In the past decade, rapid advances in genetics have increased diagnostic precision and allowed for further characterization of phenotypes of many genetic syndromes, including behavioral phenotypes. An excellent example is the identification of MECP2 as the causative gene for Rett syndrome; molecular testing has refined the diagnostic process for a previously mysterious phenomenologically defined disorder and will likely result in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) nosologic reclassification. With wide availability of molecular diagnostic testing and more precise diagnostic options, increasing attention is being paid by specialists involved in the care of children with genetic conditions, including developmental psychology, child psychiatry, pediatric neurology, genetics, pediatrics, and speech language pathology (though often from singular perspectives), to define the characteristic behavioral phenotypes of genetic disorders (Table 1).
<table>
<thead>
<tr>
<th>Diagnosis (Mutation)</th>
<th>Cognitive Features</th>
<th>Psychiatric Features</th>
<th>Role in Diagnosis</th>
<th>Diagnostic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome (Trisomy 21)</td>
<td>Moderate to severe intellectual disability&lt;br&gt;Strengths: grammar&lt;br&gt;Weaknesses: expressive language&lt;br&gt;Visual processing better than auditory</td>
<td>&gt;50%: Hyperactivity, impulsiveness, inattention, and stubbornness&lt;br&gt;30% Anxiety, depression&lt;br&gt;10% Autism</td>
<td>Minimal, diagnosis made on physical or medical features</td>
<td>Karyotype</td>
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<tr>
<td>Fragile X syndrome (FMR1; triplet repeat expansion)</td>
<td>Mild to severe intellectual disability&lt;br&gt;Difficulty with abstract thinking, sequential cognitive processing, short-term memory, math, and visual-motor processing</td>
<td>Attention dysfunction, hyperarousal, social anxiety, social cognition and communication challenges&lt;br&gt;25%–50% Autism</td>
<td>Significant, often the presenting symptoms</td>
<td>FMR1 PCR and Southern blot for CGG repeat length</td>
</tr>
<tr>
<td>Rett syndrome (MECP2)</td>
<td>Severe to profound intellectual disability&lt;br&gt;Limited language acquisition and use</td>
<td>Stage I: Decreased interactions&lt;br&gt;Stage II: Social withdrawal, irritability, autistic-like behaviors, sleep disturbance&lt;br&gt;Stage III: Improvement in alertness, interactions, ongoing sleep disturbance&lt;br&gt;Stage IV: Persistence of poor communication, irritability</td>
<td>Moderate, presents simultaneously with neurologic features</td>
<td>MECP2 sequencing; del/dup testing</td>
</tr>
<tr>
<td>Prader-Willi syndrome (15q11-q13; imprinting—loss of paternal contribution)</td>
<td>Mild to borderline intellectual disability&lt;br&gt;Strengths: visuospatial performance, reading and decoding, and long-term memory. &lt;br&gt;Weaknesses: short-term memory, auditory processing, socialization, mathematical skills, and sequential processing</td>
<td>Extreme hyperphagia, self-injurious behaviors (skin picking), OCD&lt;br&gt;Social cognition deficits&lt;br&gt;Cognitive inflexibility, explosiveness, poor affect regulation&lt;br&gt;Depression/mood disorder/psychosis</td>
<td>Minimal, obesity related to hyperphagia may be a major clinical diagnostic clue</td>
<td>Methylation PCR followed by FISH</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Intellectual disability</td>
<td>Strengths/Weaknesses</td>
<td>Symptoms/Phenotypes</td>
<td>Diagnostic Testing</td>
</tr>
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<tr>
<td>Angelman syndrome</td>
<td>Severe to profound</td>
<td>Minimal expressive speech, better receptive language</td>
<td>Social and happy; frequent, inappropriate, and unexpected laughter Positive interpersonal bias, social disinhibition with a diminished fear of strangers Fear of crowds and noise, hyperactivity/inattention, sleep disturbance</td>
<td>Significant&lt;br&gt;&lt;br&gt;Diagnostic Testing: Methylation PCR followed by FISH; UBE3A sequencing</td>
</tr>
<tr>
<td>(15q11-q13; imprinting—loss of maternal contribution)</td>
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<tr>
<td>Williams syndrome</td>
<td>Mild intellectual</td>
<td>Strengths: auditory rote memory and language Weaknesses: severe visuospatial</td>
<td>Adaptive behavior less than expected for IQ Superficial sociability Externalizing: inattention, impulsivity, attention seeking, hyperactivity, and temper tantrums Internalizing: obsessions/preoccupations, fears, anxiety, sadness/depression ADHD (&gt;50%) Sleep disturbance</td>
<td>Minimal, physical and medical issues often prompt diagnosis&lt;br&gt;&lt;br&gt;Diagnostic Testing: Locus-specific FISH or CGH microarray</td>
</tr>
<tr>
<td>(deletion 7q11.23)</td>
<td>disability (75%)</td>
<td>construction deficits and language</td>
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<td></td>
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<tr>
<td>Deletion 22q11.2</td>
<td>Borderline to mild</td>
<td>Emotional dysregulation ADHD Anxiety and phobias Poor social adaptation with withdrawal Autism 30%: Psychotic symptoms</td>
<td>Moderate, particularly when there are few medical issues&lt;br&gt;&lt;br&gt;Diagnostic Testing: Locus-specific FISH or CGH microarray</td>
<td></td>
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<tr>
<td></td>
<td>intellectual disability</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Verbal IQ is higher than performance</td>
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<td></td>
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<tr>
<td></td>
<td>Strengths: language abilities</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Weaknesses: receptive and high-order language skills, abstract reasoning, and visuospatial deficits</td>
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</tr>
<tr>
<td>Smith-Magenis syndrome</td>
<td>Moderate intellectual</td>
<td>Sleep disturbance (inverted melatonin circadian rhythms Self-injurious behaviors Stereotypy: self-hug, lick-and-flip, mouthing objects, teeth grinding, body rocking, spinning Socially adult-oriented, demanding of adult attention, egocentric, delayed empathic skills</td>
<td>Significant, often predominate overall phenotype&lt;br&gt;&lt;br&gt;Diagnostic Testing: Locus-specific FISH or CGH microarray</td>
<td></td>
</tr>
<tr>
<td>(deletion 17p11.2)</td>
<td>(range from mild to severe)</td>
<td></td>
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<tr>
<td></td>
<td>Weaknesses: short-term memory, visuomotor coordination, sequencing, and response speed</td>
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<tr>
<td></td>
<td>Speech delay is common, with receptive language better than expressive</td>
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<thead>
<tr>
<th>Diagnosis (Mutation)</th>
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<th>Role in Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner syndrome (45, X and variants)</td>
<td>Infrequent intellectual disability (5%) Performance IQ lower than verbal Learning disabilities in math common Significantly impaired nonverbal abilities Impaired executive functioning skills: attention and concentration, problem-solving ability, organization and working memory, impulsivity and processing speed</td>
<td>ADHD 18 times higher than general population Social immaturity, anxiety Younger girls: immature, hyperactive and anxious Older girls: anxiety, depression, and social relationship challenges</td>
<td>Minimal, generally diagnosed on physical or medical features Diagnostic Testing: Karyotype</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome (HPRT deficiency)</td>
<td>Mild to moderate intellectual disability</td>
<td>Chronic, compulsive, self-injurious behaviors resulting in self-mutilation: biting, eye poking, fingernail pulling, psychogenic vomiting, arching, head snapping, head banging Language pattern: repeated ambivalent statements with anxiety and vulgarity Frequent compulsive aggression toward others (grabbing and pinching)</td>
<td>Significant Diagnostic Testing: Urine urate/creatinine ratio (&gt;2.0 suggestive) followed by HPRT enzyme activity determination; sequencing is available</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; FISH, fluorescent in situ hybridization; CGH, comparative genomic hybridization; HPRT, hypoxanthine-guanine phosphoribosyltransferase; OCD, obsessive compulsive disorder.
Although children with genetic diagnoses represent a small proportion of referrals to general child psychiatry practitioners, information about these conditions has a role beyond direct applicability to the diagnosed child. Given that rates of mental illness are higher in all individuals with developmental delay, children with a neurodevelopmental disorder are more likely to present to a practitioner, and awareness of phenotypic features allows for the identification of previously undiagnosed individuals, as well as for more complete evaluation of individuals with known diagnoses. From a population perspective, examining psychopathology in individuals with known genetic diagnoses leads to an increased understanding of gene-brain-behavior pathways\textsuperscript{2} that may have far-reaching implications in the general population.

