Module: Chromosomopathies

Question: A 5 y.o. boy has mental retardation and hyperactivity. His mother has anxiety and mitral valve prolapse. Her father has difficulty walking and a tremor that is not responsive to levo-dopa. What is the most likely inheritance pattern?

A. Autosomal dominant  
B. Autosomal recessive  
C. Maternal  
D. X-linked  
E. Sporadic

Question: An 11 m.o. girl is no longer reaching for objects. She has intractable epilepsy and now has microcephaly even though her head circumference was normal at birth. She also hyperventilates intermittently and has respiratory pauses at other times. What is the most likely diagnosis?

A. Angelman syndrome  
B. Rett syndrome  
C. William syndrome  
D. Leigh syndrome  
E. Canavan’s disease

Suspect a chromosomopathy if there are characteristic

◆ Dysmorphic features  
◆ Congenital malformations  
◆ Behavioral phenotypes  
◆ Neurological abnormalities

Can be diagnosed with specific genetic testing

If features not diagnostic for specific chromosomopathy, request high resolution chromosomes vs. chromosomal microarray

◆ May also need parental testing

Fragile X syndrome  
Down syndrome  
Rett syndrome  
Angelman syndrome  
Prader-Willi syndrome  
Williams syndrome  
Klinefelter syndrome  
Velocardiofacial (DiGeorge) syndrome

Notes:
Fragile X
- X-linked dominant Xq27.3
  - FMR1 mutation with CGG repeat
- Macrocephaly
- Long thin face, prominent forehead and jaw, large, protuberant ears
- Mitral valve prolapse
- Macro-orchidism
- Joint laxity – dislocated hips
- Mental retardation
- Hyperactivity
- Aversion of gaze
- Stereotypies
- Perseverative speech
- Autism
- Epilepsy

Trinucleotide Repeat Diseases
- Polyglutamine (PolyQ) diseases: CAG triplet repeat disorders
  - Dentatorubropallidoluysian atrophy (DRPLA): Chr 12
  - Huntington’s disease: Chr 4
  - Spinobulbar muscular atrophy or Kennedy disease: X
  - Spinocerebellar ataxia Type 1: Chr 6
  - Spinocerebellar ataxia Type 2: Chr 12
  - Spinocerebellar ataxia Type 3 or Machado-Joseph disease: Chr 14
  - Spinocerebellar ataxia Type 6: Chr 19
  - Spinocerebellar ataxia Type 7: Chr 3
  - Spinocerebellar ataxia Type 17: Chr 6
- Non-polyglutamine diseases
  - Fragile X syndrome: CGG on X
  - Fragile X-associated tremor/ataxia syndrome: CGG on X
  - Fragile XE mental retardation: GCC on X
  - Friedreich’s ataxia: GAA on Chr 9 AR
  - Myotonic dystrophy (DM1): CTG on Chr 19
    - DM2 is CCTG repeat on Chr 3
  - Spinocerebellar ataxia Type 8: CTG on Chr 13
  - Spinocerebellar ataxia Type 12: CAG on Chr 5
Down Syndrome Phenotype
- Trisomy 21
- Short stature
- Brachycephaly
- Epicanthal folds, upslanting palpebral fissures, Brushfield spots
- Small ears
- Protruding tongue
- Single transverse palmar crease, short & curved 5th finger
- Wide space between 1st and 2nd toes = “sandal foot”

Down Syndrome
- Congenital heart disease 50%
- Conductive hearing loss 75%
- Otitis media 50%–70%
- Eye disease 60%
  - Cataract 15%
  - Severe refractive errors 50%
- Thyroid disease 15%, 1% congenital
- Leukemia <1%
  - Leukemoid reaction 18%
- Hirschsprung disease <1%
- Gastrointestinal atresia 12%

Down Syndrome cont’d
- Hypotonia
  - Atlantoaxial instability
  - Obstructive sleep apnea 50%–75%
  - Joint laxity
    - Acquired hip dislocation 6%
- Mental retardation
- Alzheimer’s disease with onset in 40s

Rett Syndrome
- X-linked dominant Xq28
- Acquired microcephaly
- Intermittent hyperventilation
- Cardiac conduction abnormalities
- Mental retardation
- Epilepsy
- Autism
- Loss of hand use (wring of hands) ~1 y.o.

