Diagnostic flowchart for Childhood onset Chorea

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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.

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- Ataxias and Hereditary Spastic Paraplegias
- Atypical Parkinsonism and genetic Parkinson's disease
- Dystonia, Paroxysmal Disorder and Neurodegeneration with Brain Ion Accumulation
- Frontotemporal Dementia
- Huntingtons' Disease and other Choreas
- Leukodystrophies

Specific information about the network, the expert centres and the diseases covered can be found at the networks web site www.ern-rnd.eu.

Recommendation for clinical use:

The European Reference Network for Rare Neurological Diseases developed the Diagnostic Flowchart for Childhood onset Chorea to help guide the diagnosis. The Reference Network recommends the use of this Diagnostic Flowchart.

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METHODOLOGY

The development of the Diagnostic Flowchart was done by the Disease group for HD and Chorea of ERN-RND.

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Flowchart development process:

- Development of flowchart by ERN-RND partner Hospital Clínic i Provincial de Barcelona y Hospital de Sant Joan de Déu, Spain
- Consent on diagnostic flowchart during ERN-RND annual meeting 2019 – 18/06/2019

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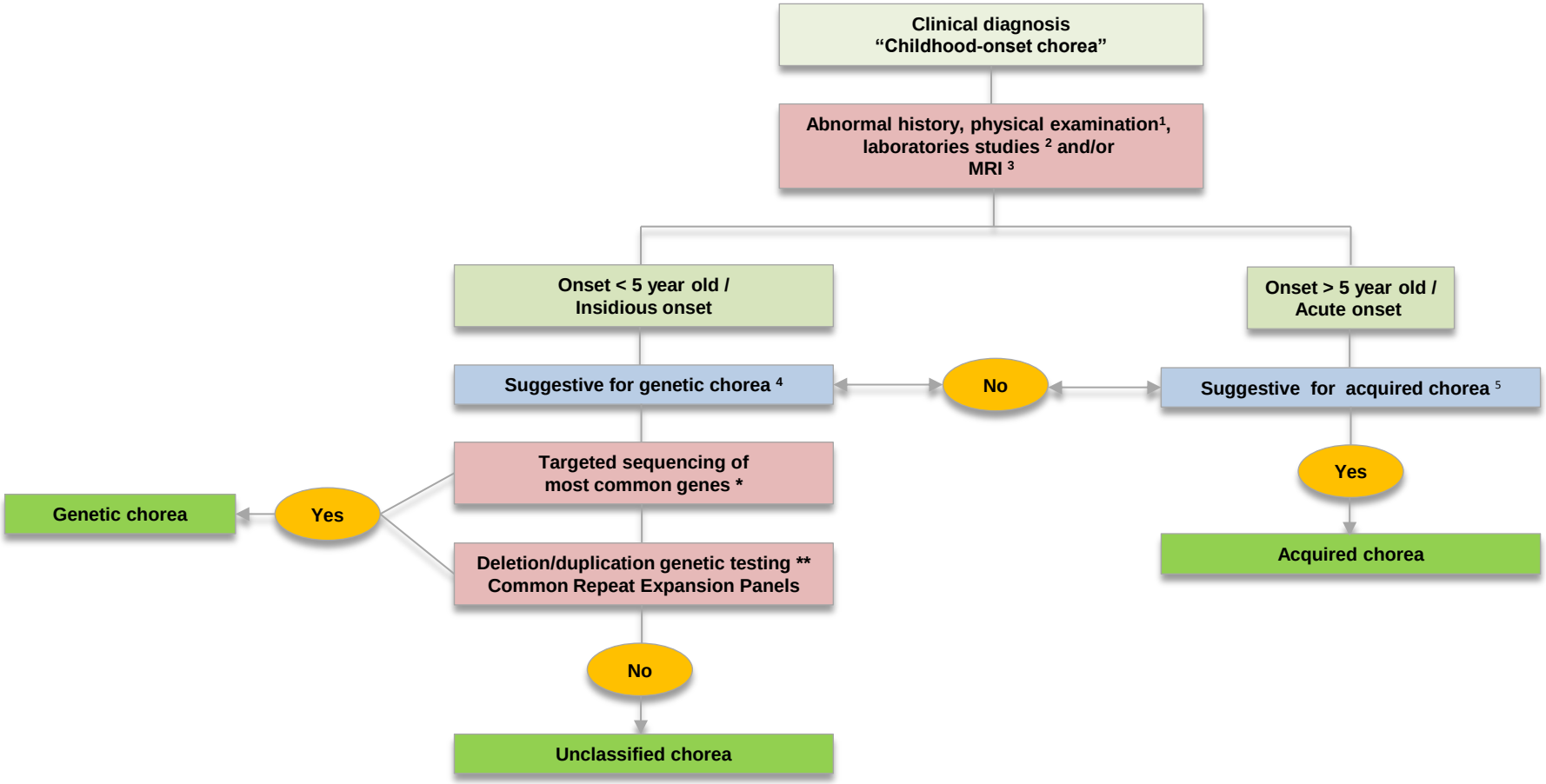

