Genetic Syndromes Associated With Autism Spectrum Disorder

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Disclosures

Relevant Financial Relationship(s)
None

Off Label Usage
None

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Learning Objectives

- Review genetic syndromes associated with ASD to appreciate the genetic diversity of the disorder
- Highlight how common ASD is in common and even some rare genetic syndromes
- Identify the commonalities of evaluation and management of genetic syndromes

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Evaluation and Management of Genetic Syndromes

- Multidisciplinary approach
- Genetics
- Other subspecialties
- Therapies as needed
- Behavioral and educational interventions
- Ongoing monitoring and surveillance

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Rett Syndrome

- 60%
- MECP2 gene
- Almost exclusively females
- Loss of speech
- Stereotypic hand movement
- Gait and coordination problems
- Seizures are common
- Abnormal respiratory pattern

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Tuberous Sclerosis Complex

- 40%
- Neurocutaneous disorder
- Hypopigmented macule, angiofibromas, shagreen patches
- Pitted teeth and small growths on gums, mouth, tongue

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Tuberous Sclerosis Complex

- Benign tumors in multiple organs
  - Kidneys, heart, lungs, eyes
- Seizures (esp. w/ ASD)
  - Infantile spasms
- Developmental delay (DD) and intellectual disability (ID)
- Behavioral concerns

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Neurofibromatosis Type 1

- 18%
- Neurocutaneous disorder
- Café au lait spots
- Axillary/inguinal freckling
- Lisch nodules on eyes
- Neurofibromas and plexiform neurofibromas

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Neurofibromatosis Type 1

- Optic gliomas
- Bone deformities
- Learning disorders (LD), ID, DD
- Macrocephaly
- Short stature

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Angelman Syndrome

- 34%
- Absence of maternally inherited UBE3A (chromosome 15q11-q13)
- Severe ID, DD
  - No or minimal speech
- Happy, excitable demeanor
- Microcephaly

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Angelman Syndrome

- Movement and balance problems
  - Stiff or jerky movements
  - Stereotypies
- Seizures are common
- Feeding difficulties
- Sleeping difficulties
- Hair, skin and eyes that are light in color

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Down Syndrome

- 16%
- Trisomy, mosaic, translocation
- Upslanting palpebral fissures, epicanthal folds
- Brachycephaly, short neck, small or unusually shaped ears

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Down Syndrome

- Hypotonia, protruding tongue, excess flexibility
- Small hands and feet, short fingers, single palmar crease
- Brushfield spots on the iris
- Short stature
- DD/ID varies

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Down Syndrome

- Seizures (infantile spasms)
- Atlantoaxial instability
- Dementia
- Congenital heart defects
- Gastrointestinal defects
- Sleep difficulties (OSA)
- Immune disorders and cancers (leukemia)

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Fragile X Syndrome

- 30%
- Most commonly inherited form of ID
  - DD, LD
- Macrocephaly, prominent forehead
- Land narrow face, large jaw, large ears
- High arching palate
- Hyperextensible joints

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Fragile X Syndrome

- Hypotonia
- Testicular enlargement in adolescence
- Pes planus
- Seizures are common
- Psychiatric and behavioral concerns
  - ADHD, depression, anxiety, OCD
  - Aggressiveness, self-injurious behaviors
- Sleep difficulties

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PTEN-Associated Macrocephaly Syndromes

- Macrocephaly/autism syndrome
  - Postnatal macrocephaly
  - Broad forehead and frontal bossing
  - Long philtrum
  - Depressed nasal bridge
  - ID

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PTEN-Associated Macrocephaly Syndromes

- Cowden/Bannayan-Riley-Ruvalcaba syndrome
  - Macrocephaly
  - "Birdlike" facies
  - Hypoplastic mandible and maxilla, high arched palate, microstomia
  - Cataract
  - Pectus excavatum
  - Skin tags, lipomas
  - GU anomalies, penile macules

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Chromosome 15q11-q13 Duplication Syndrome