Video of mouse with Rett syndrome gene vs. normal mouse

Source: http://www.dnatube.com/video/585/Rett-Syndrome-Mouse

Source: http://www.armyofangels.org/liam_school_1_sm.jpg
Angelman Syndrome
- 15q11-q13, Xq28
  - Deletion
  - Paternal disomy (missing maternal DNA)
- Microcephaly
- Epilepsy
- Mental retardation
- Prognathia, widely spaced teeth

Source: http://library.thinkquest.org/06aug/00440/images/mpraderwillisympotmweb.jpg

Prader-Willi Syndrome
- Chromosome 15q12, 15q11-q13
  - Deletion
  - Maternal disomy (missing paternal DNA)
- Failure to thrive
- Onset of obesity from 6 months to 6 years
- Mental retardation
- Treatment: growth hormone

Source: http://library.thinkquest.org/06aug/00440/images/mpraderwillisympotmweb.jpg

Notes:
Williams (Beuren) Syndrome
- Autosomal dominant, 7q11.123 deletion
- Sensorineural hearing loss
- Supravalvular stenosis (aortic and other valves)
- ASD, VSD
- Kidney abnormalities
- Mental retardation (average IQ 56)
- Relative sparing of language
- ADD
- Friendly, gregarious
- Hypercalcemia

Klinefelter Syndrome
- XXY
- Developmental delay
  - Motor
  - Language
- Infertility 95%−99%
- More breast disease, autoimmune disease and osteoporosis than normal men

Question: A pregnant woman has an amniocentesis. The amniocentesis shows a 22q microdeletion. What is the most serious complication of this condition?
A. Gastrointestinal atresia
B. Blindness
C. Liver failure
D. Congenital heart disease
E. Autonomic polyneuropathy
Velocardiofacial (DiGeorge) Syndrome
- 22q microdeletion 22q11.2DS, AD, about 93% de novo
- Congenital heart disease (conotruncal malformations) 74%
  - Tetralogy of Fallot
- Facial anomalies 69%
  - Velopharyngeal incompetence
- Immune system abnormalities 77%
  - Immunodeficiency
  - Autoimmune disease: thrombocytopenia, JRA, Grave’s disease, vitiligo, neutropenia, hemolytic anemia

Velocardiofacial (DiGeorge) Syndrome cont’d
- Hypocalcemia 50%
- Learning disabilities 70%–90%
  - Below average IQ, ADHD, autism
- Renal anomalies 37%
- Hearing loss (both conductive and sensorineural)
- Laryngotracheoesophageal anomalies
- Seizures
- Skeletal abnormalities
- Schizophrenia in 25%–30%

Source: http://migale.jouy.inra.fr/psychrophilum/transport-and-metabolism/FpsyMetabTransp.png

Notes:
**Inborn Error of Metabolism**
- Suspect when patient has
  - Neurological or developmental deterioration
  - Episodes of severe illness with common infections
  - Metabolic acidosis
  - Hypoglycemia
- Person may be asymptomatic and laboratory testing may be normal between episodes

**Caution**
- In children with suspected inborn errors of metabolism
- AVOID valproic acid
  - Especially for disorders of fatty acid metabolism or mitochondrial disease
  - Valproic acid may cause carnitine depletion
- Be careful of ketogenic diet
  - Avoid in disorders of fatty acid metabolism or mitochondrial disease

Source: http://www.noatak.com/images/carnitexpl.jpg

Notes:
General Screening for Inborn Errors of Metabolism

- Lactate
- Ammonia
- Carnitine
- Acylcarnitine
- Serum amino acids
- Urine organic acids
- CSF lactate
- CSF amino acids

Module: Mitochondrial Disorders

Electron Transport Chain
- 90 proteins
- 77 from nuclear DNA (all of complex II)
- 13 from mitochondrial DNA

Mitochondrial DNA
- 16.6 kB double stranded circular
- 2–10 copies per mitochondrial
- 13 genes for electron transport chain
- 2 genes for rRNA
- 22 genes for tRNA

Notes:
Notes:

Source: http://chemistry.umeche.maine.edu/CHY431/MitoDNA.jpg

Source: http://www.nature.com/nrg/journal/v6/n5/images/nrg1606-f3.jpg
Mitochondrial Disorders

