Genetic Causes of Autism
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Genetic Causes of Autism

• General Statements
  • Autism spectrum disorder has a large genetic component with complex inheritance
  • A genetic cause can be identified in approximately 10-20% (25-30%) of children with autism
  • Identifying the clinical phenotype of common causes of autism/underlying etiology is imperative for timely referral
  • Knowing the genetic cause can provide information regarding recurrence risk and anticipatory guidance

• Overview
  • Provide overview of features of autism
  • Present common genetic syndromes that should be considered in a child with autism

• Learning Objectives
  • List several genetic causes of autism
  • Identify the clinical phenotype/key features of several genetic conditions that may prompt genetic consultation for autism
  • What is Autism?

• Autism Spectrum Disorder (AND disorder)
  • Core symptoms include impairments in:
    • Social interaction
    • Social communication
    • Restricted, rigid and repetitive behaviors, interests and activities

• Pervasive Developmental Disorder (OR disorder)

• Developmental Delay
  • Learning difficulties or intellectual disability
  • Speech and language difficulties

Features of Autism

• Profound impairments in social functioning
• Atypical/Difficult social interaction
•Difficulty decoding non-verbal cues
• Lack of eye contact
• Impaired social emotional reciprocity/Empathy
• Social anxiety and avoidance
• Perseverative speech
• Stereotypic/repetitive behaviors
• Disregard for danger
• Sensory processing disorders (odd behaviors around food, abnormal sleep patterns)
• Impulsive aggression
• Self-injurious behaviors/Hand biting

Overview

• Conditions
  • Fragile X Syndrome (1-3%)
• Rett Syndrome (1%)
• Prader-Willi/Angelman Syndromes
• 15q11q13 Duplication Syndrome (1-3%)
• 22q13.1 Deletion Syndrome
• PTEN Macrocephaly Syndrome (1%)
• Tuberous Sclerosis Complex (1%, 0.4 to 2.8%)
• Neurofibromatosis Type 1

• **Summarize**
  • Overview
  • Inheritance
  • Frequency
  • Cause
  • Description
  • Physical/Hallmark Findings
  • Features of Autism

**Fragile X Syndrome**

• **Overview**
  • Most common cause of inherited learning disability
  • 1-3% of children with autism have Fragile X syndrome
  • Learning problems
    • Range from borderline normal IQ (females) to severe learning disability (IQ 20–35)

• **Inheritance:** X-linked dominant with reduced penetrance

• **Frequency** (full mutation): ~ 1: 5000 males, 1: 8000 females

• **Cause:** CGG (triplet) repeat expansion of FMR1 gene at Xq27.3
  • On the basis CGG repeats
    • Normal = ~ 6-45 repeats
    • Intermediate = ~ 46-54
    • Premutation = ~ 55-199 repeats
    • Full mutation = > 200
      • Female premutation carriers
        • 20% risk for premature ovarian failure
        • Mood and anxiety disorders
      • Females with full mutation
        • 33-50% show clinical signs of Fragile X syndrome

• **Physical Findings** (Full Mutation Males)
  • Macrocephaly in early childhood
  • Prominent/high forehead
  • Elongated face
  • Prognathism (after puberty)
  • Thickening of nasal bridge extending to nasal lip
  • Large ears with soft cartilage
  • Pale blue irides, epicanthal folds
  • High arched palate, dental crowding
  • Macroorchidism after puberty
  • Connective tissue weakness, hyperextensible

• **Features of Autism**
  • ~ 90% of males with Fragile X syndrome show ≥ 1 feature of autism
• Social anxiety
• Hand flapping or biting (60%)
• Poor eye contact (90%)
• Sensory disorders
• Risk for aggression

