TABLE 1- NBIA- GENES AND INHERITANCE

	GENE	INHERITANCE
NBIA 1 (Pantothenate kinase associated neurodegeneration)	PANK2	Autosomal recessive
NBIA 2 (PLA2G6 associated neurodegeneration)		
2a (Infantile neuroaxonal dystrophy)	PLA2G6	Autosomal recessive
2b (Atypical neuroaxonal dystrophy, Karak syndrome)	PLA2G6	Autosomal recessive
NBIA 3 (Neuroferritinopathy)	FTL1	Autosomal dominant
NBIA 4 (Mitochondrial membrane protein associated neurodegeneration)	c19orf12	Autosomal recessive
NBIA 5 (Beta propeller-protein associated neurodegeneration)	WDR45	X-liked dominant
NBIA 6 (CoASY protein associated neurodegeneration)	COASY	Autosomal recessive
Not yet classified		
Aceruloplasminemia	Ceruloplasmin	Autosomal recessive
Fatty acid hydroxylase associated neurodegeneration (FAHN)	Fatty acid 2 hydroxylase	Autosomal recessive
Woodhouse Sakati syndrome	DCAF17(c2orf37)	Autosomal recessive
KuforRakeb syndrome (PARK 9)	ATP13A2	Autosomal recessive

TABLE 2 THE GROSS PATHOLOGICAL FETAURES OF VARIOUS NBIA SUBTYPES

Gene	Gross morphology	Iron	Axonal spheroids	Lewy body pathology	Tau pathology	Gliosis
PANK2	Neuronal loss in GP, reduced myelin, normal SN	GP neurons, glia, microglia macrophages, perivascular and iron dusting	GP Ubq, APP ,NF	No	Occasional tangles and threads	GP and widespread
COASY	Proposed to be similar to PANK2					
C9orf12	Neuronal loss in GP, reduced myelin, GP and SN atrophy	GP neurons, macrophages, less in astrocytes	Ubq in cortex, GP, SN,caudate, putamen,brainstem	Severe Lewy bodies and Lewy neurites, GP, SN, cortex, striatum	Rare tau	widespread
PLA2G6	Cerebellar, cortical, GP and brain stem atrophy, SNPr particularly affected. Cerebellar granular cells>purkinje cells	GP and sparse in SNPr	Severe p-NF, Ubq, APP, alpha-syn	Severe Lewy bodies and Lewy neurites. Ubq, alpha-syn	Early onset hyper phosphorylated tau inclusions, threads and tangles in cortex	variable
FA2H	Proposed brainstem atrophy and demyelination		Proposed white matter lesions and enlarged axons			
WDR45	SN>GP, neuronal loss, cerebellar atrophy, purkinje and granule layer,cortical atrophy	Strongest in SN, also GP and glia	GP,SN plus thalamus	No	Tau tangles, hippocampus,cortex,putamen, few in atrophied SN and GP	Putamen and thalamus
ATP13A2			Peripheral biopsies show demyelination			

			and cytoplasmic inclusions in nerve and muscle tissue			
DCAF17/ c2orf37			Peripheral biopsies show denervation of muscle tissue			
CP	Severe neuronal loss in putamen , dentate nucleus. Neuronal atrophy and iron in visceral organs	Neuronal loss in cerebellum, GP>SN, cortex, perivascular and astrocytic terminals	Iron laden globular structures in glia and variable in neurons.	unknown	Unknown	Yes
FTL	Mild atrophy in the cerebellum, cortex, putamen. GPe and SN mildly affected	Cerebellum and putamen, glia, perivascular and perineuronal	Yes, GP , Ubq and NF. Ferritin and iron laden inclusions in glia>neurons GP,putamen,thalamus and cerebellar cortex	Unknown	Few	Yes, but some atrophy too

APP-amyloid precursor protein: GPe- globus pallidus externa, GPi- globus pallidus interna, NF- neurofilament, SNc- substantia nigra pars compacta; SNPr- substantisnigra pars reticulate, Ubq- ubiquitin, Alpha syn- alpha synuclein.

