ИНФОРМАЦИЯ ЗА:
Наименование на заболяването
PARK9
Определение на заболяването
Kufor-Rakeb синдром е рядка автозомно-рецесивна форма на атипична Паркинсонова болест с ювенилно начало (PARK9). Заболяването се асоциира със супрануклеарна погледна пареза, спастицитет и деменция. Някои пациенти имат невроизобразяващи данни за натрупване на желязо в базални ганглии, което насочваа, че патогенезата на PARK9 може да се възприема сред невродегенеративните синдроми с натрупване на желязо в мозъка (NBIA).
Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)
G23.0
Код на заболяването по Orpha code
ORPHA306674
Епидемиологични данни за заболяването в Република България
<1/1 000 000; Точните заболеваемост и болестност са неизвестни. 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. Bruggemann, N., Hagenah, J., Reetz, K., Schmidt, A., Kasten, M., Buchmann, I., Eckerle, S., Bahre, M., Munchau, A., Djarmati, A., van der Vegt, J., Siebner, H., Binkofski, F., Ramirez, A., Behrens, M. I., Klein, C. Recessively inherited parkinsonism: effect of ATP13A2 mutations on the clinical and neuroimaging phenotype. Arch. Neurol. 67: 1357-1363, 2010. 2. Najim Al-Din, A. S., Wriekat, A., Mubaidin, A., Dasouki, M., Hiari, M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol. Scand. 89: 347-352, 1994. 3. Di Fonzo, A., Chien, H. F., Socal, M., Giraudo, S., Tassorelli, C., Iliceto, G., Fabbrini, F., Marconi, R., Fincati, E., Abbruzzese, F., Marini, P., Squitieri, F., and 14 others. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 68: 1557-1562, 2007. 4. Crosiers, D., Ceulemans, B., Meeus, B., Nuytemans, K., Pals, P., Van Broeckhoven, C., Cras, P., Theuns, J. Juvenile dystonia-parkinsonism and dementia caused by a novel ATP13A2 frameshift mutation. (Letter) Parkinsonism Relat. Disord. 17: 135-138, 2011. 5. Santoro, L., Breedveld, G. J., Manganelli, F., Iodice, R., Pisciotta, C., Nolano, M., Punzo, F., Quarantelli, M., Pappata, S., Di Fonzo, A., Oostra, B. A., Bonifati, V. Novel ATP13A2 (PARK9) homozygous mutation in a family with marked phenotype

variability. Neurogenetics 12: 33-39, 2011.

Епидемиологични данни за заболяването в Европейския съюз

<1 / 1 000 000; Точните заболеваемост и болестност са неизвестни.

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

1. Bruggemann, N., Hagenah, J., Reetz, K., Schmidt, A., Kasten, M., Buchmann, I., Eckerle, S., Bahre, M., Munchau, A., Djarmati, A., van der Vegt, J., Siebner, H., Binkofski, F., Ramirez, A., Behrens, M. I., Klein, C. Recessively inherited parkinsonism: effect of ATP13A2 mutations on the clinical and neuroimaging phenotype. Arch. Neurol. 67: 1357-1363, 2010.
2. Najim Al-Din, A. S., Wriekat, A., Mubaidin, A., Dasouki, M., Hiari, M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol. Scand. 89: 347-352, 1994.
3. Di Fonzo, A., Chien, H. F., Socal, M., Giraudo, S., Tassorelli, C., Iliceto, G., Fabbrini, F., Marconi, R., Fincati, E., Abbruzzese, F., Marini, P., Squitieri, F., and 14 others. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 68: 1557-1562, 2007.
4. Crosiers, D., Ceulemans, B., Meeus, B., Nuytemans, K., Pals, P., Van Broeckhoven, C., Cras, P., Theuns, J. Juvenile dystonia-parkinsonism and dementia caused by a novel ATP13A2 frameshift mutation. (Letter) Parkinsonism Relat. Disord. 17: 135-138, 2011.
5. Santoro, L., Breedveld, G. J., Manganelli, F., Iodice, R., Pisciotta, C., Nolano, M., Punzo, F., Quarantelli, M., Pappata, S., Di Fonzo, A., Oostra, B. A., Bonifati, V. Novel ATP13A2 (PARK9) homozygous mutation in a family with marked phenotype variability. Neurogenetics 12: 33-39, 2011.

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): Kufor-Rakeb синдром е рядка автозомно-рецесивна форма на атипична Паркинсонова болест с ювенилно начало (PARK9). Заболяването се асоциира със супрануклеарна погледна пареза, спастицитет и деменция. Някои пациенти имат невроизобразяващи данни за натрупване на желязо в базални ганглии, което насочва , че патогенезата на PARK9 може да се възприема сред невродегенеративните синдроми с натрупване на желязо в мозъка (NBIA).

Признаците и симптомите на заболяването: Kufor-Rakeb синдром е рядка автозомно-рецесивна форма на атипична Паркинсонова болест с ювенилно начало (PARK9). Заболяването се асоциира със супрануклеарна погледна пареза, спастицитет и деменция.

Етиологията и патогенезата: PARK9 се причинява от хомозиготна или комбинирана хетерозиготна мутация на ATP13A2 ген, който кодира лизозомалната тип 5 АТФаза, в хромозома 1p36. Някои пациенти имат невроизобразяващи данни за натрупване на желязо в базални ганглии, което насочва, че патогенезата на PARK9 може да се възприема сред невродегенеративните синдроми с натрупване на желязо в мозъка (NBIA).

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

1. Bruggemann, N., Hagenah, J., Reetz, K., Schmidt, A., Kasten, M., Buchmann, I., Eckerle, S., Bahre, M., Munchau, A., Djarmati, A., van der Vegt, J., Siebner, H., Binkofski, F., Ramirez, A., Behrens, M. I., Klein, C. Recessively inherited parkinsonism: effect of ATP13A2 mutations on the clinical and neuroimaging phenotype. Arch. Neurol. 67: 1357-1363, 2010.
2. Najim Al-Din, A. S., Wriekat, A., Mubaidin, A., Dasouki, M., Hiari, M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol. Scand. 89: 347-352, 1994.
3. Williams, D. R., Hadeed, A., Najim al-Din, A. S., Wreikat, A.-L., Lees, A. J. Kufor Rakeb disease: autosomal recessive, levodopa-responsive parkinsonism with pyramidal degeneration, supranuclear gaze palsy, and dementia. Movement Disord. 20: 1264-1271, 2005.
4. Di Fonzo, A., Chien, H. F., Socal, M., Giraudo, S., Tassorelli, C., Iliceto, G., Fabbrini, F., Marconi, R., Fincati, E., Abbruzzese, F., Marini, P., Squitieri, F., and 14 others. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 68: 1557-1562, 2007.
5. Crosiers, D., Ceulemans, B., Meeus, B., Nuytemans, K., Pals, P., Van Broeckhoven, C., Cras, P., Theuns, J. Juvenile dystonia-parkinsonism and dementia caused by a novel ATP13A2 frameshift mutation. (Letter) Parkinsonism Relat. Disord. 17: 135-138, 2011.
6. Santoro, L., Breedveld, G. J., Manganelli, F., Iodice, R., Pisciotta, C., Nolano, M., Punzo, F., Quarantelli, M., Pappata, S., Di Fonzo, A., Oostra, B. A., Bonifati, V. Novel ATP13A2 (PARK9) homozygous mutation in a family with marked phenotype variability. Neurogenetics 12: 33-39, 2011.
7. Schneider, S. A., Paisan-Ruiz, C., Quinn, N. P., Lees, A. J., Houlden, H., Hardy, J., Bhatia, K. P. ATP13A2 mutations (PARK9) cause neurodegeneration with brain iron accumulation. Mov. Disord. 25: 979-984, 2010.

Алгоритми за диагностициране на заболяването

Алгоритми за диагностициране на заболяването: Съгласно Национален консенсус за диагностика и лечение на Паркинсоновата болест, а на когнитивните нарушения съгласно Национален консенсус за ранна диагностика и лечение на болестта на Алцхаймер и други форми на деменция.

Анамнезата: Началото на заболяването с бърза прогресия се наблюдава обичайно между 10 и 16-годишна възраст. Това включва масковиден фациес, ригидност, брадикинезия и понякога тремор. При някои пациенти се наблюдава също спастицитет, супрануклеарна погледна пареза, мини-миоклонуси, окулогирични дистонни спазми и деменция.

Диференциалната диагноза на заболяването: Идиопатична Паркинсонова болест; Палидопирамиден синдром (PARK15);

Лабораторни, образни и хистологични изследвания: Някои пациенти имат невроизобразяващи данни за натрупване на желязо в базални ганглии. МРТ на глава показва атрофия на глобус палидус и по-късно генерализирана мозъчна атрофия. PET/SPECT изследванията показват намаление на активността на допаминовия транспортер.

Генетични изследвания и медико-генетично консултиране: PARK9 се причинява от хомозиготна или комбинирана хетерозиготна мутация на ATP13A2 ген, който кодира лизозомалната тип 5 АТФаза, в хромозома 1p36.

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. Bruggemann, N., Hagenah, J., Reetz, K., Schmidt, A., Kasten, M., Buchmann, I., Eckerle, S., Bahre, M., Munchau, A., Djarmati, A., van der Vegt, J., Siebner, H., Binkofski, F., Ramirez, A., Behrens, M. I., Klein, C. Recessively inherited parkinsonism: effect of ATP13A2 mutations on the clinical and neuroimaging phenotype. Arch. Neurol. 67: 1357-1363, 2010.
4. Najim Al-Din, A. S., Wriekat, A., Mubaidin, A., Dasouki, M., Hiari, M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol. Scand. 89: 347-352, 1994.
5. Williams, D. R., Hadeed, A., Najim al-Din, A. S., Wreikat, A.-L., Lees, A. J. Kufor Rakeb disease: autosomal recessive, levodopa-responsive parkinsonism with pyramidal degeneration, supranuclear gaze palsy, and dementia. Movement Disord. 20: 1264-1271, 2005.
6. Di Fonzo, A., Chien, H. F., Socal, M., Giraudo, S., Tassorelli, C., Iliceto, G., Fabbrini, F., Marconi, R., Fincati, E., Abbruzzese, F., Marini, P., Squitieri, F., and 14 others. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 68: 1557-1562, 2007.
7. Crosiers, D., Ceulemans, B., Meeus, B., Nuytemans, K., Pals, P., Van Broeckhoven, C., Cras, P., Theuns, J. Juvenile dystonia-parkinsonism and dementia caused by a novel ATP13A2 frameshift mutation. (Letter) Parkinsonism Relat. Disord. 17: 135-138, 2011.
8. Bruggemann, N., Hagenah, J., Reetz, K., Schmidt, A., Kasten, M., Buchmann, I., Eckerle, S., Bahre, M., Munchau, A., Djarmati, A., van der Vegt, J., Siebner, H., Binkofski, F., Ramirez, A., Behrens, M. I., Klein, C. Recessively inherited parkinsonism: effect of ATP13A2 mutations on the clinical and neuroimaging phenotype. Arch. Neurol. 67: 1357-1363, 2010.
9. Schneider, S. A., Paisan-Ruiz, C., Quinn, N. P., Lees, A. J., Houlden, H., Hardy, J., Bhatia, K. P. ATP13A2 mutations (PARK9) cause neurodegeneration with brain iron accumulation. Mov. Disord. 25: 979-984, 2010.
10. Najim Al-Din, A. S., Wriekat, A., Mubaidin, A., Dasouki, M., Hiari, M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol. Scand. 89: 347-352, 1994.

