



# Diagnostic flowchart for Childhood onset Chorea

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Published by ERN-RND: 11<sup>th</sup> September 2019



This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

## 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 32 of Europe's leading expert centres in 13 Member States and includes highly active patient organizations. Centres are located in Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Slovenia, Spain and the UK.

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 Ion Accumulation
- Frontotemporal Dementia
- Huntingtons' Disease and other Chorea
- 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](http://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.

### **Disease group for HD and Chorea:**

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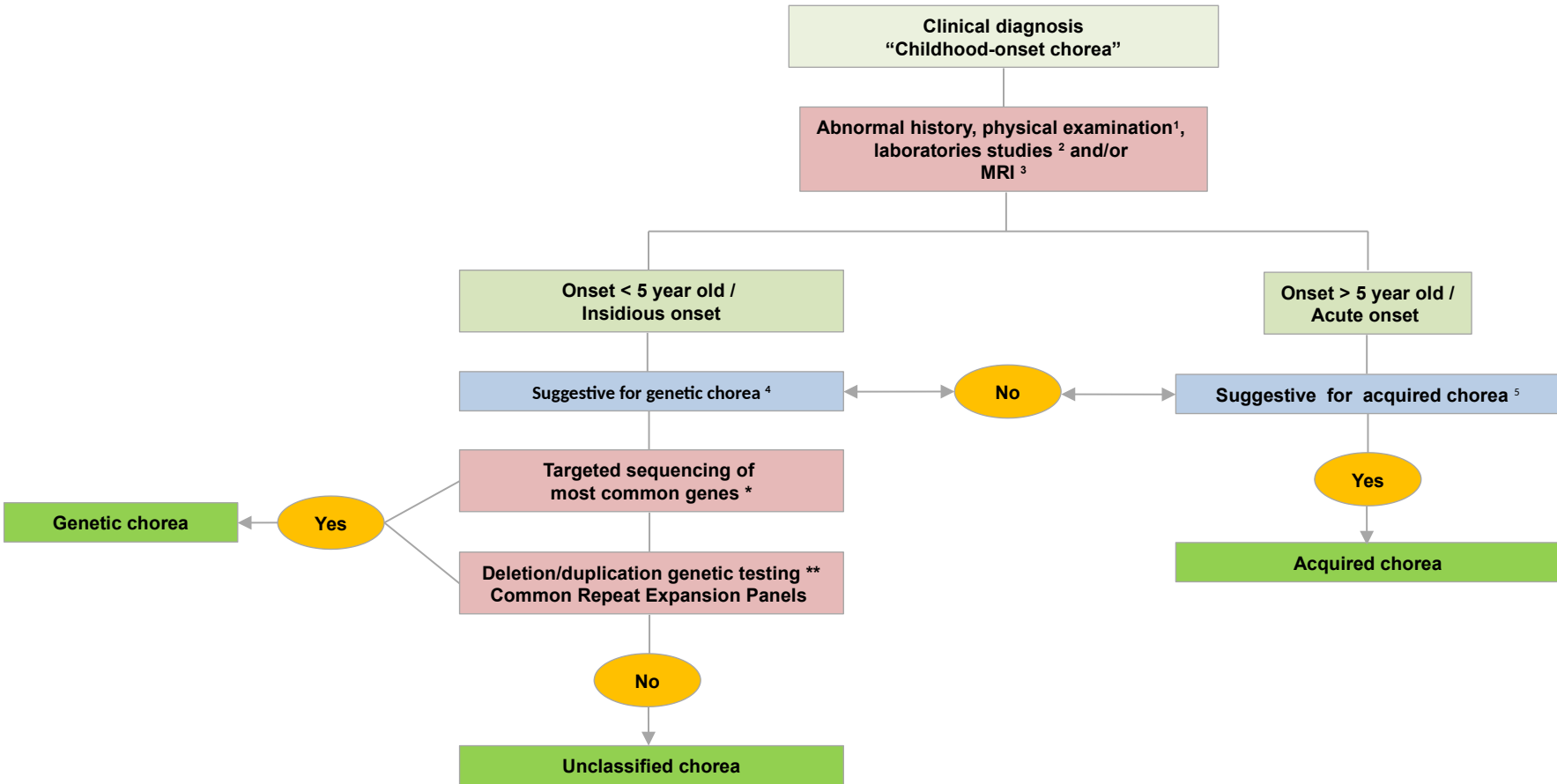
### Patient representatives:

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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



\* 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

## Acquired chorea <sup>5</sup>

### 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/hyponatremia  
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

## Genetic chorea <sup>4</sup>

### 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*  
 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*  
 Aceruloplasminemia – *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* - 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

# Genetic chorea <sup>4</sup>

## <sup>1</sup>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, KCNQ2, KCNQ3, MECP2, NKX2-1, PANK2, PDGFB, PDGFRB, PDE10A, PLA2G6, POLG, 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, 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, NKX2-1, NUP62, OPA3, PDE10A, PDHA1, PIGN, PLA2G6, PLP1, PRRT2, SCN8A, SPR, TBP, TRAPCC11, SCN8A, SLC6A8, SOUX, XPA*
- Microcephaly: *AARS, ARX, ATP7A, ERRC2, ERCC6, FBXL4, 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, SLC6A8, 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, TRAPCC11, XPA, XPR1*
- Sun sensitivity: *ERRC2, ERCC6, SCN2A, XPA*



# Genetic chorea <sup>4</sup>

## <sup>1</sup>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, 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*

# Genetic chorea <sup>4</sup>

## <sup>2</sup>Laboratories studies

### BLOOD

- Acanthocytosis: *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.

# Genetic chorea <sup>4</sup>

## <sup>3</sup> MRI

### Basal ganglia abnormalities

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

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

Hypoplastic globus pallidus *NKX2-1*

Hyperintensity: *ATP7B, DLAT, FBXL4, FTL, GCDH, KCNQ2, MICU1, MUT, NADK2, NDK2, NUP62, PDE10A, PDHA1, PNPT1, POLG, 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, 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, KCNQ2, MECP2, NADK2, PDHA1, PIGN, POLG, SCN8A, ST3GAL5, TBP, TYROBP, VPS13A, XPA*

Cerebellar atrophy: *APTX, ATM, ATXN1, ATXN7, CTDP1, ERRC6, HTT, MECP2, MRE11, OPA3, PIGN, PLA2G6, POLG, 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, ERRC6, FOXG1, HTT, MECP2, NADK2, PDGFB, PDGFRB, PDHA1, PIGN, TSEN2, TYROBP, SLC6A8, SLC20A2, VPS13A, XPA, XPR1, XK*