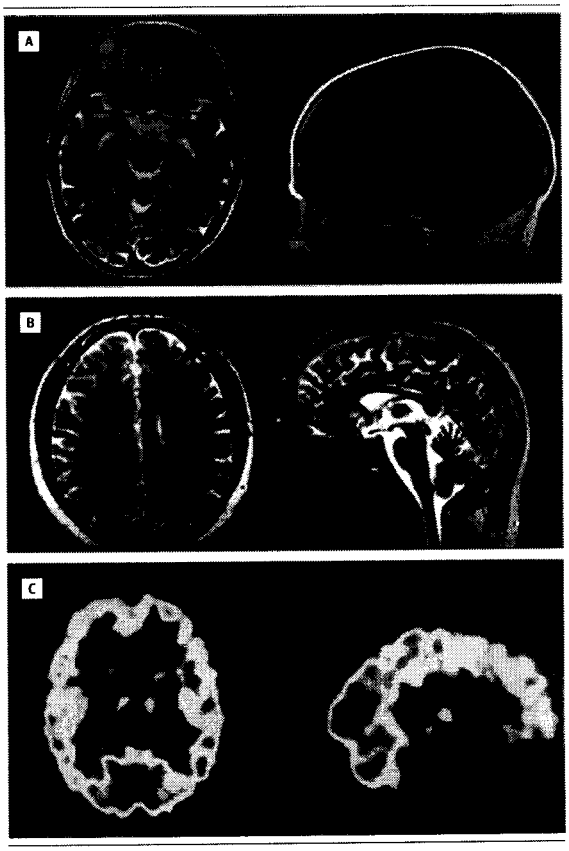
(SD) duration of disease was 6 (4) years (range, 3-14 years). The disease duration was long (14 years) in one patient (Table 1).

Four patients (III-5, II-7, III-12, and III-7) had uncommon presentations. Patient III-5 manifested apathy at age 59 years. At age 61 years, he developed bilateral blepharospasm, environmental adherence, and predominant axial akinetic-rigid parkinsonism. Brain magnetic resonance imaging revealed mild midbrain atrophy (**Figure 2A**), and brain ethyl cysteinate dimer-single-photon emission computed tomography showed prefrontal superior hypoperfusion. At age 62 years, the patient manifested anxiety, collectionism, and loss of interest, in the absence of depression. Examination showed marked axial rigid-akinetic parkinsonism with perseverations, buccolingual apraxia, bilateral grasping reflex, and severe postural instability. Examination of gaze showed slowing of voluntary vertical saccades. An electroneuromyogram was normal. Eye movement recording showed severe hypometry (gain = 0.75) but normal latency and velocity of horizontal visually guided saccades (225 milliseconds for right latency, 221 milliseconds for left latency; normal value 130-220). Saccade velocity was slightly reduced in downward vertical movements. Antisaccades were mildly abnormal (errors of 47% on the right side and 20% on the left side). A dysexecutive syndrome with perseverations, poor lexical phonological evocation, and attention and working memory deficits was present (**Table 2**). A diagnosis of PSP was made based on the clinical phenotype. The disease rapidly worsened, and death occurred at age 64 years.

From age 49 years, patient II-7 demonstrated obsessional personality traits; severe panic attacks characterized his disease, which led to a diagnosis of hypochondria. At age 51 years, the patient developed severe axial parkinsonian rigidity with postural instability associated with right upper limb dystonia. Parkinsonism only partially responded to levodopa treatment. An examination revealed a massive frontal syndrome with grasping reflex. Eye movement recording showed saccade hypometry. A diagnosis of PSP was made based on the clinical presentation. The disease rapidly worsened. Death occurred from pulmonary infection and acute respiratory failure at age 52 years.

Patient III-12 had depression and anxiety associated with behavioral changes at age 39 years. He progressively developed apathy, hyperorality, personal neglect, loss of initiative, indifference to others, and eating conduct changes. An examination at age 41 years revealed severe psychomotor slowness and reduction of speech output. Perseverative errors were present on the Wisconsin Card Sorting Test[19] (Table 2). Mild frontal atrophy was seen on brain magnetic resonance imaging, and brain single-photon emission computed tomography showed bilateral frontal hypoperfusion (Figure 2B and C). A diagnosis of bvFTD was made. An electroneuromyogram was normal. A polysomnographic recording revealed a sleep apnea syndrome. At age 42 years, he developed predominant axial rigidity associated with moderate right upper and lower limb tremor and rigidity. Levodopa treatment was complicated by drug-induced dyskinesia and hallucinations. The patient manifested severe depression with suicidal ideation (score of 20 on the Montgomery-Åsberg Depression Rating Scale[22]) that was resistant to antidepressant treatment. He later developed alcohol abuse, motor stereotypies, and progressive weight loss. Death occurred at age 43 years during an episode of acute alcoholism.

Figure 2. Brain Magnetic Resonance Imaging in Patients III-5 and III-12 and Single-Photon Emission Computed Tomography in Patient III-12




A, Brain magnetic resonance imaging in patient III-5 showing mild midbrain and frontal atrophy. B, Brain magnetic resonance imaging in patient III-12 showing mild frontal atrophy. C, Ethyl cysteinate dimer-single-photon emission computed tomography in patient III-12 showing marked frontotemporal hypoperfusion. According to radiological convention, right is left.

Patient III-7 had a long history of depression with numerous suicide attempts. He demonstrated loss of balance, a gait in small steps, and falls at age 40 years. A behavioral disorder with puerilism, coarseness, hyperorality, anosognosia, bizarre conduct, and disinhibition with seductress behavior was consistent with a diagnosis of bvFTD. The patient died at age 54 years of respiratory arrest.

Other patients (I-1, II-2, II-3, and III-3) are summarized in Table 1. Patients I-1, II-2, and III-3 had a diagnosis of early-onset parkinsonism. The phenotype of the other patient (II-3) included hypoventilation, severe depression, and associated parkinsonism with respiratory failure, which was consistent with the diagnostic criteria of Perry syndrome.

Table 2. Cognitive Profiles of Patients III-5 and III-12

| Variable | III-5 | III-12 |
|---|---|---|
| Age at examination, y | 62 | 39 |
| Evolution time, y | 3 | 2 |
| Mini-Mental State Examination[16] score (range, 1-30) | 24 | 30 |
| Mattis Dementia Rating Scale[17] | | NA |
| Score (range, 1-144) | 137 | |
| Attention (range, 1-37) | 37 | |
| Initiation (range, 1-37) | 31 | |
| Construction (range, 1-6) | 6 | |
| Concepts (range, 1-39) | 39 | |
| Memory (range, 1-25) | 24 | |
| Digit Span Forward | 5 | NA |
| Digit Span Backward | 4 | NA |
| Free and Cued Recall Test[18] | | |
| Identifications (range, 1-16) | 16 | 16 |
| Immediate cued recall (range, 1-16) | 14 | 15 |
| Immediate free recall (range, 1-48) | 20[a] | 26[a] |
| Immediate total recall (range, 1-48) | 48 | 47 |
| Delayed free recall (range, 1-16) | 11[a] | 12 |
| Delayed total recall (range, 1-16) | 16 | 16 |
| Recognitions (range, 1-16) | 16 | 16 |
| Wisconsin Card Sorting Test[19] | | |
| Criteria (range, 1-6) | 2 | 6 |
| Errors, % | 16[a] | 5[a] |
| Perseverations, % | 25[a] | 60[a] |
| Verbal Fluency[20] | | |
| Semantic (animals) | 16 | 21 |
| Phonological (letter M) | 3[a] | 16 |
| Frontal Assessment Battery[21] | | |
| Total score (range, 1-18) | 15[a] | 16[a] |
| Similarities (range, 1-3) | 3 | 3 |
| Phonological fluency (range, 1-3) | 1[a] | 2[a] |
| Grasping (range, 1-3) | 3 | 3 |
| Motor sequences (range, 1-3) | 2[a] | 3 |
| Conflicting instructions (range, 1-3) | 3 | 3 |
| Go-no go (range, 1-3) | 3 | 2[a] |

Abbreviation: NA, not available.