* Single gene targeted, multigene targeted (TruSightOne (analyses 63/77 chorea-related genes) or Expanded TruSightOne (analyses 72/77 chorea-related genes) sequencing), WES, WGS
** quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), ArrayCGH or gene-targeted microarray

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Acquired chorea [5]

Structural basal-ganglia lesions

Athetotic cerebral palsy
Bilirubin encephalopathy (kernicterus)
Extrapontine myelinosis
Mass lesions (tumors)
Multiple sclerosis/**ADEM**
Malformation of cortical development (e.g.. holoprosencephaly, etc)
Post cardiac surgery
Vascular chorea (Moya Moya disease)/stroke

Parainfectious and autoimmune

Acute necrotizing encephalitis
Antiphospholipid antibody syndrome
Chorea gravidum
NeuroBehçet disease
NMDAr encephalitis
Paraneoplastic chorea
Postinfectious or postvaccinal
Sydenham's chorea
Systemic lupus erythematosus
CNS vasculitis

Infectious chorea

Bacterial endocarditis
Cysticercosis
Diphtheria
EBV/CMV infection
HSV encephalitis
HIV encephalopathy
Legionella
Lyme disease
Mycoplasma
Neurosyphilis
Parvovirus B19
Scarlet fever
Toxoplasmosis
Viral encephalitis (mumps, measles, varicella)

Metabolic or toxic

Acute intermittent porphyria
Hepatic/renal failure
Hypocalcemia
Hypo/hyperglycemia (Diabetes-Related Chorea)
Hypo/hypernatremia
Hypoparathyroidism
Hyperthyroidism
Poisoning (Bismuth, carbon monoxide, manganese, methanol, mercury, organophosphate, thallium, toluene)
Vitamin B12 deficiency

Drug induced chorea

Dopamine receptor blocking agents
Phenothiazines
Butyrophenones
Benzamides
Antiparkinsonian drugs
L-dopa
Dopamine agonist
Anticholinergics
Antiepileptic drugs
Phenytoin
Carbamazepine
Valproic acid
Phenobarbital
Psychostimulants
Amphetamines
Cocaine
Calcium-channel blockers
Cinnarizine
Flunarizine
Verapamil
Others
Azithromycin
Baclofen
Cyclosporine
Digoxin
Lithium
SSRIs
Steroid/oral contraceptives
Theophylline
Tricyclic antidepressants

*** Laboratories studies:**

- CBC, ESR, CRP, glucose, blood gases, electrolytes, calcium, phosphate, PTH, TSH, FT4, T3, ALP, B12, ASLO, ANA, Anti-dsDNA, antiphospholipid antibodies, hCG pregnancy test
- LP: routine (protein, glucose, cell count/differential, GRAM staining, culture), IgG index, OCB, antineuronal antibodies (antiNMDAr, MOG, Anti-neurochondrin, LGI1, GABAB, Autoantibodies, etc).
- Consider 1) infectious testing, 2) prothrombotic risk factors testing (factor V Leyden, protein C, protein S, lipoprotein(a), antithrombin III, prothrombin gene mutation, homocysteine/MTHFR gene mutation and 3) heavy metal and drug screening based on clinical scenario

