THE BAKER’S DOZEN: 13 CAN’T-MISS SYNDROMES

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Disclosure Information

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General Resources for Genetic Syndrome Diagnosis and Management:

- [www.genetests.org](http://www.genetests.org) Gene Reviews

Objectives

- Become familiar medical problems associated with these syndromes and their developmental/behavioral outcomes.
- Develop a working knowledge of genetic counseling for these syndromes.

Syndromes

- Fragile X
- Prader-Willi
- Angelman
- Beckwith-Weidemann and Hemi hyperplasia
- 22q11.2 Deletion (DiGeorge/Velo-Cardio-Facial Syndrome)
Turner
Klinefelter
Neurofibromatosis
Tuberous Sclerosis
Marfan
Achondroplasia
Wilsons
Long QTc Syndromes

Fragile X Syndrome

Genetics
- PCR/Southern blot: No. of trinucleotide CGG repeats FMR1 gene
  - Normal: 5-44  Intermediate “gray zone”: 45-54
  - Premutation carrier: 55-200  Full mutation: >200
- Genetic Anticipation: Maternal premutation carrier transmits unstable FMR1 allele to offspring. Premutation expands to full mutation >200 CGG repeats.
- Full mutation leads to hypermethylation of this expanded CGG repeat tract, silencing the FMR1 gene with consequent decrease/absence of encoded FMR1 protein: cognitive disability.
- Estimated female premutation carrier frequency in USA 1:178.
- Obtain DNA study if past diagnosis of Fragile X was based only on cytogenetic study for fragile site at Xq28.
- Genetic counseling complex; doesn’t follow standard X-linked pattern.

There is a great Fragile X algorithm available through www.genetests.org (gene reviews): http://www.ncbi.nlm.nih.gov/books/NBK1384/  Authors: RA Saul and JC Tarleton

Associated Medical Findings
- Mild overgrowth
- Mild macrocephaly (relative to family OFC)
- Feeding problems; colic
- 20% have seizures
- Strabismus, hyperopia
- Recurrent OM and sinus infections
- Mitral valve prolapse
- Macroorchidism (80-90%) – identified at puberty
- Joint hyperlaxity – pes planus
- Occassional pectus deformity
- Long face, high forehead, high arched palate, prominent ears, dental crowding

Developmental Outcomes
- Mild motor delays are common
  - Hypotonia, hyperextensibility
- Sensory integration problems and irritability may be seen
- Infants may be colicky, toddlers irritable – rigid with difficulty during transitions
- Language delays; cluttered speech
• Stereotypies and other common autistic behaviors
  o Poor eye contact, social anxiety
• Intellectual disability
  o Average IQ of 41 for fully affected adult male
  o Average IQ 88 for higher functioning males
  o Average range of 70-84 for females with the full mutation
• Hyperactivity is common and improves with age
• Enuresis is common
• Carrier females can also be affected

Recommendations
• CLINICAL REPORT
  Joseph H. Hersh, MD, Robert A. Saul, MD and Committee on Genetics.
  Health Supervision for Children With Fragile X Syndrome
  PEDIATRICS Vol. 127 No. 5 May 2011, pp. 994-1006. Published online May 1, 2011

• Echocardiogram
• Developmental Evaluation/School Supports
• Consider family member carrier testing

DDX
• ADHD, Learning Disability, Autism
• Intellectual Disability
• Hearing loss, Visual impairment
• Several X-linked intellectual disability disorders, including Lujan-Fryns Syndrome (marfanoid habitus and macroorchidism) and Atkin Syndrome (large ears, macroorchidism, and short stature)
• Sotos Syndrome (Cerebral Gigantism): Overgrowth syndrome with features of macrocephaly, prominent forehead, prominent chin/mandible, coordination dysfunction, and usually intellectual disability and difficult behavior.

Prader-Willi Syndrome
Genetics
• Genotype-Phenotype correlations
  o Type I deletions: more compulsions, poorer adaptive skills, lower IQ and lower academic achievement
• 75% microdeletion paternal chromosome 15q11.2-q13.
• 20% maternal uniparental disomy chromosome 15.
• <5% imprinting center defect within 15q11.2-q13.
• Rare paternal balanced insertion or translocation involving chromosome 15 that alters the imprinting center.
• Recurrence risk generally 1%, unless child has imprinting center mutation from carrier father (50% recurrence risk; very rare).