[a] Under the cutoff.

## Discussion

We have described herein a French family characterized by high intrafamilial variability with different phenotypes, including bvFTD, Perry syndrome, PSP-like phenotype, and isolated parkinsonism caused by the p.Gly71Glu mutation in exon 2 of the *DCTN1* gene. Another apparently unrelated French family carried the p.Gly71Glu mutation[14,15] (**Table 3**). Although these 2 families originated from different regions of France, we cannot firmly exclude a founder effect for this mutation.

*DCTN1* mutations were first identified in patients with distal spinal and bulbar muscular atrophy[33,34] and in patients with ALS.[35,36] A cluster of mutations in exon 2 of the *DCTN1* gene was identified later in 11 families with Perry syndrome, a rare autosomal dominant form of parkinsonism associated with weight loss, severe depression, and central hypoventilation (Table 3).[14,15,23-32] Clinical diagnostic criteria of Perry syndrome, as defined by Wider and Wszolek,[37] include 5 cardinal characteristics (weight loss, parkinsonism, hypoventilation, psychiatric symptoms, and familial autosomal dominant history) and 5 supportive features (rapid progression, suicidal thoughts or attempts, no or transient response to levodopa, onset between the ages of 30 and 60 years, and dyspnea or apnea with night predominance). The phenotypes associated with *DCTN1* mutations are correlated with the genotype because all the mutations located in exon 2 except one (p.Gly59Ser) are responsible for Perry syndrome. The p.Gly59Ser mutation led to slowly progressive distal spinal and bulbar muscular atrophy with vocal cord paralysis.[33] All other mutations producing ALS are in the other exons of the gene (see eTable 1 in the Supplement).[35,36]

The patient of family F187 (III-5) and his relative (II-7) manifested a clinical phenotype that matched the criteria for PSP, which is an uncommon presentation in families with *DCTN1*. A clinical diagnosis of Perry syndrome could not be considered in the 2 patients at early stages of disease. Indeed, the phenotype of III-5, with only 2 cardinal features (parkinsonism and autosomal dominant inheritance) without weight loss, hypoventilation, or psychiatric symptoms was inconsistent with probable or possible criteria for Perry syndrome (see eTable 2 in the Supplement). The phenotype of II-7 was ultimately consistent with a probable diagnosis of Perry syndrome but not at the early stage of disease. Initially, both patients manifested a progressive rigid-akinetic syndrome after age 40 years, combining early postural instability with falls, slow vertical saccades, or supranuclear gaze palsy and a disease duration shorter than 8 years, which fit well with criteria for PSP by the National Institute of Neurological Disorders-Society for Progressive Supranuclear Palsy,[1] as well as criteria by the Neuroprotection and Natural History in Parkinson Plus Syndromes.[2] Oculomotor recordings in both patients showed hypometric horizontal saccades and a speed reduction downward in vertical movements, which were unusual in Perry syndrome but were characteristic of PSP. In addition, both patients had frontal syndrome and dystonia (blepharospasm or upper limb dystonia), and midbrian atrophy was present in patient III-5; these symptoms are uncommon in Perry syndrome but suggest the diagnosis of PSP. One other patient carrying a p.Gly71Arg *DCTN1* mutation demonstrated slowing of vertical downward saccades and progressive midbrain atrophy on neuroimaging that were suggestive of PSP.[31] This patient and our series support that PSP-like phenotypes may be included in the clinical spectrum of disorders associated with *DCTN1* mutations. These cases also suggest that phenotypic presentations are related to an anatomical distribution of the lesions rather than to a specific histopathological condition because *DCTN1* mutations are associated with pathological transactive response DNA-binding protein 43 (TDP-43),[32] although most other PSP phenotypic presentations are tauopathies.[4]

Table 3. Clinical Features of Previously Reported Patients With Perry Syndrome and of Family 187

| Variable | Perry et al,[23,24] 1975, 1990 | Purdy et al,[25] 1979 | Roy et al,[26] 1988 | Lechevalier et al,[15] 1992 | Bhatia et al,[27] 1993 | Elibol et al,[28] 2002 | Tsuboi et al,[29] 2002 | Ohshima et al,[30] 2010 | Newsway et al,[31] 2010 | Wider et al,[32] 2010 | Present Study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of families (geographical origin) | 1 (Canada) | 1 (Canada) | 1 (United States) | 1 (France) | 1 (United Kingdom) | 1 (Turkey) | 1 (Japan) | 1 (Japan) | 1 (United Kingdom) | 2 (Japan) | 1 (France) |
| No. of affected participants (male-female ratio) | 10 (8:2) | 5 (3:2) | 6 (3:3) | 8 (3:5) | 6 (3:3) | 2 (1:1) | 5 (5:0) | 3 (1:2) | 1 (1:0) | 2 (First [0:2]), 2 (second [1:1]) | 8 |
| Age at onset, mean (range), y | 49 (45-52) | 46 in 2 patients | 51 (44-56) in 4 patients | 49 (45-56) in 5 patients | 43 (35-51) in 5 patients | 48 (46-50) | 41 (38-43) | 56 (46-61) | 46 | 47 (First), 61 (second) | 47 (39-59) in 6 patients |
| Duration, mean (range), y | 5 (4-6) | 2.5 (2-3) | 3 (3-5) | 8 (6-10) | 5 (3-10) in 5 patients | 4 (3-5) | 6 (6-2) | 4 | 9 | NA (first), 3 (second) | 5 (3-14) in 7 patients |
| First symptoms | Depression, weight loss | Depression, weight loss | Parkinsonism, depression | Parkinsonism, depression | Parkinsonism | Apathy | Parkinsonism, depression | Parkinsonism, weight loss | Parkinsonism, depression | Parkinsonism (first); resting tremor, weight loss (second) | Parkinsonism in 4 patients; depression, apathy, anxiety in 3 patients |
| Parkinsonism | + | + | + | + | + | + | + | + | + | + | + |
| Akinesia | - | + | + | + | + | + | + | + | + | + | + |
| Rigidity | + Axial | + | + | + | + | NA | + | + | + | + | + |
| Tremor | + | + | + | + | + | + | + | + | - | + Second | + In 2 patients |
| Levodopa or dopamine agonist response (adverse effects) | - | - | + | + | + | + | + Hypomanic state in 1 patient | - | + Levodopa-induced dyskinesia | + | + Levodopa-induced dyskinesia, hallucinations |
| Other features | - | - | - | - | - | - | - | Autonomic dysfunction | Vertical gaze palsy | - | Vertical gaze palsy in 2 patients |
| Psychiatric disturbances | + | + | + | + | + | NA | + In 4 patients | + In 1 patient | - | - | + In 4 patients |
| Hypoventilation | + | + | + | + | - | + | + In 3 patients | + | + | + | + In 3 patients |
| Weight loss | + | + | + | + | - | + | + In 4 patients | + | + | - | + In 1 patient |
| Cause of death | Suicide in 1 patient, respiratory arrest in 2 patients | Respiratory arrest | Respiratory arrest | Respiratory arrest | Pneumonia in 1 patient, sudden death in 1 patient | Respiratory arrest in 1 patient, pneumonia in 1 patient | Suicide in 1 patient, respiratory arrest in 1 patient | Respiratory and cardiac arrest | NA | Respiratory arrest | Respiratory arrest in 3 patients |

Abbreviations: NA, not available; +, present; -, absent.