- Reported in 1-2% of children with ASD
- Hypotonia, joint laxity, mild facial dysmorphisms
- Developmental delay
- Stereotypies

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Noonan Syndrome

- 15%
- Clinically and genetically heterogenous
  - Often autosomal dominant
- Coarse facial features, droopy
- Wide set eyes with downward slanting palpebral fissures and droopy eyeleids, eyes may be pale blue or green
- Ears set low and posteriorly rotated

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Noonan Syndrome

- Depressed nasal bridge, wide base and round tip, deep nasal philtrum
- High arching palate, small lower jaw
- Macrocephaly, prominent forehead, low posterior hairline
- Thin, transparent skin
- Poor growth, feeding difficulties, short stature
- Pectus excavatum, wide-set nipples, short webbed neck, spine deformities

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Noonan Syndrome

- Congenital heart disease
  - Pulmonary valve stenosis
  - Hypertrophic cardiomyopathy, congenital defects, arrhythmias
- Strabismus, nystagmus, cataracts
- Hearing loss
- Bleeding and lymphatic disorder
- GU disorders
- LD, ID, DD

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DiGeorge (22q11.2 deletion) Syndrome

- 11%
- Underdeveloped chin, wide-set eyes, hooded eyes and an enlarged nose tip
- Asymmetric cry
- Ceft palate
- Conotruncal cardiac anomalies
- Hypoplastic thymus, frequent infections, hypocalcemia
- DD, ID, LD

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Joubert Syndrome

- 40%
- Hypoplasia of the cerebellar vermis
- Neuro s/s: dysregulation of breathing pattern, developmental delay
- Retinal dystrophy
- Renal anomalies

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Cohen Syndrome

- 43%
- Microcephaly, thick hair and eyebrows, wave-shaped palpebral fissures, broad nasal tip, short or smooth philtrum
- Poor weight gain in infancy, truncal obesity in adolescence
- DD
- Hypotonia, joint hypermobility
- Neutropenia

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CHARGE Syndrome

- 50%
- CHD7 gene
- **C**oloboma of the eye
- **H**eart defects
- Choanal **A**tresia
- Growth **R**etardation
- **G**enitourinary anomalies
- **E**ar abnormalities

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Timothy Syndrome

- 70%
- CACNA1C gene
- Syndactyly
- Flat nasal bridge, low-set ears, small upper jaw, thin upper lip, small misaligned teeth, baldness at birth

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Timothy Syndrome

- Congenital heart disease, arrhythmias, ventricular tachycardia, prolonged QT
- DD, cognitive dysfunction
- Seizures are common
- Multiorgan dysfunction
  - Frequent infections
  - Hypoglycemia
  - Hypothermia

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Williams-Beuran Syndrome

- 12%
- Multisystemic genetic disorder with variable phenotypic expression
- "Elfin" facies, systemic arterial stenosis (supravalvular aortic stenosis), short stature, GU abnormalities, DD

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Smith-Lemli-Opitz Syndrome

- 10-12/14 children in a case series met criteria for ASD
- Autosomal recessive disorder of cholesterol biosynthesis
- Postnatal microcephaly, soft cleft palate/bivid uvula, micrognathia, low-set posteriorly rotated ears, syndactyly of the second and third toes, abnormal genitalia, hypotonia, ID, DD, poor weight gain

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Genetic Syndromes Not Well Characterized

- Incomplete penetrance and variable expressivity
- Chromosomal variations (eg, isodicentric 15q)
- ASD-associated copy-number variants (eg, 16p11.2 deletions or duplications)
- Pathogenic variants of ASD-risk genes (eg, CHD8)

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Resources

- American Psychiatric Association. Autism spectrum disorder. In: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, American Psychiatric Association, Washington, DC 2022. p.56.
- Autism Society. https://autismsociety.org/.
- Autism Speaks. https://www.autismspeaks.org/.
- CDC Autism Information Center. https://www.cdc.gov/ncbddd/autism/index.html.
- Cleveland Clinic. Diseases and Conditions. https://my.clevelandclinic.org/health/diseases.

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Resource

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Resources

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Questions?

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