Common Neurogenetic Syndromes

HMS Child Neurology 2015
Cambridge, MA
October 28, 2015

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Disclosures / COI

• **Curoverse**: clinical bioinformatics company

• **Veritas Genetics**: CLIA certified genetics diagnostic laboratory
Covered in other talks

- MS / demyelinating disease
- Ataxia / cerebellar disorders
- ADHD / autism
- Neurometabolic
- LSD’s / NCL
- TS
- NF
- NMD
- XLADL and other leukodystrophies
- Neuropathies
- Autonomic dysfunction
- Mitochondrial d/o’s
- Neuro-oncology
Common neurogenetic syndromes

• Some overlap with other talks
• Avoid any covered in depth elsewhere (NF, TS, VHL, LSD’s, mt d/o’s, neuro-onc, neuropathies, ataxia, metabolic, AS)
• Focus on identification to cover more disorders; less emphasis on mechanisms and treatments (characteristic features and neuro presentations bolded)
• Importance of molecular diagnosis (general – in young parents, recurrence risk - and disease specific)
• When is CGH array adequate?
• Images represent “classic” presentation; in many cases, facial features are more subtle and may be more common than the “classic” facial features; prob more recognized w/ next gen seq
Outline

Covered
- 22q11
- Alagille syndrome
- CFC
- Costello syndrome
- HHT
- Williams syndrome
- Bardet Biedl syndrome
- CHARGE syndrome
- Coffin-Lowry syndrome
- Cornelia De Lange syndrome
- Cri Du Chat (5p minus syndrome)
- Joubert syndrome
- Kabuki syndrome
- Rubinstein Taybi
- Smith-Magenis
- Wolf-Hirschorn syndrome
- BWS
- Sotos syndrome
- ***Check differential dx’s on GeneReviews

Elsewhere
- AS/PWS
- Rett syndrome
- Fragile X
- SMA
- Ataxia telangiectasia
- Greig’s cephalopolysyndactyly
- Fryn’s syndrome
- Monosomy 1p36
- VACTERL
- Friedreich’s ataxia
- Craniosynostoses
- Noonan syndrome
- McCune Albright
- Cockayne syndrome
- Muscular dystrophy: eg, Duchene’s/Becker’s
- Movement d/o’s: fragile X, FA, Huntington’s
- CVA w/leukoenceph: CADASIL
22q11 deletion syndrome

- CHD (74%): esp TOF, VSD
- Palatal abn (69%): CP, bifid uvula
- **Learning difficulties** (70-90%)
- Immune def (77%)
- Hypocalcemia (50%)
- Other: renal anomalies, HL, growth hormone def, sz, ophthalm (strabismus, posterior embryotoxin)
22q11 (cont.)

• Facial features: “long face”, hypertelorism, often subtle
• Inheritance: AD, 93% de novo
• Dx: CMA or FISH, rarely TBX1 mutation
• TX: essentially treat sx’s, manifestations
Alagille syndrome

- Cholestasis: bile duct paucity
- Skeletal: butterfly vertebrae
- Ophthalm: *posterior embryotoxin* (defect in anterior chamber identified on slit-lamp exam)
- *DD*/FTT
Alagille syndrome (cont.)

- Facial features: prominent forehead, deep set eyes, pointed chin, hypertelorism, nose w/ bulbous tip
- Dx: JAG1 (89%), NOTCH2 (1-2%)
- TX: treat manifestations, *occas liver tx*
Cardiofasciocutaneous syndrome

- Cardiac: **PS**, septal defects, HCM
- Facial features: High forehead, *macrocephaly*, bitemporal narrowing, hypertelorism, downslanting palpebral fissures, epicanthal folds, ptosis, short nose with depressed bridge and anteverted nares, ear lobe creases, low-set ears that may be posteriorly rotated, deep philtrum, high-arched palate, micrognathia
- Derm: hyperkeratosis of arms, legs, and face; eczema
- **Mild to mod intellectual disability**
- Inheritance: AD
- Genes: *BRAF* (~75%), *MAP2K1* and *MAP2K2* (~25%), and *KRAS* (<2%)
Costello syndrome

- FTT, short stature, *intellectual disability*
- Cardiac: *PS*, arrhythmia (esp, SVT)
- Facial features: coarse facial features (full lips, large mouth, full nasal tip); curly or sparse, fine hair; loose, soft skin
- 15% *lifetime risk for malignant tumors inc. rhabdomyosarcoma and neuroblastoma, transitional cell carcinoma of the bladder*
- Inheritance: AD
- Genes: *HRAS* (80-90%)
- Tx: *treat cardiac and FTT issues; consider surveillance with abd/pelvic US Q3mos until 8-10yo and UA for hematuria starting at age 10*
Hereditary Hemorrhagic Telangiectasia

- Triad: Epistaxis, mucocutaneous telangiectasias, **visceral AVM’s** *(pulm, cerebral, spinal, hepatic, GI)*
- Inheritance: AD
- Genes: **ACVRL1** (25-57%), **ENG** (39-59%), **SMAD4** (1-2%), **GDF2** (<1%)
- Tx: embolization; can be **difficult to manage**
- **Usually easy to diagnose**
Williams syndrome