Two other patients had unusual presentations of predominant behavioral disorders consistent with the diagnostic criteria of bvFTD.[38] Only mild to moderate frontal atrophy was present at brain imaging, although single-photon emission computed tomography showed marked bilateral frontal hypoperfusion in one patient. Neither patient had clinical symptoms of ALS. Another patient having FTD with a family history of ALS carried a p.Arg1101Lys mutation in exon 27. Frontotemporal type of dementia is not included in the clinical criteria for Perry syndrome,[37] but our cases showed that it may be the predominant initial phenotype in patients with *DCNT1* mutations.

It has recently been shown that Perry syndrome is a genetically and pathologically heterogeneous syndrome; however, neuropathological investigations demonstrated severe neuronal loss in the substantia nigra without Lewy bodies but with TDP-43-positive inclusions in Perry syndrome caused by *DCTN1* mutations.[32] *MAPT* mutations have also recently been identified in 2 families with associated weight loss, parkinsonism, and central hypoventilation, a phenotype resembling Perry syndrome, and with a pathological 4-repeat tau suggestive of PSP.[39] *DCTN1* codes for the large subunit p150glued of the dynein-dynactin motor protein complex are involved in retrograde axonal transport. Tau is a microtubule-binding protein that strongly interacts with tubulin to assemble and stabilize the microtubule and is crucial for axonal transport. Mutations in *DCTN1* and *MAPT* in dementia, parkinsonism, and motor neuron disor-

der support that axonal transport injury might have a key role in the pathogenesis of these conditions.[33]

The frequency of *DCTN1* mutations was low (1 of 21 patients) in our series of familial forms of PSP-like phenotypes. However, our study demonstrates that *DCTN1* mutations should be searched for in patients with clinical PSP-phenotypes, especially when bvFTD, psychiatric disturbances, associated parkinsonism, or a familial history of an autosomal dominant disorder is present.

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# Perry syndrome due to the DCTN1 G71R mutation – a distinctive L-DOPA responsive disorder with behavioural syndrome, vertical gaze palsy and respiratory failure

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## Abstract

Perry syndrome is a rare form of autosomal dominant parkinsonism with respiratory failiure recently defined as being due to mutations in the DCTN1 gene. We describe a new family carrying a G71R mutation in the DCTN1 gene. The proband displayed a series of distinctive features not previously described in Perry syndrome: a disorder of vertical downward saccades accompanied by progressive midbrain atrophy, predominant non-motor symptoms responsive to L-DOPA, distinctive cranio-cervical L-DOPA induced dyskinesias, and a good response to high dose L-DOPA therapy and respiratory support. The family was initially thought to have autosomal dominant behavioural variant frontotemporal dementia with parkinsonism. This report expands the clinical definition of this distinctive syndrome.

### Keywords

Perry Syndrome; Respiratory Failure; L-Dopa Responsive; Gaze Palsy; Dementia; Parkinsonism

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## Introduction

Perry syndrome is a rare autosomal dominant disorder (reported in 8 kindreds worldwide) with core features of hypoventilation, parkinsonism, weight loss and depression or psychiatric symptoms[1,2]. Cell loss in the substantia nigra is a uniform finding with some reports describing additional involvement of the locus coeruleus, nucleus tractus solitarius, dorsal nucleus of the vagus nerve, nucleus ambiguus and ventral medulla[3]. At a molecular level Perry syndrome is characterised by TAR DNA binding protein (TDP)-43 inclusions indicating a pathological overlap with amyotrophic lateral sclerosis and some forms of frontotemporal lobar degeneration (FTLD). Unlike in FTLD, pathological frontotemporal lobar atrophy is not a feature. Perry syndrome has recently been identified as being due to mutations in the DCTN1 gene, encoding the p150$^{glued}$ component of the dynactin complex, enabling further clinico-pathological delineation of this distinctive syndrome[4]. Penetrance is about 50%.

We report a new family with Perry syndrome presenting with features of behavioural variant frontotemporal dementia (bvFTD) later developing respiratory failure as well as autonomic disturbance, an abnormality of downgaze and distinctive L-DOPA responsive off-phenomena.

### Case report

The proband was initially referred with suspected depression and was noted to have parkinsonism. His symptoms began at the age of 46. He had worked in computer-aided design. He spent the last 5 years of his working life as a warehouse operative (with decreasing productivity), retiring on ill health grounds at the age of 47. From the age of 46 his family described him becoming apathetic, less sociable and empathetic. Fluoxetine then lofepramine were prescribed with little benefit. At the age of 48 he began to walk more slowly, developed a staring expression and had falls. He had erectile dysfunction. When he was assessed at the age of 49 he had become reckless (especially with spending), mentally rigid and lacking initiative. His previously safe and reliable driving became erratic and risk-taking. He began to hoard. He would bolt food and there was mildly disinhibited behaviour, such as licking the bowl when dining. His wife remarked that he would frequently sigh, smack his lips or hum without apparent reason: these features were more prominent during sleep when they were interspersed with periods of rapid breathing and bruxism. There was no history of hallucinations. His father had died at the age of 56 with a post-mortem diagnosis of presenile dementia, and had originally been thought to have a psychiatric disorder; his paternal grandparents had both died at a young age. His mother died age 81 with late onset Parkinson's disease.

On examination he was found to have generalized paucity of movement, axial rigidity with an *en bloc* posture on standing and turning, decreased arm swing and decreased blink rate, but no distal bradykinesia. There was no dyspraxia. His Mini-Mental State Examination score[5] (MMSE) was 30/30, and Frontal Assessment Battery score[6] was 16/18. Comprehensive neuropsychological assessment including attention span, verbal and visual memory, verbal reasoning, single word comprehension, and visuoperceptual and visuospatial construction skills revealed mildly reduced verbal fluency (total F-A-S letter

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fluency of 18 in 3 minutes) and mild slowing of information processing, but no other deficits. His recognition of emotions from facial expressions was within the control range[7]. His Neuropsychiatric Inventory Score (NPI) [8] was 20 (where a score of 0 signifies no behavioural abnormalities), with the most marked changes recorded in the domains of apathy and sleep disturbance.

He was started on L-Dopa and reported an improvement in movement and mood. At the age of 50 his family reported that he was becoming more short-tempered and he became very slow carrying out everyday activities. Later in the year there was evidence of distractibility (he left bags unattended at the airport). He had no insight into his balance problems. In the 26 months from his first hospital appointment his weight dropped from 75kg to 67kg.

At the age of 51, five years after the earliest symptoms, he developed diurnal episodes of tachypnoea lasting up to 20 minutes, on occasion associated with collapse. They were initially thought to be panic attacks. The breathing changes became more pronounced at the end of L-Dopa dose period. When reviewed eight months later he exhibited a series of autonomic and stereotypic wearing-off phenomena - hypersalivation, sweating, sniffing, repetitive facial grimacing with bruxism, worsening right leg tremor, as well as a feeling of inner tension, all responsive to L-DOPA. A year after commencement of treatment he was on 1000mg / day of L-DOPA (as co-careldopa), later building to more than 2000 mg/day of L-DOPA.

