ИНФОРМАЦИЯ ЗА:
Наименование на заболяването
PARK14 свързани заболявания
Определение на заболяването
PARK14 е рядко невродегенеративно заболяване обичайно с начало преди 30-годишна възраст. Заболяването се характеризира с дистония, паркинсонизъм отговарящ на Л-Допа, пирамидни белези и бързо когнитивно влошаване.
Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)
G24.1
Код на заболяването по Orpha code
ORPHA199351
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. 2. Gregory A., Kurian MA, Maher ER, Hogarth P., Hayflick SJ. PLA2G6-Associated Neurodegeneration, GeneReviews® Last Revision: March 19, 2015.
Епидемиологични данни за заболяването в Европейския съюз
Заболеваемостта и болестността са неизвестни. До момента са публикувани само около 14 случая в света.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Paisan-Ruiz, C., Bhatia, K. P., Li, A., Hernandez, D., Davis, M., Wood, N. W., Hardy, J., Houlden, H., Singleton, A., Schneider, S. A. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann. Neurol. 65: 19-23, 2009. 2. Yoshino, H., Tomiyama, H., Tachibana, N., Ogaki, K., Li, Y., Funayama, M., Hashimoto, T., Takashima, S., Hattori, N. Phenotypic spectrum of patients with PLA2G6 mutation and PARK14-linked parkinsonism. Neurology 75: 1356-1361, 2010. 3. Shi, C., Tang, B., Wang, L., Lv, Z., Wang, J., Luo, L., Shen, L., Jiang, H., Yan, X., Pan, Q., Xia, K., Guo, J. PLA2G6 gene mutation in autosomal recessive early-onset parkinsonism in a Chinese cohort. Neurology 77: 75-81, 2011. 4. Gregory A., Kurian MA, Maher ER, Hogarth P., Hayflick SJ. PLA2G6-Associated Neurodegeneration, GeneReviews® Last Revision: March 19, 2015.
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: Началото на заболяването е в края на юношеството или в началото на зрялата възраст (обичайно преди 30-годишна възраст). Клиничната изява е с паркинсонизъм (тремор, ригидност и брадикинезия), дистония и бързо прогресиращ когнитивен дефицит. При някои пациенти са наблюдавани също абнормни очни движения (супрануклеарна вертикална погледна пареза, апраксия на отваряне на очите), пирамидни белези и психиатрични черти като депресия и личностни промени. Етиологията и патогенезата: Дистония-паркинсонизъм с късно начало се причинява от мутация на фосфолипаза А2, група VI (PLA2G6) ген, локализиран в хромозома 22q13.1.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Paisan-Ruiz, C., Bhatia, K. P., Li, A., Hernandez, D., Davis, M., Wood, N. W., Hardy, J., Houlden, H., Singleton, A., Schneider, S. A. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann. Neurol. 65: 19-23, 2009. 2. Yoshino, H., Tomiyama, H., Tachibana, N., Ogaki, K., Li, Y., Funayama, M., Hashimoto, T., Takashima, S., Hattori, N. Phenotypic spectrum of patients with PLA2G6 mutation and PARK14-linked parkinsonism. Neurology 75: 1356-1361, 2010. 3. Shi, C., Tang, B., Wang, L., Lv, Z., Wang, J., Luo, L., Shen, L., Jiang, H., Yan, X., Pan, Q., Xia, K., Guo, J. PLA2G6 gene mutation in autosomal recessive early-onset parkinsonism in a Chinese cohort. Neurology 77: 75-81, 2011.
Алгоритми за диагностициране на заболяването
Алгоритми за диагностициране на заболяването: Анамнезата: Началото на заболяването е в края на юношеството или в началото на зрялата възраст (обичайно преди 30-годишна възраст). Клиничната изява е с паркинсонизъм (тремор, ригидност и брадикинезия), дистония и бързо прогресиращ когнитивен дефицит. При някои пациенти са наблюдавани също абнормни очни движения (супрануклеарна вертикална погледна пареза, апраксия на отваряне на очите), пирамидни белези и психиатрични черти като депресия и личностни промени. Диференциалната диагноза на заболяването: Kufor-Rakeb синдром (PARK9), PKAN, болест Уилсън и др. Лабораторни, образни и хистологични изследвания: Има съобщения за повишаване на КК при някои пациенти. МРТ на глава с данни за генерализирана мозъчна атрофия, но без натрупване на желязо. PET показва намаление на активността на допаминовия транспортер в стриатума. Генетични изследвания и медико-генетично консултиране: PARK14 се причинява от хомозиготна мутация на фосфолипаза А2, група VI (PLA2G6) ген локализиран в хромозома 22q13.1.Заболяването е с автозомно-рецесивен модел на унаследяване, като генетична консултация е възможна и препоръчителна.
В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Paisan-Ruiz, C., Bhatia, K. P., Li, A., Hernandez, D., Davis, M., Wood, N. W., Hardy, J., Houlden, H., Singleton, A., Schneider, S. A. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann. Neurol. 65: 19-23, 2009.
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3. Shi, C., Tang, B., Wang, L., Lv, Z., Wang, J., Luo, L., Shen, L., Jiang, H., Yan, X., Pan, Q., Xia, K., Guo, J. PLA2G6 gene mutation in autosomal recessive early-onset parkinsonism in a Chinese cohort. Neurology 77: 75-81, 2011.

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: Паркинсонизмът обикновено е с добър отговор на допаминергична терапия, но често впоследствие се развиват изразени дискинезии.

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. Paisan-Ruiz, C., Bhatia, K. P., Li, A., Hernandez, D., Davis, M., Wood, N. W., Hardy, J., Houlden, H., Singleton, A., Schneider, S. A. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann. Neurol. 65: 19-23, 2009.
4. Yoshino, H., Tomiyama, H., Tachibana, N., Ogaki, K., Li, Y., Funayama, M., Hashimoto, T., Takashima, S., Hattori, N. Phenotypic spectrum of patients with PLA2G6 mutation and PARK14-linked parkinsonism. Neurology 75: 1356-1361, 2010.
5. Shi, C., Tang, B., Wang, L., Lv, Z., Wang, J., Luo, L., Shen, L., Jiang, H., Yan, X., Pan, Q., Xia, K., Guo, J. PLA2G6 gene mutation in autosomal recessive early-onset parkinsonism in a Chinese cohort. Neurology 77: 75-81, 2011.

Алгоритми за проследяване на заболяването

Алгоритми за проследяване на заболяването и последващи болнични и извънболнични грижи: 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.
Прогнозата на заболяването: Паркинсонизмът обикновено е с добър отговор на допаминергична терапия, но често впоследствие се развиват изразени дискинезии.
Необходимостта от консултации с други специалисти: При поставяне на диагнозата консултация с офталмолог (за изключване на пръстен на Kayser-Fleischer и pigmentary retinopathy).
Възможни усложнения, честота и тежест: Последващи чести изразени дискинезии от Л-Допа терапията.

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

библиографска справка
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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: Дистония-паркинсонизъм с късно начало се унаследява по автозомно-рецесивен модел на унаследяване, като генетична консултация е възможна и препоръчителна.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Paisan-Ruiz, C., Bhatia, K. P., Li, A., Hernandez, D., Davis, M., Wood, N. W., Hardy, J., Houlden, H., Singleton, A., Schneider, S. A. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann. Neurol. 65: 19-23, 2009. 2. Yoshino, H., Tomiyama, H., Tachibana, N., Ogaki, K., Li, Y., Funayama, M., Hashimoto, T., Takashima, S., Hattori, N. Phenotypic spectrum of patients with PLA2G6 mutation and PARK14-linked parkinsonism. Neurology 75: 1356-1361, 2010. 3. Shi, C., Tang, B., Wang, L., Lv, Z., Wang, J., Luo, L., Shen, L., Jiang, H., Yan, X., Pan, Q., Xia, K., Guo, J. PLA2G6 gene mutation in autosomal recessive early-onset parkinsonism in a Chinese cohort. Neurology 77: 75-81, 2011.
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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9. Петрова М., Трайков Л. Особености в профила и диагностика на когнитивните нарушения при Паркинсонова болест, Неврология и Психиатрия, 2011, 1, 43.
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Neuroscience Letters 514 (2012) 156–158

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Analysis of *PLA2G6* gene mutation in sporadic early-onset parkinsonism patients from Chinese population

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ARTICLE INFO

Article history:
Received 16 October 2011
Received in revised form 13 January 2012
Accepted 23 February 2012

Keywords:
PLA2G6
Gene mutation
Sporadic early-onset parkinsonism

ABSTRACT

Recent studies have shown that *PLA2G6* is a causative gene for PARK14-linked autosomal recessive early-onset complicated dystonia-parkinsonism, early-onset parkinsonism with frontotemporal dementia and autosomal recessive early-onset Parkinsonism without added complicated clinical features. In order to investigate the characteristics of *PLA2G6* gene mutations in Chinese sporadic early-onset parkinsonism (EOP) patients, we performed polymerase chain reaction and DNA direct sequencing on a cohort of sporadic EOP patients from Chinese population. In this study, we found a novel heterozygous varient (p.G679V). Bioinformatics demonstrates that p.G679V exhibits highly conserved residues across species, which hints it might be a pathogenic mutation. Our result indicated that *PLA2G6* mutations might not be a main cause of Chinese sporadic EOP.

1. Introduction

Parkinson's disease (PD) is one of the most frequent neurodegenerative disorders, and is characterized by resting tremor, rigidity, bradykinesia, and impaired postural reflexes. The majority of PD cases appear to be sporadic, thus specific genetic defects are linked to familial forms of PD. Previously, mutations in the genes encoding *Parkin* (PARK2) [7], *PINK1* (PARK6) [18], and *DJ-1* (PARK7) [1] were considered to be responsible for typical autosomal recessive early-onset Parkinsonism (AREP), while autosomal recessive parkinsonism associated with *ATP13A2* (PARK9) [12], *FBXO7* (PARK15) [3,15] and *PLA2G6* (PARK14) [10] often exhibit more complex phenotypes, including pyramidal signs, dementia, supranuclear vertical gaze palsy, and dystonia.

PLA2G6 gene mutations were previously known to cause infantile neuroaxonal dystrophy (INAD), and were also identified as a causative gene of neurodegeneration with brain iron accumulation (NBIA) [9,6]. Recently, there have been patients who are reported to carry *PLA2G6* gene mutations and present with complicated dystonia-parkinsonism phenotype sensitive to L-dopa [10,16]. Due to the prominent parkinsonian features in these patients, the candidate gene was suspects to reside at the PARK14 locus and was thought to be a newly identified cause of complicated autosomal recessive parkinsonism [13].

Recently, *PLA2G6* gene mutations were also found in sporadic early-onset parkinsonism patients with frontotemporal dementia or AREP patients without added complicated clinical features [14,20]. This suggests that the phenotype of *PLA2G6* which were related to neurodegeneretive disordors is broader than described previously.

Until now, there is limited information about *PLA2G6* gene test in sporadic EOP patients. Here we carried *PLA2G6* gene test in a cohort of sporadic EOP patients from mainland China.

2. Materials and methods

2.1. Patients and controls

A total of 72 patients with sporadic early-onset parkinsonism were studied. The majority of the patients were from central China and all were Han Chinese. There were 42 male and 30 female sporadic patients: mean age at onset, 32.7 ± 6.4 years (range, 13–40); mean course: 4.2 ± 3.8 years (range, 1–16). All patients underwent a standardized neurological examination by two movement disorder specialists. 72 patients were selected according to the following criteria: (1) at least two of the three cardinal motor signs (resting tremor, bradykinesia, rigidity); (2) excellent response following L-Dopa therapy; (3) an age at onset ≤40 years; (4) the absence

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doi:10.1016/j.neulet.2012.02.078

of extensor plantar reflexes, ophthalmoplegia, early dementia, or early autonomic failure in the family members; (5) having previously been excluded from the homozygous mutations or compound heterozygous mutations of the *parkin*, *PINK1*, *DJ-1*, *ATP13A2*, *FBXO7* genes via direct sequencing or real-time quantitative PCR analysis [4,19,8].

A control group of 500 healthy mainland Chinese individuals from the same geographic areas was obtained. All controls were free of symptoms suggestive of PD and with a negative family history of movement disorders.

2.2. Mutation analysis

Peripheral blood samples were obtained from patients and controls. DNA extraction from venous blood was performed using standard protocols. Informed consent was received from all the study subjects. The institutional ethics committee approved the genetics study.

The entire *PLA2G6* gene coding region (17 exons) and exon-intron boundaries were amplified using PCR from genomic DNA templates. PCR primer pairs were described previously [9]. PCR reactions were performed in10 μl total volume containing 0.8 μl of 10× TaKaRa PCR buffer with $MgCl_2$, 25 μM of each dNTPs, 3 μM forward primer, 3 μM reverse primer, 0.05 units of HotStart taq Polymerase (Takara Biotechnology) and 25 ng genomic DNA or 0.5 μl total cDNA, ddH_2O up to 10 μl.

Each PCR product was purified and directly sequenced in both forward and reverse directions on an ABI 3100 automated sequencer (Applied Biosystems, Foster City, CA). Alignment and analysis was carried out with DNAStar (DNAStar, Inc., Madison, WI). The consequences of variants at the protein level were predicted according to the *PLA2G6* cDNA sequence deposited in Genbank (accession number AF117676). In all cases in which a novel variant was discovered in a patient sample, 300 unrelated controls were screened by directly DNA sequencing.

3. Results

In the 72 patients analyzed, we found a novel heterozygous variant c.G2036T (p.G679V) in a sporadic patient (Fig. 1). We aligned the human *PLA2G6* protein sequence with five other species using ClustalW2 (http://www.ebi.ac.uk/clustalw/). The result demonstrated that p.G679V exhibits highly conserved residues across species (Fig. 2). Furthermore, we searched the c.G2036T (p.G679V) variant in an ethnically matched sample of 500 healthy controls. The variant was not found in the controls, which indicated that the variant might be a mutation rather than a rare polymorphism in the Chinese population. We also found five polymorphisms in the patients (Table 1), all of the five polymorphisms had been reported previously.