Associated Medical Findings
• Prenatal – hypotonia, decreased fetal movement, abnormal fetal position
• Infantile FTT – hypotonia, poor suck
• Short stature ↔ can improve with early GROWTH HORMONE
• Central obesity and severe hyperphagia
  o Increased diabetes
• Hypothalamic insufficiency
  o GH deficiency, increased hypothyroidism
  o Abnormal pubertal development
• Increased central adrenal insufficiency
• Strabismus, myopia, hyperopia
• Central and obstructive sleep apnea
• Enamel hypoplasia and atypical saliva
• Scoliosis
  o Muscular hypotonia
• Osteopenia, osteoporosis
• Increased risk of death with febrile illnesses; particularly pneumonia

**Developmental Outcomes**
• Motor delays
  o Sitting ~12months; Walking ~24months
• Poor coordination
• Language delay
• Mild intellectual disability
  o Average IQ 60s-70s
  o Relative weakness in math, sequential processing, short term memory
  o Strength in visual spatial skills, reading – great at jigsaw puzzles and wordfinding games
• Compulsive Hyperphagia
• Typical behavioral phenotype
  o Tantrums, stubbornness, ADHD, manipulative behavior, compulsiveness, rigidity, skin picking
  o Increased incidence of psychosis
  o High pain tolerance

**DDX**
• Several obesity-intellectual disability syndromes, including
  Bardet-Biedl Syndrome (polydactyly, retinitis pigmentosa, cystic renal disease)
  Cohen Syndrome (hypotonia, prominent central incisors, retinal dystrophy)
  Alstrom Syndrome (cone-rod dystrophy, deafness, type 2 diabetes)

  • A subset of Fragile X males have early onset obesity.

**Recommendations**
• **CLINICAL REPORT**
The Committee on Genetics

  Health Supervision for Children With Prader-Willi Syndrome - AAP Policy

- Increased risk of death with febrile illnesses; particularly PNA
- Heavy involvement by Peds Endocrinology
- Growth hormone
  - through adulthood?
- Sleep study and ENT consult prior to GH
- Aggressive weight management
  - Calorie restriction

**Angelman Syndrome**

**Genetics**

- Pathogenesis: Disruption/impairment of UBE3A gene function (processing of neural synapse-related proteins in fetal brain).
- 65-70% microdeletion maternal chromosome 15q11.2-q13.
- 3-7% paternal uniparental disomy chrom. 15 (milder phenotype).
- 3% imprinting center defect within maternal 15q11.2-q13.
- 5-11% UBE3A gene mutations.
- 10-15% unknown mechanism.
- DNA methylation is most sensitive single test, but DNA sequence analysis required to identify UBE3A mutations. Recurrence risk <1% for microdeletion and pat. uniparental disomy. Recurrence risk as high as 50% for maternally inherited imprinting center defect or UBE3A mutation.

**Associated Medical Findings**

- Present with nonspecific psychomotor delay and/or seizures
- Speech delay
- Global developmental delays
- Abnormal forward gait, arms held high, flexed at elbows
- Truncal Hypotonia, hypertonic limbs
- Tremulous, jerky
- Feeding/growth problems
- Acquired microcephaly
  - Generally more than 2SD below the mean

**Developmental Outcomes**

- Intellectual disability
  - usually severe to profound, 24-30month average cognitive skills
- Receptive language is a relative strength
- Typically nonverbal with good social skills as adults
Good nonverbal social communication
- Persistent SPONTANEOUS social smiling (1-3 months) and fits of laughter (can be as early as 10 weeks!!)
- Truncal hypotonia – can be hypertonic in the limbs
- Commando crawl – not on all fours
- Hand flapping with excitement
- LOVE water, open mirrors, music toys
- Cartoons are scary
- Hyperactive, inattentive
- Oral exploration
- Abnormal sleep cycles

DDX for seizures and global developmental delay
- Metabolic, CNS embryologic developmental abnormality, genetic epilepsy syndromes.