Disinhibited behaviour was becoming more marked. He required prompting for basic daily activities. Six years after onset, the patient had an episode of probable post-micturition syncope. A Holter tape revealed a persistent sinus tachycardia. Around this time his wife noticed choking and gagging noises during sleep. Two months later during the night he was found by his wife unconscious, making little respiratory effort. On admission to hospital his Glasgow Coma Score was 3, and his respiratory rate was 4/minute. He was in type II respiratory failure with a $pO_2$ of 8.8kPa, a $pCO_2$ of 10kPa and a blood pH of 7.2. Positive end expiratory pressure ventilation was initiated, he was transferred to the intensive care unit and was found to have an aspiration pneumonia. Subsequent sleep studies showed 2 desaturations (>4%) per hour on average. The pattern of desaturation was in keeping with central hypoventilation. Commencing regular non-invasive nocturnal ventilatory therapy (BIPAP) led to marked improvement in energy levels, alertness and concentration. He gained 7kg in weight during the first 3 months of non-invasive ventilatory therapy. Subsequently he also developed dysphagia as part of his wearing-off symptom complex. By the age of 53 he had marked slowing of downward saccades with preservation of horizontal saccades.

Neuropsychological assessment at this stage showed little evidence of cognitive deterioration: MMSE score remained 30/30 and performance in a series of focal cognitive domains was essentially unchanged, with only a mild increase in NPI score for abnormal behaviours (now 29). His dopaminergic therapy had been escalated to over 2g of cocareldopa/day as well as entacapone, with continued good response. With the provision of respiratory support and high dose L-DOPA treatment he and his family reported a good quality of life.

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Serial brain MRIs were initially unremarkable but later showed mild diffuse cerebral atrophy and more pronounced focal midbrain atrophy (Figure 1). Video-EEG telemetry showed no evidence of epileptiform activity with frequent motor stereotypies.

Sequence analysis of the tau (MAPT) and progranulin (GRN) genes was normal. Sequence analysis of the DCTN1 gene revealed a G71R mutation (Figure 2). The mutation was absent in a series of 355 Welsh control subjects.

## Discussion

This case fulfilled the proposed cardinal diagnostic features for probable Perry syndrome[1]. He had autosomal dominant inheritance with parkinsonism, respiratory failiure and apathy. Weight loss was present but not sustained, and with respiratory support his weight returned to pre-morbid levels. The diagnosis of Perry syndrome was confirmed by the identification of a pathogenic mutation in DCTN1. The patient was initially thought to have FTDP, however this was not supported by progressive cognitive decline or focal lobar atrophy. The diagnosis of Perry syndrome was not suspected until the development of respiratory failure.

Proposed supportive clinical diagnostic criteria for Perry syndrome include "No response to L-DOPA, or transient (<1 year) or erratic response" and "rapid progression". This patient was strikingly L-DOPA responsive, with a variety of motor and non-motor off phenomena. Wearing off phenomena led to the escalation of L-DOPA to high levels. He did not have rapid progression, had an excellent response to respiratory support and remains largely independent nine years after the onset of symptoms. On L-DOPA treatment he displayed slow axial and cranio-cervical L-DOPA induced dyskinesia. As well as having early axial rigidity and falls this patient developed PSP-like features of slowing of vertical down-gaze and mid-brain atrophy, not previously described in Perry syndrome. Whilst dual pathology is conceivable in this case, we speculate that other patients with a familial FTDP and/or PSP like syndrome could have a mutation in DCTN-1.

This is the third family identified with the DCTN1 G71R mutation[4]. In Perry's original description the earliest and most prominent symptom is treatment resistant mental depression and axial rigidity is also described[9]. In the other previously reported family with the G71R mutation from Turkey a long prodrome of decreased social-interest and apathy as well as a good response to L-DOPA are reported[10]. There is clinical heterogeneity in mutations of the DCTN-1 gene, with the nearby G59S mutation causing a lower motor neurone syndrome[11] and the R1101K mutation causing ALS and FTD[12]. There is no consistent phenotypic variation associated with individual Perry syndrome causing mutations located in exon 2 of DCTN 1. Identification of further kindreds with pathogenic mutations of DCTN 1 and the longitudinal assessment of asymptomatic family members could broaden the phenotype further. The molecular pathology overlaps with the pathology of ALS, and the mechanism of neurodegeneration in patients with DCTN1 mutations will provide important insights into the mechanisms of TDP-43 related neurodegeneration[13].

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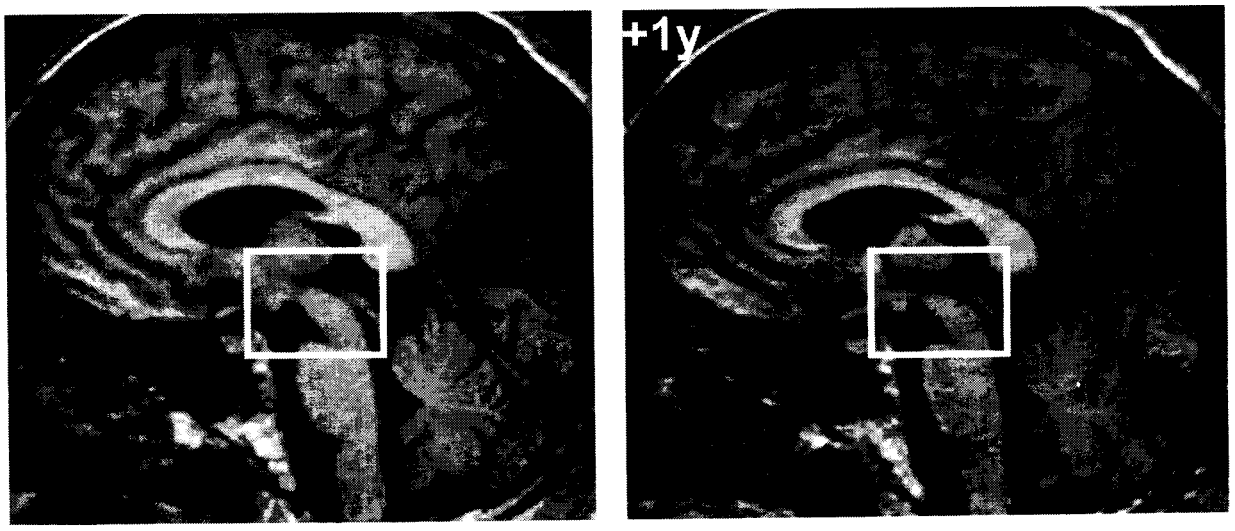


**Figure 1. MRI brain showing selective midbrain atrophy**

Sagittal T1-weighted volumetric MRI sections of the patient's brain five years after symptom onset (left) and one year later (+1y), showing relatively selective midbrain atrophy. Images have been registered into a common space for comparison (the bounding box is provided to aid visualisation of midbrain change).