- Leigh syndrome
- MERRF
- MELAS
- Kearns-Sayre syndrome and chronic progressive external ophthalmoplegia
  - POLG1 mutations
- Leber hereditary optic neuropathy

![Mitochondrial Disorders](http://www.jmda.or.jp/6/hyakka/image/zu31.jpg)

Leigh Syndrome

- Most autosomal recessive ETC proteins and pyruvate dehydrogenase, some X-linked and maternal
- Brainstem and basal ganglia
- Hypotonia
- Ophthalmoplegia
- Nystagmus
- Psychomotor regression

![Leigh Syndrome](http://www.ajnr.org/content/vol24/issue10/images/large/j41130822001.jpeg)

Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

- tRNA lysine point mutation in 90%
- Ragged red fibers
- Myoclonus
- Epilepsy
- Pseudolaminar necrosis
- Basal ganglia mineralization

![Myoclonic Epilepsy with Ragged Red Fibers](http://www.neuropathologyweb.org/chapter10/images10/10melas.jpg)

Notes:
Mitochondrial Encephalomyopathy with Lactic Acidosis and Strokelike Episodes (MELAS)
- tRNA leucine in 80%
- Dementia
- Seizures
- Recurrent strokelike events
- Myopathy
- Lactic acidosis
- Ataxia
- Deafness
- Pigmentary retinopathy

- Pigmentary retinopathy in mitochondrial myopathy
  (A) Granular (“salt and pepper”) retinopathy
  (B) Bone spicule appearance
  (C) Diffuse retinal atrophy

Source: http://www.ispub.com/ispub/jvn/volume_2_number_2_34/diagnostic_considerations_on_melas_syndrome/melas-fig1.jpg

Kearns-Sayre Syndrome and Chronic Progressive External Ophthalmoplegia
- Large mtDNA deletions (up to 50% of DNA) protein synthesis is affected, usually sporadic
- Ophthalmoplegia and ptosis
- Weakness
- Ataxia
- Pigmentary retinopathy
- Hearing loss
- Dementia
- Seizures
- Cardiomyopathy
- Cardiac conduction abnormalities
- Impaired GI motility
- Diabetes mellitus
- Endocrine
- Renal dysfunction

POLG1 mutations
- Polymerase, DNA, Gamma 1, 15q25 AR
- Used in replication of mitochondrial DNA
- May cause multiple mitochondrial DNA deletions in patients
- Mitochondrial DNA depletion syndromes
  - Alpers type
  - MNGIE type

Source: PubMed: 15702133

Source: http://content.lib.utah.edu/EHSL-WFH/image/353.jpg
Leber Hereditary Optic Neuropathy
- Maternally inherited, ETC complex I mutations
- Loss of retinal ganglia cells in perifoveal region (macula densa) and degeneration of papillomacular bundle
- Painless progressive central vision loss
- Dystonia
- Pseudobulbar palsy
- Intellectual deterioration
- Weakness
- Wolff-Parkinson-White
- Females may have multiple sclerosis like symptoms

Module: Other Inborn Errors of Metabolism

Question: A 42 y.o. man has lancinating pains in his hands and feet. He also has cloudy corneas and worsening proteinuria. What is the most likely diagnosis?
A. Refsum disease
B. Krabbe disease
C. Alexander disease
D. Niemann-Pick disease
E. Fabry disease

Lysosomal Storage Disorders ICD
- Lipid storage disorders, mainly sphingolipidoses
  - Gaucher’s
  - Niemann-Pick diseases
- Gangliosidoses
  - Tay-Sachs disease
- Leukodystrophies
- Mucopolysaccharidoses
  - Hunter syndrome
  - Hurler disease
- Glycoprotein storage disorders
- Mucolipidoses

Lysosomal Storage Disorders
- Suspect when patient has:
  - Coarse facial features
  - Hepatosplenomegaly
  - Neurological deterioration
- Order lysosomal storage disease panel

Leukodystrophies
- “Progressive degeneration of the white matter of the brain due to imperfect growth or development of the myelin sheath”
- Adrenoleukodystrophy
- Alexander disease
- Metachromatic leukodystrophy
- Krabbe’s disease or globoid cell leukodystrophy
- Canavan disease
- Childhood ataxia with central nervous system hypomyelination or vanishing white matter disease (CACH)
- Pelizaeus-Merzbacher disease
- Refsum disease
- Cerebrotendinous xanthomatosis