**** EKG**
***** MRI brain w/ and without gad**
****** Cardiac evaluation** if Sydenham's chorea is suspected

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Genetic chorea [4]

Autosomal dominant

Alternating hemiplegia of childhood – *ATP1A3*, *ATP1A2*
Basal ganglia calcification, idiopathic – *XPR1*, *PDGFB* , *PDGFRB,* and *SLC20A2*
Chorea, benign hereditary - *NKX2-1*
Dentatorubro-pallidoluysian atrophy - *ATN1*
Dyskinesia, familial, with facial myokymia – *ADCY5*
Dystonia, DOPA-responsive, with or without hyperphenylalaninemia – *GCH1*
Episodic kinesigenic dyskinesia 1 – *PRRT2, SCN8A*
Epileptic encephalopathy, early infantile – *SCN2A*, *KCNQ2*,
Huntington disease - *HTT*
Huntington disease-like - *JPH3, PRNP*
Neurodegeneration with brain iron accumulation – *FTL*, *PLA2G6*
Optic atrophy 3 with cataract – *OPA3*
Paroxysmal nonkinesigenic dyskinesia 1 - *PNKD*
Rett syndrome, congenital variant – *FOXG1*
Seizures, benign neonatal – *KCNQ2*, *KCNQ3*
Spinocerebellar ataxia 1 - *ATXN1*
Spinocerebellar ataxia 7 - *ATXN7*
Spinocerebellar ataxia 17 - *TBP*

Autosomal recessive

2,4-dienoyl-CoA reductase deficiency – *NADK2*
3-methylglutaconic aciduria, type III – *OPA3*
Aceruloplasminemina – *CP*
Aromatic L-amino acid decarboxylase deficiency - *DDC*
Ataxia-telangiectasia – *ATM*
Ataxia-telangiectasia-like disorder - *MRE11*
Ataxia, early-onset, with oculomotor apraxia and hypoalbuminemia - *APTX*
Choreoacanthocytosis - *VPS13A*
Combined oxidative phosphorylation deficiency 13 - *PNPT1*
Congenital cataracts, facial dysmorphism, and neuropathy - *CTDP1*
Dyskinesia, limb and orofacial, infantile-onset – *PDE10A* and *PDE2A*
Dystonia, DOPA-responsive, with or without hyperphenylalaninemia – *GCH1, SPR*
Epileptic encephalopathy, early 29 – *AARS*
Epileptic encephalopathy, early 17 – *GNAO1*
Glutaric aciduria, type I - *GCDH*
Hyperphenylalaninemia, BH4-deficient – *QDPR* and *PTS*
Leukodystrophy, hypomyelinating and Spastic paraplegia – *GJB2, HSPD1*
Metachromatic leukodystrophy - *ARSA*
Methylmalonic aciduria, mut(0) type – *MUT*
Mitochondrial DNA depletion - *FBXL4* and *POLG*
Multiple congenital anomalies-hypotonia-seizures syndrome 1 - *PIGN*
Muscular dystrophy, limb-girdle, type 2S - *TRAPPC11*
Myopathy with extrapyramidal signs – *MICU1*
Nasu-Hakola disease - *TREM2*, *TYROBP*
Neurodegeneration with brain iron accumulation – *PANK2*
Parkinsonism-dystonia, infantile - *SLC6A3*
Pontocerebellar hypoplasia – *TSEN2, TSEN34* and *CHMP1A*
Pyruvate dehydrogenase E2 deficiency – *DLAT*
Salt and pepper developmental regression syndrome - *ST3GAL5*
Sneddon syndrome – *CERC1*
Spinocerebellar ataxia, autosomal recessive 1 – *SETX*
Striatonigral degeneration, infantile – *NUP62*
Sulfite oxidase deficiency – *SOUX*
Woodhouse-Sakati syndrome - *DCAF17*
Xeroderma pigmentosum – *XPA, ERRC2* and *ERCC6*
Wilson disease – *ATP7B*