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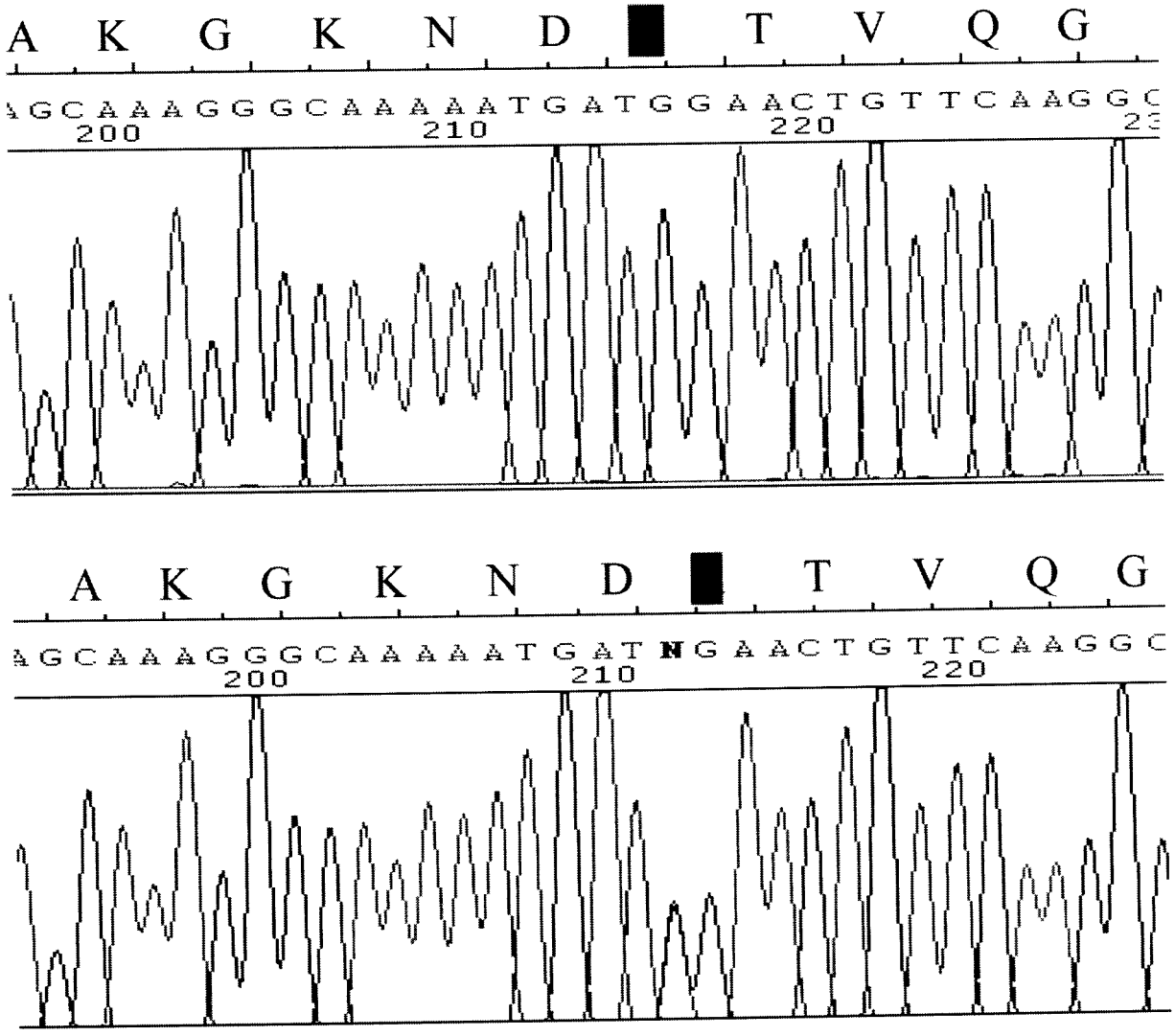


**Figure 2. Electropherogram showing mutation in DCTN1, compared to wild type**

DCTN1 G71R - Electropherogram showing the heterozygous mutation in DCTN1 exon 2 at nucleotide 212 G>A (lower panel) compared to the wild-type sequence (upper panel). Amino acid codes are given above the sequence, indicating that arginine (R) has been substituted for glycine (G) at position 71.

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# Elucidating the genetics and pathology of Perry syndrome

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ABSTRACT

Perry syndrome is characterized clinically by autosomal dominantly inherited, rapidly progressive parkinsonism, depression, weight loss and hypoventilation. In the seven families reported previously and the two new families presented herein (the Hawaii family and the Fukuoka-4 Japanese family), the mean disease onset age is 48 years (range: 35–61) and the mean disease duration five years (range: 2–10). Histology and immunohistochemistry show severe neuronal loss in the substantia nigra and locus coeruleus, with TDP-43-positive pathology in neurons (intranuclear and cytoplasmic inclusions, dystrophic neurites, axonal spheroids) and glial cells (glial cytoplasmic inclusions). Compared with other TDP-43-proteinopathies (amyotrophic lateral sclerosis and ubiquitin-positive frontotemporal lobar degeneration), the distribution is unique in Perry syndrome with pallidonigral distribution and sparing of the cortex, hippocampus and motor neurons. The genetic cause of Perry syndrome was recently identified with five mutations in the *dynactin* gene (*DCTN1*) segregating with disease in eight families. *DCTN1* encodes p150$^{glued}$, the major subunit of the dynactin protein complex, which plays a crucial role in retrograde axonal and cytoplasmic transport of various cargoes. Evidence suggests the Perry mutations alter the binding of p150$^{glued}$ to microtubules. Further studies will examine reasons for the vulnerability of selected neuronal populations in Perry syndrome, and the link between the genetic defect and TDP-43 pathology.



## 1. Introduction

In 1975, Perry and collaborators reported a Canadian family with rapidly progressive autosomal dominant parkinsonism, depression, weight loss, sleep difficulties and central hypoventilation [1,2]. Over the next 30 years six additional families have been reported from Canada, the U.S., the U.K., France, Turkey and Japan (reviewed in [3]) [4–10]. Depression, apathy, weight loss and parkinsonism are early symptoms while central hypoventilation develops in later stages. The mean onset age is 48 years (range: 35–61, including two unpublished families, see below) and the mean disease duration five years (range: 2–10). Patients die of respiratory complications, sudden unexplained death or by suicide. Initial reports highlighted reduced taurine levels in CSF from patients with Perry syndrome, however this finding was not replicated in subsequent studies [1,2,4,8,9].

An international consortium was established in 2001 by ZKW and YT to expand the clinical, pathological and genetic characterization of Perry syndrome. In so doing, we have been able to reactivate seven of the eight previously published families and to identify two additional unreported kindreds from Hawaii and Japan (Fukuoka-4 family). Materials collected included detailed clinical information (eight families), brain tissue (eight patients from five families) and DNA samples (17 affected individuals from eight families and 74 unaffected family members).

Herein we present clinical data on two unpublished families (the Hawaiian and Fukuoka-4 families) with Perry syndrome, and review our recent discoveries in the pathological and genetic characterization of the disease.

## 2. Unpublished families

Patients were examined by movement disorders neurologists, and signed IRB-approved informed consent was obtained prior to enrollment.

The Hawaiian family originates from Japan. There are six affected individuals (two men) including two with clinical information and one with pathology (Fig. 1). The proband and her second cousin presented at age 47 with parkinsonism and later developed respiratory symptoms. The proband had partial benefit from levodopa. In contrast to previously reported families, symptoms did not include depression and weight loss.

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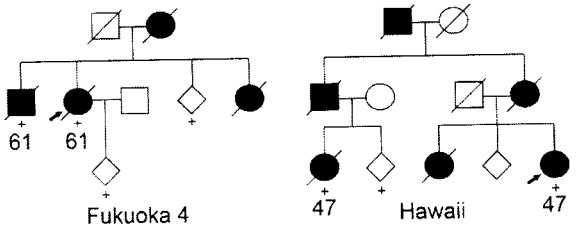


**Fig. 1.** Pedigrees of two new families with Perry syndrome. Circles, women. Squares, men. Diamonds, gender disguised. Diagonal lines, deceased. Black symbols, affected individuals. Numbers under symbols, ages of onset. "+", DNA sample available. Arrows, probands.

Neuropathologic examination of the proband's second cousin showed neuronal loss in the substantia nigra (SN) and the locus coeruleus, with no Lewy bodies.