DDx for Angelman Syndrome

Recommendations
- Anticonvulsants – Peds Neurology
- Peds Ophthalmology
- Early Intervention
- Consider adaptive equipment needs
- Structured Environment
- Family Support for abnormal sleep-wake cycles and hyperactivity
  - Very few children require stimulants or sleep aids

Beckwith-Weidemann Syndrome

Genetics
- Dysregulation of imprinted genes at chromosome 11p15.5.
- Several documented molecular mechanisms.
- Most cases sporadic; 15% familial autosomal dominant.
- 50% sporadic BWS have loss of methylation on maternal chromosome 11p15.5 at imprinting center 2 (IC2).
- 20% sporadic BWS have paternal uniparental disomy involving chrom 11p15.5 due to a post-zygotic event.
- Other genomic mechanisms: see www.genetests.org

Associated Medical Findings
- Birth: LGA, omphalocele or umbilical hernia, macroglossia, facial nevus flammeus, post. helical pits, prominent eyes, anterior ear lobe creases.
- Prenatal morbidity
  - Preterm birth, Polyhydramnios
  - Large placenta & long umbilical cord
• Perinatal mortality is ~20%
• Hypoglycemia ~30-50% of babies with BWS
  o Hyperinsulinemia, islet cell hyperplasia
• Neonatal polycythemia, hypocalcemia. Hypercholesterolemia. Hypothyroidism
• Cardiomegaly is common
  o Hypoplastic left heart (rare), mild pulm stenosis, and persistent foramen ovale
• Visceromegaly (liver, kidney, spleen)
  o Nephromegaly and a wide range of other anomalies is common
• Increased risk for cancer, especially prior to 8 years old (embryonal tumors)
  o 7.5% risk for solid tumor in BWS; 5.9% in isolated hemihyperplasia
  o Wilms, hepatoblastoma, rhabdomyosarcoma, adrenocortical carcinoma, neuroblastoma
• Children with milder phenotypes (eg. Only macroglossia and umbilical hernia) may develop tumors. Renal manifestations include hypertension, nephrocalcinosis, medullary sponge kidney, medullary dysplasia, cystic changes. Rarely, cardiomyopathy
• Over time, dental malocclusion with tendency toward maxillary underdevelopment and mandibular prognathism.

**Idiopathic Hemihyperplasia**

• Asymmetric overgrowth of one-half of the body
  o Single limb
  o Side of face, including tongue asymmetry
  o Visceromegaly
• Increased intraabdominal tumors
  o Kidney, liver, adrenal

**Developmental Outcomes**

• Development is usually normal in BWS
  o Abnormal secondary to prolonged hypoglycemia
    • Smaller OFC, lower IQ
    • Neurodevelopmental prognosis is poor if hypoglycemic seizures
  o Abnormal if duplication of 11p15
• Articulation may be poor due to macroglossia and/or asymmetric facial muscles
• Increased incidence of developmental delay (15-20%) in isolated hemihyperplasia
  o Motor problems may be seen if large discrepancy in extremities

**DDX**

• Isolated hemihyperplasia (hemihypertryophy) for which abdominal embryonal tumor surveillance is also indicated.
• Other overgrowth syndromes, especially:
  o Perlman Syndrome (AR) – macrosomia and high risk of Wilms’ tumor.
  o Simpson-Golabi-Behmel Syndrome (X-linked Recessive) – macrosomia +/- macrocephaly, visceromegaly, renal cystic dysplasia, and increased
risk for Wilms’ tumor. Distinguished by different facial appearance, frequent polydactyly, cleft lip or cleft palate, cardiac conduction abnormalities, and developmental disabilities.

Recommendations
- TREAT HYPOGLYCEMIA
- Cardiac evaluation
- Cancer screening
  - Serum alphafetoprotein every 6 weeks until age 4
  - Abdominal Ultrasounds every 3 months until age 8
- Sleep Study, ENT consult
  - Partial tongue resection (reduction glossoplasty) sometimes indicated for obstructive sleep apnea and severe articulation dysfunction associated with macroglossia
- Orthodontics
- Early Intervention for speech delay
- Craniofacial and/or Orthopedic involvement
- Consider need for adaptive equipment, shoe lift, Physical Therapy

22q11.2 Deletion Syndrome - Also known as DiGeorge Syndrome, Velocardiofacial Syndrome (VCF) and conotruncal anomaly face syndrome; Asymmetric Crying Facies and CHD associated with 22q11 deletion

Genetics
- Usually sporadic, born to normal parents. Dominant inheritance from affected parent.
- Parental F.I.S.H. analysis for microdeletion 22q11.2 indicated before genetic counseling is provided.

