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Autism Overview

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Summary

Disease characteristics. Autism, often referred to as autistic disorder or infantile autism, is a complex behavioral disorder which, by definition, develops prior to age three years. Autism is defined completely on the basis of impairments in social interaction, impairments in communication, and repetitive and stereotypic behaviors. For most children, the onset of autism is gradual; however, approximately 30% have a "regressive" onset. Fifty to seventy percent of children with autism are defined as mentally retarded by nonverbal IQ testing. Seizures develop in approximately 25% of children with autism. About 25% of children who fit the diagnostic criteria for autism at age two or three years subsequently begin to talk and communicate, and by six or seven years blend to varying degrees into the regular school population. The remaining 75% continue to have a lifelong disability requiring intensive parental, school, and societal support.

Diagnosis/testing. The standard diagnostic criteria for autism, compiled by the American Psychiatric Association Manual of Psychiatric Diseases, 4th edition (DSM-IV), are the primary diagnostic reference used in the United States. The causes of autism can be divided into "idiopathic," which comprises the majority of cases, and "secondary," in which an environmental agent, chromosome abnormality, or single-gene disorder can be identified. Approximately 5%-10% of individuals with autism can be diagnosed with secondary autism; the remaining 90%-95% have idiopathic autism. Approximately 30% of children with idiopathic autism have "complex autism," defined by the presence of dysmorphic features, microcephaly, and/or a structural brain malformation. About 70% of children with idiopathic autism have "essential autism," defined by the absence of physical abnormalities. Despite an intensive search, no genes definitely associated with idiopathic autism have been identified.

Management. Management of autism involves medical and behavioral therapies to promote conversational language and social interactions while mitigating repetitive, self-stimulatory behaviors, tantrums, aggression, and self-injurious behaviors. Therapies include predictable and routine classroom and home arrangements with planned transitions between activities and environments, with individualized intensive intervention. Visual supports, such as the Picture Exchange Communication System, are helpful in promoting language acquisition. The Visually Cued Instruction and Schedules program uses graphic clues to aid communication, organizational skills, and self management. The Social Stories intervention increases appropriate behavior by explaining social situations in ways understandable to the student. Medications, especially atypical antipsychotics, can ameliorate specific symptoms such as poor sleep or aggressive behavior; affected individuals may respond differently to the same medication.

Genetic counseling. For individuals with secondary autism, genetic counseling is based on information relevant to the primary diagnosis. For idiopathic autism, the empiric aggregate risk to sibs is 4% for autism and an additional 4-6% risk for milder conditions, including language, social, and psychiatric disorders. For families with two or more affected children, the recurrence risk approaches 35%. Male sibs (brothers) of a proband with essential autism have a 7% risk for autism and an additional 7% risk for milder autism spectrum disorders. Female sibs (sisters) of a proband with essential autism have a 1% risk for autism. The risk for a milder autism spectrum disorder is unknown. The recurrence risk to sibs of a proband with complex autism is 1% for autism and an additional 2% for a milder autism spectrum disorder.

Definition

Clinical Manifestations

Autism or autistic disorder is a complex behavioral disorder that, by definition, develops prior to age three. Infants with autism typically do not care to be held or cuddled and do not reach out to be picked up. Often they are "colicky" and hard to console, typically quieting more readily when left alone. They may avoid and fail to initiate eye contact or stare into space. Sleep disturbances and sensory issues may be noted in the first year. Despite early signs, children with autism usually do not come to medical attention until after the second year when language delays are evident.

For most children, the onset of autism is gradual; however, approximately 30% have a "regressive" onset. These children begin to speak and then, often precipitously, lose language and become distant. Within a matter of days, the child may refuse to make eye contact and stop responding to his/her name. Deafness is often suspected, although hearing tests are normal. Repetitive movements may develop immediately or not until the child is three or four years of age. It is debated whether these children are well and then become damaged by some exogenous exposure or whether they are genetically determined to regress. Retrospective analysis of first birthday videotapes and neuropathologic studies suggest the latter [Osterling & Dawson 1994, Bailey et al 1998, Kemper & Bauman 1998, Casanova et al 2002].