Алгоритми за лечение на заболяването

Алгоритми за лечение на заболяването: Съгласно 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: Има съобщения, че леводопа терапията води до подобрение на симптомите при тези пациенти.

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 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. Najim Al-Din, A. S., Wriekat, A., Mubaidin, A., Dasouki, M., Hiari, M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol. Scand. 89: 347-352, 1994.
4. Crosiers, D., Ceulemans, B., Meeus, B., Nuytemans, K., Pals, P., Van Broeckhoven, C., Cras, P., Theuns, J. Juvenile dystonia-parkinsonism and dementia caused by a novel ATP13A2 frameshift mutation. (Letter) Parkinsonism Relat. Disord. 17: 135-138, 2011.
5. Najim Al-Din, A. S., Wriekat, A., Mubaidin, A., Dasouki, M., Hiari, M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol. Scand. 89: 347-352, 1994.

Алгоритми за проследяване на заболяването

Алгоритми за проследяване на заболяването:
Прогнозата на заболяването: Williams и колеги (2005) отбелязват, че неврологичните черти са с подостро начало и водят до тежка инвалидизация още в рамките на първата година.
Възможни усложнения:Леводопа-индуцирани дискинезии

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

1. Williams, D. R., Hadeed, A., Najim al-Din, A. S., Wreikat, A.-L., Lees, A. J. Kufor Rakeb disease: autosomal recessive, levodopa-responsive parkinsonism with pyramidal degeneration, supranuclear gaze palsy, and dementia. Movement Disord. 20: 1264-1271, 2005.
2. Di Fonzo, A., Chien, H. F., Socal, M., Giraudo, S., Tassorelli, C., Iliceto, G., Fabbrini, F., Marconi, R., Fincati, E., Abbruzzese, F., Marini, P., Squitieri, F., and 14 others. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 68: 1557-1562, 2007.
3. Crosiers, D., Ceulemans, B., Meeus, B., Nuytemans, K., Pals, P., Van Broeckhoven, C., Cras, P., Theuns, J. Juvenile dystonia-parkinsonism and dementia caused by a novel ATP13A2 frameshift mutation. (Letter) Parkinsonism Relat. Disord. 17: 135-138, 2011.

Алгоритми за рехабилитация на заболяването

Алгоритми за рехабилитация на заболяването: Съгласно 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: : PARK9 се причинява от хомозиготна или комбинирана хетерозиготна мутация на ATP13A2 ген, който кодира лизозомалната тип 5 АТФаза, в хромозома 1p36. Заболяването е с автозомно-рецесивно унаследяване. Генетична консултация е възможна при семействата с установена мутация и препоръчителна.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Schneider, S. A., Paisan-Ruiz, C., Quinn, N. P., Lees, A. J., Houlden, H., Hardy, J., Bhatia, K. P. ATP13A2 mutations (PARK9) cause neurodegeneration with brain iron accumulation. Mov. Disord. 25: 979-984, 2010. 2. Di Fonzo, A., Chien, H. F., Socal, M., Giraudo, S., Tassorelli, C., Iliceto, G., Fabbrini, F., Marconi, R., Fincati, E., Abbruzzese, F., Marini, P., Squitieri, F., and 14 others. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 68: 1557-1562, 2007. 3. Ramirez, A., Heimbach, A., Grundemann, J., Stiller, B., Hampshire, D., Cid, L. P., Goebel, I., Mubaidin, A. F., Wriekat, A.-L., Roeper, J., Al-Din, A., Hillmer, A. M., Karsak, M., Liss, B., Woods, C. G., Behrens, M. I., Kubisch, C. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nature Genet. 38: 1184-1191, 2006. 4. Najim Al-Din, A. S., Wriekat, A., Mubaidin, A., Dasouki, M., Hiari, M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol. Scand. 89: 347-352, 1994.
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 CONTRIBUTION

Recessively Inherited Parkinsonism

Effect of ATP13A2 *Mutations on the Clinical and Neuroimaging Phenotype*

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Objective: To determine clinical features and to identify changes in brain structure and function in compound heterozygous and heterozygous *ATP13A2* mutation carriers.

Design: Prospective multimodal clinical and neuroimaging study.

Setting: University of Lübeck, Lübeck, Germany.

Participants: Eight family members of a large Chilean pedigree with Kufor-Rakeb syndrome (KRS).

Interventions: Clinical characterization, dopamine transporter (DAT) imaging, voxel-based morphometry (VBM), and transcranial sonography (TCS).

Main Outcome Measures: Frequency of parkinsonian signs, brain structure, and functional alterations.

Results: The only available patient with compound heterozygous KRS showed a markedly reduced striatal DAT density bilaterally. Magnetic resonance imaging revealed severe global brain atrophy as well as iron deposition in the basal ganglia. The heterozygous mother had definite parkinsonism with reduced DAT density in both putamina. While all asymptomatic heterozygous siblings displayed subtle extrapyramidal signs, DAT imaging revealed striatal tracer uptake within physiological levels. Voxel-based morphometry revealed an increase in gray matter volume in the right putamen and a decrease in the cerebellum of the heterozygous carriers. In all mutation carriers, the substantia nigra had a normal appearance on TCS.

Conclusions: Single *ATP13A2* heterozygous mutations may be associated with clinical signs of parkinsonism and contribute to structural and functional brain changes. Lack of hyperechogenicity in the substantia nigra may be a distinctive feature of this form of genetic parkinsonism. This, along with the finding of iron in the basal ganglia in our patient with KRS, implies a different underlying pathophysiology compared with other monogenic forms of parkinsonism and idiopathic PD and may place KRS among the syndromes of neurodegeneration with brain iron accumulation (NBIA).

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KUFOR-RAKEB SYNDROME (KRS) is a rare autosomal recessive form of juvenile-onset parkinsonism with subacute levodopa-responsive bradykinesia, severe dementia, supranuclear gaze palsy, and spasticity.[1,2] Recently, mutations in the *ATP13A2* gene (PARK9 locus) were found to be responsible for KRS.[3] Postmortem analysis of patients with idiopathic Parkinson disease (PD) indicated a 10-fold increased *ATP13A2* expression in dopaminergic substantia nigra (SN) neurons compared with control brains, suggesting a possible role of this gene in the etiology also of sporadic, clinically typical PD.[3]

Single heterozygous mutations in other recessive PD genes such as *Parkin* (PARK2 locus) and *PINK1* (PARK6 locus) have been discussed as susceptibility factors for late-onset PD[4,5] and tend to be associated with a later age at PD onset than homozygous mutations.[6] For *ATP13A2*, only 2 articles described a total of 5 patients with early-onset PD who harbored heterozygous *ATP13A2* mutations.[7,8]

The central aim of the study was to determine whether heterozygous *ATP13A2* mutations have a pathophysiologically relevant effect on brain function. We used a multimodal approach and clinical and neuroimaging methods to shed light on the role of single *ATP13A2* mutations. The clinical assessment comprised established motor and nonmotor features of PD. The neuroimaging part included structural and functional brain imaging. Second, we performed a multimodal examination in the affected patient for better characterization of KRS and classification among the atypical parkinsonian syndromes.

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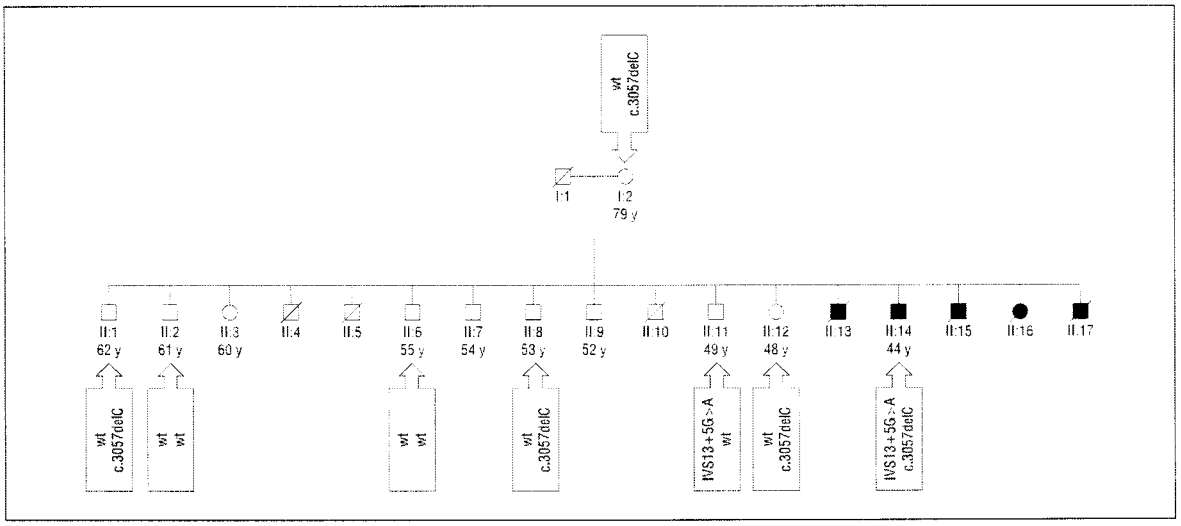

Figure 1. Family pedigree. Filled symbols indicate the subjects with Kufor-Rakeb syndrome. Slashes indicate deceased relatives. Arrows mark the examined individuals: the heterozygous mother (I.2), 4 heterozygous children (II.1, II.8, II.11, II.12), the compound-heterozygous affected son (II.14), and 2 non–mutation carriers (II.2, II.6). The genetic variations are included in the arrow box. wt indicates wild-type allele.

METHODS

SUBJECTS AND CLINICAL EVALUATION

The 5 youngest siblings from a previously described nonconsanguineous Chilean family with 17 children had typical KRS. Four died of pneumonia between 33 and 45 years of age.[3,9]

As part of the present study, a detailed clinical examination was performed in 5 *ATP13A2*-heterozygous mutation carriers (MCs), the compound heterozygous affected son (II.14), and 2 non–mutation carriers (NMCs) (**Figure 1**). After giving informed consent, all subjects underwent a neurological examination by 2 experienced movement disorders specialists (J.H. and N.B.) who were blinded to the mutational status, including the Unified Parkinson Disease Rating Scale and a standardized video protocol. Two independent raters (C.K. and A.M., who were also blinded to the genetic status, established a consensus diagnosis of PD according to the UK Brain Bank Criteria, with the exception that positive family history was not considered an exclusion criterion.[10] Because the term *PD* usually refers to the diagnosis of the idiopathic (uninherited) disease, we will use *parkinsonism* instead, to avoid confusion in terminology. Assessment of nonmotor signs of PD included the Mini-Mental State Examination, Montreal Cognitive Assessment, screening for axis I and II disorders, the Epworth Sleepiness Scale, and a PD risk factor questionnaire assessment. Smell function was determined using the University of Pennsylvania Smell Identification Test.[11] The Farnsworth Munsell 100 Hue Test was applied to estimate individual color perception, stratified according to superior (total error score, 0-16), average (20-100), and low (>100) discrimination according to normative data.