Adrenoleukodystrophy

Source: http://www.ajnr.org/cgi/content-full/22/4/773/F2
- X-linked
- Childhood cerebral form appears in mid-childhood (at ages 4-8)
- Adrenomyelopathy occurs in men in their 20s or later in life
- Impaired adrenal gland function
- Diagnostic test: very long chain fatty acids
- Treatment
  - Lorenzo’s oil = oleic acid and erucic acid
  - Docosahexanoic acid (DHA)
  - Bone marrow transplant
Alexander Disease

- Mutations in glial fibrillary acidic protein
- Often sporadic
- Rosenthal fibers = abnormal clumps of protein in astrocytes (not pathognomonic)
- Usually infantile <2 y.o.
  - Developmental delay, seizures, macrocephaly
- Juvenile 3-13 y.o.
  - Loss of motor control
- Adult rare

Source: http://www.ajnr.org/cgi/content/full/27/5/958

Metachromatic Leukodystrophy

- Autosomal recessive deficiency of arylsulfatase A
- Accumulation of the myelin lipid sulfatide in oligodendrocytes and Schwann cells
- Late infantile: blindness, seizures, dementia
- Juvenile: mental deterioration
- Adult: psychiatric symptoms and dementia
- Neuropathy
- Treatment: bone marrow transplant

Source: http://www.neuropathologyweb.org/

Notes:
**Globoid Cell Leukodystrophy or Krabbe’s Disease**

- Deficient galactocerebrosidase
- Accumulation of galactocerebroside
- Central and peripheral nervous system

**Treatment**
- Intravascular injection of cord blood
- Bone marrow transplant

**Globoid Cell Leukodystrophy**

Source: [http://www.pathology.vcu.edu/WirSelFInst/neuro_medStudents/leukodys.html](http://www.pathology.vcu.edu/WirSelFInst/neuro_medStudents/leukodys.html)

**Canavan’s Disease or Spongiform Leukodystrophy**

- Deficient enzyme: aspartoacylase
- Autosomal recessive
  - Ashkenazi Jews
- Mental retardation
- Loss of motor skills
- Feeding difficulties
- Abnormal muscle tone
- Macrocephaly
- Blindness
- Hearing loss

Source: [http://radiographics.rsnaajns.org/content/vol22/issue3/images/large/g02ma01g14b.jpeg](http://radiographics.rsnaajns.org/content/vol22/issue3/images/large/g02ma01g14b.jpeg)

Source: [http://images.the-scientist.com/content/figures/images/yr2001/sep17/normal.jpg](http://images.the-scientist.com/content/figures/images/yr2001/sep17/normal.jpg)
Vanishing White Matter Disease

or Childhood Ataxia with Diffuse CNS Hypomyelination (CACH)

- Autosomal recessive
- Mutations of one of five genes for eIF2B (eukaryotic initiation factor 2B)
- Deterioration with trauma, fever or infection
- Spasticity
- Lethargy
- Optic atrophy
- Epilepsy

Peroxisomal Disorders

- Zellweger syndrome
  - Enlarged liver
  - Facial dysmorphology – high forehead, deformed ears
  - Hypotonia
  - Glaucoma
- Infantile Refsum disease
- Neonatal adrenoleukodystrophy
- Rhizomelic chondrodysplasia

Infantile Refsum Disease

- Phytanic acid accumulation
- Neuropathy
- Retinitis pigmentosa
- Ichthyosis
- Cardiac arrhythmias

Treatment

- Restrict intake of phytanic acid (dairy, beef and lamb, fatty fish – tuna, cod, haddock)
- Plasmapheresis
Sphingolipidoses

- Sphingomyelins have a phosphorylcholine or phosphoroethanolamine molecule with an ester linkage to the 1-hydroxy group of a ceramide
- Glycosphingolipids, which differ in the substituents on their head group (see image). Glycosphingolipids are ceramides with one or more sugar residues joined in a β-glycosidic linkage at the 1-hydroxyl position
  - Cerebrosides have a single glucose or galactose at the 1-hydroxy position
  - Sulfatides are sulfated cerebrosides
- Gangliosides have at least three sugars, one of which must be sialic acid