Rett Syndrome
• Overview
  • Serious lifelong neurological disorder
  • Second most common cause of severe cognitive impairment in females after Down syndrome
  • Range from Classic Rett syndrome to Variant Rett syndrome to mild learning disabilities
  • Lethal in males: Present with severe neonatal encephalopathy/death before 2 YOA
• Inheritance: X-linked dominant (de novo)
• Frequency: Identified by the age of 15 years in 1 in 8000 females
• Cause
  • Mutations in MECP2 gene
  • Specific job of protein is not well understood but important for brain development and essential for proper function of nerve cells and communication between neurons
• Physical Findings: Unremarkable
• Description/Features of Autism: Individuals with Classic Rett syndrome
  • Stage I: Onset
    • Normal development until 6-18 months
  • Stage II: Rapid deterioration or regression (1-4 years)
    • Developmental arrest
  • Features of Autism
    • Social withdrawal, loss of language, irritability, self-abusive behavior
    • Repetitive, stereotypic hand movements (hand wringing, hand washing, clapping, patting)
    • Expressionless face, sound hypersensitivity, lack of eye-to-eye contact, environmental indifference, unresponsiveness to social cues
• Stage III: Stabilization/Pseudostationary (4–7, 2-10 years)
  • Continue to exhibit gross cognitive/motor impairments, epilepsy common
• Stage IV: Post regression phase/Late motor deterioration (5-15, > 10 years):
  • Seizures less frequent, motor deterioration continues
  • Amelioration of the social autistic-like behaviors between 5-10 y
• New Features/Behaviors of Autism
  • Bruxism
  • Night laughing/crying, screaming fits
  • Low mood and anxiety episodes (distressful events)
  • Stereotypic hand movements replace purposeful hand use
• Non-ambulant during adolescence
• Plateaus-Some survive to 60-70s in a severely debilitated state

Prader-Willi, Angelman, and 15q11-q13 Duplication Syndromes
• Overview: Loss of function or overexpression of at least one imprinted gene
• Frequency (each): ~1/15,000 to 1/30,000 live births
• **Cause**
  - Prader-Willi and Angelman syndromes
    - Deletions of a 4Mb of 15q11 to q13
    - Produces two distinct clinical syndromes (although different genes) depending on the parental origin
      - Paternal chromosome deletion: Prader-Willi syndrome
      - Maternal chromosome deletion: Angelman syndrome
    - 15q11-q13 Duplication

**Prader-Willi Syndrome**

• **Description**
  - Presentation
    - Neonatal
      - Hypotonia
      - FTT/Poor growth
      - Delayed development
    - Early childhood (70-90%)
      - Hyperphagia causing severe obesity
      - Obsessive-compulsive symptoms (skin picking)
      - Disruptive behavior (temper tantrums)/mood disorders
      - Sleep abnormalities
  - Physical Findings
    - Facial features
      - Narrow forehead
      - Almond-shaped eyes
      - Strabismus
      - Triangular mouth
    - Short stature
    - Small hands and feet
    - Hypopigmentation (unusually fair skin/hair)
    - Hypogonadism (delayed puberty/most infertile)
  - Features of Autism
    - ASD diagnosed in up to 25/100 affected individuals
    - ASD risk greater with maternal uniparental disomy than paternal deletions
      - Repetitive behavior
      - Rigidity/Stubbornness
      - Social deficits
      - Behavioral problems increased age/BMI

**Angelman Syndrome**

• **Description**
  - Complex disorder that affects nervous system
  - Epilepsy/Recurrent seizures
    - Distinctive EEG pattern
  - Delayed development apparent at 6-12 months

• **Physical Findings**
  - Microcephaly
  - Deep set eyes
  - Wide mouth/wide jaw
• Widely-spaced teeth
• Prominent chin
• Coarse facies (adulthood)
• Hypopigmentation (unusually fair skin/hair)—more common with deletion subtype
• Movement disorder with ataxia

15q11q13 Duplication Syndrome

• Overview/Description
  • One of the most frequent chromosomal changes associated with autism
  • Accounts for 1-3% of all autism causes
  • Features of both Prader-Willi and Angelman syndromes
    • Characterized by central hypotonia, developmental delay, intellectual disability, seizures and autism
  • Remarkable diversity in severity (how much material is duplicated but, even with same genotype)
  • Like PWS and AS, there appears to be parent-of-origin effect on phenotype
    • Maternally inherited (interstitial duplication/supernumerary inverted duplication)
      • 2 X more likely than paternally inherited duplications
      • Increased risk for ASD
  • Inheritance: ~60% de novo (can be inherited)
  • Frequency: Unknown, 100 cases reported in literature
  • Cause: Duplication of region

• Physical Findings (subtle)
  • High forehead
  • Flat nasal bridge and/or small button nose
  • Down-slanting palpebral fissures
  • Epicanthal folds
  • Low-set/posteriorally rotated ears
  • Hyperpigmentation (café au lait macules)
  • Growth retardation (20-30%)
  • Hypogonadism (20%)

• Associated Health Problems
  • Gastrointestinal problems (75%)
    • Feeding problems as infant/hypotonia
    • GER
    • Constipation
  • Seizures/infantile spasms (~60%) before age 5
  • Scoliosis