The study protocol was approved by the local ethics committee at the University of Lübeck.

DOPAMINE TRANSPORTER SCAN

Striatal N-ω-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl]nortropane (FP-CIT) single-photon emission computed tomographies were performed in 6 of 7 siblings, whereas the heterozygous mother underwent 2β[N,N'-bis(2-mercaptoethyl)-ethylenediamino]methyl-3β-(4-chlorophenyl)tropane (TRODAT) single photon emission computed tomography.[12] The images were taken 4 to 5 hours after intravenous injection of fluopane labeled with iodine 123 (^{123}I-fluopane; 85 MBq) or TRODAT-1 labeled with technetium 99 (38 mCi), which was given 60 minutes after thyroid blockade with sodium perchlorate. The scans were analyzed by region of interest–based semiquantitative analysis of the caudate nucleus and putamen in reference to the occipital uptake (FP-CIT) and by visual assessment (FP-CIT, TRODAT) established by a consensus panel of 3 nuclear medicine specialists who were blinded to the clinical and genetic status.

STRUCTURAL MAGNETIC RESONANCE IMAGING

Four asymptomatic MCs (II.1, II.8, II.11, II.12; mean [SD] age, 52.0 [6.7] years) were compared with 16 age- and sex-matched healthy volunteers (mean [SD] age, 52.0 [7.6] years). The symptomatic MC II.14 (age, 44 years) was compared with 10 controls (mean [SD] age, 47.5 [4.5] years). There were no significant age differences between the groups. The different control group assignment used for heterozygous MCs and the compound heterozygous MC was owing to the varying ages of the probands and the fact that one of the heterozygous MCs was female.

Structural brain magnetic resonance images were acquired on a 3.0-T whole-body scanner (Philips, Achieva, the Netherlands) using a 3-dimensional T1-weighted fast low-angle shot sequence.

Magnetic resonance images were processed with the Statistical Parametric Mapping software (SPM5, www.fil.ion.ucl.ac.uk/spm) implemented in Matlab Version 7.1 (Mathworks, Sherborn, Massachusetts). Using the voxel-based morphometry toolbox, images were bias corrected, tissue classified, and registered using linear and nonlinear transformations within the same generative model.[13] Analyses were performed on gray matter (GM) segments that were multiplied by the nonlinear components derived from the normalization matrix (modulated GM volumes). Finally, modulated GM images were smoothed with a Gaussian kernel of 12 mm full width at half maximum.

Using a general linear model, voxelwise GM differences between the 2 groups were examined using independent-sample *t* tests. To avoid possible edge effects around the border between gray and white matter and cerebrospinal fluid, an absolute GM threshold of 0.25 was used.

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Table. Demographic Data of Members of the Chilean Family With KRS[a]

Characteristic	Patient							
	II.14	I.2	II.1	II.8	II.11	II.12	II.2	II.6
Age, y	45	79	62	53	49	48	61	55
Mutational status	Compound heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous[b]	Heterozygous	Wild-type[c]	Wild-type
Clinical status/concerns	Affected	Affected	Subtle signs	Subtle signs	Subtle signs	Subtle signs	Subtle signs	Unaffected
Symptom status	Symptomatic	Symptomatic	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic
Asymmetry	Left	Right	Left	Right	Left	(left)	(right)	...
UPDRS score I/II/III/IV	6/35/53/0	0/7/17/0	0/0/6/0	0/0/2/0	0/0/4/0	1/0/0/0	0/0/3/0	1/0/0/0
Levodopa response	Poor (15%)	Not tested	Not tested	Not tested	Not tested	Not tested	Not intended	Not intended
MMSE score	Dementia	25	30	30	30	30	30	30
MoCA score	Dementia	20	30	30	30	29	30	28
ESS score	NA	9	0	1	6	1	5	8
UPSIT score/interpretation	NA	15/Anosmia	29/Moderate hyposmia	31/Mild hyposmia	28/Moderate hyposmia	28/Moderate hyposmia	26/Moderate hyposmia	32/Mild hyposmia
TES/color discrimination	NA	276/L	68/A	80/A	28/A	60/A	60/A	248/L

Abbreviations: A, average discrimination; ellipses, information not applicable because the individual is completely unaffected; ESS, Epworth Sleepiness Scale; KRS, Kufor-Rakeb syndrome; L, low discrimination; MMSE, Mini-Mental State Evaluation; MoCA, Montreal Cognitive Assessment; NA, data not available owing to severe dementia; TES, total error score; UPDRS, Unified Parkinson Disease Rating Scale; UPSIT, University of Pennsylvania Smell Identification Test.

[a] Signs were assessed by neurological examination with particular emphasis on extrapyramidal features. Symptoms were considered the reported concerns of the probands. Subjects who were conscious of their extrapyramidal signs were classified as symptomatic. Individuals unaware of their signs were classified as asymptomatic.

[b] Genetic status was predicted false negative by videotape rating (A.M.).

[c] False positive (A.M.).

For the statistical analysis, an explorative threshold of $P = .001$ (uncorrected) and clusters $P > .05$ (uncorrected at the cluster level) with a cluster extent greater than 80 voxels (the expected number of voxels per cluster) was applied.

TRANSCRANIAL ULTRASOUND

Brain parenchyma transcranial sonography (TCS) was used to determine the area of echogenicity in the SN (aSN) typically found in patients with PD and monogenic parkinsonism.[14-16] Transcranial sonography was performed with the Acuson Antares ultrasound system (Siemens, Erlangen, Germany) using a 2.0- to 2.5-MHz transducer (PX4-1) by a blinded examiner. The temporal bone window of both sides was used to visualize the SN. Only the ipsilateral SN was evaluated in a standardized axial mesencephalic plane with a maximum depth of 12 cm. The aSN was manually encircled and measured by an independent rater using a computer-based analysis. Values of less than 0.2 cm^2 were considered within the reference range, whereas values greater than 0.25 cm^2 were classified as marked hyperechogenicity.[16] The lenticular and caudate nucleus as well as the thalamus were also evaluated and considered hyperechogenic when the intensity was higher than that of the surrounding white matter.[17]

RESULTS

CLINICAL FINDINGS

Based on the clinical findings, the 2 videotape raters predicted the genetic status correctly in 6 of 8 (1 false positive [II.2], 1 false negative [II.11]) and 8 of 8 family members, respectively.

The heterozygous mother I.2 presented with parkinsonism according to Hoehn/Yahr stage 2. All heterozygous siblings showed subtle extrapyramidal signs such as slight upper limb rigidity (II.1, II.11), reduced arm swing (II.1, II.8, II.11, II.12), postural (II.8) and action tremor (II.8, II.11), and mild unilateral shoulder elevation (II.12). The signs tended to be more pronounced in older family members. One NMC presented with mild postural and kinetic arm tremor. The second NMC had an unremarkable neurological examination. Pyramidal and frontal release signs were absent in all heterozygous MCs and NMCs. All siblings were asymptomatic for the reported mild signs.

Case reports of all subjects are provided in the supplemental appendix (www.neuro.uni-luebeck.de/arch.neurol_bruggemann.et.al/; also see detailed case report of II.14[9]). Clinical characteristics and test scores are summarized in the **Table**.

OLFACTION AND COLOR DISCRIMINATION

The affected heterozygous mother I.2 had a markedly decreased sense of smell in keeping with anosmia. No differences were observed between the heterozygous siblings and NMCs, with a mean score of 29 of 40 in both groups. Sex-adjusted scores revealed mild hyposmia in 1 MC and 1 NMC as well as moderate hyposmia in 3 MCs and 1 NMC. Color discrimination was markedly impaired in the heterozygous mother and 1 NMC. The remaining siblings had average color discrimination. Smell and color testing could not be performed in the compound heterozygous proband II.14 owing to dementia.

PRESYNAPTIC DOPAMINE TRANSPORTER IMAGING

Striatal ^{123}I-fluopane uptake was markedly reduced in the caudate nucleus and putamen bilaterally in patient II.14 predominantly on the right (**Figure 2**).

Dopamine transporter (DAT) imaging in the mother (I.2) demonstrated considerably reduced tracer uptake

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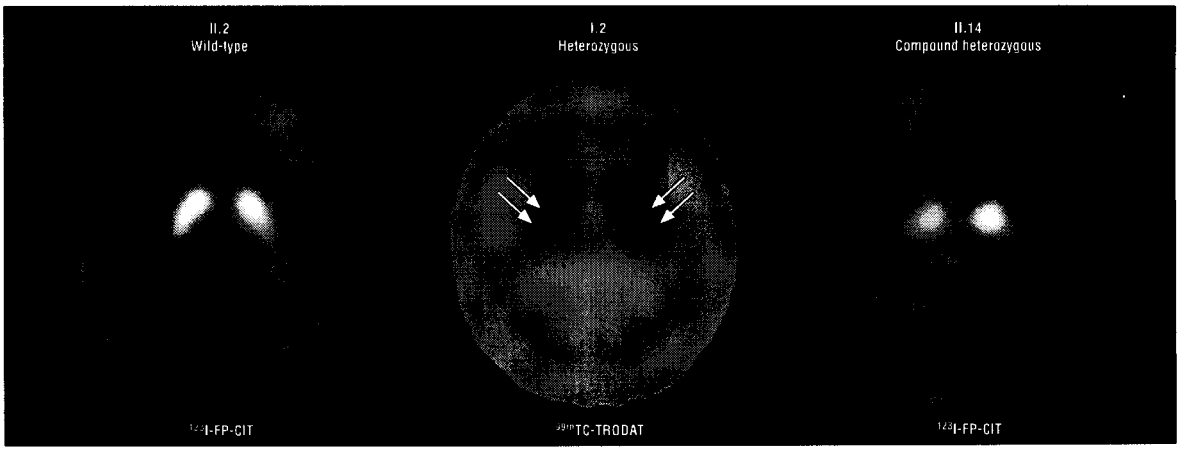

Figure 2. Dopamine transporter (DAT) scans in *ATP13A2* mutation carriers. Representative horizontal TRODAT (I.2) and FP-CIT single-photon emission computed tomographic images. The striatal tracer uptake is markedly reduced bilaterally in the carrier of compound heterozygous *ATP13A2* mutations (II.14). The heterozygous mother presented bilateral putaminal decline of uptake (I.2). Non–mutation carriers had unremarkable DAT scans (eg, proband II.2). ^{99m}TC indicates technetium 99m; ^{123}I, iodine 123.

in both putamina. The 3 heterozygous MCs (II.1, II.11, II.12) showed physiological levels of tracer uptake but the only examined carrier of the heterozygous 1306+5G>A mutation (II.11) had an asymmetric tracer distribution with a significant difference of greater than 10% reduction toward the right caudate nucleus (Figure 2; supplemental table 1; www.neuro.uni-luebeck.de/arch.neurol_bruggemann.et.al/). The 2 NMCs had no reduction of striatal tracer uptake or asymmetry.