TABLE 3- PATHOGENESIS OF NBIAS

GENES CODING FOR PROTEINS HELPING LIPID METABOLISM AND MEMBRANE HOMEOSTASIS	**EFFECT OF GENE MUTATION**
PANK2	Defective enzymatic activity- accumulation of N-pantothenyl cysteine, free cysteine- chelates iron- which accumulates[9,10].
COASY ENZYME	Decreased/absent activity of this enzyme hampers synthesis of coenzyme A and lipid synthesis - mitochondrial dysfunction.[9]
PLA2G6 ENZYME	Defective PLA2G6 activity- inability to repair the oxidized and damaged phospholipids. So axonal damage ensues leads to axonal degeneration[10.]
FATTY ACID HYDROXYLASE ENZYME	Hydroxy fatty acids are precursor to ceramide synthesis, ferritin is known to associate with myelin and faulty myelin causes iron accumulation[10]
GENES CODING FOR PROTEINS OF IRON METABOLISM	**EFFECT OF GENE MUTATION**
Mutation in the gene encoding ceruloplasmin	Absent ceruloplasmin- reduced export of iron- so accumulation of extracelluar transferrin free iron- oxidative damage and degeneration.
Mutation in the ferritin light chain.	Variant ferritin causes unsafe iron storage - increased cytosolic free iron and reactive oxygen species formation -degeneration
OTHER FORMS OF NBIA	**EFFECT OF GENE MUTATION**
WDR45	Encoding of a truncated or destabilised WDR 45- disrupted autophagy- impaired elimination of abnormal and toxic protein- celluar stress and death.
ATP13A2 is a lysososmal P type ATPase- divalent cation transporter	Its mutation leads to the disruption of autophagy[11].
mutation in DCAF17 (also called c2orf37[7])	It is a nucleolus protein and exact function is not known.

TABLE 4- IMAGING FEATURES IN NBIA

NBIA SUBTYPE	GENETIC MUTATION	RADIOLOGY (MRI BRAIN WITH T2/T2*/SWI SEQUENCES) BILATERAL HYPOTINTENSITIES IN BASAL GANGLIA
PKAN	PANK2	EYE OF THE TIGER APPERANCE IN GP, MID HYPOINTENSITY IN SN.(Figure 1a) The eye of the tiger appearance may fade as disease advances. It is neither pathognomonic nor specific to PKAN as it is found in COPAN, neurferritinopathy and non NBIA disorders like multiple sclerosis multisystem atrophy and carbon mono oxide poisoning[57]
PLAN INFANTILE NEUROAXONAL DSYTROPHY ATYPICAL NEUROAXONAL DYSTROPHY PLAN DP/PARK 14	PLA2G6	CEREBELLAR AND VERMIAN ATROPHY WITH CALLOSAL THINNING AND VERTICAL ORIENTATION, CALVAL HYPERTROPHY *Inconsistent iron deposition in GP, SN*[32] CEREBELLAR ATROPHY AND CALLOSAL CHANGES IN SOME CASES. *Inconsistent iron deposition in GP, SN. CEREBRAL T2 WHITE MATTER HYPERINTENSITIES.*
NEUROFERRITINOPATHY	FERRITIN LIGHT CHAIN	CORTICAL PENCIL SIGN[58] (Figure 1b) HYPOINTENSE CAUDATE, PUTAMEN, THALAMUS,GP,SN AND RED NUCLEUS
MPAN	C19orf12	GP AND SN HYPOINTENSE WITH HYPERINTENSE STREAKING OF MEDIAL MEDULLARY LAMINA OF GP CORTICAL AND CEREBELLAR ATROPHY
BPAN	WDR45	"HALO" IN SN (T1 HYPERINTENSITY) WITH T2 GP AND CEREBRAL PEDUNCLES.
COPAN	COASY	EYE OF THE TIGER HYPOINTENSE SN, GP WITH SWELLING OF CAUDATE AND PUTAMEN
ACERULOPLASMINEMIA	CERULOPLASMIN	HYPOINTENSE CAUDATE, PUTAMEN, THALAMUS,GP,SN AND RED NUCLEUS HYPOINTENSITIES IN CEREBELLUM
FAHN	FATTY ACID 2 HYDROXYLASE	GP MORE HYPOINTENSE THAN SN CONFLUENT SUBCORTICAL AND PERIVENTRICULAR CEREBRAL T2 WHITE MATTER HYPERINTENSITIES ATROPHY OF CEREBELLUM, MEDULLA AND SPINAL CORD[1]
KUFOR RAKEB SYNDROME	ATP13A2	HYPOINTENSE GP, CAUDATE AND PUTAMEN. CEREBELLAR BRAINSTEM AND PYRAMIDAL ATROPHY.
WOODHOUSE SAKATI SYNDROME	DCAF17/c2orf37	HYPOINTENSE GP,SN WITH WIDESPREAD AND CONFLUENT CEREBRAL T2 WHITE MATTER HYPERINTENSITIES.
LEUKOENCEPHALOPATHY WITH DYSTONIA AND MOTOR NEUROPATHY	SCP2	HYPOINTENSE GP AND SN WITH BUTTERFLY LIKE LESIONS IN THALAMUS AND PONS
NEW NBIA	GTPBP2	HYPOTINTENSE GP AND SN WITH CEREBELLAR VERMIAN ATROPHY