• Features of Autism
  • Speech/Language delays (some non-verbal, intent poor/absent)—Expressive language delay
  • Echolalia with pronoun reversal
  • Inappropriate social interactions (no peers/absent symbolic play)
  • Contact avoidance
  • Tantrums, shouting, aggressiveness/stubborn refusal, anxiety
  • Sleep problems (trouble “turning off”)
  • ± Increased pain threshold
• Stereotypies
  • Hand flapping, clapping, or wringing
  • Finger biting
  • Head turning
  • Repeated spinning

22q13.3 Deletion Syndrome (Phelan-McDermid Syndrome)
• Overview
  • Contiguous gene microdeletion (distal long arm of chromosome 22) syndrome
  • Almost all deletions include SHANK3 “hot spot”
  • SHANK3 protein important in formation of synapses
• Inheritance: Most cases occur de novo
• Incidence: > 500 cases
• Cause
  • Deletion (majority)
  • Unbalanced translocation (10%-inherited or de novo)
  • Ring chromosome
• Description
  • Rare neurodevelopmental syndrome
  • Correlation between deletion size and neurological deficit
    • Larger deletion = Greater intellectual disability/risk/severity of ASD
  • Characterized by (>75%)
    • Normal or accelerated growth
    • Neonatal hypotonia (poor feeding, FTT)
    • Global developmental delay
    • Absent to severely delayed speech
      • Expressive language delayed
      • Loss/regression of speech common
• Associated Health Problems
  • Low perception of pain (90%)
  • Decreased sweating (70%)
  • Seizures (slightly more common than general population)
  • SNHL
  • Cardiac defects (< 20%)
• Features of Autism (>50%)
  • Impaired communication (absent/severely delayed speech)
  • Reduced social interaction, poor eye contact, anxiety
  • Blunted facial expression (73%)
  • Self-stimulation/sensory seeking behaviors (68%)/Sensitivity to touch
  • Chew/mouth/suck on non-food items (clothing, toys, furniture) (80%)
  • Bruxism (75%)
  • Stereotypic movements (75%) repetitive movements, hand flapping
  • Aggressive behaviors (small minority)

PTEN Hamartoma Tumor Syndrome, PTEN Macrocephaly, PTEN-ASD
• Overview: Overlapping syndromes
  • Cowden
    • +/- Macrocephaly
    • Multiple hamartomas
• Increased risk of developing cancers (breast, thyroid, endometrial, colorectal, renal, melanoma) develop 30s and 40s
• Rare, noncancerous brain tumor (Lhermitte-Duclos disease)
• Small % may have delayed development/intellectual disability
• Bannayan-Riley-Ruvalcaba
  • Macrocephaly
  • Multiple hamartomas (noncancerous tumors/tumor-like growths)
  • Dark freckles on penis
• PTEN Proteus, Proteus-like
• **PTEN Macrocephaly, PTEN-ASD**
  • Approximately 10-20% with autism with macrocephaly have PTEN mutations (high diagnostic yield)
  • Unknown how PTEN mutations are related to autism
  • Unclear how these mutations can cause different disorders

**PTEN Macrocephaly, PTEN-ASD**
• **Inheritance**: 50% Autosomal dominant (inherited), 50% de novo
• **Frequency**: ?
• **Cause**: Mutation in PTEN, tumor suppressor gene, 10q23.31
• **Description**: Characterized by
  • Macrocephaly
  • Specific brain abnormalities
  • Unique thinking skills
    • Reduced information processing speed and memory
    • Motor difficulties/delayed psychomotor development
    • Autism behaviors and intellectual disability
  • PTEN-ASD
• **Brain Findings**
  • Overgrowth of white matter with hypointensities
  • PTEN Macrocephaly, PTEN-ASD
• PTEN testing recommended
  • HC ≥ 2 SD from norm (+2.5 to +8 SD)
  • Autism or developmental delay
• **Physical Features**
  • **Macrocephaly** (dolicocephaly/bitemporal narrowing)
  • Broad forehead
  • Mild hypertelorism
  • Midface hypoplasia
  • Depressed nasal bridge/short nose
  • Long philtrum
• **Features of Autism**
  • Non-specific