STRUCTURAL MRI

Patient II.14 showed a marked T2 hypointensity in the caudate nucleus and putamen bilaterally. The heterozygous MCs and NMCs had no T2 signal alterations (supplemental table 1; www.neuro.uni-luebeck.de/arch.neurol_bruggemann.et.al/).

On voxel-based morphometry, the main findings in the symptomatic *ATP13A2* MC were 3 large clusters demonstrating a decrease in GM volume in the cerebellum. Furthermore, we observed pronounced bilateral loss of GM volume in the premotor and supplementary motor cortex, caudate, thalamus, prefrontal cortex, cingulate, and somatosensory association cortex (**Figure 3**; supplemental table 2; www.neuro.uni-luebeck.de/arch.neurol_bruggemann.et.al/).

In asymptomatic *ATP13A2* MCs, we detected 1 large cluster of significantly increased GM volume in the right putamen when compared with healthy controls. We found an increase in GM volume in the bilateral somatosensory and motor cortex as well as in the parietal association cortex and the middle occipital gyrus. In contrast, the analysis revealed a decrease in GM volume in the cerebellum bilaterally and the right hippocampus (Figure 3; supplemental table 3; www.neuro.uni-luebeck.de/arch.neurol_bruggemann.et.al/).

BRAIN PARENCHYMA TCS

The mother had an insufficient temporal bone window bilaterally. None of the examined probands showed nigral hyperechogenicity of greater than 0.25 cm^2 (supplemental table 1; www.neuro.uni-luebeck.de/arch.neurol_bruggemann.et.al/). One MC (II.11) demonstrated a slightly increased aSN between 0.20 and 0.25 cm^2. No abnormal echogenicity was found in any other parts of the basal ganglia nor in the thalamus in any of the subjects.

COMMENTS

This detailed multimodal clinical and neuroimaging study collectively provides evidence for a possible pathogenic role of single *ATP13A2* mutations in the development of parkinsonian signs. Heterozygous *ATP13A2* mutations may cause an age-dependent measurable impairment of nigrostriatal function and altered brain plasticity. Second, we demonstrate that the neurodegenerative process in classical KRS involves several brain structures including the basal ganglia, cortical areas, and cerebellum. The presence of iron accumulation in the basal ganglia of patients with KRS may place this syndrome among the disorders of neurodegeneration with brain iron accumulation (NBIA).

EFFECT OF SINGLE *ATP13A2* MUTATIONS

Detailed clinical assessment revealed mild extrapyramidal signs in all examined heterozygous MCs and parkinsonism in the mother. Determining subtle motor findings is a diagnostic challenge, especially in genetic studies in which family members are examined for mild signs, which may be indicative of milder phenotypes or formes frustes. Such subtle signs do not necessarily equate parkinsonism and could alternatively be attributed to dystonia, or may still be within the physiological spectrum.[18] One of the 2 NMCs presented with mild symmetric action tremor. The response to alcohol and β-blocking agents was not tested. Family history for tremor was negative. Rest tremor as a cardinal PD sign, and other PD-defining signs were absent in this subject.

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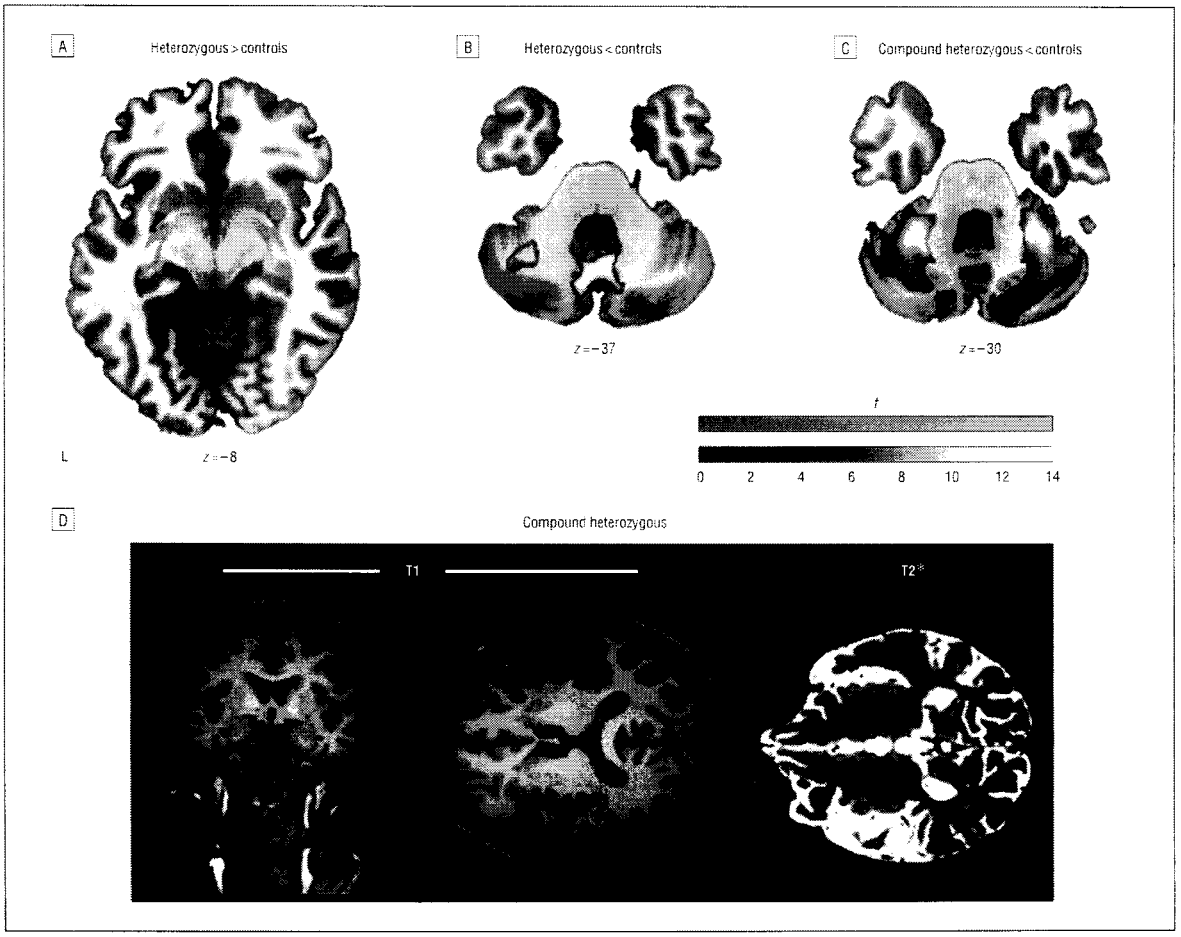

Figure 3. Gray matter (GM) volume changes in *ATP13A2* mutation carriers (MCs). The axial left image (A) visualizes the increase in GM volume in the right putamen in heterozygous *ATP13A2* MCs compared with controls. B, The main finding of cerebellar decrease in GM volume in heterozygous *ATP13A2* MCs is shown. C, The most prominent finding of pronounced bilateral loss of GM volume in the cerebellum in the compound heterozygous MC compared with healthy controls is presented. D, T1-weighted coronal and axial brain magnetic resonance images of the affected compound heterozygous MC II.14 are shown to visualize the severe global brain atrophy. The axial $T2^*$ image on the left reflects the increased bilateral iron accumulation in the caudate and putamen. The color intensity represents *t* values at the voxel level for the voxel-based morphometry findings. The results are visualized on a T1-weighted template and presented in neurological convention (the right side of brain is the part of the image on the right).

Unlike his heterozygous siblings, tremor was the only sign. We conclude that this subject presented with either an accentuated physiological tremor or a mild essential tremor. In keeping with her clinical status, the mother had a clear reduction in putaminal tracer uptake on both sides, whereas none of the remaining investigated heterozygous MCs had pathologically decreased values. It remains questionable whether the observed asymmetric tracer uptake in subject II.11 represents a true abnormality indicative of the first evidence of a possible nigrostriatal decline. Alternatively, some carriers may display a subtle nigrostriatal dopaminergic abnormality that can only be detected with more sensitive mapping techniques such as positron emission tomography.[19] Although the sensitivity of DAT scans is reported to be high, a certain proportion of probands with degenerative parkinsonism demonstrates results in the reference range and may fall below the detection threshold. A recent single-photon emission computed tomographic study revealed that 22 of 112 clinically diagnosed patients with PD had DAT imaging that appeared normal initially, a fraction of whom showed abnormal results on follow-up scans.[20] Only long-term clinical and neuroimaging follow-up investigations will help determine whether these at-risk subjects will develop definite parkinsonism later in life, like their mother.

Former DAT scan and fluorine-18-L-dihydroxyphenylalanine positron emission tomographic studies in patients with mutations in the more frequently mutated recessive genes *Parkin* and *PINK1* revealed bilaterally reduced striatal uptake, particularly in the posterior putamen, comparable with idiopathic PD.[21-24] Progression of the nigrostriatal decline in both monogenic forms was slower compared with idiopathic PD.[22,24] Also, asymptomatic carriers of heterozygous *Parkin* mutations showed subclinical striatal PET changes, suggesting a correlation between nigrostriatal dysfunction and the number of mutated alleles.[23,24] A subset of these individuals who were at risk exhibited unequivocal extrapyramidal signs and, in part, a parkinsonian phenotype. Of note, striatal

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PET changes were given as group differences between several carriers of single mutations and healthy controls and therefore need to be interpreted with caution when referring to individual probands, as in our study.

Structural neuroimaging suggests that single *ATP13A2* mutations lead to unilateral putaminal hypertrophy and to increased GM volume in the precentral and postcentral gyrus as well as the precuneus/cuneus bilaterally. The side of putaminal GM increase matches the clinically affected side in 3 of 4 heterozygous MCs that were included in the analysis. These findings are consistent with an effect of heterozygous mutations in modifying the structural brain organization. The described alterations support a previously demonstrated hypertrophy in the putamen and internal globus pallidus in carriers of heterozygous *Parkin* and *PINK1* mutations.[25,26] The morphometric changes may result from a latent striatal dopamine deficiency. Evidence supporting this hypothesis is gleaned from a study on long-term treatment with antidopaminergic drugs over a period of 2 years. The mean basal ganglia volume increased in patients who were treated with typical neuroleptics and decreased after the change to atypical neuroleptics.[27] Hypertrophy in different brain regions, especially in the putamen, may point toward compensatory plasticity in the younger and middle-aged heterozygous MCs, leading to a preserved striatal dopaminergic innervation, as shown by DAT imaging. However, the underlying biochemical alterations and the type of the involved tissue of these adaptive mechanisms remain to be elucidated.

