Table 1 NBIA disorders

Disease	Gene	Inheritance	Clinical presentation	MRI
Classic form: Early onset – rapid progression				
Pantothenate kinase-associated neurodegeneration (PKAN)	*PANK2*	autosomal recessive	Gait abnormality, dystonia, dysarthria, corticospinal involvement	"Eye-of-the-tiger" sign in the GP
Mitochondrial membrane protein-associated neurodegeneration (MPAN)	*C19orf12*	autosomal recessive	Speech and gait difficulties, progressive spastic paraparesis, dystonia, optic atrophy, axonal motor neuropathy, cognitive decline	Increased iron in GP and SN; "Eye of the tiger" sign very rare
Fatty-acid hydroxylase-associated neurodegeneration (FAHN)	*FA2H*	autosomal recessive	Onset with focal dystonia and gait impairment, ataxia, dysarthria, spastic quadriparesis, nystagmus, visual loss, no or mild cognitive impairment and seizures in late stages; overlaps with some HSP syndromes and phenotypes of leukodystrophies	Abnormal iron in GP and SN, optic, cerebellar and brainstem atrophy, confluent subcortical and periventricular hyperintensity, thinning of the CC
PLA2G6-associated neurodegeneration (PLAN) – Infantile neuroaxonal dystrophy (INAD)	*PLA2G*	autosomal recessive	Severe psychomotor regression, hypotonia, peripheral motor neuropathy, hyperreflexia, tetraparesis, ataxia, gait abnormalities	Cerebellar atrophy, abnormal iron in GP and other nuclei
Atypical form: Later onset – slower progression				
Atypical pantothenate kinase-associated neurodegeneration (PKAN)	*PANK2*	autosomal recessive	Speech abnormalities, depression, impulsivity, aggression, emotional instability, pigmentary retinopathy	Eye-of-the-tiger sign or variants of it in the GP or other signs of increased iron and gliosis in the GP

Atypical mitochondrial membrane protein-associated neurodegeneration (MPAN)	*C19orf12*	autosomal recessive	Psychiatric features, parkinsonism, dystonia-parkinsonism, motor axonal neuropathy, mild gait difficulty, optic atrophy, cognitive decline	Increased iron in GP and SN
Neuroferritinopathy	*FTL*	autosomal dominant	Huntington´s disease-like presentation: adult-onset chorea or dystonia, orofacial action dystonia, cognitive decline	Abnormal iron and later cystic changes in the basal ganglia
Aceruloplasminemia	*CP*	autosomal recessive	Diabetes mellitus, retinal degeneration, blepharospasm, facial and neck dystonia, chorea, tremor, dysarthria, ataxia – typically adult onset	Pathological iron in both the brain and viscera; in the brain: GP, striatum, thalami, dentate nuclei In the viscera: liver
PLA2G6-associated neurodegeneration (PLAN) – neuroaxonal dystrophy (NAD)	*PLA2G6*	autosomal recessive	Progressive dystonia, dysarthria, language delay, corticospinal signs, psychiatric features and social difficulties or similar to but later onset version of INAD	Cerebellar and optic nerve atrophy Iron may or may not be increased
PLA2G6-associated neurodegeneration (PLAN) – dystonia-parkinsonism	*PLA2G6*	autosomal recessive	Parkinsonism, dystonia-parkinsonism	Iron may be increased in SN an striatum
Other NBIA form				
Kufor-Rakeb syndrome	*ATP13A2*	autosomal recessive	Juvenile onset parkinsonism, corticospinal signs, supranuclear gate palsy and cognitive decline, facial-faucial-finger myoclonus, visual hallucinations, oculogyric crisis	Generalized brain atrophy, increased iron in the caudate and lenticular nuclei, but increased iron is not always present
Woodhouse-Sakati Syndrome	*C2orf37*	autosomal recessive	Hypogonadism, diabetes, alopecia, hearing loss, mental retardation, progressive generalized and focal dystonia, dysarthria, cognitive decline	Increased iron in GP, SN and other nuclei; white matter abnormalities

Beta-propeller protein-associated neurodegeneration (BPAN) formerly Static Encephalopathy with Neurodegeneration in Adulthood (SENDA)	*In progress*	autosomal recessive	Childhood onset cognitive impairment without progression; in adult age sudden onset progressive dystonia-parkinsonism and corticospinal signs.	Increased iron in the GP and SN; on T1W MRI, hyperintensity with central band of hypointensity in the SN; cerebral and cerebellar atrophy

Legend to Table

The table summarizes the currently known entities collected under the umbrella of NBIA. Transitional phenotypes are increasingly observed within the spectrum between the extremes of the early and late onset forms due to the routine use of molecular genetics in clinical practice.

Increased iron in the brain is reflected by hypointensity on T2-weighted MRI scans, and is typically detected in nuclei where some iron is normally present: GP, SN, putamen, caudate, dentate nuclei and red nuclei. The “eye of the tiger” sign refers to an ovoid area of hypointensity with a hyperintense center corresponding to increased iron and gliosis, respectively, within the GP. The histological substrates of iron accumulation include the astrocytes, microglia / macrophages, neurons, neuropil and the perivascular space. In the same regions, axonal spheroids, neuronal loss, gliosis and demyelination may also be present. Ceroid lipofuscin and neuromelanin may accumulate intracellularly and extracellularly. The numbers of histopathological studies on genetically defined subentities are limited, but so far have revealed a differential occurrence of various neuronal inclusions.

GP: Globus pallidus
SN: Substantia nigra
CC: Corpus callosum
T1W MRI: T1-weighted magnetic resonance imaging
T2W MRI: T2-weighted magnetic resonance imaging
NA: not available