European Reference Networks

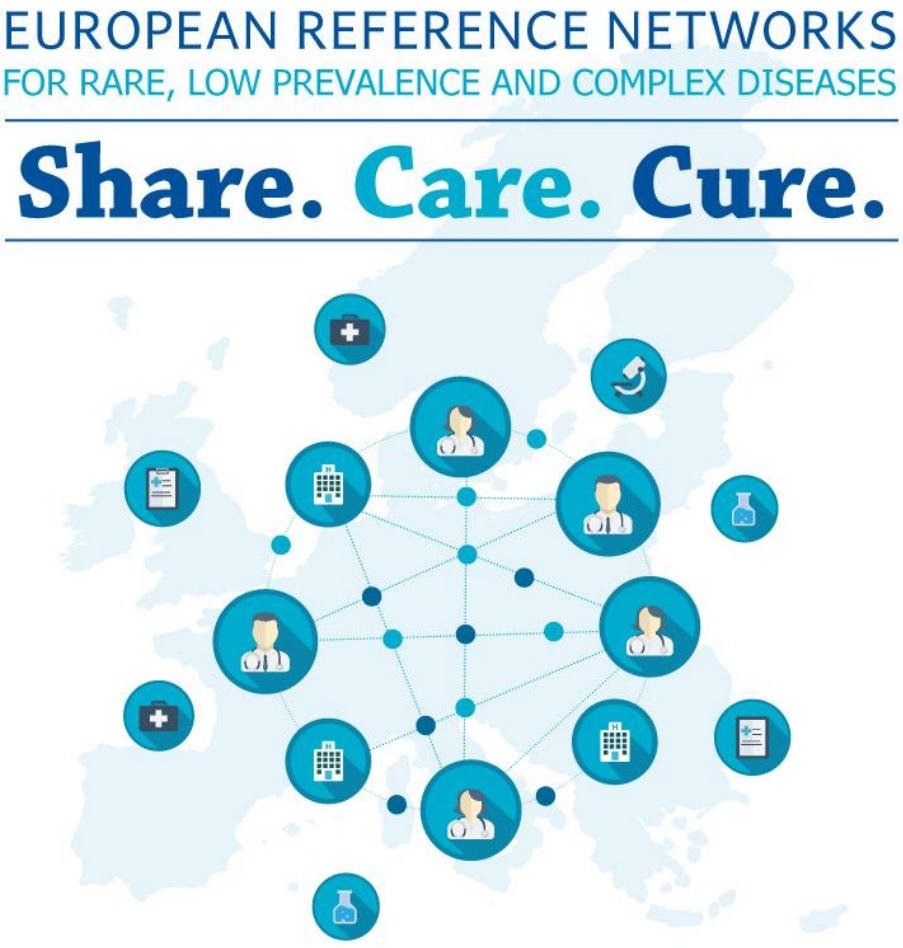
European Reference Network for rare or low prevalence complex diseases

Network: Neurological Diseases (ERN-RND)

Coordinator: Universitätsklinikum Tübingen — Deutschland

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION DISORDERS OVERVIEW

In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews®



Published by ERN-RND: May 2019

Update published: 29 January 2026

Disclaimer:

"The European Commission support for the production of this publication does not constitute endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein."

More information on the European Union is available on the Internet (http://europa.eu).

Luxembourg: Publications Office of the European Union, 2019

INTRODUCTION TO THE EUROPEAN REFERENCE NETWORK FOR RARE NEUROLOGICAL DISEASES (ERN-RND)

ERN-RND is a European Reference Network established and approved by the European Union. ERN-RND is a healthcare infrastructure which focuses on rare neurological diseases (RND). The three main pillars of ERN-RND are (i) network of experts and expertise centres, (ii) generation, pooling and dissemination of RND knowledge, and (iii) implementation of e-health to allow the expertise to travel instead of patients and families.

ERN-RND unites 64 of Europe's leading expert centers as well as 4 affiliated partners in 24 member states and includes highly active patient organizations. Centers are located in Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Slovenia, Spain and Sweden.

The following disease groups are covered by ERN-RND:

- Ataxias and Hereditary Spastic Paraplegias
- Atypical Parkinsonism and Genetic Parkinson's Disease
- Dystonia, Paroxysmal Disorder and Neurodegeneration with Brain Iron Accumulation
- Frontotemporal Dementia
- Huntington's Disease and other Chorea
- Leukoencephalopathies

Specific information about the network, the expert centers and the covered diseases can be found on the network's website ***www.ern-rnd.eu***.

Affirmation of value:
The European Reference Network for Rare Neurological Diseases has affirmed the value of this guideline as best clinical practice for Neurodegeneration with Brain Iron Accumulation (NBIA) Disorders.

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews and other guidance published, endorsed or affirmed by ERN-RND are assessments of current scientific and clinical information provided as an educational service.

The information (1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new information may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgement of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ERN-RND provided this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. ERN-RND specifically disclaims any warranties of merchantability or fitness for a particular use or purpose.

ERN-RND assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

METHODOLOGY

The guideline for Neurodegeneration with Brain Iron Accumulation was endorsed by the Disease Group for Dystonia, Paroxysmal Disorders and NBIA of ERN-RND after revision of an earlier endorsement of the consensus guideline for treatment of Pantothenate Kinase Associated Neurodegeneration (PKAN) and as per anonymous majority voting

Disease group for Dystonia, Paroxysmal Disorders and NBIA:

Disease group coordinators:

Javier Perez Sanchez[15]; Sylvia Boesch[26]

Disease group members:

Health care professionals:

Mette Møller[1]; Erik Johnsen[1]; Erik Hvid Danielsen[1]; Laura van de Pol[2]; Anna De Rosa[3]; Myriam Carecchio[4]; Roberto Ceravolo[5]; Elisa Unti[5]; Giovanni Palermo[5]; Andrea Mignarri[6]; Antonio Federico[6]; Marie Vidailhet[7]; Aurelie Meneret[7]; Marta Blázquez Estrada[8]; Pierre Kolber[9]; Giorgos Pitsas[10]; Christos Koros[11]; Evangelos Anagnostou[11]; Leonidas Stefanis[11]; Heli Helander[13]; Jiri Klempir[14]; Sára Davisonová[14]; Francisco Grandas[15]; Dirk Dressler[16]; Alejandra Darling[17]; Juan Dario Ortigoza Escobar[17]; Eugenia Amato[17]; Maria Jose Marti[17]; Yaroslau Compta[17]; Marta Skowronska[18]; Michal Sobstyl[18]; Antonio Elia[19]; Giovanna Zorzi[19]; Roberto Cilia[19]; Roberto Eleopra[19]; Alberto Albanese[20]; Giulia Giannini[21]; Luca Solina[21]; Duccio Maria Cordelli[21]; Caterina Garone[21]; Veronica Di Pisa[21]; Anna Fetta[21]; Richard Walsh[22]; Kathleen Gorman[22]; Aoife Mahony[22]; Ana Rodríguez[23]; Soledad Serrano[23]; Franziska Höpfner[24]; Thomas Klopstock[24]; Jeroen Vermeulen[25]; Philipp Mahlknecht[26]; Daniel Boesch[26]; Wolfgang Nachbauer[26]; Krista Ladzdovska[27]; Ramona Valante[27]; Elina Pucite[27]; Enrico Bertini[28]; Francesco Nicita[28]; Giacomo Garone28; Bart Post[29]; Michèl Willemsen[29]; Anke Snijders[29]; Manuel Dafotakis[30]; Rocío García-Ramos[31]; Maria Judit Molnar[32]; Marek Baláž[33]; Martina Bočková[33]; Ognyana Burgazlieva[34]; Andras Salamon[35]; Aive Liigant[36]; Pawel Tacik[37]; Fran Borovecki[38]; Ivana Jurjevic[38]; Malgorazate Dec-Cwiek[39]; Katarzyna Sawczynska[39]; Alexander Münchau[40]; Katja Lohmann[40]; Norbert Brüggemann[40]; Sebastian Löns[40]; Tobias Bäumer[40]; Ebba Lohmann[41]; Kathrin Grundmann[41]; Thomas Gasser[41]; Hendrik Rosewich[41]; Bernhard Landwehrmeier[42]; Thomas Musacchio[43]; Martin Reich[43]; Marina de Koning-Tijssen[44]; Tom de Koning[44]; Damjan Osredkar[45]; Maja Kojovic[45]; Kinga Hadzsiev[46]; Norbert Kovacs[46]; Belén Pérez Dueñas[47]; Maria Victoria Gonzalez Martinez[47]; Silvia Jesús Maestre[48]; Astrid Daniela Adarmes[48]; Pablo Mir[48]; Elena Ojeda Lepe[48]; Marta Correa[48]