Approximately 25% of children who fit the diagnostic criteria for autistic disorder at age two or three years subsequently begin to talk and communicate and by six or seven years blend to varying degrees into the regular school population. Even for this group, social impairments generally continue. For the remaining 75%, most have some improvement with age but continue to require parent, school, and societal support. An excellent review of outcome studies is provided by Seltzer et al (2004). Some studies indicate that fewer than 5% of children with autism completely recover [Nordin & Gillberg 1998]. Autistic disorder is defined completely on the basis of three areas of behavioral impairment.

- **Impairments in social interaction.** Impairment in social interaction separates individuals with autism from the people around them. Children with autism are unable to "read" other people, ignoring them and often strenuously avoiding eye contact. Typically, they do not comfort others or seek comfort and do not share interests with others, such as bringing toys or pictures to their parents. Rather, they use their parents as objects, and may climb on them to get to a desired object, pull the parent by the hand, or place the parent's hand on the object, as if the child were using a tool. In clinic, the child who is content to turn pages of a magazine or spin the wheels of a car may become agitated when a simple examination is attempted. At home, the child with autism usually prefers to be by himself, engaging in his own, often repetitive, activities. The lack of functional or spontaneous make-believe play is characteristic. Toys are lined up, sorted, twirled, or hurled, but are not used for imaginative games or imitation of day-to-day activities, such as feeding the baby or washing the dishes. When play emerges later, it is stylized and not spontaneous. Children with autism fail to develop friendships with peers and siblings. In school, they often stand and watch other children from a distance. Some children respond to social overtures but take little social initiative, while others seek interaction but have little sense of how to proceed toward normal friendships.

- **Impairments in communication.** Most children with autism fail to develop reciprocal communication either by speech, gestures, or facial expressions. Characteristically, young children fail to use eye gaze or pointing to communicate and direct attention. Early pragmatic

skills are limited and are characterized by typical rates of requesting but substantially reduced rates of joint attention and social interaction. Deficits in pragmatic skills are present throughout life and affect both language and social interaction. The young child appears unable to grasp the concept that speech can be used to name objects, to request a toy, or to engage others. In contrast to the child with nonspecific mental retardation or a primary developmental language disorder, who usually has better receptive than expressive language, the child with autism has impaired receptive language. When children with autism learn to talk, they display stereotypic speech that may involve echolalia, pronoun reversal, and unusual inflections and intonations. Unlike typically developing children who begin talking using one-word utterances, children with autism may begin talking in "chunks" composed of commercials, movies, or others' speech. These chunks often convey idiosyncratic meanings and the child with autism has no understanding of the conventional meaning of any of the individual words. Pragmatic difficulties including difficulties sustaining a conversation, turn taking, and allowing the conversational partners to introduce their topics, usually continue despite improvement in expressive speech. [reviewed in Lord et al 2004].

- **Repetitive and stereotypic behaviors.** Infants may stare or rock. Toddlers may have motor "stereotypies" such as movements of fingers, twirling strings, flicking pages of books, or licking. Repetitive whole body movements may include spinning and running back and forth. The repetitive behaviors often have a visual component such as holding the fingers to the side of the face and watching them with a sideways glance. Sometimes the movements become more complex with an individualized sequence of patting, rubbing, or twirling. These stereotypies may last for hours. Though the cause of the repetitive movements is unclear, they seem to have a calming effect and may, especially in the older child, surface in times of stress. This repetitiveness is reflected in a rigid need for sameness in daily routines. Children with autism can develop elaborate rituals in which the order of events, the exact words, and the arrangement of objects must be followed. Failure of parents/caretakers to follow the proscribed order of events results in inconsolable outbursts.