Associated Medical Findings
- Congenital Heart Defects
  - Tetralogy of Fallot, VSD, Interrupted aortic arch
- Palatal anomalies, velopharyngeal incompetence, submucosal CP, craniosynostosis, facial anomalies
  - Commonly a long tubular nose with hypoplastic alae nasi, “crumpled ears”, hypertelorism, malar hypoplasia,
  - Facial features vary with ethnicity
- Hypotonia, hypocalcemic seizures
- Immunodeficiency is common – impaired T cell function
- Hypoparathyroidism, hypocalcemia, growth hormone deficiency
- ~30% have renal anomalies
- Early feeding problems
  - Secondary to cardiac anomalies/palatal defects
  - Nasal regurgitation
  - Pharyngeal hypotonia
- Vomiting, chronic constipation
• Chronic otitis media and chronic sinusitis
  o CHL > SNHL
• Polydactyly, clubfoot, vertebral anomalies
• Ophthalmologic abnormalities – strabismus; posterior embryotoxon

Developmental Outcomes
• >90% have developmental disability
• 20% have autism
• Communication disorder
  o Delayed speech
  o Severe hypernasality leads to poor articulation and atypical pattern of language development
  o May appear apraxic or dyspraxic
• Increased psychiatric disorders
  o Bipolar, schizophrenia, mood disorders

DDX
• Cayler Cardiofacial Syndrome (asymmetric crying facies + conotruncal cardiac malformation): also 22q11.2 deletion
• CHARGE Syndrome also features congenital heart disease, immunodeficiency, hypocalcemia, and hearing loss.
• Some overlap with oculo-auriculo-vertebral spectrum
• (Goldenhar Syndrome), Kabuki Syndrome, Alagille Syndrome

Recommendations
• Cardiology evaluation
• Endocrine evaluation
  o Calcium, hypoparathyroid studies
• Renal ultrasound
• Developmental evaluation
• Early referral for Speech Therapy
• Monitor for Hearing Loss
• Immunology evaluation

Turner Syndrome
Genetics
• Sporadic; less than 1% recurrence risk.
• Deficiency of one copy SHOX (short stature homeobox gene) on Xp considered to have role in short stature.
• Karyotype:
  o 50-60% 45,X
  o 20-25% 45,X/46,X(X)* ie. Structural defect of one X
  o 10-20% 45,X/46,XX mosaic (2 cell lines): often only short stature

Associated Medical Findings
• Short neck – webbing; low posterior hair line
• Prominent post. rotated ears with upturned ear lobes, ptosis, micrognathia
• Cubitus valgus
• Short 4th, 5th metacarpals (50%)
• Disproportionately short legs
• Hyperconvex nails
• Cardiac
  o Bicuspid aortic valve, Coarctation of aorta, Hypoplastic left heart with heart failure
  o Risk of aortic dilatation 9%; aortic dissection uncommon in childhood
  o Hypertension
• Musculoskeletal
  o Hip dysplasia (5-10%)
  o Scoliosis and/or kyphosis (10-20%)
• Renal structural abnormalities (> 60% )
  o horseshoe kidney, ectopic kidney, aplasia, double collecting system, UPJ obstruction
• ENT
  o Chronic otitis, conductive hearing loss common,
• Dermatology
  o Dysplasia, Keloids, Vitiligo
• Autoimmune
  o Obesity, hyperlipidemia, hyperinsulinism, thyroiditis
  o Inflammatory bowel disease
  o Celiac Disease
• Endocrine
  o Short stature for family history. May otherwise be normal. 50% are <5% by age 18 mos.;75% are <5% by age 3.5 yr.
  o Delayed Puberty, infertility
  o Menarche 1-3%

Neonatal Presentation of Turner Syndrome
• Fetus: Edema, hydrops
  o 98% spontaneous abortion
• Newborn: Puffy edema of feet, hands; nuchal webbing; broad chest with wide-spaced nipples; left sided cardiac defect

Developmental Outcomes
• NONVERBAL LEARNING DISABILITIES
  o Generally normal IQ
  o verbal and language IQ > performance IQ
  o many are successful in college
• Scattered profile of specific learning disabilities
  o visual spatial organization
  o nonverbal problem solving (math)
  o visual – motor tasks
- social cognition (subtle clues)
- ADHD (24%)
- Increased depression, anxiety
- 50% experience hearing loss
  - conductive HL, chronic OM
  - sensorineural HL > age 6 yrs
- Vision impairment
  - Strabismus, Cataracts, Ptosis

**DDX**
- Noonan Syndrome
- Pseudohypoparathyroidism-Albright Hereditary Osteodystrophy
- Congenital lymphedema disorders (eg. Milroy lymphedema)

**Recommendations**
- **Care of Girls and Women With Turner Syndrome: A Guideline of the Turner Syndrome Study Group**
  Pediatrics 2009 123: 1423

  **AFFIRMATION OF VALUE**
  On October 7, 2008, the American Academy of Pediatrics determined that the following clinical practice guideline may be of educational value to its members:

  Available at: [http://jcem.endojournals.org/cgi/content/full/92/1/10](http://jcem.endojournals.org/cgi/content/full/92/1/10).

  *Note: With the affirmation of value of this publication, the American Academy of Pediatrics statement "Health Supervision for Children With Turner Syndrome" (Pediatrics. 2003;111[3]:692–702) was retired as of October 2008.*

- Cardiac: Initial evaluation and then yearly ECHO
  - BP checks at all visits
- Endocrine:
  - Growth Hormone to increase stature
  - Estrogen replacement therapy
- Early treatment of scoliosis
- Annual skin exams
- Annual thyroid function
- Monitor LH and FSH after age 10 years
- School accommodations
- *Motherhood generally through adoption*

**Klinefelter Syndrome**

**Genetics**
- Karyotype
  - 79% XXY
  - 20% 46XY/47XXY mosaicism (2 cell lines)
1% 48XXXY; 48XXYY; 49XXXXY; etc.

- Serum testosterone: FSH; LH; hCG; TSH
- Sporadic; < 1% recurrence risk.

**Associated Medical Findings**

- **Malignancy**
  - Male breast cancer 20 fold over XY men
  - ALL; Hodgkins and non-Hodgkins lymphoma
  - hCG secreting tumors (extragonadal germ cell tumors)
- **Hypercoagulable state (DVT and PE risk in adults)**
- **Relatively tall; long arm span > Height**
- **Endocrine**
  - Infertility; azospermia; XY/XXY mosaic males occasionally fertile (25% risk of XXY sons).
  - Small penis, cryptorchidism or small testes
  - Gynecomastia; skin striae
  - Delayed puberty; low testosterone and increased LH and FSH by ages 12 to 14 yr
- **Decreased energy, endurance, poor coordination**
- **Autoimmune disorders (SLE, RA, Thyroid, NIDDM)**
- **Scoliosis; osteoporosis**
- **Taurodontism (thin tooth surface; enlarged pulp chamber); dental decay**

**Developmental Outcomes**

- **Delayed Expressive Language**
  - Dyspraxia – poor phonemic development, motor imitation, decreased vocalizations
- **Incidence of MR not increased**
- **Lower verbal IQ for normal performance IQ**
- **Specific learning disabilities, Dyslexia, memory problems, difficulty with written language**
- **Behavioral: shy or withdrawn, low maturity for age, some with low self-esteem, anxiety, neuroses, depression**
- **ADHD**

**DDX**

- Hearing loss, autism
- Kallman Syndrome (deficient olfaction) and other causes of hypogonadotropic hypogonadism
- Prepubertally, the milder spectrum of Fragile X Syndrome

**Recommendations**

- Peter A. Lee, Christopher P. Houk, S. Faisal Ahmed, Ieuan A. Hughes in collaboration with the participants in the International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology
Consensus Statement on Management of Intersex Disorders
Pediatrics 2006 118: e488-e500

- Reassure regarding gender identity
- Peds Endocrinologist for testosterone replacement IM or patch
  - Begin age 11-12 yr.
  - More masculine pubertal development; muscle mass
  - Improves bone mineral density
  - Improves self-esteem, mood and behavior
- Plastic surgery available for gynecomastia
- Monitor for male breast cancer
- School accommodations/Early Intervention for language problems
- Behavioral support
- Klinefelter’s Syndrome Association, Inc.
  www.genetic.org (888)999-9428

Neurofibromatosis-1 (NF-1)
Genetics
- Autosomal dominant mutations (90%) or whole gene deletions (5%) of NF1 gene at chromosome 17q11.2. NF1 gene: tumor suppressor as negative regulator of ras-mediated signal transduction pathway.
- 50% born to “normal parents” (new spontaneous gene mutations). Refer for parental medical history, physical exam, slit lamp exam.
- Somatic mosaicism (localized to a body region) has much lower transmission risk to a child. Parental germline mosaicism reported, but rare.
- High penetrance; widely variable expressivity. Cells of neural crest origin (eg. melanocytes) are most affected. DNA mutation analysis not necessary, unless affected parent considers assistive reproductive technology (ART).

NF-1 Diagnostic Criteria
Two or more of the following:
- Two or more neurofibromas or one plexiform neurofibroma
  - 6 or more CALM >5mm in prepubertal
  - 6 or more CALM >15mm postpubertal
- Axillary or inguinal freckling (Crowe’s sign)
- Optic nerve tumor
- Two or more Lisch nodules (iris hamartoma)
- Distinctive osseous lesion: sphenoid dysplasia or long-bone bowing with or without pseudoarthrosis
- First degree relative with NF-1

Associated Medical Findings
- Neurofibromas
- Optic nerve tumors
- Increased solid tumors and leukemia, CNS gliomas
- Sphenoid wing dysplasia
Psuedoarthrosis
Scoliosis
HTN, increased cardiac defects (pulmonic stenosis, aortic coarctation, CAD)

Developmental Outcomes
- Learning disabilities (40-60%)
- Impaired executive function
  - inattention, impulsivity
- Delayed speech and communication
- Learning problems tend to improve with age

DDX
- Legius Syndrome (SPRED1 gene): CAL + axillary/inguinal freckling; no neurofibromas or ophthalmologic manifestations of NF1. McCune-Albright Syndrome (polyostotic fibrous dysplasia). Neurofibromatosis Type 2. Multiple autosomal dominant CAL macules without neurofibromas.

Recommendations
- Health Supervision Guidelines
  - Joseph H. Hersh, MD and Committee on Genetics Health Supervision for Children With Neurofibromatosis PEDIATRICS Vol. 121 No. 3 March 2008, pp. 633-642
- Developmental assessment/school support
- MRI any suspected plexiform neurofibromas
- Low threshold for Brain MRI
- Manage scoliosis
- Routine BP checks
- Annual Peds Ophtho exams
- Children’s Tumor Foundation website is excellent for NF1: www.ctf.org

Tuberous Sclerosis
Genetics
- Mutations of two genes identified to date:
  - TSC1 (protein product hamartin) at chromosome 9q34.3
  - TSC2 (protein product tuberin) at chromosome 16p13.3
- 75-85 of individuals who meet diagnostic criteria have a TSC1 or TSC2 mutation. 6% have a large gene deletion. For diagnostic criteria, see Gene Review for tuberous sclerosis (TS) in www.genetests.org.
- Autosomal dominant. If parents normal, spontaneous gene mutation is likely, but parental germline mosaicism is reported, so recurrence risk is about 1% for normal parents with negative DNA mutation analysis and normal Woods lamp and retinal exams, renal ultrasound, and brain neuroimaging.
Associated Medical Findings
- Cortical brain tubers
  - Seizures
- Subependymal nodules → astrocytomas
- Ash leaf spots, angiofibromas, shagreen patches, ungual fibromas
- Retinal astrocytic hamartomas
- Cardiac rhabdomyosarcomas
  - Most resolve spontaneously

Developmental Outcomes
- Intellectual Disability (45-75%)
- Autism (50%)
- Learning disabilities
  - Memory impairment, dyscalculia, visuospatial disturbances, dyspraxia

DDX
  - Facial angiofibromas of TS resemble acne to some extent.
- Note that one to three hypopigmented macules can be present on skin of normal persons. Cardiac rhabdomyomas or renal angiomyolipomas can develop sporadically, unrelated to TS

Recommendations
- Clinical Guidelines: UK Tuberous Sclerosis Association
  - http://www.tuberous-sclerosis.org/?page_id=103
- CT/MRI at diagnosis
- Echocardiogram in infancy
- Renal US at diagnosis
- Peds Ophthalmology at diagnosis
- Early Developmental Evaluation

Achondroplasia
Genetics
- Completely penetrant, autosomal dominant, most common skeletal dysplasia. Unique single base pair substitution mutation involving fibroblast growth factor receptor 3 gene (FGFR3) at chrom. 4p16.3.
- Most commonly born to parents of normal stature from spontaneous gene mutation.
Recurrence risks:
- Normal parents: <1%. Germline mosaicism reported, but very rare.
- Parent with achondroplasia: 50%.
- Two parents with achondroplasia: 50% achondroplasia + 25% unaffected child + 25% homozygous achondroplasia (severe; lethal).
- Use achondroplasia specific growth charts in primary care.
Associated Medical Findings

- Disproportionate limbs, rhizomelic shortening, “trident” fingers
- Short stature (mean height 49-51in)
- Macrocephaly, frontal bossing, depressed nasal bridge, malar hypoplasia
  - 5% may have symptomatic hydrocephalus
- Fatal apnea (~10%) especially before age 2yrs
  - Misshaped and small foramen magnum
  - Vascular and cervicomедullary constriction
- OSA is very common
  - Obesity, small airway, lymphatic hypertrophy
- Chronic hypoxemia can be associated with small thoraces/constricted chest
- Middle ear dysfunction – CHL
- Kyphosis resolves in most
- Spinal stenosis is uniformly present
- Knee instability in toddlers, varus deformity (bowlegs)
- Orthodontic problems associated with crowding and overbite
- Anesthesia risks (cervical spinal stenosis, small airway, OSA, restrictive lung disease)

Developmental Outcomes

- Cognitive development and function is typically normal
  - ~10% may have severe learning disabilities, intellectual disability or ASD
- Motor development is delayed and atypical due to hypotonia, disproportion, joint hypermobility
  - Sit 9-20months
  - Walk 14-27months
- Increased language delays
  - Associated with chronic OME and conductive hearing loss
- If marked developmental delays or hypotonia evaluate for craniocervical junction compression!

DDX

- Other skeletal dysplasias + disproportionate short stature, incl.
  - Hypochondroplasia (milder bone dysplasia; often also FGFR3).
  - Thanatophoric dysplasia (severe; usually lethal; also FGFR3).
  - Pseudoachondroplasia (epiphyseal + metaphyseal dysplasia;COMP gene).

Recommendations

- CLINICAL REPORTS
  Tracy L. Trotter, Judith G. Hall and the Committee on Genetics
  Health Supervision for Children With Achondroplasia

- Standardized linear growth charts
- Environmental and adaptive modifications
Driving, reaching, etc
- MRI or CT brain and C-spine after diagnosis during neonatal period or early infancy
  - Close monitoring of OFC
- Sleep study
- Audiology
- Avoid poor infant positioning (<12 months)
  - NO unsupported sitting, umbrella strollers, swings
- Close neurologic monitoring with regular exams
- Little People of America
  [http://www.lpaonline.org](http://www.lpaonline.org)

**Marfan Syndrome**

*Genetics*
- Autosomal dominant connective tissue disorder, full penetrance, variable expressivity. Fibrillin (FBN1) mutation chrom. 15q21.1.
- Pathogenesis: Reduced fibrillin-containing microfibrils in elastic tissue results in fewer binding sites for transforming growth factor beta (TGFβ) and overactive TGFβ signaling in tissue (role in vascular wall modeling).
- Mutation detection 90% in patients meeting clinical diagnostic criteria (see ref. for revised Ghent criteria, 2010; Gene Review at [www.genetests.org](http://www.genetests.org))
- 75% Marfan Syndrome patients have an affected parent, whose recurrence risk for offspring is 50%. If both parents clinically unaffected, recurrence risk is < 1%. Germline mosaicism reported.

*Associated Medical Findings*
- Tall stature, long limbs - dolichostenomelia, arachnodactyly
  - Disproportionate upper-to-lower segment ratio (<0.85 in adults)
  - Increased arm span-to-height ratio (>1.05)
- Aortic root dilatation/dissection, mitral valve prolapse and/or regurgitation
- Ectopia lentis, myopia, cataracts, glaucoma, retinal detachment, exotropia/strabismus
- Apical blebs \(\rightarrow\) Increased spontaneous pneumothorax
- Connective tissue involvement
  - Pectus deformities, Scoliosis, Dural ectasia (weakness of spinal cord sac), Joint hyperextensibility, Contractures
  - Increased hernias, striae,
- *Neonatal Marfan Syndrome is often fatal in first year of life due to CHF*

*Developmental Outcomes*
- Typical cognitive development
- Motor development may be affected by joint hyperextensibility
- Increased risk for psychosocial morbidity
  - Associated with individual and family response to increased risk of death

**DDX**
- Homocystinuria: Often Rx Vit. B6. Plasma homocysteine and serum amino acids indicated for all patients with clinically normal parents
- Loeys-Dietz Syndrome - dilated tortuous aorta, cleft palate or bifid uvula, hypertelorism, occasional craniosynostosis, arachnodactyly, often translucent skin
- Stickler Syndrome - marfanoid habitus, cleft palate including Robin Sequence, mid-facial hypoplasia, hearing loss, severe myopia with risk for cataract and retinal detachment, spondyloepiphyseal dysplasia on skeletal radiographs
- Familial Thoracic Aortic Aneurysms & Dissection
- Ehlers-Danlos Syndrome
- Congenital Contractural Arachnodactyly (Beals Syndrome) – joint contractures, arachnodactyly, crumpled ear, mitral valve prolapse with regurgitation, occasional aortic root dilatation.
- Other connective tissue disease