Patient representative:

Monika Benson[12]

[1]Aarhus University Hospital, Denmark; [2]Amsterdam UMC - Amsterdam University Medical Center, Netherlands; [3]AOU - Federico II University Hospital, Naples, Italy; [4]AOU - University Hospital Padua, Italy; [5]AOU - University Hospital Pisa, Italy; [6]AOU - University Hospital Siena, Italy; [7]APHP - Reference Centre for Rare Diseases 'Neurogenetics', Pitié-Salpêtrière Hospital, Paris, France; [8]Asturias Central University Hospital, Oviedo, Spain; [9]CHL - Luxembourg Hospital Center, Luxembourg; [10]Cyprus Institute of Neurology and Genetics, Egkomi, Cyprus; [11]Eginitio Hospital, National and Kapodistrian University of Athens, Greece; [12]ePAG representative; [13]Finland Consortium: University Hospitals in Oulu, Tampere and Helsinki, Finland; [14]General University Hospital Prague, Czech Republic; [15]Gregorio Marañón General University Hospital, Madrid, Spain; [16]Hannover Medical School, Germany; [17]Hospital Clinic Barcelona and Sant Joan de Déu Hospital, Barcelona, Spain; [18]Institute of Psychiatry and Neurology, Warsaw, Poland; [19]IRCCS - Foundation of the Carlo Besta Neurological Institute, Milan, Italy; [20]IRCCS - Humanitas Clinical Institute of Rozzano, Milan, Italy; [21]IRCCS - Institute of Neurological Sciences of Bologna, Italy; [22]Irish Consortium: Tallaght University Hospital and Children's Health Ireland; [23]La Paz University Hospital, Madrid, Spain; [24]Ludwig Maximilian University Hospital, Munich, Germany; [25]Maastricht University Medical Center, Netherlands; [26]Medical University Innsbruck, Austria; [27]Pauls Stradins Clinical University Hospital, Riga, Latvia; [28]Pediatric Hospital Bambino Gesù, Rome, Italy; [29]Radboud University Medical Centre, Nijmegen, Netherlands; [30]RWTH - University Hospital Aachen, Germany; [31]San Carlos Clinical Hospital, Madrid, Spain; [32]Semmelweis University, Budapest, Hungary; [33]St. Anne´s University Hospital Brno, Czech Republic; [34]St. Naum University Neurological Hospital, Sofia, Bulgaria; [35]Szent-Györgyi Albert Medical Center, Szeged, Hungary; [36]Tartu University Hospital, Estonia; [37]University Hospital Bonn, Germany; [38]University Hospital Center Zagreb, Croatia; [39]University Hospital in Krakow, Poland; [40]University Hospital Schleswig-Holstein, Lübeck, Germany; [41]University Hospital Tübingen, Germany; [42]University Hospital Ulm, Germany; [43]University Hospital Würzburg, Germany; [44]University Medical Center Groningen, Netherlands; [45]University Medical Centre Ljubljana, Slovenia; [46]University of Pécs, Hungary; [47]Vall d'Hebron University Hospital, Barcelona, Spain; [48]Virgen del Rocio University Hospital, Sevilla, Spain

Endorsement process:

- Consent on *Consensus clinical management guideline for Pantothenate Kinase-Associated Neurodegeneration (PKAN)* as best clinical practice by whole disease group: May 2019
- Revision of guideline document: October 2024 – October 2025
- Endorsement of *Neurodegeneration with Brain Iron Accumulation Disorders Overview* by whole disease group: 27 October 2025
- Publication of updated document: 29 January 2026

REFERENCE

Gregory A, Kurian MA, Wilson J, et al. **Neurodegeneration with Brain Iron Accumulation Disorders Overview.** 2013 Feb 28 [Updated 2025 Mar 6]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026.

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION DISORDERS OVERVIEW

Source: http://www.genereviews.org/

Link to publication: https://www.ncbi.nlm.nih.gov/books/NBK121988/pdf/Bookshelf_NBK121988.pdf

U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Gregory A, Kurian MA, Wilson J, et al. Neurodegeneration with Brain Iron Accumulation Disorders Overview. 2013 Feb 28 [Updated 2025 Mar 6]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Neurodegeneration with Brain Iron Accumulation Disorders Overview

Allison Gregory, MS, CGC,[1] Manju A Kurian, MA, MBBChir, PhD,[2] Jenny Wilson, MD,[1] and Susan Hayflick, MD[1]

Created: February 28, 2013; Updated: March 6, 2025.

Summary

The purpose of this overview is to:

1. Briefly describe the clinical characteristics of neurodegeneration with brain iron accumulation (NBIA);
2. Review the genetic causes of NBIA;
3. Review the differential diagnosis of NBIA with a focus on genetic conditions;
4. Provide an evaluation strategy to identify the genetic cause of NBIA in a proband (when possible);
5. Review high-level management of NBIA;
6. Inform genetic counseling of family members of an individual with NBIA.

1. Clinical Characteristics of Neurodegeneration with Brain Iron Accumulation

Neurodegeneration with brain iron accumulation (NBIA) disorders are a group of inherited neurologic disorders characterized by abnormal accumulation of iron in the basal ganglia (most often in the globus pallidus and/or substantia nigra).

Additional brain abnormalities such as generalized cerebral atrophy and cerebellar atrophy are frequently observed.

The hallmark clinical manifestations of NBIA vary by genetic subtype and generally include progressive dystonia, dysarthria, spasticity, parkinsonism, neuropsychiatric abnormalities, and optic atrophy or retinal degeneration. Cognitive decline occurs in some types.

Onset ranges from infancy to adulthood. Progression can be rapid or slow with long periods of stability. In general, the early-onset forms tend to progress more rapidly than late-onset, protracted forms of NBIA.

Author Affiliations: 1 Oregon Health & Science University Portland, Oregon; Email: gregorya@ohsu.edu; Email: wilsjen@ohsu.edu; Email: hayflick@ohsu.edu. 2 UCL Great Ormond Street Institute of Child Health, London, United Kingdom; Email: manju.kurian@ucl.ac.uk.

The distinctive clinical and neuroimaging findings of the 11 genetically defined NBIA types are summarized in Table 1 and Table 2, respectively.