Other symptoms occurring in a substantial number of individuals with autistic disorder:

- **Hyper- and hyposensitivities to sound and touch.** Loud or high-pitched noises such as the vacuum cleaner cause great discomfort, resulting in the child holding his hands over his ears. The feel of certain clothes or of being touched may be unbearable; conversely, truly painful stimuli like a burn or laceration are ignored.
- **Odd behaviors around foods** and their presentation, such as accepting a limited number of foods
- **Abnormal sleep patterns** (60%), such as never sleeping through the night, trouble going to sleep, or getting up for the day at 2:00 am
- **Tantrums and/or self-injurious and aggressive behaviors** brought on by a change in routine, an offending touch, being asked to do something they do not want to do, or no apparent reason
- **Impaired motor development** with toe walking early in life and general clumsiness
- **Total disregard for danger,** resulting in high risk of early death, commonly from drowning

Although no known methods can reliably distinguish those children who will improve from those who will have lifetime disability, the following characteristic findings are used to classify affected individuals:

- IQ scores obtained from children with autism may change over time and with intensive therapy; however, the cognitive level revealed in early childhood remains an important predictor of long-term outcome [Lord & Schopler 1989, Kobayashi et al 1992, Volkmar 1992, National Research Council 2001, Howlin et al 2004]. Fifty to seventy percent of autistic children are defined as mentally retarded by nonverbal IQ testing [reviewed by Fombonne 2003]. Stevens et al (2000) reported that children who tested during preschool as low functioning (based on nonverbal IQ, receptive vocabulary, and socialization) either remained low functioning or dropped significantly in their level of functioning when retested at school age. The authors concluded that early normal or near-normal nonverbal IQ is the best

predictor of adequate functioning by grade school; however, in the presence of significant language and social delays, it is not sufficient to insure recovery. Howlin et al (2000) reported that childhood scores on the Peabody Picture Vocabulary Test of receptive vocabulary accounted for 32% of the variance in a composite rating of outcome in adulthood.

- **Seizures** develop in aapproximately 25% of children with autism; more have nonspecific EEG changes [Tuchman & Rapin 2002]. As in the general population, seizures alone are not a predictor of outcome.

- **A structural brain malformation,** typically identified by MRI, usually portends a poor outcome [Miles & Hillman 2000].

- **Significant dysmorphology,** present in 25% of individuals with autism, indicates an insult in early development [Miles & Hillman 2000]. Using a classification system that defines significant dysmorphology as having more than six dysmorphic features including minor anomalies, measurement abnormalities, and descriptive features not present in their non-autistic parents, Miles et al (2005) found that dysmorphology was 81% predictive of a poor outcome, defined as nonverbal with an IQ lower than 55 by age eight years. In addition, presence of significant dysmorphology was the top predictor of a poor response to early intensive behavioral therapy [Stoelb et al 2004].

- **Microcephaly** (head circumference <2nd centile) occurs in 5% to 15% of children with autism [Fombonne et al 1999, Miles et al 2000, Miles et al 2005] and is highly associated with poor outcome.

- **Macrocephaly** (head circumference greater than the 98th centile), found in approximately 30% of children with autism, does not appear to correlate strongly with outcome [Miles et al 2000]. Recently, Conciatori et al (2004) presented evidence that the *HOXA1* G allele correlates with larger head circumferences, explaining approximately 5% of the variance in head circumference in their population. Butler et al (2005) identified *PTEN* mutations in three of 18 young boys with both autism and macrocephaly. There were no features suggestive of Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome (see *PTEN* Hamartoma Tumor Syndrome) except for pigmented macules on the glans penis in one boy.

Establishing the Diagnosis

The standard diagnostic criteria, compiled by the American Psychiatric Association Manual of Psychiatric Diseases, 4th edition (DSM-IV), are the primary diagnostic reference used in the United States.

DSM-IV Diagnostic Criteria for 299.00 Autistic Disorder

I A total of six (or more) items from A, B, and C, with at least two from A, and one each from B and C:

A Qualitative impairment in social interaction, as manifested by at least two of the following:

1 Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction

2 Failure to develop peer relationships appropriate to developmental level

3 A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)

4 Lack of social or emotional reciprocity

B Qualitative impairments in communication as manifested by at least one of the following:

1 Delay in, or total lack of, the development of spoken language

(not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)

2 In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others

3 Stereotyped and repetitive use of language or idiosyncratic language

4 Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

C Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

1 Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus

2 Apparently inflexible adherence to specific, nonfunctional routines or rituals

3 Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting or complex whole-body movements)

4 Persistent preoccupation with parts of objects

II Delays or abnormal functioning in at least one of the following areas, with onset prior to age three years: 1) social interaction, 2) language as used in social communication, or 3) symbolic or imaginative play

III The disturbance is not better accounted for by Rett syndrome or childhood disintegrative disorder.