X-linked

Cerebral creatine deficiency - *SLC6A8*
Epileptic encephalopathy, early infantile, 1 - *ARX*
Dystonia-Parkinsonism, X-linked – *TAF1*
HSD10 mitochondrial disease - *HSD17B10*
Lesch-Nyhan syndrome - *HPRT1*
McLeod syndrome - *XK*
Menkes disease – *ATP7A*
Methylmalonic acidemia and homocysteinemia, cblX type - *HCFC1*
Pelizaeus-Merzbacher disease and spastic paraplegia 2 – *PLP1*
Pyruvate dehydrogenase E1-alpha deficiency – *PDHA1*
Rett syndrome – *MECP2*

* HTT, JPH3, PRNP - Consensus holds that asymptomatic individuals younger than age 18 years who are at risk for adult-onset disorders should not have testing. Individuals younger than 18 years of age who are symptomatic usually benefit from having a specific diagnosis established/ ** The genes in shadow font are caused by Repeat Expansion

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Genetic chorea [4]

[1] History and Physical examination

Neurological symptoms

- Ataxia: *APTX, ARSA, ATM, ATN1, ATP1A3, ATXN1, ATXN7, FBXL4, GCH1, HTT, MECP2, MICU1, MRE11, PLA2G6, POLG, OPA3, PLP1, SETX, TBP*
- Behavioral abnormality/Autism spectrum disorder: *ADA2, ADCY5, ARSA, ATN1, ATP1A3, ATP7A, ATP7B, CERC1, CP, DECAF17, DDC, DELAT, ERC2, ERC6, FOXG1, FTL, GCDH, GCH1, HSD17B10, HTT, JPH3, KCNQ2, KCNQ3, MECP2, NKX2-1, PANK2, PDGFB, PDGFRB, PDE10A, PLA2G6, POLG, PRNP, PRRT2, PTS, QDPR, SCN2A, SCN8A, TBP, TREM2, TYROBP, VPS13A, XPA, XPR1*
- Developmental regression: *ADA2, ARX, ATP7A, ERCC2, FOXG1, FTL, GCDH, HTT, MECP2, NUP62, POLG, PLA2G6, SCN2A, SCN8A, ST3GAL5, TREM2, VPS13A, XPA*
- Diminished or absent deep tendon stretch reflexes: *AARS, ARSA, ATP7A, ERRC2, ERCC6, PIGN, SETX, XPA*
- Dystonia – parkinsonism: *AARS, ADCY5, APTX, ARSA, ATM, ATP1A2, ATP1A3, ATP7B, CP, DCAF17, DDC, DLAT, FBXL4, FOXG1, FTL, GCDH, GCH1, GNAO1, GCDH, HCFC1, HPRT1, KCNQ2, JPH3, MECP2, MICU1, MUT, NDK2, NKX2-1, NUP62, PDGFB, PDGFRB, PDHA1, PLA2G6, PLP1, PRRT2, PTS, SETX, SLC6A3, SPR, SUOX, TAF1 (Philippines), TBP, TSEN2, TSEN34, VPS13A*
- Hypotonia: *ADCY5, ARSA, ARX, ATP7A, DDC, FBXL4, FOXG1, HCFC1, HPRT1, HSD17B10, HSPD1, MECP2, NADK2, PDE10A, PLP1, PIGN, SLC6A3, SLC6A8, SCN2A, SCN8A, SPR, SUOX*
- Infantile spasms: *ARX, KCNQ2, SCN2A, SCN8A*
- Intellectual disability: *ARSA, ARX, ATN1, ATXN7, ATP1A2, ATP1A3, ATP7A, ATP7B, DCAF17, DLAT, ERRC2, ERCC6, FOXG1, FTL, GNAO1, HCFC1, HPRT1, HSD17B10, HSPD1, KCNQ2, KCNQ3, MECP2, MICU1, MUT, NXK2-1, NUP62, OPA3, PDE10A, PDHA1, PIGN, PLA2G6, PLP1, PRRT2, SCN8A, SPR, TBP, TRAPPC11, SCN8A, SLC6A8, SOUX, XPA*
- Microcephaly: *AARS, ARX, ATP7A, ERRC2, ERCC6, FBXLA, FOXG1, HCFC1, MECP2, MICU1, MRE11, NADK2, PDGFB, PDGFRB, PDHA1, PLP1, POLG, SCN8A, SOUX, ST3GAL5, XPA, XPR1*
- Myoclonus: *ARX, ATN1, ATM, KCNQ2, KCNQ3, POLG, PRRT2, TAF1 (Philippines), TYROBP,*
- Myopathy: *POLG, VPS13A, XK*
- Paroxysmal chorea: *ADCY5, ATP1A3, ATP1A2, PKND, PRRT2, SCN8A*
- Peripheral neuropathy: *ADA2, AARS, APTX, ARSA, ATM, ATP7A, ATP7B, ATXN1, ERRC2, ERCC6, GJB2, KCNQ2, KCNQ3, MICU1, OPA3, PLP1, POLG, PRRT2, SCL2A1, SCN2A, SCN8A, SETX, XPA, VPS13A*
- Pyramidal signs: *ARSA, ATN1, ATP1A3, ATXN1, ATXN7, DDC, FTL, GCDH, GCH1, GJB2, HPRT1, HSPD1, HSD17B10, TBP, MECP2, NDK2, OPA3, PANK2, PDGFB, PDGFRB, PLA2G6, PLP1, SCL6A8, SPR, SETX, ST3GAL5, TAF1*
- Seizures: ADA2, *ARSA, ARX, ATM, ATN1, ATP1A3, ATP7A, CERC1, ERRC2, ERCC6, FBXL4, FOXG1, GJB2, GNAO1, HCFC1, HSD17B10, HSPD1, HTT, KCNQ2, KCNQ3, MECP2, MUT, NDK2, PDGFB, PDGFRB, PIGN, PLA2G6, POLG, PRRT2, SCN2A, SCN8A, SLC2A1, SLC6A8, ST3GAL5, SOUX, TBP, TYROBP, VPS13A, XPA, XPR1, XK*
- Self-mutilation: *HPRT1,SLC6A8, VPS13A*
- Tremor: *ADA2, ADCY5, APTX, ATM, ATP7B, ATXN7, CP, ERRC6, FTL, GCH1, GJB2, MECP2, MICU1, OPA3, PDE10A, PDGFB, PDGFRB, PIGN, PLA2G6, PLP1, POLG, SCN2A, SETX, SLC20A2, SPR, SLC6A3, TAF1 (Philippines), TRAPCC11, VPS13C*

Skin manifestations

- Alopecia: *DCAF17*
- Skin abnormalities: *ADA2, ATP7A, ARX, ATM, CERC1, ERRC2, ERRC6, GJB2, KCNQ2, MECP2, MRE11, PANK2, PDGFB, PDGFRB, SCN2A, SETX, SLC2A1, ST3GAL5 , SUOX, TRAPPC11, XPA, XPR1*
- Sun sensitivity: *ERRC2, ERCC6, SCN2A, XPA*

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Genetic chorea [4]

[1] History and Physical examination

Eye abnormalities

- Cataracts: *CTDP1, ERCC2, ERCC6, FBXL4, FTL, POLG, OPA3, TRAPPC11, VPS13A, XPA*
- Ectopia lentis: *SOUX*
- Eye movement abnormalities, including nystagmus: *AARS, APTX, ARX, ATM, ATN1, ATP1A2, ATP1A3, ATXN1, ATXN7, DLAT, ERCC2, ERRC6, FBXL4, HSPD1, MICU1, MRE11, NDK2, NUP62, OPA3, PDHA1, PDGFRB, PIGN, PLA2G6, PLP1, POLG, PRNP, PRRT2, SCN8A, SETX, SLC2A1, SLC6A3, ST3GAL5, VPS13A*
- Optic atrophy: *ADA2, ARSA, ARX, ATXN1, ATXN7, ATP1A3, ERCC2, ERCC6, FTL, GJB2, HSD17B10, MICU1, MUT, NUP62, OPA3, PANK2, PLA2G6, PLP1, POLG, ST3GAL5, XPA*
- Retinopathy: *ATXN7*, ERCC2, *HSD17B10, OPA3*
- Kayser-Fleischer rings: *ATP7B*

Others

- Anemia: *ADA2, ATP7B, CP, HPRT1, MUT, OPA3*
- Bone cysts *PDGFRB, TREM2, TYROBP*
- Cardiomyopathy/congestive heart failure: *ADCY5, FBXL4, HSD17B10, MUT, POLG, VPS13A, XK*
- Dysmorphic features: *ARX, ATP7A, DCAF17, ERRC2, ERCC6, HCFC1, NKX2-1, PDHA1, PIGN, SLC6A8, ST3GAL5, SOUX, XPA*
- Hearing impairment: *AARS, ATP1A2, ATP1A3, DCAF17, ERRC2, ERCC6, GJB2, HSD17B10, PLA2G6, POLG, PRRT2, TRAPCC11, XPA*
- Hypogonadism: *ATM, DCAF17, ERCC2, ERRC6, POLG, XPA*
- Hypospadias: *ARX, FBXL4, HCFC1, MECP2, PIGN*

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Genetic chorea [4]

[2] Laboratories studies

BLOOD

- Acanthocytosis: *JPH3, PANK2, VPS13A, XK*
- Immunoglobulin deficiency: *ADA2, ATM, ERRC2,*
- Lymphopenia *ATM*
- Increased creatinquinase: *FBXL4, MICU1, PLA2G6, POLG, SETX, TRAPPC11, VPS13A, XK*
- Increased transaminases: *ADA2, ATM, ATP7B, FBXL4, POLG, TRAPPC11, VPS13A*
- Increased alpha-fetoprotein: *ATM, SETX*
- Lactic acidemia: *DLAT, FBXL4, HSD17B10, HSPD1, MUT, NADK2, PNPT1 , PDHA1, POLG*
- Hyperammonemia: *FBXL4, MUT*
- Low insulin-like growth factor 1 (IGF-1): *DCAF17*
- Hypothyroidism: *CP, DCAF17, NKX2-1*
- Hypoalbuminemia: *APTX*
- Hyperuricemia: *HPRT1*
- Reduced total homocysteine: *SUOX*
- Increased total homocysteine: *HCFC1*
- *CP:* Not detectable serum ceruloplasmin, serum copper concentration <10 µg/dL, serum iron concentration < 45 µg/dL, serum ferritin concentration is 850-4000 ng/mL and plasma ceruloplasmin ferroxidase activity is not detectable.
- *ATP7A*: low copper 0-55 µg/dL and low ceruloplasmin 10-160 mg/L
- *ATP7B*: serum ceruloplasmin < 20 mg/dl,
- *NDK2*: elevated plasma C10:2-carnitine, hyperlysinemia
- Hyperphenylalaninemia: *PTS, QDPR*

CSF

- *Increased lactate: DLAT, FBXL4, HSPD1, NDK2, PDHA1, PNPT1, POLG*
- *DDC:* normal CSF pterins profile, reduced HVA, 5-HIAA and MHPG, increased OMD and levodopa
- *GCH1*: normal or reduced CSF pterins, normal Phe, normal or reduced HVA and 5-HIAA
- *HCFC1:* elevated glycine and methylmalonic acid
- *NDK2*: elevated lysine
- *PTS:* increased Phe, increased neopterin, decreased biopterin, HVA and 5-HIAA
- *QDPR:* increased Phe, normal neopterin, increased biopterin, decreased HVA, 5-HIAA and folate
- *SLC6A3:* Raised HVA, normal 5-HIAA, HVA:5-HIAA ratio >4.0, normal CSF pterins
- *SPR*: low HVA and 5-HIAA and high levels of biopterin and dihydrobiopterin with the presence of sepiapterin

URINE

- *ATP7B*: 24-h urine Cu> 40 mcg
- GCSH: increased 3-hydroxy glutaric acid and glutaric acid
- *HCFC1, HSPD1, MUT*: increased urinary methylmalonic acid
- *HPRT1:* Urate/creatinine ratio > 2.0
- *HSD17B10*: elevation of 2-methyl-3-hydroxybutyrate and tiglylglycine
- *NDK2*: elevated lysine
- *OPA3*: Increased urinary excretion of 3-methylglutaconate and 3-methylglutaric acid.
- *SLC6A8* Males: Guanidinoacetate normal, Creatine normal to elevated and Creatine/creatinine ratio elevated
  Females Guanidinoacetate normal Creatine normal to elevated Creatine/creatinine ratio normal to mildly elevated
- SUOX: Urinary sulfite identified on a dipstick screening test. Elevated urinary thiosulfate and S-sulfocysteine and low urinary organic sulfate.

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Genetic chorea [4]

[3] MRI

Basal ganglia abnormalities

Iron deposition: *CP, DCAF17, FTL, PANK2, PL2G6*

Caudate atrophy: *HPRT1, HTT, JPH3, TREM2, TYROBP, VPS13A*

Hypoplastic globus pallidus *NKX2-1*

Hyperintensity: *ATP7B, DLAT, FBXL4, FTL, GCDH, KCNQ2, MICU1, MUT, NADK2, NDK2, NUP62, PDE10A, PDHA1, PNPT1, POLG, PRNP, SCN2A, SCN8A, XK*

Calcification

ATP7A, ERRC2, ERCC6, PDGFB, PDGFRB, PTS, QDPR, SLC20A2, SOUX, XPA, XPR1

White matter abnormalities

Hypomyelination/defective myelination - *AARS, ARX, ATP7A, CTDP1, DDC, FBXL4, FOXG1, GNAO1, HCFC1, SCN2A, PLP1, PNPT1, PTS*

Leukoencephalopathy / Unspecific periventricular gliosis - *ARSA, ATM, CTDP1, DCAF17, DDC, FBXL4, GJB2, HSPD1, NADK2, POLG, PRNP, PTS, QDPR, SCN2A, SLC6A8, ST3GAL5, TREM2, TYROBP*

MR Spectroscopy

Lactate peak – *DLAT, FBXL4, HSD17B10, PNPT1, PDHA1, POLG*
Cerebral creatine deficiency - *SLC6A8*
Abnormal white matter N-acetyl aspartate (NAA) levels – *PLP1, MECP2, HSPD1*
Elevated citrate, glycine and creatine *AARS*

Normal

ADCY5, ATP1A3, ATP1A2, KCNQ3, DDC, GCH1, PDE2A, PKND, SLC6A3, SPR, TAF1 , TRAPPC11

Others

Arachnoid cysts: *FBXL4*

Brain atrophy: *AARS, ARX, ATRX, ATXN7, ATN1, CTDP1, DDC, ERRC2, ERRC6, FBXL4, FOXG1, GJB2, GNAO1, HPRT1, HSD17B10, HTT, JPH3, KCNQ2, MECP2, NADK2, PDHA1, PIGN, POLG, SCN8A, ST3GAL5, TBP, TYROBP, VPS13A, XPA*

Cerebellar atrophy: *APTX, ATM, ATXN1, ATXN7, CTDP1, ERRCC6, HTT, MECP2, MRE11, OPA3, PIGN, PLA2G6, POLG, PRNP, SCN2A, SCN8A, SETX, TBP*

Hypoxic-ischemic encephalopathy-like, including cystic leukomalacia: *SOUX*

Ischemic lesions: *CERC1, FBXL4*

Malformation of cortical development: *ARX*

Pontocerebellar atrophy - *ATXN1, ATN1, CHMP1A, HSPD1, SETX, TSEN2, TSEN34*

Sella turca cysts *NKX2-1*

Spinal cord atrophy – *CTDP1*

Thin corpus callosum - *ARX, AARS, CTDP1, FBXL4, FOXG1, GJB2, GNAO1, KCNQ2, MECP2, SCN8A, TYROBP*

Vascular tortuosity - *ATP7A*

Ventricular enlargement – *AARS*, ARX, *ATP7A, ERRC2, ERCC6, FOXG1, HTT, JPH3, MECP2, NADK2, PDGFB, PDGFRB, PDHA1, PIGN, TSEN2, TYROBP, SLC6A8, SLC20A2, VPS13A, XPA, XPR1, XK*