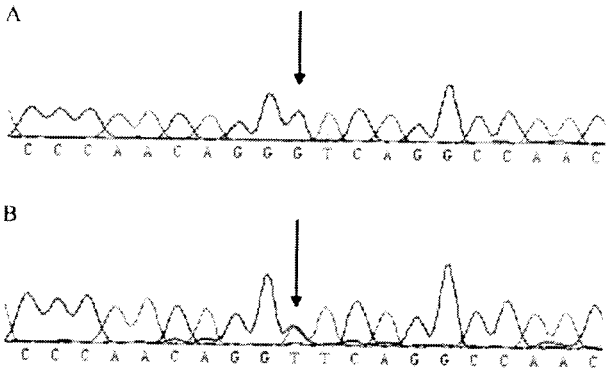

Fig. 1. Chromatogram illustrating the *PLA2G6* gene new mutation (A) wile type (arrow points). (B) Heterozygous c.G2036T (p.G679V) mutation (arrow points).

Table 1
PLA2G6 polymorphisms detected in this study.

SNP ID	Nucleotide change	Protein change
rs2267368	Ivs2 + 16C → C/T	None
rs2267369	c.G87A	None
rs4375	Ivs4 + 71A → G	None
rs12329956	Ivs5 + 43C → T	None
rs2076114	Ivs15 + 55G → G/A	None

The patient carried the p.G679V heterozygous variant was born in a family with no family history of neurological diseases. The individual's birth, early milestones, and childhood were normal. At the age of 30, she developed rigidity and bilateral bradykinesia which resulted walking difficulty without intelligence impairment. Then the patient was diagnosed EOPD and treated with levodopa. Her response to levodopa was excellent. The complicated added features such as dementia, pyramidal signs and dystonia were absent in the patient when she was 42 years old.

4. Discussion

We discovered a heterozygous variant p.G679V in a sporadic patient. It had not been reported previously and was not found in the matched controls and the 679 amino acid site in *PLA2G6* protein is conserved in mammals. All these meant this variant might be a novel mutation and possibly contribute to the pathogenesis of PD. However, because single heterozygous mutation is not pathogenic in the recessive inherited model, the heterozygous p.G679V mutation can not be proved disease-causing in the sporadic EOP patient.

There may be some explanations to clarify the phenomenon. The most likely explanation is that the second heterozygous missense or copy number variation (CNV) mutation were not found in the patient who bear the single heterozygous mutation. In fact, in

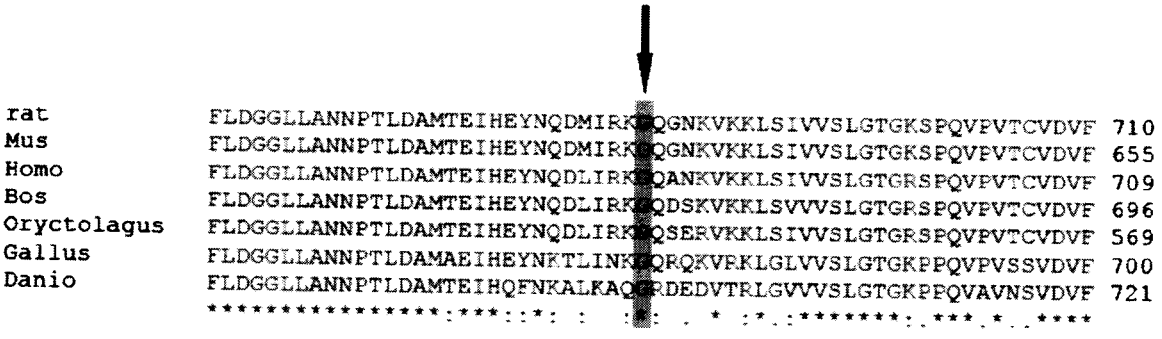

Fig. 2. Conservation of the *PLA2G6* protein residue 679 site targeted by the arrow. The closest homologues of the *PLA2G6* protein were aligned using the program Clustal-X.

the INAD patients, some were found to carry only one single heterozygous *PLA2G6* gene mutation previously, but in further study was reported to have another CNV mutation [2]. On the other hand, another possible explanation is that the heterozygous *PLA2G6* missense mutation already affected the biological function and increased the susceptibility to disease, just like *parkin*, *PINK-1* but not *DJ-1* heterozygous missense mutation [5]. However, in an earlier study, the function of dopamine transporter was proved not affected in heterozygous *PLA2G6* missense mutation carriers by PET study [14].

The role of single heterozygous mutations in PD is a vividly debated issue, whether single heterozygous mutation plays a role in the disease process remains to be determined. Haploinsufficiency, a dominant negative effect or a risk factor associated to an environmental or another genetic cause have been used as hypotheses supporting the role of a single recessive mutation in promoting parkinsonism in these patients [11,17]. More evidence is needed to reveal the biological effect of heterozygous *PLA2G6* missense mutation.

Our gene test shows that the rate of *PLA2G6* mutation is low in sporadic EOP patients, at least in our population. The result indicated that *PLA2G6* gene mutations was not a main cause of sporadic EOP and might be rare in sporadic EOP patients. But further studies including a larger sample size from different ethnic group are needed to reveal the role of *PLA2G6* gene mutations in Parkinson disease.

Conflict of interest

The authors have no actual or potential conflicts of interest to report.

Acknowledgments

This work was supported by grant 2011CB510000 from the Major State Basic Research Development Program of China (973 Program) (to Drs. Bei-sha Tang), grant 2006AA02A408 from the National "863" High-Tech Research and Development Program of China (to Drs. Bei-sha Tang), grants 30570638, 30770735 and 30971035 from the National Natural Science Foundation of China (to Drs. Bei-sha Tang), grant 30900469 from the National Natural Science Foundation of China (to Drs. Ji-feng Guo).

We would like to thank the family for their participation in this study.

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PLA2G6-Associated Neurodegeneration

Synonyms: NBIA2, *PLA2G6*-Related Disorders, PLAN

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Initial Posting: June 19, 2008; Last Revision: March 19, 2015.

Summary

Clinical characteristics.

PLA2G6-associated neurodegeneration (PLAN) comprises a continuum of three phenotypes with overlapping clinical and radiologic features:

- Classic infantile neuroaxonal dystrophy (INAD)
- Atypical neuroaxonal dystrophy (atypical NAD)
- *PLA2G6*-related dystonia-parkinsonism

INAD usually begins between ages six months and three years with developmental regression, hypotonia, progressive psychomotor delay, and progressive spastic tetraparesis. Strabismus, nystagmus, and optic atrophy are common. Disease progression is rapid. Many affected children never learn to walk or lose the ability shortly after attaining it. Severe spasticity, progressive cognitive decline, and visual impairment typically result in death during the first decade.