Sphingolipidoses cont’d

- Gangliosides: gangliosidosis
  - GM1 gangliosidoses
  - GM2 gangliosidoses
    - Tay-Sachs disease
    - Sandhoff disease
- Glycolipids
  - Fabry’s disease
  - Krabbe disease
  - Metachromatic leukodystrophy
- Sphingomyelin
  - Niemann-Pick disease
  - Gaucher’s disease

Notes:

Tay-Sachs Disease
- Hexosaminidase A deficiency, AR
- Ashkenazi Jewish heritage
- Onset 3-6 months of age, usually death before 4 years
- Storage of glycosphingolipid GM2 ganglioside
- Progressive weakness
- Loss of motor skills
- Decreased attentiveness
- Increased startle response
- Seizures
- Blindness, cherry red spot of fovea centralis of macula
- Normal size spleen and liver
- Spasticity

Fabry Disease
- Deficiency of α-galactosidase (α-Gal A), X linked
  - <1% classic
  - >1% variants: LV hypertrophy or renal
- Lysosomal deposition of globotriaosylceramide (GL-3)
- Neuropathy with acroparesthesias and lancinating pains
- Angiokeratomas
- Hypohidrosis
- Corneal and lenticular opacities
- Proteinuria
  - ESRD in 3rd to 5th decade
Niemann-Pick Disease Type C
- Autosomal recessive, NCP1 and NCP2
- Cannot esterify cholesterol
- Hypotonia, developmental delay
- Ataxia
- Supranuclear vertical gaze palsy
- Dementia
- Dystonia
- Seizures
- Ascites, liver disease
- MRI: late findings
  - Thin corpus callosum, cerebral and cerebellar vermis atrophy
  - Increased signal periatrial white matter

Mucolipidoses
- Sialidosis II (ML I)
  - Deficiency of sialidase
  - Sialidosis I milder
- Mucolipidosis types II and III
  - Deficiency of the enzyme N-acetylglucosamine-1-phosphotransferase
  - Type 2 more severe, type 3 milder
- Mucolipidosis type IV
  - Deficiency of mucolipin-1

Notes:
Mucopolysaccharidoses
■ Normal intellect to profoundly retarded
■ Developmental delay
■ Severe behavioral problems
■ Coarse or rough facial features
  ◆ Thick lips
  ◆ Enlarged mouth and tongue
■ Short stature with a disproportionately short trunk (dwarfism)
■ Abnormal bone size or shape (and other skeletal irregularities)
■ Thickened skin
■ Enlarged organs such as the liver or spleen
■ Hernias
■ Excessive body hair growth
■ Recurrent upper respiratory tract and ear infections
■ Cloudy corneas
■ Treatment
  ◆ Alpha-L-iduronidase for MPS I (Scheie syndrome and Hurler-Scheie syndrome: AR)
  ◆ Idursulfase for MPS II (Hunter syndrome: X linked recessive)
  ◆ Arylsulfatase B for MPS VI (Maroteaux-Lamy syndrome)

Neuronal Ceroid Lipofuscinosis (NCL or CLN) or Batten Disease
■ Abnormal apoptosis of neurons
■ Dysregulated sphingolipid metabolism
  ◆ Lysosomal enzymes
  ◆ Lysosomal membrane proteins
  ◆ Proteins in endoplasmic reticulum
■ Neurological symptoms
  ◆ Epilepsy
  ◆ Ataxia
  ◆ Cognitive decline
  ◆ Loss of vision
■ Diagnosis: DNA testing, EM of lymphocytes

Batten Disease (NCL or CLN)
■ CLN1 infantile
■ CLN2 late infantile
■ CLN3 adult
■ CLN4 adult
■ CLN5 Finnish VLINCL
■ CLN6
■ CLN7 Turkish (Northern epilepsy)
■ CLN9
■ Santavuori-Haltia
■ Jansky-Bielschowsky
■ Spielmeyer-Sjögren
■ Kufs disease

Source: http://www.ncbi.nlm.nih.gov/books/NBK1428/

Notes:
Answer Key

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E. Autonomic polyneuropathy

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C. Alexander disease
D. Niemann-Pick disease
E. Fabry disease

Resources

- NIH site for neurological disorders
- Leukodystrophies
- Neuropathology pictures
  - http://www.neuropathologyweb.org/
- Genetic or metabolic testing
  - http://www.genetests.org/
- Clinical trials
  - http://www.clinicaltrials.gov/

Notes: