THE BAKER’S DOZEN: Genetic Syndromes with Developmental Disabilities

General Resources for Genetic Syndrome Diagnosis and Management:
- www.genetests.org  Gene Reviews

Objectives
- Recognize features of common genetic syndromes associated with developmental disabilities.
- Become familiar medical problems associated with these syndromes and their developmental/behavioral outcomes.
- Become familiar with basic genetic counseling for these syndromes.

Syndromes
- Fragile X
- Prader-Willi
- Angelman
- Beckwith-Wiedemann
- Chromosome 22q11.2 Deletion (DiGeorge/Velo-Cardio-Facial Syndrome)
- Turner
- Noonan
- Klinefelter
- Neurofibromatosis
- Tuberous Sclerosis
- Achondroplasia
- Williams
- Wilson Disease

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 inheritance pattern.

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
- Occasional 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
  - Poor eye contact, social anxiety
- Intellectual disability
  - Average IQ of 41 for fully affected adult male
  - Average IQ 88 for higher functioning males
  - 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

**DDX**
- Non-specific Intellectual Disability
- Autism, Severe Learning Disability +/- ADHD
- Several X-linked intellectual disability disorders.
- 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**
  - 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
  - Increased diabetes
- Hypothalamic insufficiency
  - GH deficiency, increased hypothyroidism
  - Abnormal pubertal development
- Increased central adrenal insufficiency
- Strabismus, myopia, hyperopia
- Central and obstructive sleep apnea
- Enamel hypoplasia and atypical saliva
- Scoliosis
  - Muscular hypotonia
- Osteopenia, osteoporosis
- Increased risk of death with febrile illnesses; particularly pneumonia

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

**DDX:** Several obesity-intellectual disability syndromes. 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
  *Pediatrics* Vol. 127 No. 1 January 2011, pp. 195-204


- Increased risk of death with febrile illnesses; particularly PNA
- Growth hormone management by pediatric endocrinology
  - through adulthood?
- Sleep study and ENT consult prior to growth hormone
- 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 chromosome 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 ataxic 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 improved social skills as adults
  - Good nonverbal social communication
- Persistent SPONTANEOUS social smiling (1-3months) and fits of laughter (can be as early as 10weeks!!)
- 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**
- Rett Syndrome, autism, ataxic CP

**Recommendations**
- Anticonvulsants – Pediatric Neurology
- Pediatric 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 aides

**Beckwith-Wiedemann Syndrome (BWS)**

**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).
- Other genomic mechanisms: see www.genetests.org

**Associated Medical Findings**
- Birth: LGA, omphalocele or umbilical hernia, macroglossia, facial nevus flammeus, posterior ear pits on helix, 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
  - Hyperinsulinemia, islet cell hyperplasia
- Neonatal polycythemia, hypocalcemia. Hypercholesterolemia. Hypothyroidism
- Cardiomegaly is common
  - Hypoplastic left heart (rare), mild pulmonic stenosis, and persistent foramen ovale; occasionally, cardiomyopathy
- Visceromegaly (liver, kidney, spleen)
  - Nephromegaly is common. Renal manifestations may include hypertension, nephrocalcinosis, medullary sponge kidney, medullary dysplasia, cystic changes.
- Increased risk for cancer, especially prior to 8 years old (embryonal tumors)
  - 7.5% risk for solid tumor in BWS; 5.9% in isolated hemihyperplasia
Wilms tumor, hepatoblastoma, rhabdomyosarcoma, adrenocortical carcinoma, neuroblastoma

- Children with milder phenotypes (eg. only macroglossia and umbilical hernia) may develop tumors.
- Over time, dental malocclusion with tendency toward maxillary underdevelopment and mandibular prognathism.

**Developmental Outcomes**

- Development is usually normal in BWS
  - Neurodevelopmental disabilities secondary to prolonged hypoglycemia
    - Smaller OFC, lower IQ
    - Neurodevelopmental prognosis is poor if hypoglycemic seizures
  - Abnormal if duplication of 11p15
- Articulation may be poor due to macroglossia and/or asymmetric facial muscles

**DDX**

- Isolated hemihyperplasia (hemihypertryophy) for which abdominal embryonal tumor surveillance is also indicated.
- Other overgrowth syndromes

**Recommendations**

- TREAT HYPOGLYCEMIA
- Cardiac evaluation
- Cancer screening
  - Serum alpha-fetoprotein every 6 weeks until age 4
  - Abdominal Ultrasounds every 3 months until age 8
- Sleep Study, ENT consult
  - Partial tongue resection surgery (ie. reduction glossoplasty) often 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

**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, ventricular septal defect, interrupted aortic arch
• Palatal anomalies, velopharyngeal incompetence, submucosal cleft palate, craniosynostosis, facial anomalies
  o Commonly a long tubular nose with hypoplastic alae nasi, “crumpled ears”, hypertelorism, malar hypoplasia,
  o 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
  o Secondary to cardiac anomalies/palatal defects
  o Nasal regurgitation
  o 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.

Recommendations
• Cardiology evaluation
• Endocrine evaluation
  o Calcium, parathyroid 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:
  - 50-60% 45,X
  - 20-25% 45,X/46,X(X)* ie. structural defect of one X chromosome
  - 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
  - Bicuspid aortic valve, coarctation of aorta; rarely hypoplastic left heart with early onset heart failure
  - Risk of aortic dilatation over the years is 9%; aortic dissection uncommon in childhood
  - Hypertension
- Musculoskeletal
  - Hip dysplasia (5-10%)
  - Scoliosis and/or kyphosis (10-20%)
- Renal structural abnormalities (> 60%)
  - horseshoe kidney, ectopic kidney, aplasia, double collecting system, uretero-pelvic junction obstruction
- ENT
  - Chronic otitis, conductive hearing loss common,
- Dermatology: skin dysplasia, keloids, vitiligo
- Autoimmune
  - Obesity, hyperlipidemia, hyperinsulinism, thyroiditis
  - Inflammatory bowel disease
  - Celiac disease
- Endocrine
  - Short stature for family history. May otherwise be normal. 50% are <5% by age 18 mos.; 75% are <5% by age 3.5 yr.
  - Delayed puberty, infertility
  - Menarche 1-3%

**Neonatal Presentation of Turner Syndrome**
- Fetus: Edema, hydrops
  - 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**
  - Generally normal IQ
  - Verbal and language IQ > performance IQ
  - Many are successful in college
- Scattered profile of specific learning disabilities
  - Visual spatial organization
  - Nonverbal problem solving (math)
  - Visual – motor tasks
  - Social cognition (subtle clues)
- ADHD (24%)
- Increased depression, anxiety
- 50% experience hearing loss
  - Conductive hearing loss, chronic otitis
  - Sensorineural hearing loss > age 6 yrs
- Vision impairment
  - Strabismus, cataracts, ptosis

**DDX**
- Noonan Syndrome (short stature, webbed neck, right-sided cardiac defect (esp. pulmonic stenosis), pectus deformity of chest, frequent developmental disabilities that may include intellectual disability or specific learning disabilities.

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


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

**Klinefelter Syndrome**

**Genetics**
- Karyotype
  - 79% XXY
  - 20% 46,XY/47,XXY mosaicism (2 cell lines)
  - 1% 48,XXXXY; 48,XXYY; 49,XXXXXY; etc.
- Sporadic; < 1% recurrence risk.
Associated Medical Findings

- Malignancy
  - Male breast cancer 20 fold over XY men
  - Acute lymphoblastic leukemia; Hodgkins and non-Hodgkins lymphoma
  - hCG secreting tumors (extragonadal germ cell tumors)
- Hypercoagulable state (deep vein thrombosis and pulmonary embolus 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 (systemic lupus erythematosis, rheumatoid arthritis, thyroid dysfunction, diabetes)
- Scoliosis; osteoporosis
- Dental decay

Developmental Outcomes

- Delayed expressive language development
  - Dyspraxia – poor phonemic development, motor imitation, decreased vocalizations
- Incidence of intellectual disability not increased in XXY males
- 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 pubertal insufficiency
- Prepubertally, the milder spectrum of Fragile X Syndrome

Recommendations

- Reassure regarding gender identity
- Pediatric Endocrinology for testosterone replacement
  - 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.
Neurofibromatosis-1 (NF-1)

Genetics
- Autosomal dominant mutations (90%) or whole gene deletions (5%) of NF1 gene at chromosome 17q11.2.
- 50% born to “normal parents” (new spontaneous gene mutations).
- Somatic mosaicism (localized to a body region) has much lower transmission risk to a child.
- High penetrance; widely variable expressivity. DNA mutation analysis not necessary, unless affected parent considers assistive reproductive technology.

NF-1 Diagnostic Criteria
Two or more of the following:
- Two or more neurofibromas or one plexiform neurofibroma
  - 6 or more café au lait macules (CALM) >5mm (prepubertal)
  - 6 or more café au lait macules (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
- Pseudoarthrosis
- Scoliosis
- Hypertension (sometimes secondary to renal artery stenosis); occasional cardiac defects (pulmonic stenosis, coarctation of aorta); coronary artery disease in adulthood

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
Developmental assessment/school support
- MRI any suspected plexiform neurofibromas
- Low threshold for Brain MRI
- Manage scoliosis
- Routine BP checks
- Annual Pediatric Ophthalmology 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
- CNS subependymal nodules → astrocytomas
- Dermatologic: 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.

Recommendations
- Clinical Guidelines: UK Tuberous Sclerosis Association
  - http://www.tuberous-sclerosis.org/?page_id=103
- Brain CT/MRI at diagnosis
- Echocardiogram in infancy
- Renal ultrasound at diagnosis
Pediatric Ophthalmology consultation for retinal examination
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 chromosome 4p16.3.
- Most commonly born to parents of normal stature secondary to spontaneous gene mutation.

Recurrence risks:
- Normal parents: <1%.
- 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
- Disproportionately short limbs relative to trunk
- 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 cervico-medullary constriction
- Obstructive sleep apnea is very common
  - Obesity, small airway, lymphatic hypertrophy
- Chronic hypoxemia can be associated with small thorax or restrictive lung disease
- Middle ear dysfunction – conductive hearing loss
- Kyphosis
- 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 otitis media with effusion and conductive hearing loss
- **If marked developmental delays or severe hypotonia → evaluate for craniocervical junction compression!**

DDX
- Other skeletal dysplasias + disproportionate short stature, incl.
  - Hypochondroplasia (milder bone dysplasia; often also FGFR3).
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 head circumference growth
- Sleep study
- Audiology
- Avoid poor infant positioning (<12months)
  - NO unsupported sitting, umbrella strollers, swings
- Close neurologic monitoring with regular exams
- Little People of America
  - [http://www.lpaonline.org](http://www.lpaonline.org)

**Williams Syndrome**

**Genetics**

- Usually sporadic, born to normal parents. Autosomal dominant inheritance from affected parent (ie. 50% risk of transmission).
- Clinical diagnosis is confirmed with F.I.S.H. analysis for microdeletion chromosome 7q11.23, locus of elastin gene.

**Associated Medical Findings**

- Congenital heart defects in 50%-75%; most common supravalvular aortic stenosis; also ventricular septal defect, atrial septal defect, and pulmonary artery stenosis.
- 15% hypercalcemia of infancy that gradually resolves over time. Multi-system disorder of stenoses and gradual calcification of major arterial blood vessels with resulting predisposition to hypertension.
- Facial features: open mouth with prominent lips, long philtrum, epicanthal folds; blue eyes common with stellate iris pattern; upper lateral periorbital fullness of subcutaneous tissue.
- Short stature; occasional scoliosis
- Renal malformations in 15%
- GI: Some have celiac disease, gastro-esophageal reflux disease, constipation
- Increased prevalence of diabetes mellitus in adolescents and adults
- Joint hypermobility during childhood; development of joint contractures and tight heel cords during adolescence and young adulthood.

**Developmental outcomes**

- Average full scale IQ 56 with range 41 to 80.
- Close to normal peers in verbal skills, expressive language, speech proficiency, and verbal memory.
- Deficits in visual-motor perceptual skills (eg. building, puzzles, drawing); impaired working spatial memory.
- Reading achievement is highest domain in educational performance.
• Low math skills achievement; difficulty with money concepts, including calculating simple change.
• Often proficient in musical talent, including playing some instruments.
• Loquacious personality: “Everyone is my friend” with consequent risk for unrealistic trusting of strangers; deeply empathetic; excellent reading of others’ feelings and facial expression; 12% with anxiety disorder.

Recommendations and Resources
• Developmental preschool emphasis on augmenting linguistic and verbal learning skills; speech and language therapy; special education services in elementary school with emphasis on reading development with systematic phonics approach, building phonemic awareness and concrete vocabulary.
• Occupational therapy
• Safety: Within home and school environment, reinforce education regarding stranger awareness and proper behavioral response when encountering strangers; safety code words when it is necessary to delegate someone other than immediate family member to meet child at school bus stop or home.
• Family support websites: Williams Syndrome Association at www.Williams-syndrome.org and Williams Syndrome Foundation at www.wsf.org

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 assay can be normal.
• 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 if undiagnosed and untreated:
• Lifelong neurologic impairment
  o Drooling
  o Tremors
• Fulminant hepatic failure
• Cirrhosis, portal hypertension
• 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 cirrhosis/liver failure and academic/neurobehavioral deterioration.
- Consultation with Pediatric Gastroenterology
- Copper chelation therapy
  - Penicillamine or triethylene tetramine dihydrochloride + oral zinc
- Dietary copper avoidance
  - Shellfish, nuts, liver, chocolate

Family support website: Wilson’s Disease Association [www.wilsonsdisease.org](http://www.wilsonsdisease.org)

ADDITIONAL REFERENCES (see other sources above)