Atypical NAD shows more phenotypic variability than INAD. In general, onset is in early childhood but can be as late as the end of the second decade. The presenting signs may be gait instability or ataxia (as in the classic form) or speech delay and autistic features, which are sometimes the only evidence of disease for a year or more. The course is fairly stable during early childhood and resembles static encephalopathy but is followed by neurologic deterioration between ages seven and 12 years.

PLA2G6-related dystonia-parkinsonism presents with subacute onset of dystonia-parkinsonism in late adolescence/early adulthood. Other findings are eye movement abnormalities, pyramidal tract signs, and marked cognitive decline.

Diagnosis/testing.

Before 2006, the diagnosis of INAD was established by clinical and pathologic findings alone. Since the discovery of *PLA2G6*, the gene in which mutation causes *PLA2G6*-associated neurodegeneration, molecular genetic testing has been used to help confirm the diagnosis, and in many cases eliminates the need for tissue biopsy.

Management.

Treatment of manifestations: For INAD and atypical NAD: Routine pharmacologic treatment of spasticity and seizures; trial of oral or intrathecal baclofen for dystonia associated with atypical INAD; treatment by a psychiatrist for those with later-onset neuropsychiatric symptoms; fiber supplements and/or stool softener treatment for constipation; control of secretions with transdermal scopolamine patch as needed; feeding modifications as needed to prevent aspiration pneumonia and achieve adequate nutrition.

For *PLA2G6*-related dystonia-parkinsonism: Consider treatment with dopaminergic agents; treatment of neuropsychiatric symptoms by a psychiatrist; evaluation by physical therapy for management of postural instability and gait difficulties; occupational therapy to assist with activities of daily living.

Prevention of secondary complications: Early physical therapy and orthopedic management to prevent contractures as the disease progresses.

Surveillance: Periodic assessment of vision and hearing.

Genetic counseling.

PLA2G6-associated neurodegeneration is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family are known.

GeneReview Scope

PLA2G6-associated Neurodegeneration: Included Phenotypes

- Infantile neuroaxonal dystrophy
- Atypical neuroaxonal dystrophy
- *PLA2G6*-related dystonia-parkinsonism

For synonyms and outdated names see Nomenclature.

Diagnosis

PLA2G6-associated neurodegeneration comprises a continuum of three phenotypes with overlapping clinical and radiologic features:

- Infantile neuroaxonal dystrophy (INAD)
- Atypical neuroaxonal dystrophy [Gregory et al 2008, Kurian et al 2008]
- *PLA2G6*-related dystonia-parkinsonism [Paisán-Ruiz et al 2009]

Infantile Neuroaxonal Dystrophy (INAD)

Predominant features

- Onset before age three years
- Psychomotor regression (most common presenting feature)
- Cerebellar atrophy (see Figure 1)
- Optic atrophy
- Characteristic pattern of early truncal hypotonia followed by development of spastic tetraparesis (usually with hyperreflexia in the early disease stages with progression to areflexia later in the disease course)
- Histopathologic evidence of dystrophic axons on biopsy from one or more of the following tissues: conjunctiva, skin, rectum, muscle, or other peripheral nerve (sural). Dystrophic axons viewed by electron microscopy (EM) exhibit:

- Membranotubular profiles;
- Mitochondrial aggregates;
- Increased axonal diameter and thinned membrane.

Other common features

- Symmetric pyramidal tract signs
- Nystagmus
- Strabismus
- Bulbar dysfunction
- Ataxia
- EMG (electromyogram): evidence of denervation
- EEG (electroencephalogram): fast rhythms
- VEP (visual evoked potential): delayed with reduced amplitudes
- NCV (nerve conduction velocity): distal axonal-type sensorimotor neuropathy
- T_2-weighted MRI of the brain: hypointense globus pallidus (indicating iron accumulation), cortical cerebellar hyperintensities consistent with cerebellar gliosis, white matter abnormalities, thin vertically oriented corpus callosum (see Figure 1), and hypertrophy of the clava [Illingworth et al 2014].
- Seizures that may present early or late in the disease course [Wu et al 2009]

Note: MRI of the brain and ophthalmologic examination are keys to establishing strong clinical features of INAD.

Atypical Neuroaxonal Dystrophy (Atypical NAD)

Predominant features

- Onset before age 20 years
- Psychomotor regression
- Gait abnormalities
- Prominent expressive language difficulties and autistic-like behavior
- Disease progression slower than in classic disease
- Cerebellar atrophy
- Optic atrophy

- Progressive dystonia and dysarthria
- T_2-weighted MRI of the brain: hypointense globus pallidus (indicating iron accumulation)
- Histopathologic evidence of dystrophic axons identical to that described for classic INAD

Other common features

- Psychiatric/behavioral abnormalities
- Spasticity (without preceding hypotonia)
- Joint contractures
- Seizures
- Nystagmus
- VEP: delayed with reduced amplitudes

Note: As with INAD, MRI of the brain and ophthalmologic examination are also keys to establishing the strong clinical features of atypical NAD.

***PLA2G6*-Related Dystonia-Parkinsonism**

Predominant features

- Onset varies from childhood to young adulthood
- Parkinsonism (tremor, bradykinesia, rigidity, and markedly impaired postural responses)
- Dystonia
- Cognitive decline
- Neuropsychiatric changes
- Initial dramatic response to dopaminergic treatment followed by the early development of dyskinesias

Note: Abnormal brain iron accumulation in the globus pallidus, substantia nigra, and/or striatum is variable and may not be evident on MRI studies until late in the disease course for some individuals.

Other common features

- Dysarthria
- Autonomic involvement
- Mild cerebral atrophy

- In some cases, frontotemporal atrophy/hypoperfusion on single-photon emission computed tomography (SPECT)

Testing

Tissue biopsy. Before the availability of molecular genetic testing, identification of dystrophic axons on electron microscopic examination of nerve ultrastructure in a tissue biopsy of conjunctiva, skin, muscle, sural nerve, or rectum was the finding necessary to establish the diagnosis of INAD. Because axonal spheroids accumulate with age and may not be evident in all tissues, individuals with INAD and atypical NAD may require multiple biopsies over time before axonal spheroids are identified. Furthermore, some individuals with convincing INAD phenotypes, including evidence of peripheral spheroids, do not have identifiable *PLA2G6* pathogenic variants. Therefore, molecular genetic testing is now considered the most reliable method of identifying PLAN.

Note: Peripheral spheroids have not been described in pathologic specimens from persons with *PLA2G6*-associated dystonia-parkinsonism; however, limited pathologic material has been available thus far from this group.

Molecular Genetic Testing

Gene. *PLA2G6* is the only gene in which pathogenic variants are known to cause *PLA2G6*-associated neurodegeneration. (See Table 1 and Table A. Genes and Databases.)

Table 1.

Summary of Molecular Genetic Testing Used in *PLA2G6*-Associated Neurodegeneration

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant Detectable by This Method
PLA2G6	Sequence analysis [2]	~85% [3]
	Deletion/duplication analysis [4]	Proposed ≤12.5% [5]
Unknown [6]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein name. See Molecular Genetics for information on allelic variants.

2.

Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

3.
Of all individuals identified with *PLA2G6* pathogenic variants, approximately 10% have only one mutated allele identified [NBIA International Mutation Database, unpublished data]. Large intragenic deletions have now been identified in several cases. Crompton et al [2010] describe the first reported use of multiplex ligation-dependent probe amplification (MLPA) in *PLA2G6* analysis.

4.
Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, MLPA, and chromosomal microarray (CMA) that includes this gene/chromosome segment.

5.
Morgan et al [2006] reported one large contiguous gene deletion (see Molecular Genetics, **Pathogenic allelic variants**).

6.
Linkage data support the presence of at least one additional INAD locus [Morgan et al 2006].

Testing Strategy

The steps to confirm the diagnosis in a proband have been altered by the advent of molecular genetic testing.

INAD or atypical NAD. When the clinician suspects a diagnosis of INAD or atypical NAD, an ophthalmologic examination and brain MRI are recommended first because optic atrophy and cerebellar atrophy are strong clinical features:

- If suspicion remains high, molecular genetic testing by sequence analysis followed by deletion/duplication testing of *PLA2G6* is recommended as the next step instead of an invasive biopsy.
- If no *PLA2G6* pathogenic variants are identified but the evolving phenotype remains most consistent with INAD or atypical NAD, a biopsy to assess for axonal spheroids could be considered. Preferred tissues are, in order: conjunctiva, skin, rectum, other peripheral nerve.

***PLA2G6*-related dystonia-parkinsonism.** When the clinician suspects a diagnosis of *PLA2G6*-related dystonia-parkinsonism, brain MRI is recommended if it has not already been performed. Note: Abnormal brain iron accumulation has been documented in some individuals with

PLA2G6-related dystonia-parkinsonism, but not all [Paisán-Ruiz et al 2009, Yoshino et al 2010, Bower et al 2011].

One genetic testing strategy is molecular genetic testing of *PLA2G6,* the only gene in which pathogenic variants are known to cause *PLA2G6*-related dystonia-parkinsonsim.

An alternative genetic testing strategy is use of a multi-gene panel that includes *PLA2G6* and other genes associated with early-onset dystonia-parkinsonism (see Differential Diagnosis). Note: The genes included and the methods used in multi-gene panels vary by laboratory and over time.

Clinical Characteristics

Clinical Description

Infantile neuroaxonal dystrophy (INAD). Onset of INAD usually occurs between ages six months and three years. The disease presents with psychomotor regression (i.e., loss of previously acquired milestones) or delay, delayed walking, or gait disturbance.

Truncal hypotonia is observed early in disease course. Over time, affected persons develop a spastic tetraparesis, with symmetric pyramidal tract signs on clinical examination.

Visual signs and symptoms are common. Strabismus and nystagmus are early features of the disease. Later optic atrophy occurs in most cases. Optic atrophy may be observed early as optic nerve pallor; thin optic chiasm and tracts have also been reported on brain MRI [Farina et al 1999].

Seizures occur in a minority of individuals as a later symptom [Nardocci et al 1999, Wu et al 2009].

The progression of disease is usually rapid. Many affected children never learn to walk or lose this ability shortly after attaining it. During the end stages of disease, severe spasticity, progressive cognitive decline, and visual impairment result in a vegetative state. Death occurs as a result of secondary illnesses such as aspiration pneumonia, associated with bulbar dysfunction. Many affected children do not survive beyond their first decade, but some survive into their teens or later. Supportive care can contribute to a longer life span by reducing the risk of infection and other complications.

Atypical NAD. Whereas the features of INAD are relatively homogeneous, atypical disease is quite varied.

In general, onset in atypical cases is in early childhood but can be as late as the late teens. In a series of 13 individuals, four had onset by age three years but a fairly stable course during early childhood resembling static encephalopathy, followed by neurologic deterioration between ages seven and 12 years [Nardocci et al 1999].

The presenting signs and symptoms may be similar to classic INAD, including gait instability or ataxia. Others may present with speech delay and autistic features, which may remain as the only evidence of disease for a year or more, given the slow progression of atypical disease compared to classic disease [Gregory et al 2008].

Although spastic tetraparesis is evident late in the disease, it is rarely preceded by early truncal hypotonia. In contrast to classic disease, extrapyramidal findings (i.e., dystonia and dysarthria) predominate in atypical cases. Eye findings are similar to those seen in classic INAD. Neuropsychiatric disturbances including impulsivity, poor attention span, hyperactivity, and emotional lability are also common [Gregory et al 2008].

Atypical cases are rare, and the life span is not known; however, it is expected to be longer than that observed in classic disease.

***PLA2G6*-related dystonia-parkinsonism.** To date, only a small number of affected individuals have been described. Although the age at onset has varied from four to 30 years [Paisán-Ruiz et al 2009, Paisán-Ruiz et al 2010, Yoshino et al 2010, Bower et al 2011, Paisán-Ruiz et al 2012, Virmani et al 2014], the majority have presented in early adulthood (late teens to 20s). Of those with childhood onset, one presented with foot drag and dystonia at age ten years and another with stuttering speech, clumsiness, and dyslexia at age four years – findings which may not be related to the *PLA2G6*-associated neurodegeneration (PLAN). In young adults, initial symptoms are frequently neuropsychiatric, including depression, personality changes, aggression, delusions, or paranoia. Gait disturbance is also common at presentation.

Regardless of the age at onset, affected individuals consistently develop dystonia and parkinsonism (which may be accompanied by rapid cognitive decline) in their late teens to early twenties. Neuropsychiatric changes may precede the movement disorder or occur concomitantly. Dystonia is most common in the hands and feet but may be more generalized. The most common features of parkinsonism in these individuals are bradykinesia, resting tremor, rigidity, and postural instability. Of note, it is common to have an initially dramatic positive response to dopaminergic agents; however, this tends to be short-lived and followed quickly by the development of motor fluctuations and dyskinesias.

Neuropathology. Paisán-Ruiz et al [2012] described the neuropathologic findings in seven people who spanned the three forms of PLAN. Numerous axonal swellings in the basal ganglia and brain stem were observed in individuals with infant-onset and adult-onset PLAN. They were also found in the spinal cord in the two individuals for whom cord tissue was available. Lewy bodies were widespread in both those with adult-onset and those with infantile-onset PLAN. In two affected individuals, one with onset at 18 years and the other only specified as "childhood," the Lewy body pathology was comparable to that seen in severe, end-stage Parkinson disease. Tau pathology, to varying degrees, was also found across the PLAN spectrum.

Genotype-Phenotype Correlations

Genotype correlates with phenotype to a limited extent:

- All individuals with two null alleles of *PLA2G6* have INAD.

- The less severe atypical NAD phenotype is caused almost exclusively by pathogenic missense variants.

- Common pathogenic variants associated with INAD impair the catalytic activity of the PLA2G6 protein, whereas three pathogenic variants associated with *PLA2G6*-related dystonia-parkinsonism did not [Engel et al 2010].

Nomenclature

Outdated terms

- Seitelberger [1952] first described this condition, which was originally named Seitelberger disease.