In genetics, a clinical diagnosis is often suspected on the basis of specific physical, developmental, medical, and behavioral features; all of these features comprise the overall phenotype of the individual. The behavioral phenotype of genetic conditions encompasses specific cognitive, language, and social aspects as well as behavioral deviance and psychopathology. It is important to remember that despite a common diagnosis, a “classic” behavioral phenotype may not occur in all affected individuals and may be affected by genotype, environmental factors, and intellectual disability.\textsuperscript{2}

The mental health field historically has struggled with the concept of distinct psychiatric or neurobehavioral illness in a person with developmental delay, sometimes termed dual diagnosis. Reiss and colleagues\textsuperscript{3} have eloquently described the troublesome issue of diagnostic overshadowing, whereby all features of an individual’s presentation are ascribed to developmental delay. Such an error of attribution leads to the underdiagnosis of distinct and treatable disorders or impairments, and increases illness burden. Social traits, in particular, have been difficult for clinicians to evaluate, specifically whether deficits are due to a particular genetic diagnosis, a common downstream effect of psychosocial disadvantage and stigmatization, or secondary to developmental delay and intellectual disability.\textsuperscript{4} In contrast, clinicians must be alert to the possibility of overpathologizing developmentally appropriate behavior in a delayed child.

A common conundrum for the child psychiatrist is that neither psychiatric nor behavioral models fully capture the individual presenting phenotype. The field has evolved from detailed narrative descriptions of characteristic behavioral traits for a specific disorder to a second generation of research that uses validated instruments applying DSM criteria to define prevalence rates of psychopathology. Concerns have been raised that creating a behavioral or psychiatric phenotype solely from studies measuring psychopathology based on DSM criteria is reductionistic,\textsuperscript{5} as many individuals with genetic syndromes have behaviors or features that do not appear in the DSM, and if a particular diagnostic category is not assessed in the research, it is then omitted from the evidence base. The neurodevelopmental disorders with well-described genetic bases have far more specificity than DSM disorders, and social phenotypes or traits, in particular, are not well characterized in the DSM Fourth Edition, Text Revised.

Behavioral phenotypes themselves, however, do not fully capture what a child psychiatrist is evaluating, which should be particularly focused on what may contribute to impairment in functioning. Such an evaluation requires the integration of cognitive, social, psychiatric, and behavioral features that contribute to impairment, leading to description and possible understanding of an individual functioning phenotype. With this context in mind, here the authors review several readily identified genetic syndromes, with a particular focus on psychiatric features that affect the functional phenotype.
Significant advances have been made in methods and availability of genetic testing in the past decade, allowing for increased precision in establishing a diagnosis for many individuals. In fact, the long-honored chromosome analysis (or karyotype), once the mainstay of genetic testing, is now often replaced as a first-line test with molecular methods, including fluorescent in situ hybridization (FISH), comparative genomic hybridization (CGH) microarray, and gene sequencing. A good analogy for genetic testing is a set of encyclopedias on a shelf. A karyotype can determine how many volumes are present or if large sections are rearranged onto other volumes. FISH testing can indicate whether a specific section or chapter is missing; CGH can determine if any chapter is missing. DNA sequencing can tell if there is a typo in a specific sentence.

A karyotype remains the primary means of documenting chromosome number and structure; this is the only testing method able to diagnose chromosome translocations. A karyotype is obtained by inducing living cells to replicate in the laboratory but halting the process in metaphase when the chromatin is condensed into the characteristic chromosomes; these chromosomes are then stained and the banding patterns are compared to identify and sort the individual chromosome pairs.

FISH is a method used to detect the presence or absence of a specific portion of DNA as determined by the probe used. Patient DNA is collected and denatured to a single-stranded form; a locus-specific DNA probe with an attached fluorescent marker is then hybridized to the patient DNA. If the probe target is present in patient DNA, the probe binds and its presence is detected using a fluorescent microscope. Absence of the locus-specific DNA probe indicates that the target area is deleted from the patient DNA.

CGH, or microarray, uses a multiplex platform to compare numerous (tens of thousands) segments of patient DNA to control DNA using a computerized reading method. Patient DNA and control DNA are allowed to hybridize and bind to a computer chip where specific chromosome loci are represented by specific locations on the chip. A computer then assesses whether the patient DNA and control DNA are present in equal amounts at each test locus. If excess control DNA is detected at a particular location, the inference is that this area was deleted in the patient sample; if excess patient DNA is detected, a duplication of patient DNA is implied. CGH is being used increasingly as a first-line diagnostic tool.

For disorders in which a specific gene is identified to be causative, targeted DNA testing is often used to establish a diagnosis. The specific type of DNA testing method used depends on the molecular cause of the condition. For diagnoses in which point mutations (single nucleotide alterations, insertions, or deletions) are the main etiology, gene sequencing is often used. For well-characterized conditions, sequencing may be simplified into common mutation testing or exon-specific sequencing if there are particular “hot spots” within the known gene. It is important to remember that gene sequencing only tests for alterations in the specific gene targeted and will not provide any other genetic information.

An excellent resource for information about genetic testing, including available testing options for many genetic diagnoses, is www.genetests.org, a National Institutes of Health supported Web site designed to provide current genetic diagnostic information via a searchable laboratory directory.

Pre- and posttest genetic counseling is a necessary component of all genetic testing. Families must be informed of the advantages and limitations of various tests, particularly the sensitivity and specificity of testing and implications of test results for other family members. This counseling is often complex and should be provided by
a someone who is very familiar with all of the potential issues; genetic counselors are Masters degree trained individuals with board certification from the American Board of Genetic Counseling.

TRISOMY 21 (DOWN SYNDROME)
Genetics, Etiology, and Epidemiology

Initially described by John Langdon Down in 1866, the condition known eponymously as Down syndrome (DS) was determined to be caused by trisomy of chromosome 21 in the 1950s. Whereas the vast majority of individuals (more than 95%) with trisomy 21 have an entire additional chromosome 21 secondary to nondisjunction during gametogenesis, a smaller percentage of individuals will have trisomy 21 related to a chromosome translocation. An even smaller percentage of affected individuals will have variable physical features related to somatic mosaicism or partial duplication of chromosome 21q22 involved in other chromosome rearrangements. A diagnosis of trisomy 21 can be confirmed with chromosome analysis, although determining low-level mosaicism may require additional testing.

The incidence of trisomy 21 varies during gestation, but is thought to be approximately 1 in 800 live births. There is no identified ethnic, population, or socioeconomic predilection. The risk of trisomy 21 increases with increasing maternal age, related to maternal nondisjunction; however, the vast majority of babies with trisomy 21 are born into families without advanced parental age.

Advances in medical and surgical care of individuals with chromosome abnormalities has had a tremendous impact on the life expectancy of individuals with trisomy 21. Although mortality within the first several years of life is increased over the general population, related in part to higher neonatal mortality and congenital structural cardiac disease, current life expectancy is estimated to be greater than 50 to 60 years.

Physical Features and Medical Issues

The overwhelming majority of individuals with trisomy 21 will be diagnosed in the neonatal period based on characteristic facial features and concomitant medical issues. An increasing proportion of infants are also diagnosed prenatally through widely available screening tests offered to all pregnant women.

The characteristic facial features of individuals with trisomy 21 vary slightly over time, but the overall facial gestalt is always present. Microcephaly with occipital flattening is common, and midface hypoplasia tends to center the facial features. Notably, the palpebral fissures are up-slanting and there is often an exaggerated inner-canthal or epicanthal fold that accentuates a flat and broad nasal bridge. The nose and mouth are small. The ears tend to be small and round, and are often low set (the peak of the pinna is not intersected by an imaginary line drawn through the inner and outer canthal folds) and posteriorly rotated. The neck is short and there is frequently thickening or redundant skin posteriorly. Individuals with trisomy 21 are shorter than their family prediction, and this is most apparent in the proximal arms and legs as well as the hands and feet.