NEURODEGENERATIVE PROCESS AND BRAIN IRON ACCUMULATION IN KRS

In the index patient, presynaptic DAT imaging revealed a marked striatal uptake decrease, indicating severely impaired nigrostriatal function, with the most prominent reduction in the dorsal portions of the putamen. Accordingly, fluorine-18-L-dihydroxyphenylalanine positron emission tomography showed diminished bilateral striatal uptake in a previously described Japanese patient with a homozygous *ATP13A2* mutation.[25] We detected marked iron deposition in the basal ganglia of the patient with KRS and pronounced bilateral loss of GM volume in several brain regions on observer-independent voxel-based morphometry. Unlike the heterozygous MCs, the patient with KRS did not show an increase in GM volume in the basal ganglia but a marked decline. Apparently, regions with an accumulation of iron seem to be associated with neuronal death in this neurodegenerative syndrome. The compensatory capacity for avoiding neuronal death is obviously lost in the patient with KRS in contrast to younger and middle-aged heterozygous subjects. Whether the increased iron content in KRS reflects a pathophysiologically relevant mechanism or a secondary epiphenomenon remains to be elucidated in future studies. Interestingly, the yeast orthologue of the human *ATP13A2* protein, YPK9p, might play a role in the sequestration of divalent heavy metals.[29] Despite the lack of post mortem data, *ATP13A2*-associated parkinsonism may be considered the latest member in the growing list of neurodegenerative diseases with brain iron accumulation such as pantothenate kinase-associated neurodegeneration.[30]

Unlike patients with idiopathic PD and carriers of heterozygous and homozygous *Parkin* and *PINK1* mutations, subjects with *ATP13A2*-associated parkinsonism and heterozygous *ATP13A2* mutations showed no increased aSN in TCS.[14,15] Substantia nigra hyperechogenicity in idiopathic PD is thought to be associated with increased iron content, bound to proteins other than ferritin.[31] The lack of this TCS sign in the present study may be explained by the putative presence of different iron compounds and binding partners in KRS and other atypical forms of parkinsonism.[16] Only limited data are currently available regarding the hyperechogenicity of the lenticular and caudate nuclei. Apart from increased metal tissue content, signal alterations may result from minor calcifications, enlarged perivascular spaces, and gliosis. The underlying neurodegenerative process in *ATP13A2*-associated atypical parkinsonism may differ from other forms of inherited as well as uninherited PD.

The pathophysiological role of heterozygous mutations in recessive parkinsonism genes currently remains a matter of vivid debate.[32] Their potential effect on the development of parkinsonism is influenced by a variety of parameters including changes in other genes or gene-regulating elements as well as epigenetic and environmental factors. Our data from this multilayered investigation collectively provide evidence for a relevant pathophysiologic effect of single *ATP13A2* mutations in the development of parkinsonian signs and demonstrate possible compensatory brain plasticity mechanisms in heterozygous subjects. The question whether the measured phenotypic effects are consistently caused by single *ATP13A2* mutations should be clarified in an independent, larger sample of carriers with a different genetic and environmental background. This approach will help to better interpret the role of heterozygous mutations in putatively recessive parkinsonism genes.

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Author Contributions: Dr Klein had full access to all of the data in the study and takes responsibility for the integ-

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rity of the data and the accuracy of the data analysis. *Study concept and design:* Brüggemann, Hagenah, Münchau, Siebner, Binkofski, and Klein. *Acquisition of data:* Brüggemann, Hagenah, Schmidt, Kasten, Buchmann, Eckerle, Bähre, Münchau, Djarmati, van der Vegt, Behrens, and Klein. *Analysis and interpretation of data:* Brüggemann, Hagenah, Reetz, Buchmann, Bähre, Münchau, Siebner, Binkofski, Ramirez, Behrens, and Klein. *Drafting of the manuscript:* Brüggemann, Eckerle, and Bähre. *Critical revision of the manuscript for important intellectual content:* Hagenah, Reetz, Schmidt, Kasten, Buchmann, Münchau, Djarmati, van der Vegt, Binkofski, Ramirez, Behrens, and Klein. *Statistical analysis:* Reetz and Siebner. *Obtained funding:* Siebner and Klein. *Administrative, technical, and material support:* Brüggemann, Reetz, Schmidt, Kasten, Buchmann, Eckerle, Bähre, van der Vegt, and Klein. *Study supervision:* Buchmann, Münchau, Binkofski, Ramirez, and Klein.

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Letter to the Editor

Juvenile dystonia-parkinsonism and dementia caused by a novel ATP13A2 frameshift mutation☆

Keywords:
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The Kufor-Rakeb syndrome (KRS, MIM 606693) is a rare form of juvenile parkinsonism marked by dementia, supranuclear gaze palsy and pyramidal signs. The syndrome was first described in 1994 in a Jordanian consanguineous family [1]. More than ten years later, a compound heterozygous mutation in the *ATP13A2* gene (c.3057delC/c.1306+5G > A) was demonstrated to be responsible for KRS in a large Chilean non-consanguineous family [2]. Subsequently, a homozygous 22 bp duplication in *ATP13A2* (c.1632_1653dup22) was identified in the original Jordanian family [2]. More recently, mutations in *ATP13A2* were also implicated in other cases of KRS and early-onset Parkinson's disease (PD) [3–6].

Here we describe the identification of a novel *ATP13A2* mutation in a consanguineous Afghan family with an index patient suffering from KRS.

The index patient (II.3) was 10 years of age at presentation and was born to consanguineous Afghan parents, who were related as first cousins (Fig. 1A). Pre-, perinatal history as well as developmental milestones of the index patient are generally unremarkable. However, no detailed clinical records are available due to the family's immigration to Belgium when the index patient was 6 years of age. Familial history was negative for neurological or metabolic disease, with exception of the eldest sibling (II.1) who suffers from mild mental retardation and intentional tremor. Mild mental retardation was also diagnosed in the index patient prior to the onset of motor symptoms. At age 10, he experienced slowing of writing, due to impairment of fine motor control of the right hand (video 1). Fine tremor in the hands was observed (more pronounced on the right side). Further examination showed severe dystonic posturing of the neck to the right side, dextroconvex cervical scoliosis and sinistroconvex thoracolumbar scoliosis. Cranial nerve function was normal, with exception of slow vertical saccades and hypomimia. We observed irregular small-amplitude jerky movements in the perioral muscles. Strength in the right arm was reduced with dystonic flexion posturing (video 2). Tendon reflexes were symmetrical and brisk. Plantar reflexes were in flexion. Finger-to-nose testing showed no ataxia. Cognitive function declined very quickly, leading to a clinical picture of dementia at age 11 years. A total IQ score of 45 (verbal IQ score of <55 and performance IQ score of <55) was observed on the Wechsler Intelligence Scale for Children (WISC-III) at age 12. Medical treatment included trihexyphenidyl, levodopa and ropinirole. Bradykinesia and rigidity were partially responsive to levodopa, while no improvement of the dystonic symptoms was observed. Shortly after treatment onset, dyskinesias, athetosis (video 3) and camptocormia (video 4) appeared. Visual hallucinations and psychosis occurred during the disease course and limited the use of dopaminergic medication. Magnetic resonance imaging of the brain at age 11 years was unremarkable and did not show hypodensities in the basal ganglia on T2* sequences. ^{123}I-FP-CIT nuclear imaging [7] at age 11 years however showed decreased ligand binding in the right caudate nucleus and severely decreased ligand binding in both putamina (Fig. 2). In the oldest sibling (II.1) a reduced uptake was observed in both putamina (left > right) on ^{123}I-FP-CIT nuclear imaging. The other members of the family DR447 do not show extrapyramidal nor overt cognitive symptoms on neurological examination. However, the youngest sibling (individual II.5) of the index patient has currently not been examined.

Supplementary data related to this article can be found online at doi:10.1016/j.parkreldis.2010.10.011.

Genomic DNA (gDNA) was isolated from peripheral blood using optimized techniques. All 29 exons, including exon–intron boundaries and the proximal promoter region of *ATP13A2* were sequenced. Primer sequences and PCR conditions are available upon request.

In the index patient (II.3) a novel homozygous 2-bp deletion (c.2742_2743delTT) in exon 23 of *ATP13A2* was identified, while the eldest sibling carries the same deletion in a heterozygous state (Fig. 1C). This deletion is predicted to cause a premature stop codon at position 856 (p.F851Cfs856X) and most likely leads to truncation of 324 amino acids and loss-of-function of the protein. We did not observe evidence for non-sense mediated decay based on RT-PCR analysis of RNA isolated from cycloheximide-treated lymphoblasts versus non-treated lymphoblasts of the index patient.

The clinical phenotype of the index patient (II.3) in family DR447 can be described as asymmetric dystonia-parkinsonism with dementia. Interestingly, the prominent and early dystonia has not yet been described in previously reported KRS patients with exception of the KRS patient reported by Schneider et al. in which early leg dystonia progressing to generalized dystonia, was noted [6]. The extrapyramidal symptoms in the index patient

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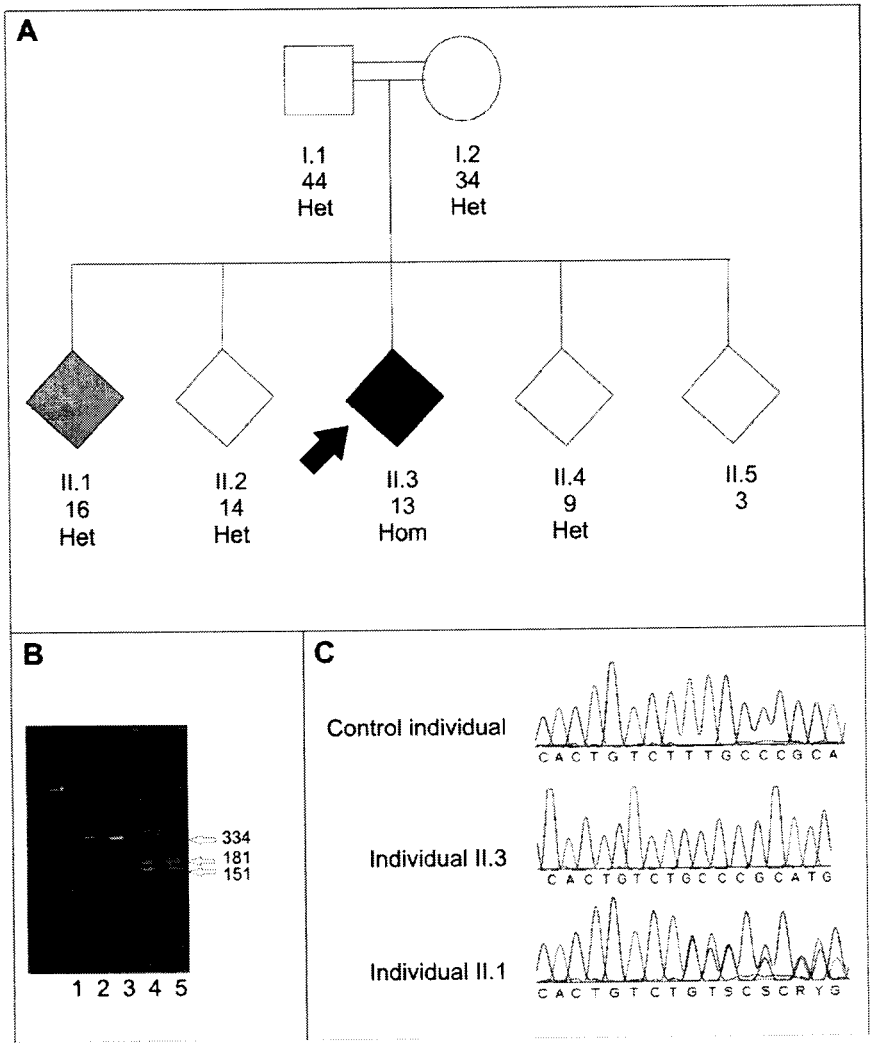