**Tuberous Sclerosis Complex**
• **Overview**
  • Causes benign tumors/lesions in different organs (brain, skin, eyes, heart, kidneys, lungs)
  • Impact extremely variable (some go undiagnosed) whereas others suffer seizures, severe learning disabilities, autism
• Tuberous growths in temporal lobe associated with autism, especially with epileptic activity in early development.
• Females tend to have milder disease than males
• **Inheritance:** Autosomal dominant (1/3 inherited, 2/3 de novo)
• **Frequency:** 1: 6000 births
• **Cause:** Mutations in TSC1 (24-31%) or TSC2 (66-69%) (tumor suppressor genes)
  • Autism, low IQ and infantile spasms more frequently associated with changes in TSC2

**Physical/Hallmark Findings**
• **Major Features**
  • Angiofibromas/fibrous cephalic plaque
  • Cardiac rhabdomyoma
  • Cortical dysplasias/tubers/cerebral white matter migration lines
  • Hypomelanotic macules
  • Lymphangioleiomyomatosis
  • Multiple retinal nodular hamartomas
  • Renal angiomyolipoma
  • Shagreen patch
  • Subependymal giant cell astrocytoma/nodules
  • Ungual fibromas
• **Minor Features**
  • “Confetti” skin lesions
  • Dental enamel pits
  • Intraoral fibromas
  • Multiple renal cysts
  • Nonrenal hamartomas
  • Retinal achromic patch
  • Tuberous Sclerosis Complex

**Description**
• Co-occurrence of TSC and autism well established (16% to 61%)
  • ¼- ½ with TSC develop ASD
    • Frequency of classic autism in those with TS is about 25%
    • Frequency of anyone with PDD with TS increases to 44%
  • Intellectual disability/seizures increases risk for autism
  • Children with TSC and autism show gradual decline in nonverbal intelligence (1-3 YOA)
  • Observed association but underlying pathogenesis remains largely unknown

**Features of Autism**
• Impaired language pathways
• Atypical face processing

**Neurofibromatosis Type 1**
• **Overview**
  • One of the most common dominantly inherited genetic disorders
  • Characterized by pigmentation and tumor growth
  • Symptoms vary widely
• **Inheritance:** Autosomal dominant, 50% inherited, 50% de novo
• **Frequency:** 1:3000-4000
• **Cause**
  • Mutation in *NF1* (*tumor suppressor gene*)
  • Long arm of chromosome 17 (17q11.2)

• **Description**
  • Most with NF1 have normal intelligence
    • Learning disabilities or behavioral problems (50%-80%)
      • Visual-spatial performance
      • Attention
      • Motor function
      • Executive function, memory and language
  • Overt intellectual disability (6%-7%)
  • ASD features (up to 30%) (social competence)
    • ASD is underrecognized in NF1

• **Physical/Hallmark Findings**
  • Multiple café-au-lait macules
  • Axillary/groin freckling
  • Lisch nodules (iris hamartomas)
  • Neurofibromas
  • Plexiform neurofibromas (50%, most internal)
  • Macrocephaly
  • Relative short stature

• **Features of Autism** (distinct phenotype)
  • Pronounced social-communicative impairments
  • Fewer restrictive/repetitive behaviors

**Genetic Testing and Detection Rates**

<table>
<thead>
<tr>
<th>Test</th>
<th>Yield</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Cytogenetic</td>
<td>3%</td>
<td>Important if suspect balanced translocation, ≥ 2 miscarriages</td>
</tr>
<tr>
<td>Chromosomal microarray</td>
<td>~ 10% (30% complex)</td>
<td>First line test in all patients with autism</td>
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<tr>
<td>Fragile X</td>
<td>0.5-0.6% (males)</td>
<td>Recommended for all males</td>
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<tr>
<td>MECP2 (sequencing and deletion)</td>
<td>1-4% (females)</td>
<td>Recommended for all females</td>
</tr>
<tr>
<td>X-linked intellectual disability panel</td>
<td></td>
<td>If family history suggests X-linked inheritance</td>
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<tr>
<td>PTEN (sequencing and deletion)</td>
<td>5-16%</td>
<td>Recommended for all patients with significant macrocephaly</td>
</tr>
<tr>
<td>Whole Exome Sequencing</td>
<td>25.8%*</td>
<td></td>
</tr>
<tr>
<td>Targeted metabolic evaluation</td>
<td>Unknown</td>
<td>If suggestive clinical, physical or laboratory findings</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td>Targeted MRI considered with neurological regression, macrocephaly, abnormal neurological findings</td>
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General References

- Unique: The Rare Chromosome Disorder Support Group.

Other References