- Karak syndrome was described in two sibs with early-onset cerebellar ataxia, dystonia, spasticity, and intellectual decline. Brain MRI findings included cerebellar atrophy and iron accumulation in the globus pallidus and substantia nigra [Mubaidin et al 2003]. Morgan et al [2006] identified pathogenic variants in *PLA2G6* in individuals with Karak syndrome, which is now included in the phenotypic spectrum of PLAN and no longer considered a clinically distinct entity; what had been described as Karak syndrome is now referred to as atypical NAD.

Current nomenclature. In addition to INAD, later-onset variants have been called late-infantile, juvenile, or atypical neuroaxonal dystrophy and neurodegeneration with brain iron accumulation (NBIA).

The authors propose the following usage:

- **INAD** for early-onset, rapidly progressive disease

- **Atypical NAD** for later childhood-onset disease with slower progression and predominant extrapyramidal findings (dystonia, dysarthria). The atypical NAD phenotype is expected to include a broad range of presentations including Karak syndrome.

- ***PLA2G6*-related dystonia-parkinsonism** for adult-onset dystonia-parkinsonism accompanied by cognitive decline and neuropsychiatric changes.

Prevalence

Disease prevalence is not established; it is estimated at 1:1,000,000.

Genetically Related (Allelic) Disorders

Though still only speculative, pathogenic variants in *PLA2G6* may underlie Schindler disease as well. This may explain the discordance between the clinical and biochemical phenotypes observed in Schindler disease, which is categorized as a neuroaxonal dystrophy. Schindler disease was originally reported in sibs with early-onset, rapidly progressive psychomotor

regression, evidence of axonal spheroids, and deficiency of α-N-acetylgalactosaminidase (α-NAGA) [Schindler et al 1989]. Alpha-NAGA deficiency underlies the oligosaccharidiuria found in Schindler disease, but its causal role in the neurologic phenotype has been questioned because other persons with α-NAGA deficiency have a spectrum of clinical findings ranging from angiokeratoma to no abnormalities [Keulemans et al 1996, Bakker et al 2001].

The authors have proposed that pathogenic variants in *PLA2G6* account for the early-onset neurodegenerative phenotype that occurs in a subset of individuals with Schindler disease based on their common clinical and pathologic features, their interrelatedness, and the proximity of *PLA2G6* to *NAGA* on chromosome 22 [Westaway et al 2007]. Molecular genetic testing of samples from the original sibs diagnosed with Schindler disease should resolve this question; such samples have not been available.

Differential Diagnosis

Infantile neuroaxonal dystrophy (INAD). Early diagnosis is challenging because the initial symptoms of psychomotor regression and progression are also observed in other conditions.

The degree of weakness early in the disease course may initially direct the clinician toward a myopathy or spinal muscular atrophy.

Cerebellar atrophy can be detected by brain MRI before age two years in some children [Farina et al 1999]. The differential diagnosis for childhood cerebellar atrophy includes infantile neuronal ceroid-lipofuscinosis (Santavuori-Haltia), ataxia-telangiectasia, and hereditary ataxia; however, cerebellar atrophy usually presents later for these disorders.

An estimated 40%-50% of individuals with INAD have abnormal iron accumulation in the basal ganglia (primarily the globus pallidus), which is best detected on T_2-weighted MRI. For this reason, conditions included in the neurodegeneration with brain iron accumulation (NBIA) category should also be considered in the differential diagnosis of INAD. Individuals with INAD have not been found to have an eye-of-the-tiger sign, which correlates very highly with pantothenate kinase-associated neurodegeneration (PKAN) [Hayflick et al 2003].

Since the identification of *PLA2G6* pathogenic variants as causative of INAD, the need for invasive nerve biopsy to aid in diagnosis has decreased. While the presence of axonal spheroids in peripheral tissues remains specific to INAD, spheroids are found in the brain in a few other conditions, including PKAN, idiopathic NBIA, infantile GM2 gangliosidosis (see Hexosaminidase A Deficiency), Niemann-Pick disease type C, and Menkes disease (see *ATP7A*-Related Copper Transport Disorders).

Atypical neuroaxonal dystrophy (NAD). Initial speech delay and limited social interaction may be consistent with autism.

Spasticity, dystonia, and dysarthria, findings similar to those of other forms of NBIA, eventually predominate; high brain iron in the globus pallidus and substantia nigra has been observed in nearly all cases, although ascertainment is likely to be biased [Gregory et al 2008]. Therefore,

idiopathic NBIA should also be considered in the differential diagnosis of atypical NAD. PKAN may present with similar features.

***PLA2G6*-related dystonia-parkinsonism.** When high brain iron is present and pathogenic variants in *PLA2G6* have been ruled out, other forms of NBIA should be considered in the differential diagnosis. Atypical PKAN, Kufor-Rakeb syndrome, and MPAN (mitochondrial membrane protein-associated neurodegeneration) can present with neuropsychiatric changes, parkinsonism, and dystonia in late childhood or early adulthood. As in *PLA2G6*-related dystonia-parkinsonism, individuals with MPAN and Kufor-Rakeb syndrome also exhibit cognitive decline.

Other forms of early-onset dystonia-parkinsonism must also be considered, including dopa-responsive dystonia, Wilson disease, Parkinson disease 2 (PARK2), PARK6, PARK7, PARK15, *SLC6A3*-related dystonia-parkinsonism, dystonia 3 (DYT3), DYT12, DYT16, and spatacsin-related hereditary spastic paraplegia (SPG11) [Schneider & Bhatia 2010].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PLA2G6*-associated neurodegeneration (PLAN), the following evaluations are recommended:

- Thorough ophthalmologic examination (if not performed during the diagnostic evaluation) to assess for optic atrophy
- EEG for the possibility of unrecognized seizure activity
- Clinical genetics consultation

Note: The extent of disease is often well characterized by the time of diagnosis, since the diagnostic work-up frequently includes neurophysiologic studies (EEG, EMG, nerve conduction studies, ERG [electroretinogram], and/or VEP) and brain MRI.

Treatment of Manifestations

The following treatments for **infantile neuroaxonal dystrophy (INAD)** and **atypical NAD** are palliative:

- Pharmacologic treatment of spasticity and seizures
- Trial of oral or intrathecal baclofen for those with atypical INAD who have significant dystonia (see Dystonia Overview)
  - Deep brain stimulation has been successfully utilized in one individual with atypical NAD who had intractable dystonia [Cif et al 2014].
- Treatment by a psychiatrist for those with a later-onset, more protracted course accompanied by neuropsychiatric symptoms

- Over-the-counter fiber supplements and/or stool softeners to treat constipation that is likely caused by a combination of immobility, diet, and medications
- Transdermal scopolamine patch to reduce the volume of secretions in those with excessive drooling or difficulty controlling secretions
- Measures such as a gastric feeding tube or tracheostomy as needed to prevent aspiration pneumonia

Treatments for ***PLA2G6*-related dystonia-parkinsonism** are also palliative but differ somewhat:

- Treatment with dopaminergic agents is likely to be beneficial for the motor symptoms of parkinsonism and dystonia and may initially produce a dramatic response. In cases to date, this response diminished over time, and affected individuals often developed prominent early dyskinesias, complicating medical management. Despite the dyskinesias, treatment with dopaminergic agents may still be indicated, as affected individuals typically experience benefit for a period of time and the dyskinesias are expected to decline after discontinuation of treatment. In one case report, an individual age 32 years with dystonia-parkinsonism developed episodes of non-painful, fixed upward gaze with neck extension that started shortly after levodopa administration and persisted until the drug wore off [Virmani et al 2014]. The use of deep brain stimulation for *PLA2G6*-associated dystonia-parkinsonism has not been reported.
- Treatment by a psychiatrist for neuropsychiatric symptoms is indicated.
- Evaluation by physical therapy may guide the management of postural instability and gait difficulties. Occupational therapy may offer tools to assist with activities of daily living.
- Interventions such as a gastric feeding tube or tracheostomy may be needed to reduce the risk of aspiration pneumonia.