Diagnostic tools. To diagnose autism, one must precisely enumerate the autism symptoms and their age of occurrence. This can be done by using a copy of the DSM-IV or a number of checklists [Filipek et al 2000, California DDS 2002].

The most commonly used diagnostic checklist is the CARS (Childhood Autism Rating Scale) [Schopler et al 1986], which consists of 15 questions scored by the parent and the tester. The CARS is a reliable, well-verified measure, which is relatively fast and easy to administer. A score of 30 to 35 indicates mild autism and 36 or higher moderate-to-severe autism. Other similar checklists, including the ABC (Autism Behavior Checklist) [Aman et al 1985] and the GARS (Gilliam Autism Rating Scale) [Gilliam 1995], are commonly used. The CHAT (Checklist for Autism in Toddlers) [Baron-Cohen et al 1992] is a 14-item checklist designed as a screening tool for primary care providers to identify at-risk toddlers at the 18-month visit. Although its sensitivity has been questioned [Baird et al 2000], the CHAT is recommended by the Neurology Quality Standards Subcommittee [Filipek et al 1999, 2000]. The M-CHAT (Modified) [Robins et al 2001] is an expanded American version with 23 items that parents can fill out in the waiting room;it is available in Spanish and English [California DDS 2002].

School systems usually use educationally based criteria that are similar but not identical to the medical criteria, sometimes leading to conflicts. This is particularly true for the higher-functioning or Asperger syndrome students whose autism, although equally in need of consideration and remediation through the schools, may not meet the educational criteria for an autism diagnosis.

The diagnosis of Asperger syndrome is problematic, with poor concordance between the various diagnostic instruments [Klin et al 2005]. The Autism Spectrum Screening Questionnaire (ASSQ) [Ehlers et al 1999], the Asperger Syndrome Diagnositic Interview (ASDI) [Gillberg et al 2001], the Australian Scale for Asperger's Syndrome [Garnett & Atwood 1997], and the Childhood Asperger Syndrome Test (CAST) [Scott et al 2002], are commonly used for children. A new video, Asperger's Diagnostic Assessment [Attwood 2004] provides a hands-on tutorial which should be useful to the clinician.

In North America, research criteria for autism depend primarily on the ADI-R (Autism Diagnostic Interview-Revised) [Lord et al 1994], which is a detailed parent interview, and the somewhat shorter ADOS (Autism Diagnostic Observation Schedule) [Lord et al 1989]. Both scales follow the DSM-IV criteria and were

developed in an attempt to sort autism by its behavioral symptoms to permit identification of homogeneous affected populations. Although required for research studies, these scales are not widely used in clinical practice because of the time and expense to administer them, though the shorter ADOS is being used in some clinics.

Differential Diagnosis

Pervasive developmental disorder (PDD) is the umbrella diagnosis that encompasses autism/autistic disorder, Asperger syndrome, Rett syndrome, and childhood disintegrative disorder.

- **Asperger syndrome** [Asperger 1944, reprinted in English in Frith 1991] is characterized by relatively normal language development (which includes timing, grammar, and vocabulary) but includes all the other DSM-IV diagnostic criteria. Individuals with Asperger syndrome are generally loners, are uncomfortable in groups, cannot empathize with others, do not chat, follow a literal interpretation of speech with no understanding of idioms or jokes, maintain a sameness in routine, follow strict rules, and have an encompassing preoccupation with one domain, such as the weather or computers. Speech may be pedantic or repetitive with odd intonations. IQ is usually normal. Clumsiness is common. Whether Asperger syndrome is the expression of the high end of the autism spectrum or is a discrete genetic entity is unclear.

- **Childhood disintegrative disorder** is an extremely rare condition manifesting before age ten years in which children who have developed normally for at least two years deteriorate and lose previously acquired language, social, and play skills. The condition may resemble autism in clinical presentation but differs from autism in the pattern of onset, course, and outcome.