Table 1. Neurodegeneration with Brain Iron Accumulation Disorders: Clinical Characteristics by Genetic Type

NBIA Genetic Type		Onset	Typical Presentation	Other Key Clinical Manifestations
PKAN	Classic PKAN	Early (w/rapid progression)	Gait abnormalities at age ~2-3 yrs, speech delay, clumsiness / poor balance	• Progressive generalized dystonia w/prominent bulbar/ oromandibular involvement, dysarthria, rigidity, spasticity, hyperreflexia, & striatal toe signs • Retinal degeneration is common & may be detected by ERG several yrs before onset of visual symptoms. • Neuropsychiatric symptoms (more frequent in later-onset form)
	Atypical PKAN	Age >10 yrs (w/ slower progression)	Dysarthria, balance &/or gait change	
PLAN (Parkinson disease 14; PARK14)	Infantile PLAN (INAD)	Age 6 mos to 2 yrs	Developmental regression, initial hypotonia, progressive psychomotor delay, & progressive spastic tetraparesis	• Progressive cognitive decline • Strabismus, nystagmus, & optic atrophy • Rapid disease progression
	Juvenile PLAN [1]	Childhood or, more rarely, adolescence	Gait instability, ataxia, speech delay, & autistic features	• Neuropsychiatric changes • Dystonia & spastic tetraparesis • Cognitive decline • Slower progression
	Adult PLAN	Early adulthood	Gait disturbance &/or neuropsychiatric changes	• Marked cognitive decline • Subacute onset of dystonia-parkinsonism • Eye movement abnormalities • Pyramidal tract signs
MPAN [2]		Childhood to early adulthood	• Children: gait abnormalities, limb spasticity, & optic atrophy • Adults: gait abnormalities & acute neuropsychiatric changes	• Progressive cognitive decline in most persons • Neuropsychiatric changes • Spasticity (more prominent than dystonia), motor neuronopathy w/ early upper motor neuron findings followed by signs of lower motor neuron dysfunction • Optic atrophy • Slowly progressive course w/ survival well into adulthood
BPAN		Infancy to childhood	Global delays w/slow motor & cognitive gains, little to no expressive language, & seizures	• Seizures of various types are more prominent in childhood & may resolve in later adolescence. • Autistic features • Stereotypies • Hyperphagia • Premature adrenarche • Motor dysfunction incl broad-based or ataxic gait, hypotonia, mild spasticity • Relatively sudden onset of progressive parkinsonism & dementia during late adolescence or adulthood

Table 1. continued from previous page.

NBIA Genetic Type	Onset	Typical Presentation	Other Key Clinical Manifestations
FAHN	Childhood	Subtle change in gait that may lead to increasingly frequent falls.	• Slowly progressive ataxia, dysarthria, dystonia, & tetraparesis • Optic atrophy leading to progressive loss of visual acuity • Seizures during later stages of disease • Progressive cognitive decline in most affected persons
Kufor-Rakeb syndrome [3] (Parkinson disease 9; PARK9)	Juvenile	Gait abnormalities & neuropsychiatric changes	• Parkinsonism • Dementia • Supranuclear gaze palsy • Facial-faucial-finger myoclonus • Visual hallucinations • Oculogyric dystonic spasms [4]
FTL-assoc neuroferritinopathy [5]	Adult	May be similar to Huntington disease w/chorea or dystonia & cognitive changes	• Progresses from extremity involvement to more generalized movement disorder • Characteristic orofacial action-specific dystonia related to speech
FTH1-assoc neuroferritinopathy [6]	Childhood	Microcephaly, global delays, & feeding difficulties	• Limited speech, intellectual disability • Progressive spasticity • Dystonia, dysphagia • Seizures
Aceruloplasminemia	Adult (age 25-60 yrs)	Clinical triad of retinal degeneration, diabetes mellitus, & neurologic disease	• Facial & neck dystonia, dysarthria, tremors, chorea, ataxia, & blepharospasm • ↓ serum concentrations of copper & iron & ↑ serum concentrations of ferritin can distinguish aceruloplasminemia from other forms of NBIA.
Woodhouse-Sakati syndrome (Hypogonadism, alopecia, diabetes mellitus, intellectual disability & extrapyramidal syndrome) [7]	Childhood	• Alopecia may be earliest symptom. • Intellectual disability & delayed puberty	• Progressive extrapyramidal disorder, generalized & focal dystonia, dysarthria, & cognitive decline • Endocrine abnormalities (hypogonadism, alopecia, & diabetes mellitus)

Table 1. continued from previous page.

NBIA Genetic Type	Onset	Typical Presentation	Other Key Clinical Manifestations
CoPAN [8]	Childhood	Childhood-onset dystonia & spasticity w/cognitive impairment	• Oromandibular dystonia, dysarthria, axonal neuropathy, parkinsonism, cognitive impairment, & obsessive-compulsive behavior • Slow progression; nonambulatory in 3rd decade

BPAN = beta-propeller protein-associated neurodegeneration; CoPAN = COASY protein-associated neurodegeneration; ERG = electroretinography; FAHN = fatty acid hydroxylase-associated neurodegeneration; INAD = infantile neuroaxonal dystrophy; MPAN = mitochondrial membrane protein-associated neurodegeneration; NAD = neuroaxonal dystrophy; PKAN = pantothenate kinase-associated neurodegeneration; PLAN = *PLA2G6*-associated neurodegeneration

1. Juvenile PLAN is less common than the infantile form (INAD).

2. A common *C19orf12* founder variant (NM_001031726.3:c.204_214del11 [p.Gly69ArgfsTer10]) has been observed in persons of central European descent (mainly Polish).

3. Proposed to be an NBIA disorder based on findings described by Schneider et al [2010] in a family originally reported in 1994

4. Williams et al [2005]

5. A common *FTL* pathogenic variant in exon 4 has been found in approximately 80% of affected individuals.

6. The *FTH1*-associated neuroferritinopathy phenotype will continue to evolve as additional affected individuals are recognized.

7. A founder pathogenic variant in *DCAF17* accounts for the cases in the Saudi Arabian population.

8. The CoPAN phenotype will continue to evolve as additional affected individuals are recognized.

Table 2. Neurodegeneration with Brain Iron Accumulation Disorders: Neuroimaging Findings by Genetic Type

NBIA Genetic Type	Neuroimaging Findings [1]	
	Pattern of iron distribution	Other key radiographic features
PKAN	GP, SN (GP iron > SN iron usually)	Eye of the tiger sign [2] in GP (virtually pathognomonic for PKAN [3])
PLAN (Parkinson disease 14; PARK14)	Variable GP & SN; usually develops in all 3 forms w/time	Cerebellar atrophy & optic atrophy are hallmark features; other features incl cortical cerebellar hyperintensities, cortical atrophy, thin vertically oriented corpus callosum, & apparent hypertrophy of the clava.
MPAN	GP, SN	Cerebellar & cortical atrophy; on T_2-weighted images hyperintense streaking of medial medullary lamina between GP interna & externa that could be mistaken for eye-of-the-tiger sign
BPAN	GP, SN (SN iron > GP iron)	Early childhood hypomyelination & thin corpus callosum; later development of T_2-weighted signal hypointensity in SN & GP & T_1-weighted signal hyperintensity w/central band of hypointensity in SN; cerebellar & cerebral atrophy may also be present at any age
FAHN	GP, SN	Pontocerebellar atrophy, diffuse cerebral atrophy, thinning of corpus callosum, periventricular & subcortical white matter hyperintensity on T_2-weighted images & optic atrophy
Kufor-Rakeb syndrome (Parkinson disease 9; PARK9)	Variable GP, putamen, caudate, or no iron accumulation [4]	Cerebral, cerebellar, & brain stem atrophy

Table 2. continued from previous page.