Fig. 1. A. Pedigree of the family DR447: For each individual, an identification code and current age is noted. Dark-filled individual II.3 is the affected proband; suffering from Kufor-Rakeb syndrome. Gray-filled individual II.1 suffers from mild mental retardation and intentional tremor. *Het*: Heterozygous carrier of deletion c.2742_2743delTT in *ATP13A2*. *Hom*: Homozygous carrier of deletion c.2742_2743delTT in *ATP13A2*. B. Restriction enzyme digestion (BstAPI) of PCR product of exon 23 of *ATP13A2*. 1: 100 bp ladder; 2 and 3: control individuals; 4 and 5: individual II.3. Base pair length of the fragments is indicated with open arrows. C. Electrophoretogram of direct sequencing of exon 23 of *ATP13A2* in a control individual, the index patient II.3 and the eldest sibling II.1. A deletion of two thymidines (c.2742_2743delTT or p.F851Cfs856X) is identified in the index patient II.3 (homozygous) and in the eldest sibling II.1 (heterozygous). Coding DNA mutation numbering is relative to Genbank accession number NM_022089.2 and starts at nucleotide 1. Amino acid variation numbering is relative to Genbank accession number NP_071372.1.

Fig. 2. ^{123}I-FP-CIT SPECT scan of individual II.3 at age 11. Ligand binding in both putamina is almost absent and severely decreased in the right caudate nucleus.

II.3 were responsive to dopamine agonists and levodopa, but dyskinesias developed quickly. We did not observe clinical evidence for supranuclear gaze palsy, but slowing of vertical saccades was present. The fine tremor in the hands and the irregular jerky movements in the lower face could be related to the facial-faucial-finger mini-myoclonus, which was also previously described in KRS [2,6].

The onset age of the index patient of family DR447 is the youngest onset age ever reported for KRS suggesting a severe impact of this novel frameshift mutation on the protein's function. It is conceivable that the mental retardation which preceded the motor symptoms in the index patient, forms an integral part of KRS, possibly indicating an even earlier onset age. The eldest sibling (II.1) of the index patient is a heterozygous carrier of the truncating mutation and suffers from intentional tremor and mild cognitive symptoms. Both parents (I.1 and I.2) and two other siblings (II.2 and II.4) are also heterozygous carriers. Interestingly, only individual II.1 has developed mild symptoms to date. Possibly, other siblings may not have reached the onset age of symptoms yet, but the parents clearly have. Although only homozygous *ATP13A2* mutations are considered to cause classical KRS, heterozygous *ATP13A2* missense mutations have been reported in two young-onset Parkinson's disease patients with atypical clinical features [4]. Therefore, we can speculate about the variable penetrance of this truncating mutation in heterozygous individuals of this family. It is conceivable that heterozygous mutations in *ATP13A2* lead to a milder phenotype. Additionally, environmental or genetic factors could modify the penetrance of the mutation for heterozygous carriers.

Further clinical follow-up of this family will increase the knowledge on the natural history and clinical features of KRS, which seems to be a rare disorder. Only five KRS families and 13 patients suffering from KRS have been reported today. In order to understand the clinical heterogeneity of *ATP13A2* homozygous, compound heterozygous and single heterozygous mutations, we will have to unravel the mutational spectrum and function of this protein. The possible role of the ATP13A2 protein in the lysosomal-autophagy pathway can lead to further knowledge of the pathogenesis of Parkinson's disease and neurodegeneration in general.

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ORIGINAL ARTICLE

Novel *ATP13A2* (*PARK9*) homozygous mutation in a family with marked phenotype variability

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Abstract Mutations in the *ATP13A2* (*PARK9*) and *FBXO7* (*PARK15*) genes are linked to different forms of autosomal recessive juvenile-onset neurodegenerative diseases with overlapping phenotypes, including levodopa-responsive parkinsonism, pyramidal disturbances, cognitive decline, and supranuclear gaze disturbance. However, the associated genotypes and phenotypes are poorly characterized due to the small number of patients described. Here, we report clinical, instrumental, and genetic findings in an Italian family with novel *PARK9* and *PARK15* mutations. The proband developed a severe progressive phenotype including juvenile-onset parkinsonism, pyramidal disturbances, cognitive decline, and oculomotor abnormalities. On the contrary, his brother only shows mild abnormalities (pyramidal, cognitive, and oculomotor) on the neurological examination at the age of 31 years. These two brothers both carry a novel homozygous *PARK9* missense (p.G877R) and a novel heterozygous *PARK15* mutation (p.R481C). The *PARK9* mutation replaces a crucial residue for the ATPase activity, and is therefore most likely a loss-of-function mutation and disease-causing in homozygous state. The pathogenic significance of the *PARK15* single heterozygous mutation remains unclear. In both sibs, DaTSCAN single photon emission computed tomography showed marked nigrostriatal dopaminergic defects, and transcranial magnetic stimulation detected prolonged central motor conduction time. MRI, including T2*-weighted imaging, detected no evidence of brain iron accumulation. This family, the third reported with homozygous *PARK9* mutations and the first with mutations in two genes for atypical juvenile parkinsonism, illustrates that PARK9-linked disease might display wide intra-familial clinical variability and milder phenotypes, suggesting the existence of strong, still unknown, modifiers.

Keywords Parkinsonism · Movement disorders · PARK9 · PARK15 · ATP13A2 · FBXO7

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Introduction

PARK9, or Kufor-Rakeb syndrome (KRS), is characterized by juvenile-onset, levodopa-responsive parkinsonism,

pyramidal signs, dementia, and supranuclear gaze palsy [1, 2], caused by recessive mutations in the *ATP13A2* gene [3]. Since the initial report, only six definitely disease-causing (homozygous or compound heterozygous) mutations have been described in two families [3] and three isolated KRS patients [4–6]. For another seven mutations identified in single heterozygous state in patients with early-onset Parkinson's disease (PD) [4, 7, 8], the role in the disease causation remains unclear.

The *ATPA13A2* gene encodes a large lysosomal transmembrane protein, belonging to the group 5 P-type ATPase family. P-type ATPases use the energy deriving from ATP hydrolysis to generate gradients of ions across membranes [9]. The substrate specificity of the ATP13A2 protein remains unknown, but there is evidence that this protein is involved in the transport of several cations from the cytosol to the lysosomal lumen, including manganese, cadmium, nickel, and selenium [10, 11].

Recessive mutations in the *FBXO7* gene have been recently linked to PARK15, a different rare juvenile neurodegenerative disorder, presenting as a parkinsonian-pyramidal syndrome and reported so far in only three families [12, 13].

In this study, we describe two brothers from a southern Italian family, who both carry a novel homozygous *ATP13A2* mutation and a single heterozygous *FBXO7* mutation. Despite the identical genotypes, the brothers were affected with markedly different severity.

Subjects and methods

A simplified pedigree is shown in Fig. 1. A healthy couple had two offspring, who both developed different degrees of a progressive neurological disease. The parents report no known consanguinity, but they both originate from the same small village in the Campania region of southern Italy. The project was approved by the relevant ethical authorities, and written informed consent was obtained from all subjects.

Genetic studies

Genomic DNA was isolated from peripheral blood samples following standard procedures. We first screened the proband for mutations in the *parkin* (*PARK2*), *PINK1* (*PARK6*), *DJ-1* (*PARK7*), *ATP13A2* (*PARK9*), *PLA2G6* (*PARK14*), and *FBXO7* (*PARK15*) genes. All exons and exon–intron boundaries of the above-mentioned genes were sequenced in both strands. The PCR protocols and primers are available on request from the authors. Direct sequencing was performed using Big Dye Terminator chemistry ver.3.1 (Applied Biosystems). Fragments were loaded on an Applied Biosystems 3130XL automated sequencer and analyzed with DNA Sequencing Analysis (ver.5.3) and SeqScape (ver.2.6) software (Applied Biosystems). The mutations were numbered from the "A" of the ATG-translation initiation codon, according to the GenBank reference sequences, accession numbers NM_022089.2 (*ATP13A2*) and NM_012179.3 (*FBXO7*). We also screened the proband for copy number aberrations in the *parkin*, *PINK1*, *DJ-1*, *ATP13A2*, and *SNCA* (*alpha-synuclein*) genes, using a multiplex ligation-dependent probe amplification (MLPA) assay (probe mix P051 and P052) according to the manufacturer's protocol (MRC-Holland). The *PARK9* and *PARK15* mutations detected in the proband were studied in the whole family, as well as in a panel of unrelated healthy controls from the same region of southern Italy, and using the same sequencing techniques. In order to analyze the evolutionary conservation of the mutated amino acids, the ATP13A2 and FBXO7 protein homologues were aligned using the program ClustalW.

Brain imaging

Brain single photon emission computed tomography (SPECT) studies were performed 4 h after intravenous administration of 185 MBq of [123I]FP-CIT (DaTSCAN, GE-Healthcare) using a dual-headed camera (E.CAM, Siemens Medical Systems, Hoffman Estates, IL) equipped with low-energy high-resolution collimators (zoom, 1.23; pixel size, 3.90×3.90 mm). Outcome measures were the specific-to-nondisplaceable binding ratio, V''_3 for the putamen and caudate.

The brain MRI studies included T2-weighted turbo spin-echo (TSE) (TR/TE 4,400/100 ms) and FLAIR (TR/TE/TI 8,000/100/2,200 ms) sequences, as well as T1-weighted conventional SE (TR/TE 580/15 ms), and DWI (EPI, TR/TE 3,500/90 ms) images (1.5 T, Achieva, Philips Medical Systems, Eindhoven, Netherlands). In addition, T2*-weighted axial images (Gradient echo, TR/TE 600/15 ms, Flip Angle 20°) were acquired (3 T, Magnetom Trio, Siemens Medical Systems, Erlangen, Germany).

Results

Clinical findings

The proband (NAPO-6 in Fig. 1) is a 41-year-old man with referred perinatal asphyxia and slight delay in reaching the developmental milestones. At the age of 10 years, he developed a slowly progressive gait disturbance with slowing and stiffness of legs. An asymmetric onset of symptoms was not recorded. Treatment with levodopa yielded marked improvement in gait and in limb rigidity.