- **Pervasive developmental disorder - not otherwise specified (PDD-NOS).** Children with autistic symptoms who do not meet full criteria in all three diagnostic domains can be diagnosed with a pervasive developmental disorder - not otherwise specified (PDD-NOS). PDD-NOS includes children with milder symptoms in all three domains as well as those who fit full autism criteria in two of the three domains. Sometimes PDD-NOS is used as an initial or tentative diagnosis for younger children or before diagnostic evaluations are completed.

- **Broader autism phenotype** may designate siblings or other family members with some autism symptoms [Piven & Palmer 1999, Pickles et al 2000, Geschwind et al 2001]. This terminology has been adopted by researchers to identify sibs who are likely to have mutations in putative autism genes and reflects the growing awareness that the phenotypic spectrum of autism is broad.

Prevalence

An increase in the apparent prevalence of all the pervasive developmental disorders is being reported worldwide. Prior to 1990, most studies estimated a general population prevalence for autism of four to five per 10,000 [Jorde et al 1990, Fombonne 2001]. During the 1990s, studies of preschool children in Japan, England, and Sweden reported prevalence rates for autism of 21 to 31 per 10,000 [Honda et al 1996, Arvidsson et al 1997, Baird et al 2000]. A recent CDC case-finding study in Brick Township, New Jersey reported prevalence at 40 per 10,000 for autism and 67 per 10,000 for all PDDs [CDC 2000]. An important epidemiologic study from the United Kingdom utilizing specialized visiting nurses who monitored child health and development at seven months, 18 to 24 months, and three years of age reported a prevalence rate of 16.8 per 10,000 for autism and 63 per 10,000 for all PDDs in children younger than five years of age [Chakrabarti & Fombonne 2001]. Those rates were recently confirmed, reporting a prevalence rate of 22 per 10,000 for autism and 59 per 10,000 for all PDDs in children younger than six years of age [Chakrabarti & Fombonne 2005].

Evidence suggests that more complete case finding together with broadening of the diagnostic criteria are most responsible for the apparent increased incidence of autism [Gernsbacher et al 2005]. Studies finding the greatest increase in the non-autism PDDs are also recording lower rates of mental retardation in these children. Only 30% of children with PDDs ascertained by Chakrabarti & Fombonne (2005) were mentally retarded compared with 70% of children in earlier studies. This suggests that many of the higher-functioning children with milder autistic symptoms had not been counted in past epidemiologic surveys. The California study [MIND Institute 2002], however, contends that changes in diagnostic criteria did not

account for the 273% increase in autism between 1987 and 1998 recorded in children receiving care through the California Regional Center system, raising the question of an environmental effect.

Causes

The causes of autism can be divided into "idiopathic," which comprises the majority of cases, and "secondary," in which chromosome abnormality, single-gene disorder or environmental agent can be identified. Approximately 10% of individuals with autism can be diagnosed with secondary autism; the remaining 90-95% have idiopathic autism.

Environmental Causes

In utero exposures, including rubella (German measles), valproic acid, and thalidomide, are recognized causes of secondary autism; however, it remains unclear whether those who develop autism after such an exposure are also genetically predisposed. The search for new environmental causes of secondary autism has centered primarily on childhood immunizations given around the time that regressive-onset autism is recognized. Organic mercury in the preservative thimerosal, used for certain injectable vaccines, and the measles-mumps-rubella (MMR) vaccine, which never contained mercury, have both been under scrutiny; however no scientific evidence for a relationship between vaccines and autism has been identified [Institute of Medicine 2001, 2004; DeStefano & Thompson 2004; Gernsbacher et al 2005].

Heritable Causes

Chromosomal Causes of Autism

- Approximately 3% of individuals with autism have a maternally inherited chromosomal duplication in the Prader-Willi syndrome/Angelman syndrome region of 15q11-q13. Most commonly, this is a supernumerary isodicentric 15q chromosome detectable by routine cytogenetic studies; less commonly, an interstitial duplication of the region detected by interphase FISH analysis of the *SNRPN* gene. (For laboratories offering FISH testing, see Testing.) These two chromosome abnormalities have only subtle effects on the physical phenotype, though the phenotype associated with isodicentric 15 is typically more severe than with an interstitial duplication [Borgatti et al 2001, Dykens et al 2004].

- An additional 3-5% of individuals with autism have other chromosome abnormalities, including apparently balanced and unbalanced translocations, inversions, rings, interstitial deletions and duplications, and marker chromosomes [Wassink et al 2001, Reddy 2005]. Although cytogenetic abnormalities on almost every chromosome have been found in association with autism, only a few occur commonly enough to be regarded as possible indicators of putative autism genes. Chromosome abnormalities (in addition to 15q duplications) that have been reported on more than one occasion are deletions of 2q,18q, 22q13, Xp, and the sex chromosome aneuploidies, 47,XYY and 45,X [Gillberg 1998, Manning et al 2004].

  Routine chromosome analysis detects most abnormalities; however, high-resolution chromosome studies, subtelomere FISH studies, or chromosomal microarray analysis are recommended for some persons. Reddy (2005) reported that 28% of the cytogenetic abnormalities detected were subtle, requiring high resolution analysis. Takahashi et al (2005) found unbalanced chromosome abnormalies exclusively in probands with autism who had significant dysmorphology (13/387 - 3.4%). All reported terminal deletions of 2q and 22q have been associated with dysmorphology [Lukusa et al 2004, Manning et al 2004].

  The yield of subtelomeric FISH studies remains controversial. Although Wolff et al (2002) found that one out of ten unselected individuals with autism had a subtelomeric deletion detected by FISH analysis, Keller et al (2003) found no terminal deletions in 49 children with autism. Medne et al (2003) performed both routine chromosome analysis and subtelomeric FISH analysis in 108 individuals with autism; 7.4% (8/108) had a chromosome abnormality,

only one of which required subtelomeric FISH analysis for detection. In a retrospective study of 29 mentally retarded individuals with submicrocopic chromosome defects, de Vries et al (2001) found that prenatal growth retardation and a family history of mental retardation were important predictors of subtelomeric abnormalities.

Chromosomal microarray analysis (CMA) can identify small deletions and duplications of the subtelomeres, each pericentromeric region, and other chromosome regions. Some of the abnormalities detected by CMA have been associated with autism; thus, CMA may replace subtelomeric FISH as the second-tier cytogenetic study.

- Children with Down syndrome have autism more commonly than expected. The incidence was at least 7% in one study [Kent et al 1999]. This finding suggests that chromosome abnormalities may lower the threshold for the expression of autism.

- **Fragile X syndrome**. Whereas a very small percentage of children with autism have fragile X syndrome, at least half of children with fragile X syndrome have autistic behaviors, including avoidance of eye contact, language delays, repetitive behaviors, sleep disturbances, tantrums, self-injurious behaviors, hyperactivity, impulsiveness, inattention, and sound sensitivities. Rogers et al (2001) reported that 33% of two- to four-year-old children with fragile X syndrome had autism. Fragile X syndrome is caused by expansion of the CGG trinucleotide repeat in the *FMR1* gene into a full mutation (>200 CGG repeats). Reports of *FMR1* premutations (55-200 CGG repeats) and mosaicism for *FMR1* full mutations associated with autism spectrum disorders indicate that molecular genetic testing of *FMR1* should be performed in all children who present with autism or PDD [Goodlin-Jones et al 2004, Cornish et al 2005,Reddy 2005]. Further studies are needed to determine the rate of autism spectrum diagnoses in individuals who are premutation carriers.

- **Rett syndrome**. One of the DSM-IV-defined pervasive developmental disorders, Rett syndrome exhibits considerable phenotypic overlap with autism; children with both disorders often have a period of normal development followed by loss of language with stereotypic hand movements. Decreasing rate of head growth over time and hand-wringing in female individuals may suggest the diagnosis of Rett syndrome. Molecular genetic testing for *MECP2* mutations that cause Rett syndrome is clinically available. However, only 1% of individuals with the diagnosis of autism have been reported to have a *MECP2* coding region mutation [Voure'h et al 2001, Lam et al 2000, Zapella et al 2003, Lobo-Menendez et al 2003, Carney et al 2003]. Nevertheless, it appears that these two disorders may be causally related based on reports of variants in the 3'-UTR of *MECP2* in three of 24 individuals with autism [Shibayama et al 2004] and variable MeCP2 expression in the brains of individuals with both Rett syndrome and autism [Samaco et al 2004]. The latter study suggests that defects in pathways that regulate MeCP2 expression may be involved in autism pathogenesis

- **Tuberous sclerosis complex**. Although 25% of mentally retarded individuals with tuberous sclerosis complex (TSC) have autism, only 1.1% to 1.3% of individuals with autism have TSC [Hunt & Dennis 1987, Smalley et al 1992, Gillberg et al 1994, Baker et al 1998].