**Recommendations**

Proper multidisciplinary management = improved life expectancy

- AAP Health Supervision Guidelines (1996)

- Cardiovascular
  - Yearly echocardiography
  - Beta-blockers reduce hemodynamic stress on aortic wall
  - Surgical aortoplasty (aortic diameter > 5cm or smaller diameter but rapid progression of dilatation in very young children)
  - Mitral and aortic valve replacement for progressive MI, AISBE prophylaxis essential
  - Avoid competitive sports and isometric exercise

- Ocular: Experienced Peds Ophthalmology is essential
  - Lens dislocation may require surgical lens implantation

- Progressive scoliosis: surgical stabilization
- Severe pectus excavatum may limit cardiopulmonary function

- National Marfan Foundation
  - [www.marfan.org](http://www.marfan.org); Email staff @ marfan.org
  - 1-800-8MARFAN

- Canadian Marfan Association
  - [www.marfan.ca](http://www.marfan.ca); Email info@marfan.ca
  - 1-866-722-1722

**Ghent Diagnostic Criteria for Marfan:** [www.genetests.org](http://www.genetests.org) (gene reviews)

**Wilson Disease**

Genetics
- Autosomal recessive. Defective transport of copper from liver into apoceruloplasmin and into the biliary system. Excess copper accumulation in liver.
- Diagnosis: ATP7B gene DNA sequence analysis. Most patients carry two different mutations (compound heterozygotes). Kayser-Fleischer rings may be absent and serum ceruloplasmin can be nl.
- Once proband is diagnosed, screen all siblings for same mutation(s) with DNA analysis, because affected individuals can be asymptomatic for many years, and Wilson Disease is treatable.

Associated Medical Findings
- Lifelong neurologic impairment
  - Drooling
  - Tremors
- Fulminant hepatic failure
- Cirrhosis, portal hypertensions
- Hemolytic crisis (can be fatal)
- Cerebral and brain stem atrophy
- White matter changes on brain MRI
- Kayser-Fleischer Rings
- Low serum ceruloplasmin

Developmental Outcomes
- Adolescence
  - Deteriorating handwriting
  - Tremors
  - Clumsiness
  - Spasticity
  - Academic decline
  - Behavior disturbance
- Psychiatric symptoms are common, especially Bipolar Disorder, Depression and Dysthymia, psychosis, schizophrenia
- Cognitive decline (leading to intellectual disability)
- Personality changes (irritability, disinhibition, impulsivity)

DDX
- Other causes of non-alcoholic chronic liver disease, or acute RBC hemolysis especially if recurrent, or movement disorders (tremors, rigid dystonia, deterioration in coordination).

Recommendations
- Early Diagnosis and treatment can prevent progression
- Partner with Peds GI
- Copper chelation therapy
  - Penicillamine or triethylene tetramine dihydrochloride + oral zinc
- Copper avoidance
  - Shellfish, nuts, liver, chocolate
Long QTc Syndrome

- Congenital form of Long QTc
  - Positive family history in 60%
- Romano-Ward Syndrome
  - Less severe
- Jervell and Lange-Nielsen Syndrome
  - Suspect when history of near drowning, syncope, family history of sudden death

Jervell and Lange-Nielsen Syndrome

- Autosomal recessive Long QTc
- Profound sensorineural deafness
  - The deaf child with syncope
- Ventricular tachyarrhythmia
- High risk of sudden cardiac death
- Gene mutations in cardiac potassium channels

Romano-Ward Syndrome

- Long QTc
- Familial syncope or sudden death
- Syncope, seizures, palpitations with exercise or intense emotions
- Sudden cardiac death, especially with swimming, diving and vigorous exercise
- Personally screen family members, involve Cardiologist, beta blockers, supervised swimming, recreational sports only
- Six distinct molecular genotypes documented

Recommendations

- **Screening for Long QT Syndrome.**  Mike Dubik.  AAP Grand Rounds 2006; 16(5):49-50.  Family members must be screened once proband is diagnosed. Depending upon results, extended family screening may be necessary.

- Consider screening ECG in patients with congenital profound sensorineural deafness
- High index of suspicion if FH is positive for drowning/SCD
- Beta blockers
- Avoid high risk situations – vigorous exercise, swimming alone

ADDITIONAL REFERENCES (see other sources above)