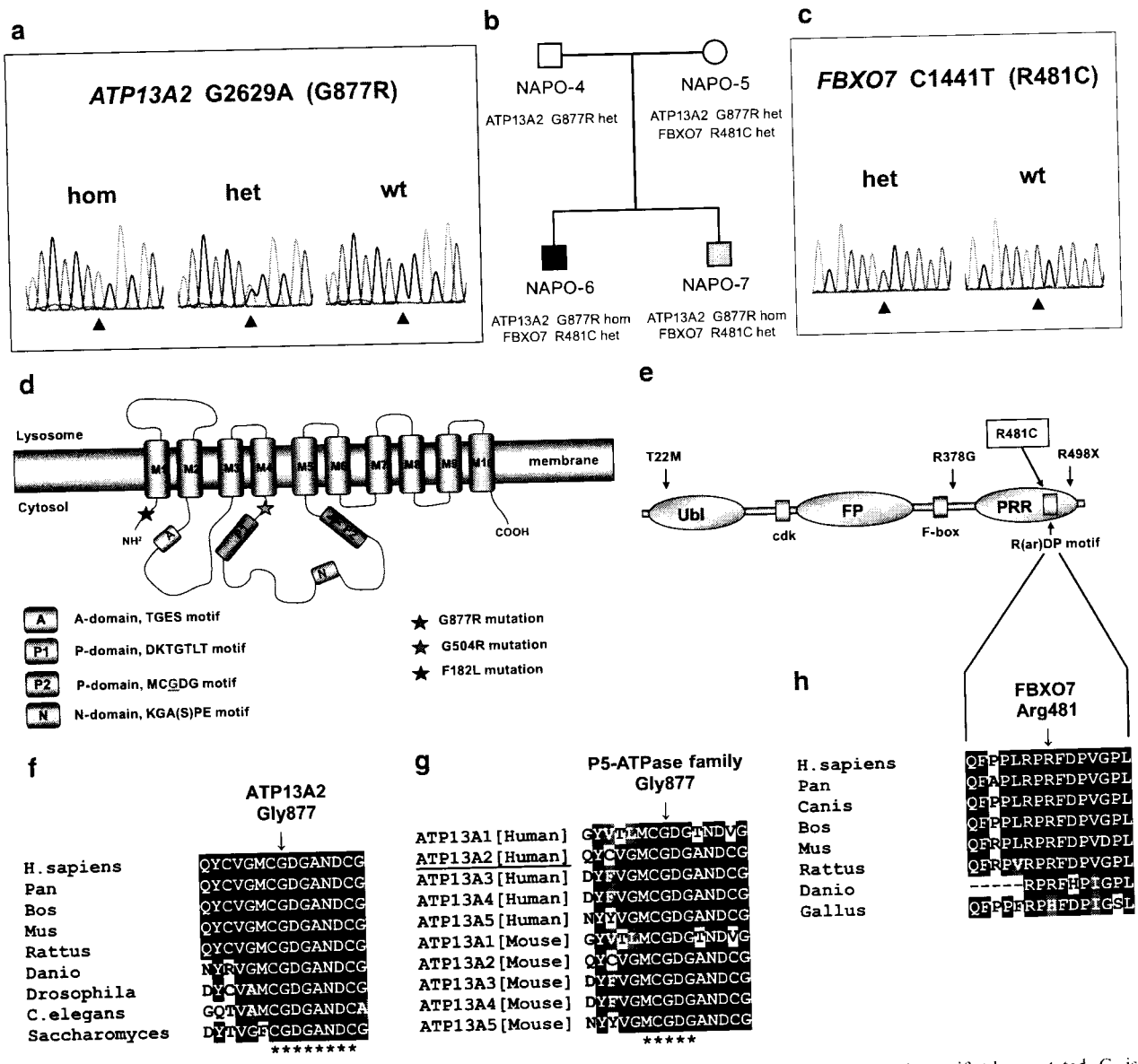

Fig. 1 Genetic findings in the family with *PARK9* and *PARK15* mutations. **a** Electropherograms of a fragment of *ATP13A2* (*PARK9*) exon 24; *hom* homozygous mutation, *het* heterozygous mutation, *wt* wild-type sequence. **b** Simplified pedigree. The proband is highlighted by a *black symbol*; his brother is highlighted in *gray*. The *ATP13A2* (*PARK9*) and *FBXO7* (*PARK15*) mutations are shown below the individual symbols. **c** Electropherograms of a fragment of *FBXO7* (*PARK15*) exon 9; *het* heterozygous mutation, *wt* wild-type sequence. **d** Schematic representation of the ATP13A2 protein, its known functional domains and amino acid motifs. The position of the G877R mutation detected in the Italian family is indicated within the P2 domain and within the MCGDG motif (the mutated G is *underlined*). The other two missense mutations reported previously in homozygous state in PARK9 patients are also shown. **e** Schematic representation of the FBXO7 protein. The R481C mutation detected in the Italian family is framed. The other disease-causing mutations reported previously in PARK15 patients are also shown. **f** Alignment of ATP13A2 protein homologues in the region of the G877R mutation. **g** Alignment of P5-ATPase protein family in the region corresponding to the G877R mutation. **h** Alignment of FBXO7 protein homologues in the region of the R481C mutation

Nonetheless, over time, his motor performance progressively deteriorated, and a mild cognitive impairment became apparent. At the age of 18 year, he received the diagnosis of "extra-pyramidal and pyramidal syndrome with cognitive impairment". Since then, the patient complained of dysarthria and dysphagia, and some years later, the arm and leg stiffness became so severe to determine the complete dependence on others for all daily living activities. Our neurological examination, 30 years after the disease onset, showed a moderate limitation of the up-gaze

and right lateral gaze. The saccadic eye movements were slow both in upward and downward direction and bilaterally hypometric on lateral gaze. A severe hypomimia was present, and the speech was almost incomprehensible. There was also mild dysphagia, allowing a normal feeding. Sub-continuous mini-myoclonus was present in the lower facial muscles. The gait was only possible with bilateral support, and dystonic posturing was present. The muscle tone was markedly increased in all limbs with prevalence of rigidity in the arms and spasticity in the legs. The deep tendon reflexes were all brisk, and the Babinski sign and palmomental reflex were present bilaterally. Cerebellar signs and tremor were absent. The unified PD rating scale (UPDRS) motor score was 67, and it was not modified by the acute administration of levodopa. The administration of the mini-mental state examination (MMSE) was not possible. Blood chemistry, including manganese, selenium, cadmium, and nickel dosage, was normal. Needle EMG (biceps brachii, rectus femori, and tibialis anterior muscles), surface antidromic sensory (median, ulnar, sural, and peroneal nerves) and orthodromic motor nerve (median, ulnar, and tibial nerves) conduction studies (NCS), and somatosensory evoked potentials (SSEPs) following median and tibial nerve were all normal. Transcranial Magnetic Stimulation (TMS) showed a prolonged central motor conduction time (CMCT) for upper (10.3 ms; normal upper limit, 8 ms) and lower (30.5 ms; normal upper limit, 15 ms) limbs, while motor evoked potential (MEP) amplitude was normal in the upper and reduced in the lower limbs (0.7 mV; normal lower limit, 1.2 mV).

The proband's brother (NAPO-7 in Fig. 1), a 31-year-old man, had a normal birth and developmental motor milestones, but he did not perform normally at school and received a diagnosis of "mild mental retardation". At the time of neurological examination (age 31), he was otherwise asymptomatic. However, the neurological evaluation showed a slight limitation of upward and downward gaze, moderate increase of axial tone, and slight upper limb rigidity. The deep tendon reflexes were brisk, and the Babinski sign was bilaterally present. Finger tapping and stepping were moderately decreased in frequency and amplitude. Cerebellar signs and tremor were absent. The UPDRS motor score was 16. He had never used anti-parkinsonian drugs. The MMSE score was 23. Blood chemistry, including manganese, selenium, cadmium, and nickel dosage, was normal. Needle EMG (biceps brachii, rectus femori, and tibialis anterior muscles), surface antidromic sensory (median, ulnar, sural, and peroneal nerves) and orthodromic motor (median, ulnar, and tibial nerves) NCS, and SSEPs following median and tibial nerve were normal. TMS showed a prolonged CMCT for upper (11.8 ms; normal upper limit, 8 ms) and lower (24.2 ms; normal upper limit, 15 ms) limbs, while MEP amplitude was normal in the upper and reduced in the lower limbs (0.4 mV; normal lower limit, 1.2 mV).

Genetic findings

By sequencing the genomic DNA in the proband, we detected a homozygous mutation in exon 24 of the *ATP13A2* gene (c.G2629A, predicted to lead to the p.G877R missense change in the encoded protein) and a heterozygous mutation in exon 9 of the *FBXO7* gene (c.C1441T, predicted to result in the missense change p.R481C) (Fig. 1a–c). Direct sequencing revealed no additional mutations in these or other screened genes for autosomal recessive parkinsonism (*parkin*, *PINK1*, *DJ-1*, *PLA2G6*). Furthermore, gene dosage aberrations were not detected by the MLPA assays in any of the screened genes. The *ATP13A2* c.G2629A mutation was detected in heterozygous state in both the proband's parents, while it was absent from a large number of control chromosomes (n=336) from the same region of southern Italy. The *FBXO7* c.C1441T mutation was detected in heterozygous state in the proband's mother, while it was absent from the father and from control chromosomes from the region (n=318). The proband's brother (NAPO-7) carried a homozygous *ATP13A2* and heterozygous *FBXO7* mutation, a situation identical to that found in the proband (Fig. 1b). The cDNA studies confirmed the genotypes detected in genomic DNA in the whole family (not shown). Both mutations introduce drastic replacements in amino acid positions that have been highly conserved in the evolution of the ATP13A2 and FBXO7 protein homologues (Fig. 1d–h).

Imaging findings

The [123I]FP-CIT–SPECT showed in both brothers a decrease of dopamine transporter (DaT) density in the striatum (Fig. 2). Compared to controls, the proband showed a marked and widespread striatal reduction of V''_3 (75% in the caudate and 85% in the putamen) (Fig. 2a). In the brother, the specific-to-nondisplaceable binding ratio V''_3 was also symmetrically reduced, mostly in the putamen (40% in the caudate and 65% in the putamen) (Fig. 2b). In both brothers the brain MRI showed diffuse cerebral and cerebellar cortex atrophy, which was more severe in the proband (Fig. 3). The T2* scans detected no evidence of metal accumulation in the basal ganglia of both sibs (Fig. 3c, f).

Discussion

Several arguments support the view that the G877R mutation is harmful for the ATP13A2 protein function.

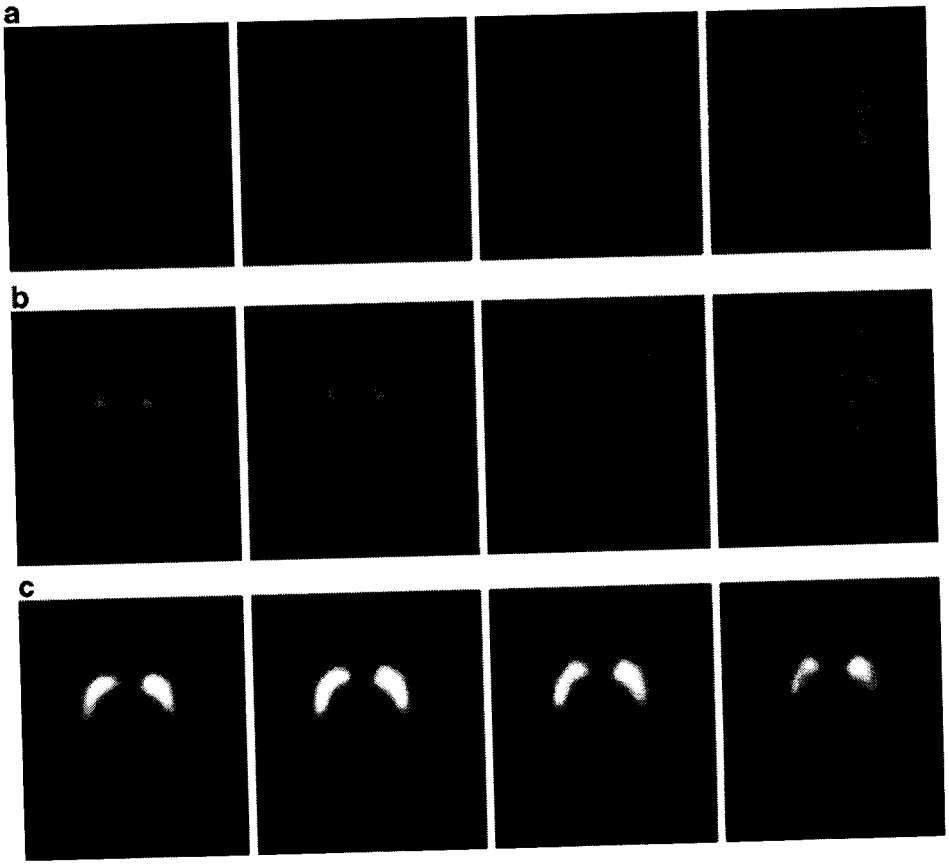

Fig. 2 DaTSCAN SPECT imaging. Brain [123I]FP-CIT (DaTSCAN SPECT) in the proband (**a**), his brother (**b**), and a normal unrelated subject (**c**): a severe presynaptic defect of the nigrostriatal dopaminergic systems is present in the two brothers, more marked in the proband

The glycine 877 lies in a stretch of five amino acids that have not only been conserved in the evolution of ATP13A2 homologues until the yeasts but are also invariably present in all members of the ATPase P5 protein family (Fig. 1f–g), suggesting a crucial role for the protein function. Furthermore, the G877R mutation replaces a small non-polar amino acid (glycine) with a larger polar one (arginine). The large cytoplasmic loop located between the M4 and M5

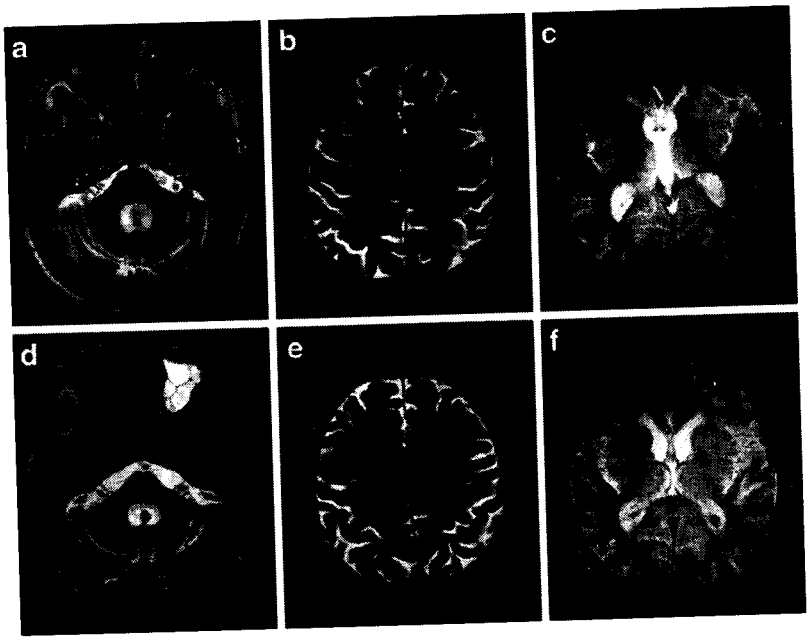

Fig. 3 Brain MRI imaging. T2-weighted TSE axial scans (1.5 T) at the level of the cerebellar hemispheres (**a, d**) and centra semiovalia (**b, e**) and T2*-weighted scans (3 T) at the level of the basal ganglia (**c, f**), in the proband (**a–c**) and his brother (**d–f**). Diffuse supra- and sub-tentorial atrophy is present. The T2*-weighted scans show normal intensity of the basal ganglia in both individuals. Incidental left maxillary sinusitis is also present (**d**)

transmembrane domains of the ATP13A2 protein (Fig. 1d) contains the catalytic autophosphorylation domain (P domain, including an N-terminal and C-terminal part) and the nucleotide binding domain (N domain, necessary for ATP binding) [9, 14]. The presence of an arginine in position 877 places a net positive charge next to the highly conserved negatively charged aspartic acid in position 878, in a very important motif within the C-terminal part of the P domain (Fig. 1d).

Structural studies of a similar P-type cationic pump, the calcium ATPase of skeletal muscle sarcoplasmic reticulum (SERCA1), revealed that the conserved aspartic acid corresponding to Asp-878 in ATP13A2 is one of the most critical residues for the ATP hydrolysis and is spatially very close to the aspartic acid residue (Asp351, corresponding to Asp513 in ATP13A2) which provides the autophosphorylation site [14]. Thus, the G877R mutation is very likely to interfere with the ATPase and autophosphorylation activity of ATP13A2, necessary for the function as cationic pump. Taken together, these considerations argue strongly that the G877R mutation is deleterious for the ATP13A2 function and disease-causing when present in homozygous state.

The R481C mutation replaces a highly conserved arginine residue in the FBXO7 protein, within the so called R(Ar)DP motif (where Ar indicates any aromatic amino acid) in the C-terminal proline-rich region of the protein (Fig. 1e, h) [15]. The function of the R(Ar)DP motif remains undetermined, but the proline-rich region is important for binding of the known FBXO7 substrates [15–17]. The mutation might therefore also be deleterious for the FBXO7 function. However, being found as a single heterozygous mutation in the two affected brothers and their unaffected mother, its significance for the disease causation remains unclear. This could be a coincidental finding, or the mutation could act as a disease modifier, or play some pathogenic role, together with still unknown mutations in other genes.

Different research lines point to an important role for the lysosomes in the pathogenesis of common, late-onset PD. Lysosomes are important for the degradation of the alpha-synuclein protein [18], and heterozygous mutations in the *GBA* gene, encoding the lysosomal enzyme glucocerebrosidase, are an important risk factor for PD [19]. Intriguingly, the ATP13A2 mRNA is highly expressed in the brain, particularly in substantia nigra, and it might be up-regulated in the brain of patients with the common late-onset idiopathic PD [3]. Moreover, the ATP13A2 protein has been recently identified as a potent modifier of the toxicity induced by alpha-synuclein in animal models of PD [10]. On the other hand, manganese, one possible substrate of ATP13A2, is a well-known cause of toxic parkinsonism in humans [20]. Despite the rarity of PARK9 mutations, the ATP13A2 protein might therefore offer clues for understanding the pathogenesis of the common, late-onset forms of PD, linking genetic (alpha-synuclein), and environmental (manganese) factors in the disease etiology.

The clinical phenotype associated with *PARK9* mutations remains poorly defined, as only few patients with clear disease-causing genotypes have been reported. Some phenotypic variability has been described (i.e., variable presence and degrees of dementia, behavior disorders, visual hallucinations, L-dopa responsiveness, and disease progression). Our proband resembles indeed the previously reported PARK9 cases, and his phenotype is compatible with the clinical diagnosis of KRS. The sub-continuous mini-myoclonus present in the lower facial muscles is reminiscent of the facial–faucial–finger mini-myoclonus described in the original KRS patients [2] and other PARK9 cases [3, 5]. Remarkably, the younger brother, apart from a moderate cognitive deficit, remains otherwise asymptomatic at the age of 31 years, and only the neurological examination revealed a mild pyramidal–extra-pyramidal involvement. This marked phenotypic variability has not been previously described in patients with identical PARK9 mutations. It could be the result of the action of genetic or environmental modifiers, or both. An aggravating effect for the perinatal brain sufferance in the proband could not be excluded; however, the severity of his phenotype is similar to that in the other PARK9 patients, and therefore, a protective effect in the proband's brother appears more likely. Mutations in the other known genes for early-onset PD (apart from the *FBXO7* heterozygous mutation) were excluded in the proband, and therefore they cannot play a role as aggravating factors. Environmental factors could include the role of some cations, according to the evidence that the ATP13A2 protein is involved in their transport from the cytosol to the lysosomal lumen [10, 11]. However, the blood levels of manganese, cadmium, nickel, and selenium were normal in both sibs. Furthermore, the siblings have been living with their parents in the same place, being likely exposed to the same environment.

In both sibs, the brain MRI showed diffuse brain atrophy, more marked in the proband, and the DaTSCAN SPECT showed marked nigrostriatal dopaminergic defects, again more marked in the proband, and similar to those reported in advanced idiopathic PD. The neurophysiologic investigation confirmed the involvement of the pyramidal tract and showed the normality of the large myelinated peripheral fibers and of the somatosensory system.

Recently, hypointense signals in the basal ganglia in MRI T2*-weighted scans, suggesting iron accumulation, have been reported in a patient with homozygous PARK9 mutation [6]. Based on this finding, it has been suggested to classify PARK9 within the neurodegenerations with brain iron accumulation [6]. The MRI studies in other previously reported PARK9 cases did not include T2*-weighted scans [2, 5] and were therefore inconclusive concerning the iron

accumulation. Using a comprehensive MRI protocol that includes T2*-weighted scans, we did not find evidence of metal accumulation in the basal ganglia of both sibs reported here. Brain metal accumulation seems therefore not a constant feature in PARK9, even after three decades of disease course. Perhaps brain metal accumulation occurs in the cases with *ATP13A2* mutations leading to the most severe loss of protein function, such as that present in the patient reported elsewhere [6] (p.Thr367ArgfsX29, causing frameshift and protein truncation), while in some patients with missense mutations a residual protein function is retained and brain metal accumulation does not occur.

In conclusion, this family, the third reported with homozygous PARK9 mutations and the first with mutations in two genes for atypical juvenile parkinsonism, illustrates that PARK9-linked disease might display wide intra-familial clinical variability and present with milder phenotypes, suggesting the existence of strong, still unknown, modifiers.

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Disclosure All experiments comply with the current laws of the country in which they were performed. The authors declare that they have no conflict of interest.

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