Cardiac malformations of multiple organ systems may be seen in trisomy 21. Cardiac malformations are seen in 40% to 50% of individuals and include most commonly ventricular septal defects, endocardial cushion defects, and persistent patent ductus arteriosus as well as a variety of other malformations. Gastrointestinal malformations, including duodenal atresia, and Hirschsprung disease are seen at rate higher than in the general population. Other common medical issues include an...
increased risk for seizures, refractive errors, strabismus, hearing loss, eustachian tube dysfunction, occipito-atlanto-axial instability, and acute leukemia as well as an increased susceptibility to infections. Appropriate growth charts and Health Care Supervision recommendations are available from the American Academy of Pediatrics as well as the major DS awareness and support organizations.

Cognitive and Psychiatric Features

Developmental delay is universally present in individuals with DS, most commonly moderate to severe intellectual disability, with a wide range in severity. Language delay is common, with greater impairment in expressive skills as compared with receptive skills. Language pragmatics are spared, while there are challenges for grammar. Visual processing is more developed than auditory processing.

Individuals with DS historically were described as placid and good tempered, but this generalization has not been supported. Several investigators have characterized a pattern of hyperactivity, impulsivity, inattention, and stubbornness/disobedience, with Pueschel and colleagues describing this pattern in more than half of the 40 school-age children with DS studied. Some children demonstrate a stubborn persistence, need for sameness, and repetitive or perseverative qualities.

Rates of comorbid psychiatric disorders are higher than in the general population, although lower than rates in the total population with intellectual disability. Up to one-third of children with DS meet criteria for at least one psychiatric disorder including attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and anxiety disorder.

Psychiatric features change with developmental level. Preschool- to school-age children with DS commonly display hyperactivity and impulsivity, noncompliance and tantruming, agitation, anxiety or disruptiveness, repetitive movements, and sensory dysregulation, but are rarely disinterested in social interaction. Postpubertal individuals show a significant decrease in hyperactivity but increased internalizing symptoms, including social withdrawal. Depression has been described in children and adolescents with DS. Symptoms observed are those typical of depressive disorders (ie, depressed mood, crying, decreased interests, and so forth), and self-care may deteriorate. The differential diagnosis of a mood disorder in DS individuals should include hypothyroidism, B-12 deficiency, bereavement, and obstructive sleep apnea. Increased anxiety and extreme social withdrawal may be present in DS children with major depressive disorder. In addition, 7% to 10% of individuals with DS meet criteria for autism, and when it occurs there is a high probability of one or more family members displaying a broader autism phenotype.

Accurate psychiatric diagnosis can be a challenge, and experts in the treatment of individuals with DS encourage a focus “beyond overt behaviors in search of diagnostic clues, such as alterations in mood, arousal or activity level, physiologic disturbance, atypical development or neurocognitive function.”

The evidence base for DS-specific psychopharmacologic treatment is limited. At this time treatment borrows from conventional intervention pathways for psychiatric illness in the general population. In one group of children with DS, a small open-label trial of rivastigmine showed positive effects on several aspects of cognitive functioning.

Fragile X Syndrome

Genetics, Etiology, and Epidemiology

Fragile X syndrome (FXS) is recognized as the most common inherited form of mental retardation, with an incidence of approximately 1 in 3000, including affected males.
and females. The premutation/intermediate length mutation carrier frequency is much higher, approximately 1% in females\textsuperscript{26} and 1 in 800 males.

FXS is one of several “triplet repeat” neurologic disorders caused by expansion of a disease-specific trinucleotide repeat within a disease-specific gene. In FXS this trinucleotide repeat, CGG, expands within the promoter of the \textit{FMR1} gene located at Xq27.3. Expansion of the number of CGG repeats leads to decreased or absent formation of FMRP, a protein critical to the translation of molecular messages within the developing brain.

In the general population, the number of CGG repeats in \textit{FMR1} is typically 20 to 50. CGG repeats within this range can be stable over generations and carry no risk of expansion to a full mutation in the next generation. When the number of CGG repeats expands to greater than 50, the risk of expansion to a full mutation, more than 200 CGG repeats, increases. CGG repeats between 50 and 200 are termed premutations; premutation carriers may have mild features, but are often indistinguishable from nonpremutation carriers. When a premutation in \textit{FMR1} is passed from a carrier mother to a child, there is a substantial risk of expansion to produce a full mutation in the child; full mutations of \textit{FMR1} are methylated and FMRP is not expressed. This situation results in FXS in males (who have only one copy of \textit{FMR1}) and variable features, ranging from mild to complete FXS, in females, because of X-inactivation and the contribution of the normal \textit{FMR1} gene to cellular functioning.

Molecular testing for FXS in affected individuals and individuals at risk for being carriers is readily available.\textsuperscript{27} More than 99% of patients can be diagnosed using the polymerase chain reaction (PCR) to determine CGG repeat size (most accurate for CGG repeat lengths within the normal or low permutation range) and Southern blotting to determine the size of large mutations as well as methylation status. Determining methylation status in males with a full mutation can provide some prognostic information. Determination of premutation size in at risk family members is essential for accurate genetic counseling. Methylation PCR is frequently used to rapidly identify individuals who require more in-depth testing. Point mutations in \textit{FMR1} have been identified in a very small percentage of affected individuals. Cytogenetic studies cannot be used reliably for detection of a fragile site in either affected individuals or carriers; this is important as cytogenetics was the primary means of diagnosis until well into the 1990s.

\textit{Physical Features and Medical Issues}

The classic physical and facial features associated with FXS in males may not be evident until later childhood, if at all. These features include macrocephaly, large and prominent ears, a long face, postpubertal macroorchidism, and a subtle connective tissue disorder characterized by a highly arched palate, small joint hyperextensibility, flat feet, and mitral valve prolapse.\textsuperscript{28} In early childhood clinical suspicion is most often raised by the developmental and behavioral phenotype, as physical examination features are not as clear.\textsuperscript{29,30}

In infancy, boys with FXS may have feeding difficulties related to hypotonia, gastroesophageal reflux, or oral motor/sensory issues.\textsuperscript{31} Medical problems in childhood can include seizures in approximately one-third of affected individuals, recurrent sinus or middle ear infections in up to 25%, mild scoliosis in 20%, and problems with small joint hyperextensibility, particularly in the hands in the vast majority of boys.\textsuperscript{32} Older adolescents and adults may develop mitral valve prolapse (50%) and hypertension. The hyperextensibility generally improves.
American Academy of Pediatrics has published Health Care Supervision guidelines for individuals with FXS.33

**Cognitive and Psychiatric Features**

Affected males typically show mild to severe intellectual disability and difficulty with abstract thinking, sequential cognitive processing, short-term memory, math, and visual-motor processing.34 IQ correlates inversely with the number of trinucleotide repeats, and executive functioning, visual-spatial skills, and attention are more impaired than would be expected for IQ level.35 Language skills plateau at approximately 48 months, and speech is typically rapid with tangentiality and perseveration. One-third of patients have a significant decline in IQ in middle to late childhood due to peaking in the rate of development relative to chronologic age. Large prospective longitudinal studies have shown that children with FXS do not lose skills, but do not maintain the same developmental trajectory as same-age peers.36

Individuals with FXS struggle with attentional dysfunction, hyperarousal, social anxiety, and communication challenges. Females with the full mutation may show social anxiety, social awkwardness, and schizotypal features.37 Female premutation carriers have an elevated rate of emotional problems; 30% show anxiety, social phobia or depression, but no cognitive deficits.38 This statistic suggests that the behavioral features of social avoidance and anxiety are independent of the effects of cognitive deficits. Adult male premutation carriers have attention-switching problems including a preference for fixed routines and a tendency to focus on details.39

Anxiety has been widely recognized as a major focus of impairment.40 Avoidance of social interactions may be due to hyperarousal, as children with FXS have enhanced autonomic reactivity to sensory stimuli and a decrease in prepulse inhibition.41,42 Gaze aversion is a prominent feature, particularly over the age of 8 to 9 years, and may disrupt social interactions. Of note, the gaze aversion is accompanied by an appropriate recognition of the other person. Studies have shown neuronal dysfunction involving the fusiform gyrus, plus evidence that direct gaze is processed abnormally.43 Direct gaze, eye contact, and socialization are associated with hyperarousal and a high level of stress.44

There are high rates of autistic-like symptoms, such as gaze aversion, hand flapping, language impairment and perseveration, and social cognition deficits,45 and one-quarter to one-half of children with FXS meet criteria for autism, although individuals with FXS account for only 1% of those diagnosed with autism. In one study, autistic and psychiatric symptoms were found to be stable over time in 18 males with FXS through adulthood.46

Treatment of emotional and behavioral problems in children with FXS is best approached from a multimodal perspective. Speech and language therapy, behavioral interventions, special education, and psychopharmacology all have a role.