- Cardiac: especially *supravalvular AS* (75%)
- Also hoarse voice overly friendly, anxious, ADD
- Endo: hypocalcemia, hypercalcuria, hypothy
- FTT in infancy
- Inheritance: AD; most de novo
- DX: contiguous 7q11.23 del; in 99% cases involving *ELN*
- Tx: supportive
Bardet-Biedl syndrome

- **Cone-rod dystrophy**
- Truncal obesity
- Postaxial polydactyly
- **Cognitive impairment**
- Hypogonadal
- Renal abn
- **Blindness by age 15.5 yrs usu**
- **Inheritance: AR; tri-alleleic!**
- **Dx:** **BBS genes (around 19 now)**
  - BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14), WDPCP (BBS15), SDCCAG8 (BBS16), LZTFL1 (BBS17), BBIP1 (BBS18), and IFT27 (BBS19)
- **TX:** supportive
CHARGE syndrome

- Coloboma
- Heart anomaly
- Choanal atresia
- Mental retardation
- Genitourinary malformations
- Ear anomalies +/- deafness
- Inheritance: AD
- DX: CHD7 seq (65-70%)
- Tx: supportive
Coffin-Lowry

- Profound MR
- Soft, fleshy hands w/ tapering fingers
- Males <3% ht
- Microcephaly
- Kyphoscoliosis
- “drop episodes”
- Thickened skull with ant vertebral beaking
- NL to profound MR in females
- Inheritance: XLD
- DX: RPS6KA3 seq (35-40%)
- Tx: respiridone, echo Q5-10yrs
Cornelia De Lange

- Growth retardation
- Low anterior hairline
- **Synophrys; coarse features**
- Cardiac anomalies
- Diaphragmatic hernia
- Ptosis
- **Mod-severe MR**
- Inheritance: AD and XLR
- DX: *NIPBL* (60%), *SMC1A* (4%; X chr), *SMC3* (<1%) seq
- Tx: supportive
Cri Du Chat (5p minus syn)

- **Cat-like cry** (abn laryngeal dev)
- FTT, hypotonia, strabismus
- **Mod-severe MR**
- Inheritance: AD
- DX: 5p15.2 del
- Tx: supportive
Joubert syndrome

- **Hypotonia in infancy**
- **Ataxia**
- **Pigmentary retinopathy**
- **Molar tooth sign on MRI from cerebellar vermis hypoplasia**
- Renal disease
- DD
- Inheritance: **AR (except OFD1; XL)**
- DX: **19 genes** are identified in about 50% of individuals with a JSRD: *NPHP1*, *CEP290*, *AHI1*, *TMEM67* (*MKS3*), *RPGRIP1L*, *CC2D2A*, *ARL13B*, *INPP5E*, *OFD1*, *TMEM216*, *KIF7*, *TCTN1*, *TCTN2*, *TMEM237*, *CEP41*, *TMEM138*, *C5orf42*, *TMEM231*, and *TCTN3*
- Tx: supportive
Kabuki syndrome

- Speech delay
- HL
- Fetal pads
- **IQ<80**
  - typical facial features (elongated palpebral fissures with eversion of the lateral third of the lower eyelid; arched and broad eyebrows; short columella with depressed nasal tip; large, prominent, or cupped ears)
- CHD
- Renal anomalies
- Joint laxity
- High arch palate, CL/CP
- Inheritance: AD, XLD
- DX: *MLL2, KDM6A (exome success)*
- Tx: supportive
Rubinstein Taybi

- CHD
- *Microcephaly*
- *Beaked nose*
- *Broad thumbs/toes*
- Cryptorchidism
- Growth delay
- Inheritance: AD
- DX: *CREBBP* (40-50%), *EP300* (3-8%)
- Tx: supportive
Smith Magenis

- Hypotonia
- FTT
- Short stature
- Brachydactyly
- *Sleep issues*
- *Behavioral, coarse features*
- Inheritance: AD
- DX: *RAI1*
- Tx: supportive
Wolf Hirschorn syndrome (4pminus)

- **Greek helmet appearance** (wide bridge of the nose continuing to the forehead)
- Microcephaly
- **Sz** (90-100%)
- DD
- IgA def
- CL/CP
- Renal anomalies
- Inheritance: AD
- DX: 4p16.3 del
- Tx: supportive; 2/3 of absence sz responsive to valproate (Carbamazepine may worsen atypical absence seizures.)
BWS

- hemihypertrophy
- Macrosomia
- Visceromegaly
- Embryonal tumors
- Neonatal hypoglycemia
- Ear pits
- Renal anomalies
- Inheritance: AD (15%)
- DX: abn methylation 11p15
- Tx: 20% mort (prob old overestimate), screen for embryonal tumors abd us q3mos w/ AFP (may be elevated prior to U/S findings) until 8yo
Sotos syndrome

- Macrocephaly
- Inverted pear shape
- CHD
- Sz’s
- Behavioral issues
- DD (can have nl IQ)
- Inheritance: AD
- DX: NSD1 (80-90%)
- Tx: supportive
Thank you