Prevention of Secondary Complications

A rehabilitation program including physical therapy and orthopedic management should be initiated early in the disease course to prevent contractures when the individual is permanently nonambulatory.

Surveillance

Periodic assessment of vision and hearing of nonverbal children is indicated as needed to determine the level of sensory deficits.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Women with the INAD and atypical NAD forms of PLAN have not been known to reproduce due to the relatively early onset and severity of disease.

Two women with *PLA2G6*-related dystonia-parkinsonism have been reported to reproduce [Paisán-Ruiz et al 2010, Virmani et al 2014]. Since onset of manifestations of PLAN has been reported as late as age 30 years, some women may become pregnant before onset of symptoms or early in the disease course. For those who may be symptomatic, the main issue is the potential for teratogenic effects of medications taken during pregnancy. It is not known whether pregnancy itself may have short- or long-term effects on the disease course for the affected pregnant woman.

Therapies Under Investigation

Because some individuals with PLAN have high brain iron and this disorder falls into the category of NBIA, the option of chelation therapy is sometimes raised. The chelator deferiprone is currently under investigation for the PKAN form of NBIA. Results may inform its use in PLAN and/or lead to additional trials.

A proof-of-concept gene therapy strategy is currently under investigation in murine disease models of PLAN [Dr. Manju Kurian, personal communication].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Docosahexaenoic acid (DHA) is selectively hydrolyzed from phospholipids by the action of the iPLA2beta enzyme, the protein encoded by *PLA2G6*. Although not yet tested as an intervention in individuals with PLAN, a *Pla2g6*-mutant mouse model showed reduced DHA metabolism and signaling [Basselin et al 2010]; evidence from a more recent study showed that DHA can reverse selective iPLA2beta inhibition [Mazzocchi-Jones 2015]. Given the low risk of harm from DHA supplementation, the authors recommend its administration at a dose that is age appropriate.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

PLA2G6-associated neurodegeneration (PLAN) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes for a *PLA2G6* pathogenic variant and therefore carry one mutated allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier of a *PLA2G6* pathogenic variant is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- Individuals with infantile neuroaxonal dystrophy (INAD) and atypical NAD have not been known to reproduce.
- All offspring of individuals with later-onset *PLA2G6*-related dystonia-parkinsonism will be obligate (unaffected) carriers.
- If the reproductive partner of a person with *PLA2G6*-related dystonia-parkinsonism is a carrier, the risk to their offspring of being homozygous is 50% and of being heterozygous (unaffected carriers) is 50%. The phenotype of the homozygous offspring within the PLAN spectrum will be influenced by the type of pathogenic variant present in the carrier partner; current data are not sufficient to predict which PLAN phenotype the homozygous offspring will display.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier of a *PLA2G6* pathogenic variant.

Carrier Detection

Carrier testing for at-risk family members is possible if the pathogenic variants in the family are known. The following situations may arise when carrier detection is pursued by at-risk individuals and their reproductive partners:

- **Two *PLA2G6* pathogenic variants are identified in the proband.** In this case, the at-risk family members can be offered testing for the family-specific pathogenic variants to clarify their carrier status.
- **Only one *PLA2G6* pathogenic variant is identified in the proband.** Molecular genetic testing will be informative for relatives of the parent with the identifiable pathogenic variant.

Molecular genetic testing will not be informative for relatives of the carrier parent in whom no pathogenic variant has been identified.

- **Neither pathogenic variant is identified in the proband.** Molecular genetic testing of relatives will not be informative.

- **The proband is deceased, and no DNA-based testing was performed.** It is appropriate to attempt to obtain any available tissue samples for DNA extraction for *PLA2G6* molecular genetic testing. If DNA cannot be obtained, it is appropriate to test at-risk family members following genetic counseling in which the limitations of testing are explained. For those family members in whom a *PLA2G6* pathogenic variant is not identified, a revised carrier risk can be calculated.

- **A person has a reproductive partner who is a known carrier or is at risk of being a carrier.** The reproductive partners of carriers or those at risk of being carriers can be offered molecular genetic testing with the understanding that a negative result can reduce but does not eliminate their risk of being a carrier.

Related Genetic Counseling Issues

Testing of at-risk sibs. The proband may have sibs younger or close in age who could be affected. Although early diagnosis is not likely to significantly reduce morbidity or mortality, testing of at-risk sibs may be desired:

- If both *PLA2G6* pathogenic variants have been identified in the proband, the sibs may be tested to determine if they have inherited both *PLA2G6* pathogenic variants.

- If the *PLA2G6* pathogenic variants have not been identified in the proband, a plan for assessing at-risk sibs should be designed based on the primary findings in the proband and the established clinical criteria for INAD/atypical NAD/*PLA2G6*-related dystonia-darkinsonism. Evaluations are likely to include brain MRI, ophthalmologic assessment, and possibly biopsy for histologic examination of peripheral nerves (see Diagnosis).

Note: Neither the absence of axonal spheroids nor a normal brain MRI rules out INAD or atypical NAD, as these findings develop over time and spheroids vary by location. Diagnostic tests may need to be repeated at a later age for at-risk sibs in families without identified *PLA2G6* pathogenic variants. A normal MRI and absence of other symptoms (including regression) in a sib who is older than the affected sibling was when cerebellar atrophy and/or other symptoms presented is reassuring.

- Predictions of clinical course and age of onset are more challenging in asymptomatic individuals diagnosed with *PLA2G6*-related dystonia-parkinsonism than in individuals with INAD or atypical NAD. Age of onset can vary widely in individuals from the same family; additionally, some of the neuropsychiatric changes that may be present early in disease course (e.g., anxiety or depression) are also common in the general population and thus may not be attributable to the onset of *PLA2G6*-related dystonia-parkinsonism.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once both *PLA2G6* pathogenic variants have been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk for PLAN are possible options.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **NBIA Disorders Association**

2082 Monaco Court

El Cajon CA 92019-4235

Phone: 619-588-2315

Fax: 619-588-4093

Email: info@NBIAdisorders.org

www.nbiadisorders.org

- **eyeGENE - National Ophthalmic Disease Genotyping Network Registry**

Phone: 301-435-3032

Email: eyeGENEinfo@nei.nih.gov

www.nei.nih.gov/eyegene

- **NBIA Disorders Association Research Registry and Treat Iron-Related Childhood-Onset Neurodegeneration (TIRCON) Registry**

CA 92019-4235

Phone: 619-588-2315

Fax: 619-588-4093

Email: pwood@nbiadisorders.org

International Patient Registry & Biomaterial Bank

- **Registry for NBIA and Related Disorders**

Oregon Health & Science University

Phone: 503-494-4344

Fax: 503-494-6886

Email: gregorya@ohsu.edu

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

PLA2G6-Associated Neurodegeneration: Genes and Databases

Gene	Chromosome Locus	Protein	Locus Specific	HGMD
PLA2G6	22q13.1	85/88 kDa calcium-independent phospholipase A2	PLA2G6 @ LOVD	PLA2G6

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

Table B.