Treatment of emotional dysregulation and behavioral outbursts has been investigated from behavioral and pharmacologic perspectives. In controlled studies, most problem behaviors in FXS children were maintained by social escape, suggesting that an exposure protocol treatment for social interaction paired with social skills training may be an effective intervention. A pilot study of behavioral shaping to increase eye contact was recently published by Hall47 and suggests the ability to use cognitive behavioral techniques to improve core behavioral deficits in FXS. Treatment with a selective serotonin reuptake inhibitor (SSRI) targeting social anxiety may be helpful, and a survey of fluoxetine usage in FXS suggested that it may be effective for depression and mood lability in females and aggression in males.48
Aggression, agitation, and mood dysregulation may respond to an atypical antipsychotic—anecdotal reports from topic experts indicate low doses of aripiprazole, 2.5 to 5 mg at night, may be beneficial.\footnote{Aggression, agitation, and mood dysregulation may respond to an atypical antipsychotic—anecdotal reports from topic experts indicate low doses of aripiprazole, 2.5 to 5 mg at night, may be beneficial.} Lithium has also been anecdotally reported to be helpful with aggression and mood stabilization in adolescents; opinion on the use of propranolol, a β-blocking agent, is mixed, although one case report suggested improvement.\footnote{Lithium has also been anecdotally reported to be helpful with aggression and mood stabilization in adolescents; opinion on the use of propranolol, a β-blocking agent, is mixed, although one case report suggested improvement.}

There have been 3 controlled studies of treatment of ADHD in FXS: 15 children with FXS, 3 to 11 years old, received methylphenidate (MPH), 0.3 mg/kg twice a day or dextroamphetamine, 0.2 mg/kg daily for 1 week. Ten of the 15 were judged to be responders to MPH; however, improvements could not be demonstrated on most outcome measures.\footnote{There have been 3 controlled studies of treatment of ADHD in FXS: 15 children with FXS, 3 to 11 years old, received methylphenidate (MPH), 0.3 mg/kg twice a day or dextroamphetamine, 0.2 mg/kg daily for 1 week. Ten of the 15 were judged to be responders to MPH; however, improvements could not be demonstrated on most outcome measures.} A double-blind randomized controlled trial using L-acetylcarnitine, 50 mg/kg twice a day, reported improvement in hyperactivity at the 1-year mark in boys with FXS.\footnote{A double-blind randomized controlled trial using L-acetylcarnitine, 50 mg/kg twice a day, reported improvement in hyperactivity at the 1-year mark in boys with FXS.} A survey of parents whose children were taking clonidine suggested beneficial effects in a majority,\footnote{A survey of parents whose children were taking clonidine suggested beneficial effects in a majority,} and the same author has suggested clonidine or tenex as an intervention of choice for children with sensory hypersensitivity and hyperarousal.

Sporadic case reports have looked at other agents including imipramine.\footnote{Sporadic case reports have looked at other agents including imipramine.} Several attempts have also been made to use compounds targeting neurobiologic deficits produced by the absence of FMRP.\footnote{Several attempts have also been made to use compounds targeting neurobiologic deficits produced by the absence of FMRP.}

### RETT SYNDROME

#### Genetics, Etiology, and Epidemiology

Classic Rett syndrome has a prevalence of approximately 1 in 10,000 females,\footnote{Classic Rett syndrome has a prevalence of approximately 1 in 10,000 females, although emerging information regarding the range of phenotypes associated with MECP2 alterations in both males and females will expand the clinical impact of this gene over time.} although emerging information regarding the range of phenotypes associated with MECP2 alterations in both males and females will expand the clinical impact of this gene over time. MECP2 is located at Xq28 and encodes the MeCP2 protein responsible for decreasing transcription, and thus expression, of other genes. Loss of this inhibition in the brain probably results in overexpression of normally tightly regulated genes in brain development.\footnote{MECP2 is located at Xq28 and encodes the MeCP2 protein responsible for decreasing transcription, and thus expression, of other genes. Loss of this inhibition in the brain probably results in overexpression of normally tightly regulated genes in brain development.}

Molecular testing is available to confirm a clinical diagnosis of Rett syndrome; however, mutations are found by sequencing the MECP2 gene in only approximately 80% of girls with classic features and 40% with variant phenotypes.\footnote{Molecular testing is available to confirm a clinical diagnosis of Rett syndrome; however, mutations are found by sequencing the MECP2 gene in only approximately 80% of girls with classic features and 40% with variant phenotypes.} Reliable genotype-phenotype correlations cannot be made for most identified mutations.\footnote{Reliable genotype-phenotype correlations cannot be made for most identified mutations.} Other methods are used to detect deletions and duplications; the latter are more common in severe MECP2-related phenotypes.\footnote{Other methods are used to detect deletions and duplications; the latter are more common in severe MECP2-related phenotypes.} Most MECP2 mutations associated with classic Rett syndrome are not inherited, although asymptomatic mothers have been identified.

#### Physical Features and Medical Issues

Clinical diagnostic criteria are available for establishing a diagnosis of Rett syndrome along with variant phenotypes.\footnote{Clinical diagnostic criteria are available for establishing a diagnosis of Rett syndrome along with variant phenotypes.} These criteria highlight the more specific features of the syndrome and place less emphasis on the nonspecific features to reduce erroneous diagnosis and exclude other potential causes of similar generalized features.

Rett syndrome is most often diagnosed in childhood once the developmental trajectory of affected girls is recognized. Classic Rett syndrome typically progresses through recognizable clinical stages throughout the lifetime.\footnote{Rett syndrome is most often diagnosed in childhood once the developmental trajectory of affected girls is recognized. Classic Rett syndrome typically progresses through recognizable clinical stages throughout the lifetime.} Stage I is the “early-onset stagnation” phase marked by mildly delayed development, although continued progress, and reduced interactions with others. This stage typically begins in toddlerhood and lasts weeks or months, only to be followed by a similarly brief State II. Stage II is the “rapid developmental regression” phase during which there is true loss of acquired motor,
language, and social skills, which may happen quite dramatically or over time. This phase is accompanied by a more pronounced decrease in interaction with others and objects, and development of atypical behaviors or actions such as hair pulling. Growth failure develops during this time, with slowing of linear growth and head circumference. By early childhood, length and head circumference are usually at least 2 standard deviations below the mean, and the head circumference may continue to decrease to more than 3 standard deviations below the mean by late childhood.

Following State II is Stage III, the “pseudostationary phase,” when the stereotypical, repetitive hand motions (wringing, washing motions, or clapping) are most obvious. Breathing patterns can change, and sleep/wake cycles are often disturbed. Interaction skills and elements of personality reappear, leading to an apparent “wake-up.” Seizures are seen in some affected girls, and dystonia is not infrequent leading to orthopedic complications. This phase can last for many years. Stage IV, “late motor deterioration,” commences when the ability to walk is lost. During this phase there is progressive neurologic deterioration leading to rigidity, although purposeful eye movements and intense visual awareness are often preserved. Autonomic dysfunction is also common.

Medical complications are related to the developmental and neurologic issues. Feeding problems due to neurologic impairment can be compounded by gastroesophageal reflux. Seizures are common, and are diagnosed in 80% of affected individuals, although they can resolve with time. Orthopedic complications secondary to neurologic manifestations are typical. Cardiac rhythm disturbances due to prolonged QTc interval are seen and have been associated with sudden death.