- **Mitochondrial disorders**. Although mitochondrial respiratory chain disorders have only been reported in autism on rare occasion, elevated plasma concentration of lactate has been frequently noted [reviewed by Coleman 2005]. A population-based study of 69 children with autism reported elevated plasma lactate concentration in 20%; five of the eleven children (7.2%) undergoing muscle biopsy had a confirmed respiratory chain disorder based on enzymatic complex activity less than 20% of normal [Oliveira et al 2005]. If this percentage is confirmed, it will indicate the largest etiologic subgroup of autism. Mitochondrial disorders are a consideration in autistic children with atypical features such as hypotonia, failure to thrive, and recurrent episodes of regression or flare-ups.

- **Sotos syndrome**. An autosomal dominant disorder of macrocephaly and overgrowth, Sotos syndrome should be considered in children with autism who also have macrocephaly.

- **Neurofibromatosis type 1 (NF1).** Although NF1 has been diagnosed in children with autism, it is unclear whether this is a true association or the chance simultaneous occurrence of two relatively common childhood disorders.

- **Joubert syndrome**. In one study, three of 11 children with Joubert syndrome met diagnostic criteria for autism and one of 11 for PDD-NOS [Ozonoff et al 1999]. However, Takahashi & Miles (in preparation) clearly delineated the behavioral and genetic differences between autism and Joubert syndrome. In a report by Muhle et al (2004) of monozygotic twins with Joubert syndrome, the twin with the more severe cerebellar abnormality had autism, suggesting that some disorders may have the potential to cause the autism phenotype if as yet unidentified autism regions or circuits of the brain are affected.

- **Timothy syndrome.** A disorder of calcium conductivity caused by a mutation in the *CACNA1C* gene, Timothy syndrome is characterized by severe QT prolongation, syndactyly, cardiac defects, dysmorphic faces, developmental delays, and autistic symptoms [Splawski et al 2004].

Idiopathic Autism

Idiopathic autism, defined as autism with no identifiable cause, is used to designate an individual in whom secondary autism has been eliminated by physical examination and appropriate testing. For these individuals, it is practical to make a distinction between "essential autism" and "complex autism" [Miles et al 2005]. It is anticipated that both essential and complex autism will be further divided as more is learned about specific genetic mechanisms associated with each.

- Essential autism is defined by the absence of physical abnormalities. Approximately 70% of children with idiopathic autism have essential autism. Children with essential autism are more likely to be male, and have a higher sibling recurrence risk and greater family history of autism and autism-related disorders such as alcoholism and depression. As a group, the outcome is better for essential autism, but most children still do poorly.

- Complex autism is defined by the presence of dysmorphic features and/or microcephaly, features that indicate some alteration of early morphogenesis. Approximately 20-30% of children with idiopathic autism have complex autism. Complex autism is associated with a poorer prognosis, a lower male-to-female ratio, and a lower sibling recurrence risk.

No genes definitely associated with idiopathic autism have been identified. Although whole-genome-wide scans have identified consensus regions of interest (see Table 1) including 2q31-33, 3q25-27, 6q14, 7q22, 7q32, 13q21, 15q11-13, 16p13, 17q11,17q31, and 19p13, the studies have been difficult to replicate. This difficulty is variously attributed to (1) heterogeneity within and between populations studied; (2) the hypothesis that the effect of each of the several genes working in concert to produce the autism phenotype is modest; and (3) as-yet-undiscovered epigenetic effects. Additional regions of interest from study of chromosomal rearrangements in autism include 15q11-q13 and 7q.

Reviews of the current status of candidate genes and loci include [Bespalova & Buxbaum 2003, Wassink et al 2004, Veenstra-VanderWeele & Cook 2004, Muhle et al 2004, and OMIM].