NBIA Genetic Type	Neuroimaging Findings [1]	
	Pattern of iron distribution	Other key radiographic features
FTL-assoc neuroferritinopathy	GP, putamen, caudate, dentate, SN, & RN	Cystic changes & cavitation in caudate & putamen (unique to neuroferritinopathy); mild cortical & cerebellar atrophy, cortical "pencil lining" that reflects iron deposition in periphery of cortex and & gray matter structures may be observed.
FTH1-assoc neuroferritinopathy	Variable in structures of BG & thalamus	Cerebellar hypoplasia & selective cerebellar atrophy of vermis, thin corpus callosum, & white matter loss; eye of the tiger sign similar to PKAN reported in 1 case; pontocerebellar hypoplasia w/figure eight appearance on axial plane & hot cross bun sign in another case
Aceruloplasminemia	GP, putamen, caudate, thalamus, RN, & dentate [5]	Cerebellar atrophy
Woodhouse-Sakati syndrome (Hypogonadism, alopecia, diabetes mellitus, intellectual disability, & extrapyramidal syndrome)	GP	White matter disease is common.
CoPAN	GP, SN	T_2-weighted images: hyperintense caudate, putamina, & medial & posterior thalami in early disease; [6] GP calcifications

BG = basal ganglia; BPAN = beta-propeller protein-associated neurodegeneration; CoPAN = COASY protein-associated neurodegeneration; FAHN = fatty acid hydroxylase-associated neurodegeneration; GP = globus pallidus; MPAN = mitochondrial membrane protein-associated neurodegeneration; PKAN = pantothenate kinase-associated neurodegeneration; PLAN = *PLA2G6*-associated neurodegeneration; RN = red nucleus; SN = substantia nigra

1. For a more comprehensive overview of the radiographic findings in NBIA disorders, see Lee et al [2020].

2. The eye of the tiger sign is a T_2-weighted hypointense signal in the globus pallidus with a central region of hyperintensity.

3. Hayflick et al [2003]

4. Similar to *PLA2G6*-associated neurodegeneration (PLAN), it has been suggested that some individuals may not have iron accumulation, it may develop late in the disease course, or it may only be associated with more severe pathogenic variants [Chien et al 2011].

5. Abnormal hypointensities in the liver are common (liver iron content > basal ganglia iron content).

6. In one individual early in the disease course, T_2-weighted sequences showed hyperintense and swollen caudate nuclei and putamen and mild hyperintensity in the medial and posterior thalami, which may help distinguish CoPAN from other NBIA disorders if these features are observed in additional cases.

Diagnosis of Neurodegeneration with Brain Iron Accumulation

NBIA can be diagnosed in individuals with suggestive clinical features as well as characteristic neuroimaging findings.

Note: The quality of the neuroimaging, including magnet strength and spacing of image slices, can limit the ability to accurately identify abnormal brain iron accumulation. Iron-sensitive sequences, such as SWI, GRE, and T_2, should be used as a first-line diagnostic investigation to identify the characteristic changes in NBIA disorders. By the time clear neurologic features are present, the brain MRI almost always shows characteristic changes, although iron may be visible only later in the disease course.

Neuropathologic findings may include basal ganglia iron accumulation or axonal spheroids in the central nervous system (both identified postmortem) and, in some types, in peripheral nerves that can be identified with a biopsy as part of the diagnostic workup.

2. Genetic Causes of Neurodegeneration with Brain Iron Accumulation

The 11 genes known to be associated with types of neurodegeneration with brain iron accumulation (NBIA) are *ATP13A2*, *C19orf12*, *COASY*, *CP*, *DCAF17*, *FA2H*, *FTH1*, *FTL*, *PANK2*, *PLA2G6*, and *WDR45* [Hayflick 2023] (see Table 3). The clinical findings associated with these genes include abnormal iron accumulation confirmed with brain autopsy.

Table 3. Neurodegeneration with Brain Iron Accumulation: Genetic Types

Gene [1]	NBIA Genetic Type	MOI	% of All NBIA Disorders
ATP13A2	Kufor-Rakeb syndrome (OMIM 606693)	AR	Rare [2]
C19orf12	Mitochondrial membrane protein-associated neurodegeneration (MPAN)	AR, AD [3]	5%-10% [4]
COASY	COASY protein-associated neurodegeneration [5] (CoPAN) (OMIM 615643)	AR	Rare [5]
CP	Aceruloplasminemia	AR	Rare
DCAF17	Woodhouse-Sakati syndrome	AR	Rare [6]
FA2H	Fatty acid hydroxylase-associated neurodegeneration (FAHN)	AR	Rare [7]
FTH1	*FTH1*-associated neuroferritinopathy	AD	Rare [8]
FTL	*FTL*-associated neuroferritinopathy	AD	Rare
PANK2	Pantothenate kinase-associated neurodegeneration (PKAN)	AR	30%-35% [4]
PLA2G6	*PLA2G6*-associated neurodegeneration (PLAN)	AR	10%-15% [4]
WDR45	Beta-propeller protein-associated neurodegeneration (BPAN)	XL	40%-45% [4]

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Genes are listed alphabetically.

2. Pathogenic variants in *ATP13A2* were identified in the family originally reported with Kufor-Rakeb syndrome and a handful of other individuals worldwide [Behrens et al 2010, Brüggemann et al 2010, Schneider et al 2010, Chien et al 2011, Eiberg et al 2012].

3. Autosomal dominant inheritance and *de novo* dominant pathogenic sequence variants have been reported in some families [Gregory et al 2019].

4. Based on prevalence in the International Registry for NBIA and Related Disorders from the Hayflick laboratory

5. Dusi et al [2014], Annesi et al [2016], Evers et al [2017]

6. Described in a few case reports and one larger series of 12 families [Al-Semari & Bohlega 2007]

7. First reported as an NBIA disorder by Kruer et al [2010]; fewer than 15 families documented in various case reports

8. Shieh et al [2023]

NBIA of unknown cause. A significant portion of individuals with clinical, radiographic, and sometimes neuropathologic evidence of NBIA do not have pathogenic variants identified in one of the 11 known NBIA-related genes [Hogarth et al 2013] (see Figure 1). For the most part, these individuals do not stratify into clear phenotypic groups.

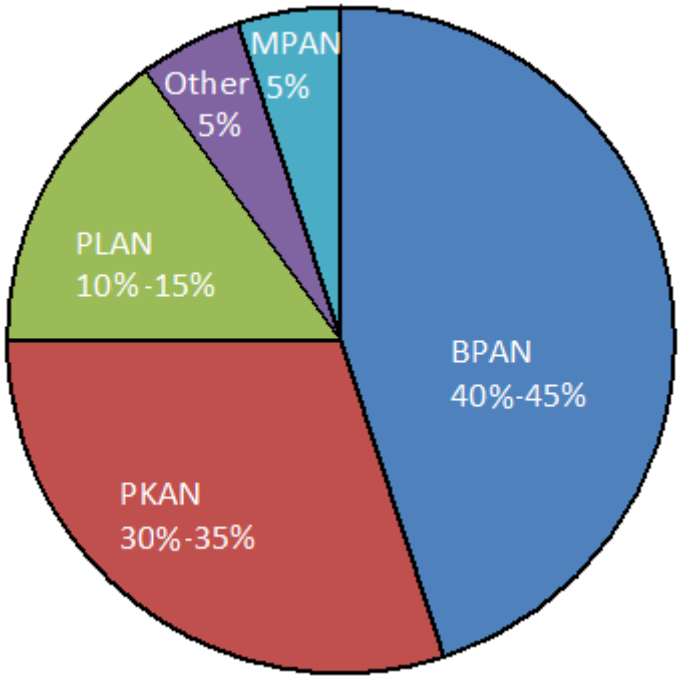


Figure 1. Neurodegeneration with brain iron accumulation types

BPAN = beta-propeller protein-associated neurodegeneration

PKAN = pantothenate kinase-associated neurodegeneration

PLAN = *PLA2G6*-associated neurodegeneration

MPAN = mitochondrial membrane protein-associated neurodegeneration

Minor forms include those associated with pathogenic variants in *ATP13A2*, *FA2H*, *FTH1*, *FTL*, *CP*, and *DCAF17*. Frequencies are based on 850 families worldwide collected over 25 years in a repository of neurodegeneration with brain iron accumulation.