Cognitive and Psychiatric Features

Most affected girls experience severe to profound intellectual disability, but there is little evidence for deterioration over time.66 There is severe impairment in the development of expressive and receptive language, and most girls lose all speech by 40 months, although use of some words may be preserved.67

Behavioral and emotional features vary by stage of progression. In Stage I subtle symptoms include decreased eye contact and reduced interest in toys. During Stage II the emergence of stereotypic hand movements is paired with social withdrawal, and autistic-like behaviors with irritability, sleep disturbance, and screaming and crying episodes.

In Stage III there is generally an improvement in behavior, less irritability and fewer autistic-like features, better social and communication skills, and better alertness and attention span. Stereotypical, midline, asymmetric hand movements are almost constant but can be voluntarily controlled for short periods of time.68 Stage III is also characterized by sleep disturbance with initial insomnia, frequent arousals, and daytime napping. Stage IV (late motor deterioration) heralds reduced mobility and increased rigidity, spasticity, and dystonic posturing, but no decline in cognition, communication, or hand skills.69 Eye gaze becomes the most important interactional mode.

There are no proven pharmacologic treatments for the syndrome. Topic experts have suggested that agitation can be treated with low-dose neuroleptics or SSRIs, and sleep disturbance can be ameliorated with melatonin or antihistamines.70
controlled by imprinting, by which methylation of the DNA causes the selective silencing of genes from either the paternal or the maternal homolog. The genes within this region are variably expressed, with some genes expressed only when inherited paternally and others only when inherited maternally.

Loss of the paternally expressed genetic information at 15q11-q13 results in the medical and physical features recognized as Prader-Willi syndrome (PWS). PWS has an estimated incidence of 1 in 10,000 to 1 in 15,000, and has no racial or ethnic predilection. There are several different molecular etiologies for PWS including a common 4-Mb deletion of the paternally inherited chromosome 15 (75%), maternal uniparental disomy (UPD; inheritance of both copies of chromosome 15 from the mother), or an imprinting defect (<5%).

Molecular testing for PWS is readily available. Most testing algorithms begin with methylation-sensitive PCR, which can diagnose PWS independent of molecular etiology by determining whether both a methylated (maternal) and unmethylated (paternal) signal are detected. The absence of the unmethylated (paternal) contribution confirms the diagnosis. Additional testing, including FISH and UPD studies, are required to distinguish the underlying cause and provide appropriate genetic counseling.

**Physical Features and Medical Issues**

The medical and physical features of PWS change dramatically within the first few years of life. Infancy is universally marked by profound central hypotonia and feeding difficulties, often leading to failure to thrive. With time the hypotonia improves, but global developmental delays become more prominent. In childhood, central obesity results from extreme hyperphagia, usually beginning between 1 and 6 years of age.

Physical features include short stature, small and narrow hands and feet, hypogonadism, and fair pigmentation as compared with family members. The facial features are notable for bitemporal narrowing, almond-shaped eyes, and a narrow nasal bridge. Medical issues are often related to obesity, with a high proportion of fat mass to lean body mass. Decreased vomiting and a high pain threshold may predispose affected individuals to acute injuries.

Clinical criteria have been developed and validated to allow for prompt diagnosis in suggestive clinical situations. Treatment with recombinant human growth hormone has been shown to improve linear growth and, possibly, body composition.

**Cognitive and Psychiatric Features**

Mild (33%) to borderline (60%) intellectual disability is common; however, up to 5% of those with PWS have an IQ in the normal range. Individuals with PWS show challenges with short-term memory, auditory processing, socialization, mathematical skills, and sequential processing. Relative strengths are present in visuospatial performance, reading and decoding, and long-term memory. There is a particular aptitude for jigsaw puzzles.

Individuals with PWS have very high rates of maladaptive behaviors, the most striking of which is compulsive hyperphagia, characterized by compulsive food seeking, food hoarding, and gorging. Management is primarily behavioral, by restricting access to food, which can be a major challenge.

Obsessive-compulsive features are widely recognized, including ritualistic behaviors, hoarding nonfood items, hair pulling, skin picking, ordering, and “just right” behaviors. Compulsive behaviors cause significant impairment in almost half of affected individuals, but frank obsessional thinking is rare.
with a drive for sameness, usually comes to clinical attention around 5 years of age with perseveration in speech, becoming “stuck” on issues, and need for a consistent daily schedule. There is a high incidence of responding to minor frustrations with explosive tantrums. Individuals with PWS tend to be egocentric and will argue, lie, manipulate, and confabulate to change rules, obtain their wishes, or justify behavior. These characteristics may produce a picture of oppositionality and stubbornness which, when paired with typically solitary behavior and social withdrawal, leads to poor peer relations. Specific social cognition deficits have been identified, including difficulty recognizing social cues and processing social information.

In adolescence, explosiveness and poor affect regulation may evolve into prolonged periods of clinical depression, and in some cases into a hypomanic state with confusion, restlessness, and increased goal-directed behavior lasting days to weeks; 15% to 17% of individuals with PWS meet criteria for a mood disorder. In one study, 28% of individuals with PWS developed severe affective disturbance with psychotic features in late adolescence to adulthood; there are emerging genotype-phenotype correlations.

Self-injury rates are high throughout life; in one series 81% of PWS individuals engaged in self-injurious behavior (SIB). Skin picking is the most common form of self-injury followed by nose picking, nail and lip biting, nail pulling, and hair pulling.

The primary treatment for most of the functionally impairing features is behavioral and has been reviewed elsewhere. All individuals require long-term behavioral treatment, and interventions have included placing food under restricted access, token economies, video modeling, and others.

Pharmacologic management experience is anecdotal. A tendency toward effects greater than expected for dose, both therapeutic and undesired, has been noted, and dosages one-quarter to one-half of typical are often sufficient for effect. Reduced metabolism by components of cytochrome P450 complex has been documented in one-third of PWS individuals and may provide a clue to this finding. SSRIs may improve compulsive behaviors and skin picking, but careful monitoring of mood is necessary. Additional small studies and case reports have demonstrated success in improving mood and skin-picking behaviors with topiramate, reduction of violent outbursts with carbamazepine and lithium, and improvement in maladaptive behaviors without weight gain using low-dose risperidone (average of 1.6 mg/d). Methylphenidate has been noted to be helpful for ADHD symptomatology. Medications have not been effective in curbing the drive for food or decreasing appetite.

ANGELMAN SYNDROME

Genetics, Etiology, and Epidemiology

Within the 15q11-q13 region are genes with specific parent of origin expression; some genes are exclusively expressed from the paternal allele and others are expressed only from the maternal allele. When there is loss of the normal expression of maternal alleles, Angelman syndrome (AS) results. This loss of expression can result from several molecular mechanisms including a deletion within the maternal chromosome homolog (70%–75%), paternal UPD of chromosome 15 (2%–5%), and imprinting defects (2%–5%). Mutations within one gene located within this region, UBE3A, have been shown to cause AS in 20% to 25% of affected individuals.

Molecular testing to diagnose AS is available. Testing begins with methylation-sensitive PCR, which can confirm a diagnosis in most affected individuals. If an abnormal methylation pattern is detected, additional FISH or UPD studies will
determine the etiology. In individuals with classic features and normal methylation studies, UBE3A mutation analysis is indicated.

AS is seen in all ethnic groups, and has an overall incidence of approximately 1 in 12,000 to 1 in 20,000.98

Physical Features and Medical Issues

Most individuals with AS are diagnosed in childhood as the physical examination features, developmental profile and medical issues become apparent.99 Seizures, often difficult to control, dominate the medical issues, and usually emerge at 18 to 24 months. Microcephaly develops over time as well. Some individuals have hypopigmentation, strabismus or oral motor coordination difficulties.

Cognitive and Psychiatric Features

Global developmental delays in very early childhood evolve into severe to profound intellectual disability. Marked expressive speech delay is common, with many children using few, if any words; receptive language skills are often more advanced.