OMIM Entries for PLA2G6-Associated Neurodegeneration (View All in OMIM)

256600	NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 2A; NBIA2A

603604 PHOSPHOLIPASE A2, GROUP VI; PLA2G6

610217 NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 2B; NBIA2B

Molecular Genetic Pathogenesis

PLA2G6 encodes 85-kd calcium-independent phospholipase A_2 (iPLA$_2$-VIA). The iPLA$_2$ family of phospholipase A_2 enzymes catalyzes the hydrolysis of glycerophospholipids, generating a free fatty acid (usually arachidonic acid) and a lysophospholipid. The iPLA$_2$-VIA protein has proposed roles in phospholipid remodeling, arachidonic acid release, leukotriene and prostaglandin synthesis, and apoptosis [Balsinde & Balboa 2005]. The iPLA$_2$ enzymes play a critical role in cell membrane homeostasis by helping to regulate levels of phospholipids [Baburina & Jackowski 1999]. Defects in iPLA$_2$-VIA could lead to a relative abundance of membrane phospholipids or skewing of the proportions of specific species and secondary structural abnormalities, which may contribute to the axonal pathology observed in INAD [Morgan et al 2006].

Gene structure. The longest characterized *PLA2G6* transcript (NM_003560.2) has 17 exons that are alternatively spliced to create several transcript variants encoding multiple protein isoforms [Larsson et al 1998]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign allelic variants. No commonly occurring *PLA2G6* benign variants have been identified to date.

Pathogenic allelic variants. The original report of pathogenic variants in *PLA2G6* described 44 unique pathogenic variants: 32 missense variants, five small deletions leading to a frameshift, three nonsense variants, two leading to amino-acid deletions without a frameshift, one splice site variant, and one large deletion [Morgan et al 2006]. Some pathogenic variants have been identified in multiple families reported to be unrelated, although several share ethnic backgrounds [NBIA International Mutation Database, unpublished data]. The large deletion was a contiguous gene deletion involving *PLA2G6* intron 13, the remainder of *PLA2G6*, and extending into exons 1 and 2 of the adjacent putative transcript FLJ22582, now identified as the gene *BAIAP2L2* [Morgan et al 2006].

Normal gene product. The longest transcript (NM_003560.2) encodes a protein of 806 amino acids (NP_003551.2). iPLA$_2$-VIA is one of several calcium-independent phospholipases. The protein is active as a tetramer.

Abnormal gene product. The two enzymatically active isoforms of the protein are predicted to be affected by all of the pathogenic variants reported to date [Morgan et al 2006]. A subset of pathogenic variants would also alter the shorter enzymatically inactive isoforms, which seem to act as dominant-negative inhibitors when incorporated in the tetramer [Larsson et al 1998, Balsinde & Balboa 2005].

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Suggested Reading

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Chapter Notes

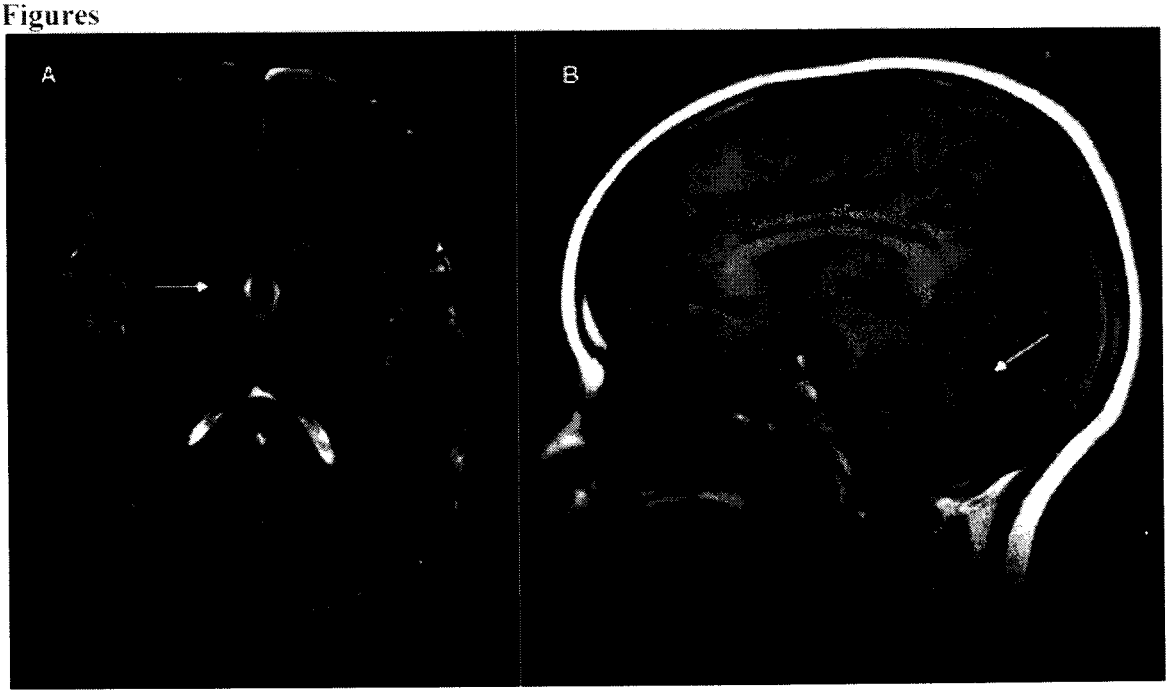
Acknowledgments

This work was supported in part by grants from the National Institute of Child Health and Human Development, the National Eye Institute, L'Association Internationale de Dystrophie Neuro Axonale Infantile, and the NBIA Disorders Association. This work was made possible by support from the Oregon Clinical and Translational Research Institute (OCTRI), grant number UL1 RR024140 01 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research.

Revision History

- 19 March 2015 (ag) Revision: docosahexaenoic acid added as a treatment for PLAN
- 21 August 2014 (me) Comprehensive update posted live
- 19 April 2012 (me) Comprehensive update posted live
- 1 September 2009 (cd) Revision: deletion/duplication analysis available clinically
- 19 June 2008 (me) Review posted live
- 14 June 2007 (ag) Original submission

Figures



A. Left axial image shows high brain iron in the globus pallidus (see arrow) on T_2-weighted MRI. B. Right sagittal image shows cerebellar atrophy (see arrow).

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