The Fukuoka-4 family has four affected individuals (one man) over two generations (Fig. 1). Disease onset (61 years) and duration (three years) were similar in the proband and her brother. The initial symptom was resting tremor in the proband and weight loss in her brother; both later developed levodopa-responsive parkinsonism, weight loss and hypoventilation. Response to levodopa was transient and did not cause motor complications. The proband died of sudden death and her brother of respiratory failure. Of notice, these two patients did not develop depression or apathy, a feature found in all previously published families with Perry syndrome. Further, onset age in this family (61 years) was five years older than the upper range of onset age in other families. No autopsy was performed on these patients.

Genetic analysis showed that although these two families are of Japanese descent, they harbor distinct mutations from two different founders (see below).

## 3. Neuropathology

Previous reports have highlighted severe neuronal loss in the SN and locus coeruleus, with few to no Lewy bodies [3]. We examined autopsy material from eight patients with Perry syndrome (fixed and frozen tissue from two, paraffin-embedded fixed tissue from five, unstained tissue on glass slides from one). All patients had severe SN neuronal loss. Surviving SN neurons had intranuclear (NII) and cytoplasmic (NCI) inclusions that stained positive for transactive-response (TAR) DNA-binding protein of 43 kD (TDP-43) [11]. TDP-43 pathology also included dystrophic neurites, axonal spheroids and glial cytoplasmic inclusions (Fig. 2). Immunohistochemistry for tau and α-synuclein was negative. These findings show TDP-43-positive inclusions are characteristic of Perry syndrome and establish this condition as a TDP-43-proteinopathy.

TDP-43 was recently identified as the major ubiquitinated component of NCI and NII in ubiquitin-positive frontotemporal lobar degeneration (FTLD-U), frontotemporal dementia–motor neuron disease (FTD–MND) and amyotrophic lateral sclerosis (ALS) [12].

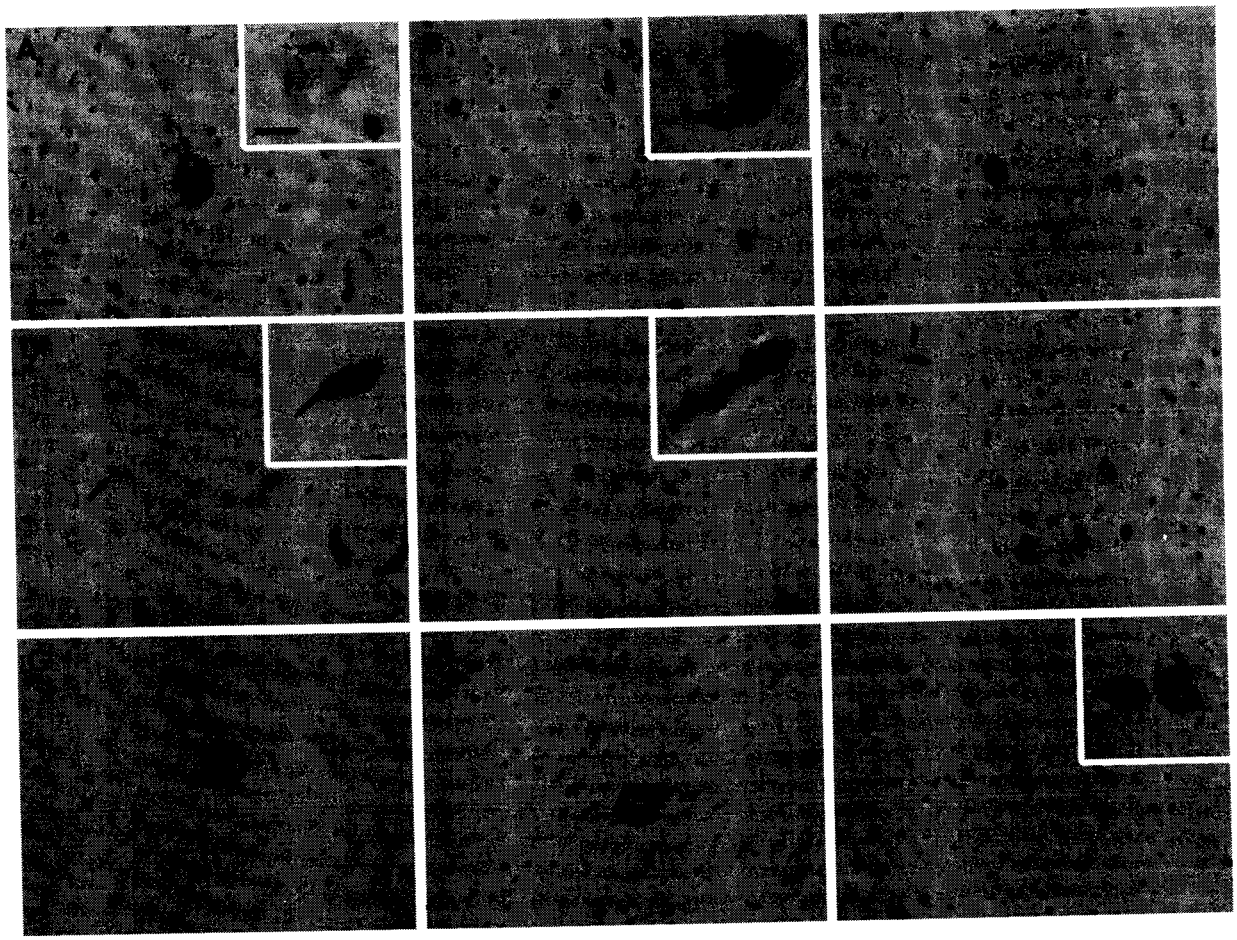

**Fig. 2.** TDP-43 immunohistochemistry of Perry patients shows NCI (A–C; higher magnification in inset of B), NII (inset in A), dystrophic neurites (D arrows, E and F; higher magnification in inset of D), axonal spheroids (G, H), glial cytoplasmic inclusions (I, arrow; higher magnification in inset of I), and a perivascular astrocytic inclusions (inset of E; cap = capillary). Scale bar: 25 μm (A–I), 10 μm (insets of A, B, D, E and I).
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**Table 1**
Comparison of Perry syndrome and distal spinal bulbar muscular atrophy.

| | Perry syndrome | Distal spinal / bulbar muscular atrophy |
|---|---|---|
| **Clinical** | | |
| Inheritance | Autosomal dominant | Autosomal dominant |
| Mean age of onset, years (range) | 48 (35–61) | 34 (23–44) |
| Number of patients | 34[a] (9 families) | 13 (1 family) |
| Disease progression | Rapid (death 2–10 years) | Slow (some patients > 30 years) |
| Parkinsonism | + | – |
| Depression | + | – |
| Hypoventilation | + | – |
| Weight loss | + | + |
| LMN symptoms/signs | – | + |
| -limbs | – | + (upper limb predominance) |
| -larynx/face | – | + |
| **EMG** | | |
| Signs of LMN disease | – | +[b] |
| **Imaging** | | |
| Brain MRI abnormalities | – | – |
| FDG-PET scan | Reduced metabolism (lateral prefrontal and temporal) | NA |
| FD-PET scan | Reduced striatal tracer uptake | NA |
| **Pathology** | | |
| Histology | SN, LC, pallidum neuronal loss | Loss of LMN (XII, ventral horn) |
| Immunohistochemistry | TDP-43-positive (some p50 and p62-positive) | P50 and dynein-positive |
| Inclusions/aggregation | NCI, NII, DN, GCI | Neuronal cytoplasmic aggregation/small inclusions |
| Distribution | Extrapyramidal | LMN |
| **Genetics** | | |
| *DCTN1* mutations | p.G71R, p.G71E, p.G71A, p.T72P, p.Q74P | p.G59S |
| $p150^{glued}$ localization of mutations | CAP-Gly, within or immediately adjacent to "GKNDG" motif | CAP-Gly 8 amino acids away from "GKNDG" motif |

CAP-Gly, cytoskeleton-associated protein, glycine rich domain. DN, dystrophic neurites. GCI, glial cytoplasmic inclusions. LC, locus ceruleus. LMN, lower motor neuron. NA, not assessed. NCI, neuronal cytoplasmic inclusions. NII, neuronal intranuclear inclusions. SN, substantia nigra.

[a] Including only patients with clinical information available.

[b] Signs of chronic denervation; fibrillation potentials, high-amplitude and long-duration motor potentials with reduced recruitment (upper limbs muscles); positive sharp waves and complex repetitive discharges at rest (bilateral thyroarytenoid muscles).

Interestingly, NCI and NII in Perry syndrome are similar to those found in FTLD-U and ALS. However, the distribution differs in Perry syndrome with pallidonigral predominance and sparing of the cortex, hippocampus and motor neurons. This accounts for the lack of dementia and motor neuron disease in Perry syndrome, in contrast with FTLD-U and ALS. The initial hypothesis that TDP-43-positive inclusions were specific to a small number of diseases such as FTLD-U, FTD–MND and ALS has been challenged by the identification of abnormal TDP-43 in Perry syndrome, Lewy body disease, Guam Parkinson dementia complex, Alzheimer's disease, and hippocampal sclerosis [3,13–15]. Such findings suggest TDP-43 pathology may not be disease-specific but rather represent a more general cellular response to a variety of genetic defects and environmental insults. However, it should be emphasized that in Perry syndrome, FTLD-U, FTD–MND and ALS, TDP-43 immunoreactive inclusions are the dominant pathologic finding, supporting a role in pathogenesis. This contrasts with other conditions such as Alzheimer's disease and Lewy body disease where the main finding is α-synuclein and tau-positive inclusions, TDP-43 pathology being less prominent. Further supporting a more direct implication of TDP-43 in a selected number of diseases, mutations in the *TDP-43* gene (*TARDBP*) were recently shown to cause ALS [16,17].

While SN neuronal loss explains parkinsonism in Perry syndrome, identifying the pathological basis of depression, weight loss and hypoventilation has proven more challenging [11]. An autopsy study of one patient from the first Japanese family found selective loss of putative respiratory neurons in the ventrolateral medulla (neurokinin-1 receptor/tyrosine hydroxylase-immunopositive neurons) and in the raphe nucleus (serotonergic neurons), which most probably accounts for central-type hypoventilation [18]. Loss of aminergic neurons in the locus ceruleus and the ventral tegmental area may contribute to depression and apathy. No specific pathological abnormality (e.g. hypothalamic) was found that would explain weight loss.

## 4. Genetics

Our group recently established mutations in the *dynactin* gene (*DCTN1*) as the genetic cause of Perry syndrome [19]. Each of the eight families examined harbored one of five mutations in exon 2 of *DCTN1* (p.G71A/E/R, p.T72P, and p.Q74P), all of which segregated with

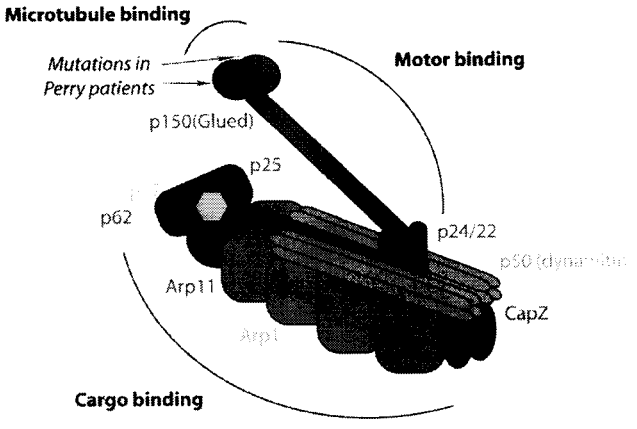


**Fig. 3.** Schematic representation of the dynactin protein complex highlighting the different subunits, the position of Perry mutations in $p150^{glued}$, and domains binding microtubules, the motor dynein, and various cargoes.
Adapted from [24], with permission from the Annual Review of Cell and Developmental Biology Volume 207 ©2004 by Annual Reviews, www.annualreviews.org.

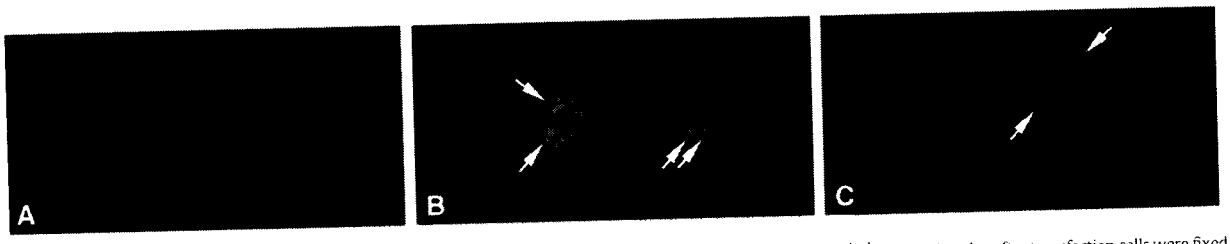


**Fig. 4.** COS7 cells were transiently transfected with plasmids encoding wild-type (A) or mutant (B, p.G59S or C, p.G71R) $p150^{glued}$ protein. One day after transfection cells were fixed in 4% formaldehyde, blocked in 3% BSA and subsequently stained for $p150^{glued}$ (green). A polyclonal goat antibody directed against C' terminal $p150^{glued}$ was used (1266–1278 aa, Abcam, 1:200 in 1%BSA in PBS) as *DCTN1* mutations may affect N' terminal epitopes and antibody affinity. Confocal pictures were taken using the 40× oil immersion objective of a Zeiss Axivert 200 M microscope equipped with LSM510META technology. White arrows indicate representative examples of inclusion bodies. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

disease. None of the mutations were identified in 949 control individuals and in 475 patients with familial parkinsonism. Another mutation in *DCTN1* (p.G59S) was previously reported in a family with a rare form of lower motor neuron disease (comparison with Perry syndrome is presented in the Table 1) [20,21]. Additional mutations have been identified in ALS patients and in a family with ALS and FTLD (clinically of the behavioral type), however evidence of pathogenicity is lacking [22,23].

*DCTN1* encodes $p150^{glued}$, the major subunit of the dynactin protein complex (Fig. 3) [24]. Present as a dimer, $p150^{glued}$ is the backbone of the dynactin complex, binding directly to microtubules, the molecular motor dynein, and different dynactin subunits (Fig. 3). Dynactin plays a major role in retrograde axonal and cytoplasmic transport of vesicles, organelles and other cargoes. Its complex multimeric structure allows dynactin to interact with microtubules and dynein (via the $p150^{glued}$ subunit) and various cargoes (via other subunits). In transgenic mice, over-expression of dynamitin (the p50 subunit of dynactin) leads to late-onset progressive motor neuron disease [25]. Interestingly the five *DCTN1* mutations which cause Perry syndrome and the previously reported p.G59S mutation are all located within the $p150^{glued}$ highly conserved N-terminal cytoskeleton-associated protein, glycine-rich (CAP-Gly) domain. The CAP-Gly domain is critical for microtubule binding and *in vitro* assays with Perry (p.G71R and p.Q74P) and p.G59S mutant $p150^{glued}$ demonstrated reduced affinity of dynactin for microtubules [19,20,26]. Further, cells transfected with *DCTN1* p.G71R, p.Q74P or p.G59S show redistribution of dynactin compared to wild-type protein (Fig. 4) [19]. *In vitro* and *in vivo* evidence suggests the p.G59S mutation leads to altered dynactin/dynein function (loss of function) as well as dynactin aggregation (toxic gain of function) [26]. In contrast, experimental data shows that $p150^{glued}$ mutations identified in ALS and FTLD, which lack evidence of pathogenicity, do not impair microtubule binding, alter the dynein–dynactin interaction or confer increased propensity to form aggregates, thus not supporting a direct role in pathogenesis [27].

## 5. From gene to inclusion: the conundrum of regional specificity

One of the crucial challenges facing researchers in neurodegenerative diseases is to understand what determines selective neuronal vulnerability. The five Perry mutations in *DCTN1* lead to a complex albeit uniform clinico-pathological entity, yet the p.G59S mutation located only 12–15 amino acids away is associated with a clearly different disease (Table 1). The bulk of the pathology in Perry syndrome is found in pallidonigral neurons (accounting for parkinsonism in patients), whereas the p.G59S mutation affects lower motor neurons (clinically manifested by lower motor neuron disease).

In addition to the CAP-Gly domain, a second $p150^{glued}$ microtubule-binding domain was identified which is basic and highly conserved across species [28]. Evidence showed the CAP-Gly domain binds microtubules firmly as an "anchor", whereas binding of the basic domain displays dynamic properties which allow "skating" along microtubules even in the absence of the motor dynein. This suggests

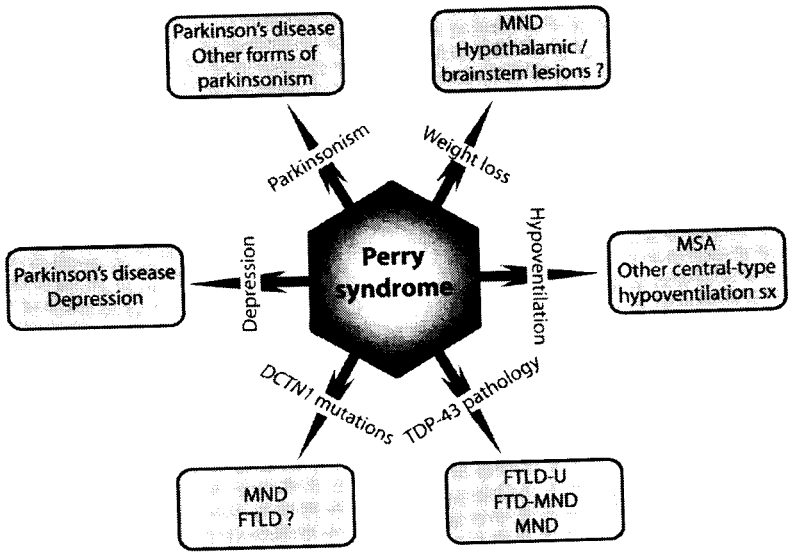


**Fig. 5.** Schematic representation of clinical, pathological and genetic overlap of Perry syndrome with other conditions. FTD–MND, frontotemporal dementia–motor neuron disease. FTLD, frontotemporal lobar degeneration (-U, ubiquitin-positive). MND, motor neuron disease. MSA, multiple system atrophy.

antagonizing effects of the two p150$^{glued}$ microtubule-binding domains on dynein-promoted motility, the CAP-Gly domain acting as a "parking brake", counteracting the dynamic properties of the basic domain [28]. Contrarily to the p.G59S mutation, Perry mutations are located within or immediately adjacent to the critical CAP-Gly "GKNDG" motif. Therefore it is conceivable that Perry mutations alter microtubule binding qualitatively by destabilizing the progression of dynactin along microtubules, favoring increased but unstable mobility. Differences in morphology, connectivity and function must explain why nigral neurons are more susceptible than motor neurons to such altered mobility. In particular, vesicular transport of potentially toxic dopamine precursors may confer nigral neurons a lower threshold to cell damage. However, patients with familial motor neuron disease and *DCTN1* p.G59S, although they have an earlier onset and a more gradual progression, do not develop parkinsonism and nigrostriatal dysfunction (Table 1). Nor do Perry patients have any signs of motor neuron disease. Of note, the p.G59S is buried within the center of the CAP-Gly domain, whereas the Perry mutations are within a hydrophobic pocket upon the surface. *In vitro*, all *DCTN1* pathogenic mutations in the CAP-Gly domain modestly impair microtubule binding, but there may be qualitative differences. In addition, p150$^{glued}$ CAP-Gly microtubule binding is only one of the many protein interactions whose binding and transport might be differentially perturbed in a cell-specific manner [29].

In physiological conditions, over 90% of the RNA-binding protein TDP-43 is located in the nucleus, where it plays a role in transcription repression, exon skipping and alternative splicing [30]. In the cytosol and in synaptic sites, TDP-43 may function as a translation regulator [30]. Two domains play a critical role in the regulation of TDP-43 trafficking between the cytosol and the nucleus, a nuclear localization signal and a nuclear export signal [31]. Under stress conditions such as starvation, and oxidation, TDP-43 levels are elevated in the cytoplasm, and its transport may require fully functional dynactin. This hypothesis is supported by the co-localization of two subunits of dynactin (p50 and p62) and TDP-43 immunohistochemistry in some NCI from patients with Perry syndrome [19]. We should point out that TDP-43 immunostaining has not been reported in the patient with the p.G59S mutation as the publication antedated the identification of TDP-43 in neurodegenerative diseases [21]. Positive TDP-43 pathology would be expected given the underlying genetic defect is similar to that of Perry syndrome. However, negative results could indicate a cell-specific propensity to TDP-43 aggregation that may shed further light on selective vulnerability.

## 6. Diagnosis and treatment

To accurately diagnose a disease, to effectively treat it, to halt its progression and to affect a cure, requires an understanding of its molecular pathogenesis. The finding of p150$^{glued}$ mutations in Perry syndrome can now be used to formally diagnose this age-associated disorder in asymptomatic subjects and may help advanced directives, family planning and therapeutic intervention. Depression and suicidal ideation in carriers can be successfully managed. Assuming that lowering the quantitative amount of p150$^{glued}$ may not be detrimental to the stoichiometry and function of the dynactin complex, specific mutant allele silencing in the brain may also prevent the core features of disease and their progression. Several approaches for transcript silencing and delivery are in development for neurodegenerative disorders, including allele-specific targeting, upon which treatments for orphan diseases such as Perry syndrome can be included [32,33].

## 7. Conclusions

Orphan diseases such as Perry syndrome are difficult to study due to lack of funding and low prevalence of disease. However, clinical, pathological and genetic features of Perry syndrome overlap with those of a number of more common conditions (Fig. 5). The distinct selective vulnerability of neuronal populations (extrapyramidal or motor neurons) is perhaps the most remarkable finding given the position of *DCTN1* CAP-Gly mutations. Insights gained from studies of Perry syndrome, and the role of dynactin in cargo trafficking are now likely to shed light on the pathogenesis of a variety of diseases, including Parkinson's disease, multiple system atrophy, depression, FTLD-U, ALS, sleep disorders and metabolic diseases.

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