The behavioral phenotype of individuals with AS is characteristic and part of available clinical diagnostic criteria.100 Individuals appear social and happy but laugh frequently, inappropriately and unexpectedly with minimal stimulation. Laughter is not uncontrollable; laughing and smiling behavior increases in the presence of adult speech, touch, eye contact, smiling or laughing.101 Although individuals with AS have a markedly positive interpersonal bias, social disinhibition, a diminished fear of strangers, fear of crowds and noise are commonly problematic.102

Hyperactivity/inattention is commonly reported, particularly in childhood, and improvement is noted with age.103 Sleep disturbance, seen in approximately 25% of individuals includes reduced total sleep time, increased sleep onset latency, disrupted sleep architecture with frequent nocturnal awakenings, reduced rapid-eye-movement sleep and periodic leg movements.104 Other less frequent but problematic behaviors include excessive mouthing/chewing, hand flapping, aggression and an attraction to water; food related behaviors include pica, gorging food and food fads.105 No controlled psychopharmacologic data exist.

WILLIAMS SYNDROME

Genetics, Etiology, and Epidemiology

The co-occurrence of idiopathic hypercalcemia and supravalvar aortic stenosis was initially described in the 1960s106–108 and the full syndrome was eponymously named after cardiologists Williams and Buren. WS is primarily a sporadic condition with an approximate incidence of 1 in 10,000. A common chromosome microdeletion of 1.5 Mb at 7q11.23 is responsible for the full phenotype; absence of the ELN gene is associated with the cardiac and connective tissue features, and loss of the LIMK1 and GTF2I genes appear to be critical for the WS cognitive and developmental phenotype, respectively.110,111 Molecular testing, via FISH or CGH microarray, is able to document the microdeletion in 99% of individuals with WS.

Physical Features and Medical Issues

Most diagnoses of WS are made early in childhood based on the classic cardiac malformations, supravalvar aortic stenosis and, less commonly, pulmonic stenosis, accompanied by short stature, typical facial features, and characteristic developmental and behavioral features. The facial features of individuals with WS change over time but are notable for bitemporal narrowing, a long philtrum, a wide mouth with full lips, a “stellate” appearance of the iris, an infraorbital crease, and full cheeks.
Because of the defect in elastin, the face ages more than expected based on chronologic age, resulting in narrowing of the face and furrowing along the nasolabial folds. Individuals with WS tend to have a deep or hoarse voice, hypotonia, ligamentous laxity, soft skin, and a predisposition to viscous organ diverticulae and rectal prolapse. Fifteen percent of individuals have variable hypercalcemia. A history of failure to thrive in infancy is common. Health care supervision guidelines are available from the American Academy of Pediatrics.  

**Cognitive and Psychiatric Features**

Seventy-five percent of individuals with WS have intellectual disability, usually in the mild range. Adaptive behavior, however, is less than expected for IQ. Strengths in auditory rote memory and language are seen, but severe visuospatial construction deficits and language disorder are problematic.

Externalizing maladaptive behaviors are common and include inattention (>90%), impulsivity, attention seeking, hyperactivity, and temper tantrums. Internalizing features are also frequent, including obsessions/preoccupations, fears, anxiety, sadness/depression, and irritability. Fights and aggressive behavior are less common than the frequency seen in the general intellectual disability (ID) population.

Individuals with WS display a superficial sociability, comprising a keen interest in people and increased empathy, appearing most clearly pathologic in their guileless approach to strangers. Affected children show increased social interest from infancy onward, and display a positive interpersonal bias when categorizing others; face-seeking and positive face stimuli are overvalued. Individuals with WS rely on superficial signals but fail to recognize more subtle cues in the interactions with others, resulting in excessive empathy and lack of social inhibition. Along with this capacity to empathize with others, affected individuals perform poorly on theory of mind tasks that require inferring mental states as a basis for others’ behavior, and in particular show deficits in the social cognition component.

The most striking psychopathologic features are on the anxiety axis, which are more prevalent than in the general ID population. Individuals show high levels of anxiety, and many develop depression as adults, which may relate to the accumulation of unsuccessful social experiences. Use of the DICA-R (Diagnostic Interview for Children and Adolescents—Revised) in WS individuals revealed minimal separation anxiety or obsessive compulsive disorder, but high rates of worry about future events. Eighteen percent met criteria for generalized anxiety disorder, and 35% met full criteria for a specific phobia, commonly with associated avoidance behavior. Unlike neurotypical children, individuals with WS show maintenance of concrete fears, out of proportion to their developmental delay. Common phobias involve natural environment fears (storms, high places), fears of being alone, and fears involving animals. Cognitive behavioral therapy using exposure and response prevention is recommended for treatment of these phobias.

More than half of affected children have ADHD, primarily inattentive and combined types. Hyperactivity and aggression, if present, may decrease with age. There have been 2 small placebo-controlled pharmacologic treatment studies, in which MPH was shown to be effective at a dose of 0.5 mg/kg or 10 mg twice a day in a majority of those studied. An increased rate of sleep disturbance, particularly initiating and maintaining sleep, has been seen in up to half of affected individuals; polysomnography showed no increased sleep apnea but increased wake time, decreased stage 1 and 2 sleep,
increased stage 3 and 4 sleep, and fivefold higher periodic limb movements. Clonazepam has been reported to be helpful.\textsuperscript{125}

**DELETION 22Q11.2 (VELO-CARDIO-FACIAL SYNDROME; DIGEORGE SYNDROME)**

*Genetics, Etiology, and Epidemiology*

Encompassing a wide range of physical phenotypes, including several eponymous syndromes, this microdeletion is thought to be the most common contiguous gene deletion, with general population estimates ranging from 1 in 3800 to 1 in 6000.\textsuperscript{126} The deletion is found in much higher frequency within populations selected for cardinal physical features including cleft lip/palate/bifid uvula and conotruncal cardiac malformations.

The classic 3-Mb deletion includes 30 genes, several of which appear to play a role in the phenotype. \textit{TBX1} has been shown to be associated with the cardiovascular malformations,\textsuperscript{127} \textit{COMT} may have a role in the behavioral and psychological issues,\textsuperscript{128} and \textit{CTLD} appears to be associated with hypotonia.\textsuperscript{129}

Deletions of 22q11.2 can be detected via specific FISH. Recently, CGH microarray has been used as first-line molecular testing for individuals with developmental delays.\textsuperscript{130} This technology is able to detect the classic deletion as well as smaller, variant deletions that would not be detected via FISH, as the probe target is not deleted. The clinical information emerging as a result of the variant deletions will likely contribute to more specific genotype-phenotype correlations, particularly with regard to the congenital anomalies and psychiatric issues.\textsuperscript{131,132}

In contrast to most other microdeletion syndromes, approximately 10% of 22q11.2 deletions are inherited from variably affected parents.\textsuperscript{133,134} As with all chromosome deletions, there is a 50% risk of passing the deletion from parent to child.

**Physical Features and Medical Issues**

Deletion 22q11.2 is known for wide phenotypic variability, and long lists of possible features have been compiled.\textsuperscript{135} Multisystem involvement is apparent in most individuals.

Velo-cardio-facial syndrome (VCFS) classically involves abnormalities of the palate, ranging from velopharyngeal insufficiency to overt clefting; structural cardiac defects involving the aorta, ventricular septum, conotruncal structures and proximal vasculature, and subtle facial features including a long face, long nose with a full tip, retrognathia, hooded eyes, and atypical ear morphology. Short stature is common, as are long, tapered fingers and hypotonia.

Several clinical diagnoses have been associated with deletions of 22q11.2, including DiGeorge syndrome, conotruncal anomaly face syndrome, Cayler syndrome, and some families with Opitz G/BBB syndrome.\textsuperscript{136–138}

**Cognitive and Psychiatric Features**

Individuals with deletion 22q11.2 commonly have IQ scores in the borderline range, with a mean of 70, although some may have mild intellectual disability. Verbal IQ is higher than performance,\textsuperscript{139} and the most common learning disability area is math. There is a relative strength in language abilities, despite frequent and dramatic early language delay. Investigators have documented receptive and high-order language deficits, abstract reasoning deficits, and visuospatial deficits.

Executive functioning challenges include distractibility, attention deficits, and abstract thinking problems.\textsuperscript{140} Individuals can be impulsive, disinhibited, and prone to temper tantrums. What is often characterized as mood swings (emotional dysregulation) has been attributed by one expert author to better represent a feature of ADHD.
or oppositional behavior, rather than a bipolar diathesis, as they occur in the absence of other symptoms of a manic disorder, such as grandiosity, increased energy, decreased need for sleep, or racing thoughts.\textsuperscript{141}

Younger children with VCFS show attention problems, anxiety and phobia symptoms, and poor social adaptation with withdrawal, shyness, and awkwardness.\textsuperscript{142} The development of anxiety may be related to gene/environment interaction whereby hypernasal speech, decreased facial expression, and poor social interaction skills are met with negative reinforcement from peers.\textsuperscript{143,144} With age, anxiety persists rather than diminishes, and 8 times as many individuals develop psychotic disorders when compared with age- and IQ-matched controls.\textsuperscript{142}

While rates of anxiety are generally high, Gothelf and colleagues\textsuperscript{143} have particularly noted obsessive compulsive disorder (OCD), the most prevalent symptoms being excessive washing and cleaning, hoarding, and somatic worries.

Two-thirds of school-aged children and adolescents will meet criteria for a psychiatric disorder; there is no correlation with IQ.\textsuperscript{144} Fifty percent of affected individuals meet criteria for autism spectrum diagnoses by the Autism Diagnostic Interview—Revised (primarily Pervasive Developmental Disorder—Not Otherwise Specified), 27% have psychotic symptoms, and 12% schizophrenia.\textsuperscript{145}

The emergence of psychotic symptoms in adolescence to early adulthood is of great concern to families. Approximately 30% of individuals develop psychotic symptoms that tend to have a chronic course and are less responsive to neuroleptic treatment than other psychoses.\textsuperscript{146} Paranoid schizophrenia has also been reported in up to 30% of adults.\textsuperscript{140} Increased rates of psychotic illnesses among relatives have also been documented.\textsuperscript{147} The presence of subthreshold psychotic symptoms, anxiety, and depression, and lower verbal IQ during childhood significantly predicted the onset of a psychotic disorder at 17.5 years, but ADHD did not put the subjects at increased risk.\textsuperscript{148} Overall, approximately 2% of all cases of schizophrenia and 6% of those with onset in childhood were found to have deletion 22q11.2\textsuperscript{148}, all deletion-positive individuals had physical features or medical history indicating this diagnosis.

Genotype/phenotype correlations are emerging regarding the remaining \textit{COMT} gene in affected individuals, the gene product involved in dopamine degradation. Two polymorphisms have been identified within this gene, a high-activity VAL allele and a lower activity MET allele. Individuals with the 22q11.2 deletion and a remaining MET allele may be at risk for more severe psychotic symptoms, and have higher rates of OCD and ADHD in childhood.\textsuperscript{149}

Treatment should be multimodal and includes behavioral treatment for anxiety disorders, social skills training, and psychopharmacology. An annual psychiatric examination by a child psychiatrist with particular attention to subthreshold psychotic symptoms, and consideration of treatment with atypical antipsychotics, is recommended. Given the high rates of cardiac involvement in individuals with this deletion, an electrocardiogram should be obtained, and QTc monitored\textsuperscript{149} particularly during treatment of ADHD. One open-label study of low-dose MPH (0.3 mg/kg) reduced ADHD symptoms in 75% of treated individuals.\textsuperscript{150} Significant improvement in OCD symptoms has been noted with fluoxetine, 30 to 60 mg/d. Metyrosine, a tyrosine hydroxylase inhibitor, has been associated with a decrease in psychiatric symptoms.\textsuperscript{151}

\textbf{SMITH-MAGENIS SYNDROME}

\textit{Genetics, Etiology, and Epidemiology}

Smith-Magenis syndrome (SMS) has been recognized since the 1980s\textsuperscript{152–154} and is caused by a deletion of chromosome 17p11.2.\textsuperscript{155,156} The phenotype changes
significantly over the life span, and diagnosis is largely dependent on the presence of structural malformations or recognition of the behavioral phenotype.

The critical region for SMS is a 1-Mb region within the classic deletion of approximately 4 Mb. Several genes within this region have been implicated in the features of SMS syndrome, including RAI1. A standard karyotype will identify the deletion in at least 90% of affected individuals. Deletion-specific FISH is available and can increase diagnostic yield to more than 95%. Smaller deletions may be detected using CGH microarray. A small number of affected individuals have been found to have mutations within RAI1.

Physical Features and Medical Issues

In contrast to many microdeletion syndromes, the behavioral and developmental features of SMS predominate the phenotype and may be the presenting symptoms prompting diagnostic testing in childhood.

The facial features of children and adults with SMS are described as “coarse” with a prominent brow ridge, deeply set eyes, and a prominent mandible. Ophthalmologic abnormalities, cardiac anomalies, hearing loss, short stature, and small hands and feet are frequent. Neurologic abnormalities, including seizures, hypotonia, diminished reflexes, and high pain tolerance are common. Hypercholesterolemia is also common.

Infants with SMS have a particular phenotype, quite different from that seen in older children. The facial features of babies are more subtle, with midface hypoplasia and up-slanting palpebral fissures. Affected infants are hypotonic, quiet, and “compliant,” often with feeding difficulties.

Cognitive and Psychiatric Features

Most individuals have moderate intellectual disability, with a range from mild to severe, with no verbal/performance difference, and the level of cognitive and adaptive functioning has been shown to depend on deletion size. Short-term memory, visuomotor coordination, sequencing, and response speed are weaknesses. Speech delay is common, with receptive language better than expressive, and there is usually limited adaptive functioning. Sleep disturbance, stereotypy, and SIB are the primary psychiatric features and are not usually recognized until the age of 18 months, and evolve with time.

A lifelong sleep disturbance can cause significant impairment. This problem begins as long naps as an infant, but evolves to become an inverted melatonin circadian rhythm problem, including difficulty falling asleep, shortened sleep cycles, frequent and prolonged awakenings at night, and daytime sleepiness. Treatment of the sleep disturbance with a β1-adrenergic antagonist (acebutolol, 10 mg/kg) during the day, and exogenous administration of melatonin in the evening have been shown in case series to lead to improved sleep and reduced behavioral problems.

SIB is seen in over 95% of affected individuals; typical topography includes wrist biting, head banging, skin picking, nail removal, and foreign body insertion. These behaviors can be severe and persistent, and the frequency and range of topography increase with age. There is also a characteristic “self-hug”—a spasmodic squeezing of the upper body, of which there are 2 subtypes: (1) self-hugging and spasmodically tensing the upper body, and (2) hand clasping at chest level and squeezing arms against body. This behavior has been interpreted as a ticlike pattern of involuntary expression of excitement. Other odd or stereotypic behaviors include lick-and-flip, mouthing objects, teeth grinding, body rocking, and spinning objects.

Children with SMS are socially adult-oriented and demanding of adult attention. These children are egocentric and have delayed empathic skills out of proportion to
their cognitive level. In fact, withdrawal of adult attention is often the primary antecedent to SIB and aggressive/disruptive behavior.\textsuperscript{172} While most children are affectionate and have a primarily positive affect, affective lability, property destruction, impulsivity, nervousness, physical aggression, and argumentative behavior are also seen.\textsuperscript{173} There is a single case report of use of risperidone to target aggression in a 13-year-old with SMS.\textsuperscript{174}

**TURNER SYNDROME**

*Genetics, Etiology, and Epidemiology*

By definition, Turner syndrome (TS) occurs only in females and has an incidence of approximately 1 in 3000 live-born infant girls. At the most basic level, TS results when there is a single functioning X chromosome as a result of loss of the second sex chromosome in its entirety or more specifically, portions of the short arm of either the second X chromosome or the Y. Half of affected individuals will have a 45,X karyotype; a wide range of other structural X-chromosome malformations and mosaic chromosome constitutions make up the remaining karyotypes.\textsuperscript{175} A standard peripheral blood karyotype will confirm a diagnosis as well as detect X-chromosome variations and mosaicism.

**Physical Features and Medical Issues**

Cardinal features of TS include lymphedema, cardiac malformations, short stature, and primary ovarian failure. The age at which a diagnosis of TS is made is highly dependent on the physical features that are present: in infancy, lymphedema of the hands and feet or characteristic cardiac malformations may prompt diagnostic testing, whereas in childhood short stature is the common diagnostic feature, as is delayed puberty or primary ovarian failure in adolescents and adults. Prenatal diagnosis, based on the presence of an increased nuchal translucency or cystic hygroma, is also possible.

Left-sided congenital structural malformations, such as aortic valve abnormalities and aortic coarctation, are seen in less than half of affected individuals.\textsuperscript{176,177} Renal malformations are also fairly common in TS, as are recurrent otitis media, strabismus, hypothyroidism, inflammatory bowel disease, overweight, and benign nevi.\textsuperscript{178,179} Subtle facial features, including down-slanting palpebral fissures and low-set ears, or physical examination findings (wide neck, low posterior hairline, broad chest) are present in some affected individuals. Appropriate growth charts and Health Care Supervision recommendations are available from the American Academy of Pediatrics.\textsuperscript{180}

**Cognitive and Psychiatric Features**

In general, affected girls have an IQ in the normal range; only 5% have intellectual disability. Performance IQ is usually lower than verbal, and learning disabilities in math are common. Nonverbal abilities are often significantly impaired, including visual-spatial, visual-perceptual, and visual-constructional abilities.\textsuperscript{181} Impaired executive functioning skills may include attention and concentration, problem-solving ability, organization and working memory, impulsivity, and processing speed. Russell and colleagues\textsuperscript{182} found an 18-fold increased prevalence for ADHD among those with TS versus controls.

Psychiatric features include social immaturity, anxiety, hyperactivity, and social challenges. Younger girls are generally immature, hyperactive, and anxious. Older girls tend to have anxiety, depression, and social relationship challenges. Girls
with TS have been shown to have more difficulty maintaining relationships, and
tend to have fewer friends and be more socially isolated than controls.\textsuperscript{183}

There is debate as to whether the shyness, anxiety, low self esteem, and depression
noted with increased prevalence in TS are due to neurodevelopmental deficits, or due
to self-consciousness over physical appearance and infertility. When compared with
their unaffected sisters, in an effort to neutralize environmental effects, girls with TS
had more social thought and attention problems.\textsuperscript{184}

Rigorous neuropsychological investigation into the social interaction difficulties and
anxiety seen in TS has demonstrated weakness with discriminating facial affect,\textsuperscript{185}
and affective prosody\textsuperscript{186} and specific significant deficits with mental rotation, object
assembly, and face recognition.\textsuperscript{187} There is a specific partial deficit in social gaze pro-
cessing, involving recognition of emotional cues expressed in the upper face, partic-
ular for expression of “fear” in the eye region.\textsuperscript{188} Impaired appraisal of facial affect and
decreased ability to habituate to fearful stimuli may stem from impaired functional
connectivity between the amygdala and fusiform gyrus, suggesting that standard
cognitive behavioral therapy exposure protocols for treatment of anxiety may have
to be modified for these individuals.\textsuperscript{189}

Although there are few treatment data psychotherapy is generally recommended,
focusing on coping and adaptive skills, social skills training, stress management,
improving self esteem, and using internal and external strategies to compensate for
cognitive weaknesses.\textsuperscript{190}

**LESCH-NYHAN SYNDROME**

**Genetics, Etiology, Epidemiology, Physical Features, and Medical Issues**

Lesch-Nyhan syndrome is an X-linked disorder of purine metabolism resulting from
decreased activity of hypoxanthine-guanine phosphoribosyltransferase. This diag-
nosis is often suspected because of the specific physical and behavioral phenotype
seen in childhood; choreoathetosis, seizures, dystonia, and dysarthria are also
frequently present. The diagnosis is established by measuring plasma or urine uric
acid levels, which are markedly elevated. Medical treatment is primarily symptomatic,
and allopurinol is used to prevent complications related to hyperuricemia/uricosuria.

**Cognitive and Psychiatric Features**

IQ is typically in the mild to moderate range of intellectual disability. The psychiatric
presentation is dominated by chronic SIB, resulting in self-mutilation.

Self-injury consists most frequently of biting, followed by eye poking, fingernail pull-
ing, and psychogenic vomiting. Biting behavior tends to target the lips and fingers, fol-
lowed by the arms and tongue, and the biting pattern is often asymmetric. Other
movements that can produce self-injury, such as arching, head snapping, and head
banging, are also seen.\textsuperscript{191} The SIB appears to be a compulsive behavior that the child
tries to control but generally is unable to resist.\textsuperscript{192} As with other compulsive behaviors,
control improves with age but affected individuals may enlist others to assist in
controlling these impulses, or may self-restrain. A characteristic language pattern
involving repeated ambivalent statements with anxiety and vulgarity is seen along
with frequent compulsive aggression toward others, grabbing, and pinching—with
resultant apologies.

Based on a theory that many of the neuropsychiatric features are related to abnor-
malities in dopamine function, treatments with the dopamine precursor levodopa have
been tried, but were unsuccessful. A case report of deep brain stimulation in
the globus pallidus pars interna in a single 19-year-old describes cessation of
self-mutilation. Other effective treatment avenues include behavioral therapy with an extinction protocol based on active withdrawal of attention. Benzodiazepines can reduce anxiety, but may exacerbate extrapyramidal side effects and behavioral features. Stress and anxiety increase self-injury, so reduction in these factors is important. Use of restraints and protective equipment is common. SSRIs can be used to treat anxiety, Risperidone at low dose has been suggested by topic experts for SIB and aggression. No controlled pharmacologic treatment data are available.

COMMON INBORN ERRORS OF METABOLISM

Several other inborn errors of metabolism are associated with marked behavioral or psychiatric manifestations. Not all of these diagnoses are established in infancy through newborn screening, and many may not be diagnosed until the behavioral phenotype is well established. Although in general these diagnoses are rare, consideration should be given to a metabolic evaluation in individuals with suggestive medical and psychological features.

Phenylketonuria (PKU), resulting from a deficiency of phenylalanine hydroxylase, is part of newborn screening programs in all 50 US states. Early diagnosis and medical management to maintain phenylalanine levels within the recommended therapeutic range of 2 to 6 mg/dL (120–360 μmol/L) in childhood reduces the risk of mental retardation, behavioral problems, and learning difficulties. Liberalization of the phenylalanine restricted diet, with subsequent elevations of blood phenylalanine levels to greater than 10 to 20 mg/dL are often accompanied by difficulty with attention, reduced executive functioning, and anxiety/depression. Many of these symptoms can be reduced by decreasing the blood phenylalanine concentration through diet modification or medications, although there does remain an increased risk for psychiatric disorders.

Most individuals with the mucopolysaccharidoses (MPS) are diagnosed based on specific physical or medical issues related to the intracellular storage of nonmetabolized mucopolysaccharides. The MPS disorders are also often associated with behavioral problems, including abnormal levels of activity (either lethargy or hyperactivity), aggression, oppositional behavior, sleep disturbance, and difficulties in interpersonal skills. The SanFillipo syndromes (MPS III) are particularly notable for the degree of behavioral involvement, which often dominates the overall phenotype. A variable period of normal development is followed by delays in language acquisition, severe temper tantrums, inattention, explosive reactions to change, sleep disturbance and, ultimately, dementia. A limited number of diagnosis-specific therapies are available, primarily targeting the medical complications.

The recurrent hyperammonemia associated with the urea cycle disorders (UCDs) has been implicated in residual developmental delays and mental retardation seen in many patients. However, neurocognitive disabilities and decreased IQ are seen in individuals without episodic hyperammonemia and in asymptomatic carriers of the most common form, X-linked ornithine transcarbamylase deficiency. There is increasing recognition of a characteristic nonverbal learning disability and difficulties with attention and executive functioning in individuals of all ages, regardless of the degree of hyperammonemic symptomatology.

SUMMARY

The identification of specific genetic diagnoses, including genotype-specific variations, presents the unique opportunity to study genotype/phenotype connections in child psychiatry. Multiple investigators have spent the last 2 decades characterizing
the psychopathologic features associated with specific diagnoses, and the latest research seeks to connect specific facets of behavioral functioning, such as social gaze processing in TS, with genetic variance. These advances have implications for understanding functional deficits in the broader population, and support a dimensional approach to psychopathologic characterization. Each disorder, as it is more fully characterized, presents a microcosm whereby particular facets of functional impairment, such as direct gaze aversion in FXS, or components of theory of mind in Williams syndrome, can be mapped and linked at a genomic level to inform highly specific treatments with potential broader application.

REFERENCES