3. Differential Diagnosis of Neurodegeneration with Brain Iron Accumulation

The differential diagnosis of neurodegeneration with brain iron accumulation (NBIA) is usually based on a brain MRI that raises the suspicion of abnormal iron accumulation (see Table 4).

Table 4. Conditions with Brain MRI Findings or Clinical Findings that Resemble Neurodegeneration with Brain Iron Accumulation

Neuroimaging Findings	Clinical Findings Overlapping NBIA Disorders	Disorders	Gene(s)
T_2-weighted hyperintensity in GP reminiscent of early PKAN [1]	Poor temperature regulation, muscle wasting	Fucosidosis (OMIM 230000)	*FUC1A*
	Psychomotor regression, complex movement disorder	Glutaric acidemia type 1	*GCDH*
	Psychomotor regression, spasticity, movement disorders	Leigh encephalopathy (See Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview & Mitochondrial DNA-Associated Leigh Syndrome Spectrum.)	15 mitochondrial genes; ~100 nuclear genes
	Dystonia, spasticity	Primary pyruvate dehydrogenase complex deficiency	7 genes incl: *DLAT* *DLD* *PDHA1* *PDHB* *PDHX*
T_2-weighted & SWI hypointensity in GP ± SN, thin splenium of corpus callosum	Hypotonia, developmental delay, seizures, progressive lower extremity weakness & spasticity	AP-4-Associated Hereditary Spastic Paraplegia	*AP4M1* *AP4S1*
T_2-weighted & SWI hypointensity in GP, SN, RN, & dentate; cerebral & cerebellar volume loss	Childhood- or adolescent-onset progressive weakness, respiratory insufficiency, fatigability, joint hyperlaxity, ↑ CK	Multiple mitochondrial dysfunctions syndrome 10	*CIAO1*
Cerebellar atrophy, thin corpus callosum, T_2-weighted hypointense GP & SN	Speech delay, gait change, slowly progressive cerebellar ataxia	*CRAT*-associated disease [2]	*CRAT*
Cerebellar hypoplasia & atrophy		Jaberi-Elahi syndrome (OMIM 617988)	*GTPBP2*
Cerebellar & cerebral atrophy, thin corpus callosum	Optic atrophy, lower extremity spasticity	Spastic paraplegia 30; hereditary sensory & autonomic neuropathy type IIC	*KIF1A*
T_2-weighted hypointense lateral streaks in external GP in affected children	Childhood-onset dystonia; prominent cervical, cranial, & laryngeal dystonia	*KMT2B*-related dystonia	*KMT2B*
Iron accumulation in BG (case report)	Early-onset dystonia-parkinsonism	Early-onset dystonia-parkinsonism [3]	*PSEN1*
T_2-weighted hypointense GP & peduncles, progressive cerebellar & cerebral atrophy	Progressive dystonia, dysarthria, spasticity, nystagmus	*REPS1*-associated disease [2]	*REPS1*
Susceptibility-weighted signal hypointensity GP & SN	Adult-onset gait change & ↑ tone	Sterol carrier protein 2 deficiency (OMIM 613724)	*SCP2*
T_2-weighted hypointensity of GP & striatum that is hyperintense on T_1-weighted imaging	Childhood-onset dystonia & spasticity	*SLC39A14*-related early-onset dystonia-parkinsonism (SLC39A14 deficiency)	*SLC39A14*

Table 4. continued from previous page.

Neuroimaging Findings	Clinical Findings Overlapping NBIA Disorders	Disorders	Gene(s)
T_2-weighted hypointensity of GP, mild cerebellar atrophy, childhood onset	Childhood onset of ataxia, dystonia, & gaze palsy	Neurodegeneration w/ataxia, dystonia, & gaze palsy, childhood onset (OMIM 617145)	*SQSTM1*
Cerebellar atrophy, thinning of corpus callosum	Dysarthria, gait change	*UBTF*-related neuroregression (OMIM 617672)	*UBTF*
T_2-weighted hypointensity of SN, hyperintensity of striatum	Progressive dystonia, dysarthria	Striatonigral degeneration, childhood onset [4]	*VAC14*
T_2-weighted signal ↑ in caudate & putamen, mild generalized cerebral cortical atrophy, striatal necrosis	Acanthocytes, oral dystonia	VPS13A disease (choreoacanthocytosis)	*VPS13A*

BG = basal ganglia; CK = creatine kinase; GP = globus pallidus; RN = red nucleus; SN = substantia nigra
1. Mohammad et al [2020] provides an excellent overview of MRI pattern recognition in childhood basal ganglia disorders, many of which have findings that overlap with NBIA disorders.
2. Drecourt et al [2018]
3. Carecchio et al [2017]
4. Lenk et al [2016]

4. Evaluation Strategies to Identify the Genetic Cause of Neurodegeneration with Brain Iron Accumulation in a Proband

Establishing a specific genetic cause of neurodegeneration with brain iron accumulation (NBIA):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*), genetic counseling, and treatment options;
- Usually involves a medical history, physical examination, family history, laboratory testing, and genomic/genetic testing.

Medical history. See Table 1 for clinical characteristics and Table 2 for neuroimaging findings that could lead a clinician to suspect or consider a specific genetic type of NBIA disorder.

Physical examination. See Table 1 for clinical characteristics that could help the clinician identify key issues in the physical examination that would cause suspicion and/or consideration of a specific genetic type of NBIA disorder.

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of NBIA and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

Molecular genetic testing approaches can include a combination of gene-targeted testing (single-gene testing, multigene panel) and comprehensive genomic testing (exome sequencing, whole genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **A multigene panel** that includes some or all of the genes listed in Table 3 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are

likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

- **Single-gene testing** (sequence analysis of one gene, followed by gene-targeted deletion/duplication analysis) is useful when the neuroimaging and/or phenotype clearly point toward one NBIA-related disorder. For example, an eye of the tiger sign on brain MRI is nearly pathognomonic for pantothenate kinase-associated neurodegeneration (PKAN) caused by biallelic *PANK2* pathogenic variants.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered when clinical/neuroimaging findings have not suggested NBIA. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: For individuals in whom a genetic cause of NBIA cannot be established, participation in research studies may be considered as new technologies may facilitate identification of additional NBIA-related genes in the future (see Resources).

5. Management of Neurodegeneration with Brain Iron Accumulation

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a neurodegeneration with brain iron accumulation (NBIA) disorder, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 5. Neurodegeneration with Brain Iron Accumulation Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• Consider EEG for clinical seizures or movements suspected to be seizures. • Neuromotor eval (tone, hyper- or hypokinetic movement disorder, balance, & gait) • Consider referral to PT, OT, orthopedics, &/or PM&R. • Assess swallowing & nutritional status; consider referral for swallow study or feeding specialist. • Assess communication (e.g., dysarthria); consider referral to SLP or AAC specialist. • Assess quality of sleep; consider referral for sleep study.
Development (children)	Developmental assessment	• To incl motor, adaptive, cognitive, & communication • Based on diagnosis, assess for autistic features (e.g., stereotypies), ADHD, anxiety, & other behaviors like abnormal breathing patterns.
Neurobehavioral/ Psychiatric	Psychiatric eval	Usually referred for specific concerns, incl OCD, anxiety, ADHD, autistic features, depression / flat affect, agitation, behavioral challenges, signs of psychosis, &/or other psychiatric issues

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Orthopedics / PM&R / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, spinal abnormalities, hip abnormalities • Mobility, ADL, & need for adaptive devices • Need for PT &/or OT
Eyes	Ophthalmology eval	To assess for optic atrophy, retinal disease, refractive errors, reduced vision, abnormal ocular movement, best corrected visual acuity, & more complex findings that may require referral for subspecialty care &/or low vision services
Ears/Hearing	Hearing eval	Screening eval with follow up as indicated given that some NBIA disorders can involve hearing loss
Endocrine	Endocrinology eval	• Only for those NBIA disorders w/known endocrine abnormalities or if there are indicators of an abnormality such as signs of premature puberty &/or advanced bone age • Persons w/Woodhouse-Sakati syndrome will require more frequent screening. • Persons w/aceruloplasminemia should include screening for diabetes mellitus.
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of NBIA disorders to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as NBIA Disorders Association • Social work involvement for parental support • Home nursing referral • Palliative care referral (may be appropriate at time of diagnosis for some persons)

AAC = augmentative and alternative communication; ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; MOI = mode of inheritance; OCD = obsessive-compulsive disorder; OT = occupational therapy; PM&R = physical medicine and rehabilitation; PT = physical therapy; SLP = speech-language pathologist

1. Clinical geneticist, certified genetic counselor, certified genetic nurse, genetics advanced practice provider (nurse practitioner or physician assistant)

Treatment of Manifestations

Treatments for NBIA disorders are palliative and should be tailored to the specific NBIA disorder and to the affected individual. Consensus management guidelines for pantothenate kinase-associated neurodegeneration (PKAN) [Hogarth et al 2017] and beta-propeller protein-associated neurodegeneration (BPAN) [Wilson et al 2021] have been published.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 7). Some of these treatments do not apply to all genetic types of NBIA.

Table 7. Neurodegeneration with Brain Iron Accumulation Disorders: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Neuropsychiatric issues / Intellectual disability	Psychiatrist / neurologist / developmental pediatrician to perform relevant testing, treat medically when indicated, & consider appropriate referrals	• Incl for persons w/a later-onset, more protracted course accompanied by neuropsychiatric symptoms • Some children may benefit from educational programs or behavioral interventions like ABA therapy (particularly for BPAN)
Tone abnormalities, movement abnormalities, & musculoskeletal issues	Neurologist / PM&R specialist / orthopedist / PT & OT	• Consider need for positioning & mobility devices (e.g., AFOs, walkers, wheelchairs, hoist), disability parking placard. • Several NBIA disorders require significant dystonia mgmt, [1] which may incl treatment w/ trihexyphenidyl, gabapentin, clonidine, clonazepam, oral or intrathecal baclofen, & other medications. • Deep brain stimulation (DBS), used clinically for dystonia w/increasing frequency, shows some evidence of benefit for some NBIA disorders. While it may reduce dystonic crises for a limited amount of time, disease will still progress. DBS may also have a role in treating parkinsonism in some forms of NBIA. • Botulinum toxin to target focal dystonia or spasticity • Some NBIA disorders will involve interventions for low tone, esp truncal hypotonia, (e.g., use of Lycra® suit & supportive seating) • Levodopa & other treatments for parkinsonism are beneficial in NBIA disorders where this is a prominent feature. [2] • Standing activities & vitamin D supplementation are beneficial for bone health.
Epilepsy	Standardized treatment w/ASM by experienced neurologist or an epileptologist for challenging cases (mainly BPAN)	• Many ASMs may be effective. • Some children w/BPAN have intractable seizures & may try interventions like ketogenic diet or vagus nerve stimulation. • Some persons w/BPAN will have infantile spasms &/or epileptic encephalopathy that require specialized mgmt.
Gastrointestinal issues	Swallowing eval as indicated & regular dietary assessments to assure adequate nutrition & manage constipation &/or reflux as needed	• Once affected person can no longer maintain an adequate diet orally, or is choking or aspirating, a gastrostomy tube should be considered. • Over-the-counter fiber supplements, laxatives, &/or stool softeners are indicated to treat constipation, which may be caused by a combination of immobility, diet, & medications.
Ocular issues	Ophthalmologist	Retinal abnormalities, optic atrophy, ocular movement abnormalities, &/or more complex findings
	Low vision services	Low vision clinic &/or community vision services / OT / mobility services

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Communication deficits	SLP / neurologist / pediatric neurologist / developmental pediatrician	• Speech delay or limited/absent speech is common in children & adults w/NBIA disorders & should be addressed by an SLP, ideally one w/expertise in AAC. • For adults & teens, dysarthria is usually identified by neurologist w/referral to SLP or other specialists, such as ENT for vocal cord botulinum toxin injections, as needed. • All affected persons w/communication deficits should have formal audiologic eval.
Orthopedic issues [3]	Orthopedist	Fracture risk, osteopenia, kyphoscoliosis, &/or hip dislocation
Chronic disease issues	Palliative care specialist / pulmonologist	• With disease progression & loss of mobility, pulmonary hygiene may become useful. • Bed sores & skin breakdown in areas exposed to friction from dystonia or spasticity require attention. • Mgmt of secretions w/medication, suction, or eventual tracheostomy may be indicated.
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

AAC = augmentative and alternative communication; ABA = applied behavior analysis; AFO = ankle-foot orthoses; ASM = anti-seizure medication; BPAN = beta-propeller protein-associated neurodegeneration; NBIA = neurodegeneration with brain iron accumulation; OT = occupational therapist/therapy; PM&R = physical medicine and rehabilitation; PT = physical therapist; SLP = speech-language pathologist

1. As some NBIA disorders progress, affected individuals may experience episodes of extreme dystonia lasting for days or weeks (status dystonicus). It is especially important during these episodes to evaluate for treatable causes of pain, which may include occult gastrointestinal bleeding, urinary tract infections, and occult bone fractures and pressure sores.

2. Some individuals will have an initially dramatic response that may diminish over time; some will develop prominent dyskinesias.

3. The combination of osteopenia in a nonambulatory person with marked stress on the long bones from dystonia places many individuals with an NBIA disorder at high risk for fractures without apparent trauma.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 8 are recommended.

Table 8. Neurodegeneration with Brain Iron Accumulation Disorders: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	• Assess for new manifestations such as seizures, changes in tone, movement disorders, & changes in speech. • Assess for changes in sleep. • Assess for pain. • Assess efficacy / side effects of current treatments. • Assess for signs of disease progression such as loss of function.	At each visit
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, contracture, functional skills	
Gastrointestinal	• Measurement of growth in children • Eval of weight/nutritional status & safety of oral intake • Monitor for constipation.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Neurobehavioral/ Psychiatric/ Developmental	• Evaluate developmental progress/changes & developmental supports. • Assess for abnormal behaviors. • Screen for anxiety, depression, & other psychiatric disorders.	When indicated
Eyes/Vision	Monitor for changes to retina, optic nerve, refractive error, & other changes.	Per treating ophthalmologist(s)
	Low vision services	Per treating clinicians
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Therapies Under Investigation

Unproven targeted compounds are listed in Table 6.

Table 6. Neurodegeneration with Brain Iron Accumulation: Therapies Under Investigation

Type of Therapy	Drug/Medication	Comments
Iron chelation therapy	Deferiprone	Deferiprone addresses the downstream effect of abnormal iron accumulation associated with PKAN and some other NBIA disorders. It has been trialed in PKAN in a limited number of studies [Spaull et al 2021] including one randomized, double-blind, placebo-controlled study, but has not been proven to significantly improve the clinical outcomes measured [Klopstock et al 2019].
Coenzyme A metabolism	Pantothenate	The existence of residual enzyme activity in some individuals with PKAN raises the possibility of treatment using high-dose pantothenate, the *PANK2* enzyme substrate. Pantothenate has no known toxicity in humans. The efficacy of pantothenate supplementation in ameliorating symptoms is currently unknown.
Ceramide metabolism	Desipramine	Cell and animal models of desipramine treatment suggest it may address the underlying ceramide metabolism abnormalities in PLAN [Lin et al 2023]. A single open-label trial of four individuals was prematurely terminated (NCT03726996).
DHA metabolism	DHA (fish oil)	A *Pla2G6*-mutated mouse model showed reduced DHA metabolism & signaling; there is evidence that DHA can reverse selective iPLA$_2$-beta inhibition. This therapy has a low risk of harm.

DHA = docosahexaenoic acid; PKAN = pantothenate kinase-associated neurodegeneration; PLAN = *PLA2G6*-associated neurodegeneration

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for NBIA disorders.

6. Genetic Counseling of Family Members of an Individual with Neurodegeneration with Brain Iron Accumulation

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Modes of Inheritance

Neurodegeneration with brain iron accumulation (NBIA) disorders can be inherited in an autosomal recessive, autosomal dominant, or X-linked manner (see Table 3).

Genetic counseling and risk assessment depend on determination of the specific cause of NBIA in an individual. Most forms of NBIA are autosomal recessive. A basic view of genetic counseling issues related to autosomal recessive NBIA is presented in this section; issues that may be specific to a given family or genetic cause of autosomal recessive NBIA are not comprehensively addressed. For review of genetic counseling issues related to:

- Autosomal dominant NBIA, see Neuroferritinopathy and Mitochondrial Membrane Protein-Associated Neurodegeneration;
- X-linked NBIA, see Beta-Propeller Protein-Associated Neurodegeneration.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an autosomal recessive NBIA-causing pathogenic variant.
- Molecular genetic testing for the pathogenic variants identified in the proband is recommended for the parents of a proband to confirm that both parents are heterozygous for an NBIA-causing pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive NBIA-related pathogenic variant, each sib of an affected individual has at conception 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.

- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Individuals with autosomal recessive forms of NBIA rarely reproduce due to the severity of the condition.
- Those with later-onset, atypical disease may have offspring; all offspring will be obligate heterozygotes.

Other family members. Each sib of the proband's parents is at 50% risk of being a carrier of an NBIA-related pathogenic variant.

Carrier detection. Carrier testing for at-risk family members requires prior identification of the pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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 heterozygous, or are at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Once the NBIA-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

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 Alliance**
  Email: Info@NBIAalliance.org
  www.nbiaalliance.org

- **NBIAcure**
  Center of Excellence for NBIA Clinical Care and Research
  International Registry for NBIA and Related Disorders
  Oregon Health & Science University
  Email: info@nbiacure.org
  nbiacure.org

- **NBIA Disorders Association**
  Email: info@NBIAdisorders.org
  nbiadisorders.org

- **Treat Iron-Related Childhood-Onset Neurodegeneration (TIRCON)**

Email: TIRCON@med.uni-muenchen.de
TIRCON.eu

Chapter Notes

Author Notes

The NBIAcure website provides information about NBIA disorders for families and clinicians, updates on research studies with links to enroll, and information about the NBIA Center of Excellence at Oregon Health & Science University and clinician-to-clinician case consultation. For general inquiries, contact info@nbiacure.org.

Susan Hayflick, MD, and Allison Gregory, MS, CGC, are interested in hearing from clinicians treating families affected by idiopathic NBIA or possible NBIA cases that have been difficult to diagnose and no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Allison Gregory to inquire about review of variants of uncertain significance.

Revision History

- 6 March 2025 (gm) Comprehensive update posted live
- 21 October 2019 (bp) Comprehensive update posted live
- 28 February 2013 (me) Review posted live
- 23 April 2012 (ag) Original submission

References

Literature Cited

Al-Semari A, Bohlega S. Autosomal-recessive syndrome with alopecia, hypogonadism, progressive extra-pyramidal disorder, white matter disease, sensory neural deafness, diabetes mellitus, and low IGF1. Am J Med Genet A. 2007;143A:149–60 PubMed PMID: 17167799.

Annesi G, Gagliardi M, Iannello G, Quattrone A. Mutational analysis of COASY in an Italian patient with NBIA. Parkinsonism Relat. Disord. 2016;28:150-1. PubMed PMID: 27021474.

Behrens MI, Brüggemann N, Chana P, Venegas P, Kägi M, Parrao T, Orellana P, Garrido C, Rojas CV, Hauke J, Hahnen E, González R, Seleme N, Fernández V, Schmidt A, Binkofski F, Kömpf D, Kubisch C, Hagenah J, Klein C, Ramirez A. Clinical spectrum of Kufor-Rakeb syndrome in the Chilean kindred with ATP13A2 mutations. Mov Disord. 2010;25:1929-37. PubMed PMID: 20683840.

Brüggemann N, Hagenah J, Reetz K, Schmidt A, Kasten M, Buchmann I, Eckerle S, Bähre M, Münchau A, Djarmati A, van der Vegt J, Siebner H, Binkofski F, Ramirez A, Behrens MI, Klein C. Recessively inherited parkinsonism: effect of ATP13A2 mutations on the clinical and neuroimaging phenotype. Arch Neurol. 2010;67:1357-63. PubMed PMID: 21060012.

Carecchio M, Picillo M, Valletta L, Elia AE, Haack TB, Cozzolino A, Vitale A, Garavaglia B, Iuso A, Bagella CF, Pappata S, Barone P, Prokisch H, Romito L, Tiranti V. Rare causes of early-onset dystonia -parkinsonism with cognitive impairment: a de novo *PSEN-1* mutation. Neurogenetics. 2017;18:175-8. PubMed PMID: 28664294.

Chien HF, Bonifati V, Barbosa ER. ATP13A2-related neurodegeneration (PARK9) without evidence of brain iron accumulation. Mov Disord. 2011;26:1364-5. PubMed PMID: 21469196.

Drecourt A, Babdor J, Dussiot M, Petit F, Goudin N, Garfa-Traore M, Habarou F, Bole-Feysot C, Nitschke P, Ottolenghi C, Metodiev MD, Serre V, Desguerre I, Boddaert N, Hermine O, Munnich A, Rotig A. Impaired

transferrin receptor palmitoylation and recycling in neurodegeneration with brain iron accumulation. Am J Hum Genet. 2018;102:266-77. PubMed PMID: 29395073.

Dusi S, Valletta L, Haack TB, Tsuchiya Y, Venco P, Pasqualato S, Goffrini P, Tigano M, Demchenko N, Wieland T, Schwarzmayr T, Strom TM, Invernizzi F, Garavaglia B, Gregory A, Sanford L, Hamada J, Bettencourt C, Houlden H, Chiapparini L, Zorzi G, Kurian MA, Nardocci N, Prokisch H, Hayflick S, Gout I, Tiranti V. Exome sequence reveals mutations in CoA synthase as a cause of neurodegeneration with brain iron accumulation. Am J Hum Genet. 2014;94:11-22. PubMed PMID: 24360804.

Eiberg H, Hansen L, Korbo L, Nielsen IM, Svenstrup K, Bech S, Pinborg LH, Friberg L, Hjermind LE, Olsen OR, Nielsen JE. Novel mutation in ATP13A2 widens the spectrum of Kufor-Rakeb syndrome (PARK9). Clin Genet. 2012;82:256-63. PubMed PMID: 21696388.

Evers C, Seitz A, Assmann B, Opladen T, Karch S, Hinderhofer K, Granzow M, Paramasivam N, Eils R, Diessl N, Bartram CR, Moog U. Diagnosis of CoPAN by whole exome sequencing: waking up a sleeping tiger's eye. Am J Med Genet. 2017;173:1878-86. PubMed PMID: 28489334.

Gregory A, Lotia M, Jeong SY, Fox R, Zhen D, Sanford L, Hamada J, Jahic A, Beetz C, Freed A, Kurian MA, Cullup T, van der Weijden MCM, Nguyen V, Setthavongsack N, Garcia D, Krajbich V, Pham T, Woltjer R, George BP, Minks KQ, Paciorkowski AR, Hogarth P, Jankovic J, Hayflick SJ. Autosomal dominant mitochondrial membrane protein-associated neurodegeneration (MPAN). Mol Genet Genomic Med. 2019;7:e00736. PubMed PMID: 31087512.

Hayflick SJ. A brief history of NBIA gene discovery. J Mov Disord. 2023;16:133-7. PubMed PMID: 37096298.

Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, Gitschier J. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. N Engl J Med. 2003;348:33-40. PubMed PMID: 12510040.

Hogarth P, Gregory A, Kruer MC, Sanford L, Wagoner W, Natowicz MR, Egel RT, Subramony SH, Goldman JG, Berry-Kravis E, Foulds NC, Hammans SR, Desguerre I, Rodriguez D, Wilson C, Diedrich A, Green S, Tran H, Reese L, Woltjer RL, Hayflick SJ. New NBIA subtype: Genetic, clinical, pathologic, and radiographic features of MPAN. Neurology. 2013;80:268-75. PubMed PMID: 23269600.

Hogarth P, Kurian MA, Gregory A, Csanyi B, Zagustin T, Kmiec T, Wood P, Klucken A, Scalise N, Sofia F, Klopstock T, Zorzi, G, Nardocci N, Hayflick SJ. Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). Mol Genet Metab. 2017;120(3):278-87. PubMed PMID: 28034613.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Klopstock T, Tricta F, Neumayr L, Karin I, Zorzi G, Fradette C, Kmiec T, Buchner B, Steele HE, Horvath R, Chinnery PF, Basu A, Kupper C, Neuhofer C, Kalman B, Dusek P, Yapici Z, Wilson I, Zhao F, Zibordi F, Nardocci N, Aguilar C, Hayflick SJ, Spino M, Blamire AM, Hogarth P, Vichinsky E. Safety and efficacy of deferiprone for pantothenate kinase-associated neurodegeneration: a randomized, double-blind, controlled trial and an open-label extension study. Lancet Neurol. 2019;18:631-42. PubMed PMID: 31202468.

Kruer MC, Paisán-Ruiz C, Boddaert N, Yoon MY, Hama H, Gregory A, Malandrini A, Woltjer RL, Munnich A, Gobin S, Polster BJ, Palmeri S, Edvardson S, Hardy J, Houlden H, Hayflick SJ. Defective FA2H leads to a novel form of neurodegeneration with brain iron accumulation (NBIA). Ann Neurol. 2010;68:611-8. PubMed PMID: 20853438.

Lee JH, Yun JY, Gregory A, Hogarth P, Hayflick SJ. Brain MRI pattern recognition in neurodegeneration with brain iron accumulation. Front Neurol. 2020;11:1024. PubMed PMID: 33013674.

Lenk GM, Szymanska K, Debska-Vielhaber G, Rydzanicz M, Walczak A, Bekiesinska-Figatowska M, Vielhaber S, Hallmann K, Stawinski P, Buehring S, Hsu DA, Kunz WS, Meisler MH, Ploski R. Biallelic mutations of VAC14 in pediatric-onset neurological disease. Am J Hum Genet. 2016;99:188-94. PubMed PMID: 27292112.

Lin G, Tepe B, McGrane G, Tipon RC, Croft G, Panwala L, Hope A, Liang AJH, Zuo Z, Wang L, Pandey A, Bellen HJ. Exploring therapeutic strategies for infantile neuroaxonal dystrophy (INAD/PARK14). eLife. 2023;12:e82555. PubMed PMID: 36645408.

Mohammad SS, Angiti RR, Biggin A, Morales-Briceno H, Goetti R, Perez-Duenas B, Gregory A, Hogarth P, Ng J, Papandreou A, Bhattacharya K, Rahman S, Prelog K, Webster RI, Wassmer E, Hayflick S, Livingston J, Kurian M, Chong WK, Dale RC; Basal Ganglia MRI Study Group. Magnetic resonance imaging pattern recognition in childhood bilateral basal ganglia disorders. Brain Commun. 2020;2:fcaa178. PubMed PMID: 33629063.

Schneider SA, Paisán-Ruiz C, Quinn NP, Lees AJ, Houlden H, Hardy J, Bhatia KP. ATP13A2 mutations (PARK9) cause neurodegeneration with brain iron accumulation. Mov Disord. 2010;25:979-84. PubMed PMID: 20310007.

Shieh JT, Tintos-Hernandez JA, Murali CN, Penon-Portman M, Flores-Mendez M, Santana A, Bulos JA, Du K, Dupuis L, Damseh N, Mendoza-Londono R, Berera C, Lee JC, Phillips JJ, Alves CAPF, Dmochowski IJ, Ortiz-Gonzalez XR. Heterozygous nonsense variants in the ferritin heavy-chain gene *FTH1* cause a neuroferritinopathy. HGG Advances. 2023;4:100236. PubMed PMID: 37660254.

Spaull RV, Soo AKS, Hogarth P, Hayflick SJ, Kurian MA. Towards precision therapies for inherited disorders of neurodegeneration with brain iron accumulation. Tremor Other Hyperkinet Mov (N Y). 2021;11:51. PubMed PMID: 34909266.

Williams DR, Hadeed A, al-Din AS, Wreikat AL, Lees AJ. Kufor Rakeb disease: autosomal recessive, levodopa-responsive parkinsonism with pyramidal degeneration, supranuclear gaze palsy, and dementia. Mov Disord. 2005;20:1264-71. PubMed PMID: 15986421.

Wilson JL, Gregory A, Kurian MA, Bushlin I, Mochel F, Emrick L, Adang L, BPAN Guideline Contributing Author Group, Hogarth P, Hayflick SJ. Consensus clinical management guideline for beta-propeller protein-associated neurodegeneration. Dev Med Child Neurol. 2021;63:1402-09. PubMed PMID: 34347296.

License

European Reference Networks

https://ec.europa.eu/health/ern_en

European Reference Network
for rare or low prevalence complex diseases

Network
Neurological Diseases
(ERN-RND)

Coordinator
Universitätsklinikum
Tübingen — Deutschland

www.ern-rnd.eu

Co-funded by the European Union