Table 1. Candidate Susceptibility Genes in Autism (Organized by Chromosomal Location)

Gene Symbol	Chromosome Locus	Gene/Protein Function	References		Test Availability
			Pro [1]	Con [2]	
SLC25A12	2q24	Mitochondrial aspartate/glutamate carrier	Ramoz et al 2004		
C4B	6p21	Complement component	Odell et al 2005		
GLO1	6p21	Zinc metalloenzyme scavenges oxoaldehydes	Junaid et al 2004		
GRIK2	6q21	Glutamate receptor 6 involved in neural development	Jamain et al 2002, Shuang et al 2004		
				Devlin et al	

HOXA1	7p15-p14.2	Homeobox gene involved in hindbrain development	Ingram et al 2000, Conciatori et al 2004	2002, Li et al 2002, Talebizadeh et al 2002, Collins et al 2003, Romano et al 2003, Gallagher et al 2004	
RELN	7q22.1	Signaling protein involved in neuron migration	Persico et al 2001, McCoy et al 2001, Zhang et al 2002	Krebs et al 2002, Devlin et al 2004, Li et al 2004	
WNT2	7q31	Signaling proteins involved in embryonic patterning, cell proliferation and cell determination	Wassink et al 2001, Hutcheson et al 2004	McCoy et al 2002, Li et al 2004	
FOXP2	7q31	Transcription factor involved in embryogenesis and neural functioning	Gong et al 2004, Li et al 2005	Gauthier et al 2003, Wassink, Piven et al 2002	
UBE2H	7q32	Ubiquitin-dependent proteolytic system enzyme	Vourc'h et al 2003		
EN2	7q36.2	Homeobox gene involved in midbrain and cerebellum development	Petit et al 1995, Gharani et al 2004	Zhong et al 2003	
PTEN	10q23.31	Tumor suppressor	Butler et al 2005		
HRAS	11p15.5	Oncogene GTPase involved in cell division, differentiation and apoptosis	Herault et al 1995, Comings et al 1996		
AVPR1A	12q14-q15	Arginine vasopressin receptor involved in social behavior	Kim, Young et al 2002, Wassink et al 2004		Research only
UBE3A	15q11-q13	Angelman syndrome causative gene encodes ubiquitin protein ligase	Nurmi et al 2001, Jiang et al 2004	Nurmi, Dowd et al 2003	
ATP10C	15q11.2-q12	Phospholipid transporter involved in CNS signaling	Nurmi, Amin et al 2003	Kim, Herzing et al 2002	
GABRB3, GABRA5, GABRG3	15q11.2-q12	GABA receptor subunits	Cook et al 1998; Martin et al 2000; Nurmi et al 2001; Buxbaum et al 2002; Nurmi, Dowd et al 2003; Menold et al 2001; Shao et al 2003; McCauley et al 2004	Nurmi et al 2001, Maestrini et al 1999, Salmon et al 1999	
SLC6A4	17q11.1-q12	Serotonin transporter	Cook et al 1997, Klauck et al 1997, Yirmiya et al 2001, Tordjman et al 2001, Kim,	Persico et al 2000, Persico et al 2002,	

			Cox et al 2002, Conroy et al 2004, Mulder et al 2005	McCauley et al 2004	
NF1	17q11.2	Ras protein regulation	Mbarek et al 1999, Marui et al 2004	Plank et al 2001	
HOXB1	17q21-q22	Homeobox gene involved in hindbrain development	Ingram et al 2000	Li et al 2002, Romano et al 2003, Gallagher et al 2004	
APOE2	19q13.2	Lipoprotein receptor involved in neuronal migration and lipid transport	Persico et al 2004		
ADA	20q13.12	Purine metabolism and immune response	Young et al 1999, Kim, Young et al 2002		
NLGN3	Xq28 ?13	Neural synapse formation	Jamain et al 2003		
NLGN4X	Xp22.33	Neural synapse formation	Jamain et al 2003, Laumonnier et al 2004	Talebizadeh et al 2004, Gauthier et al 2005, Vincent et al 2004	Clinical Testing
ARX	Xp22.13	Homeobox gene	Stromme et al 2002, Turner et al 2002		Research only

Based on a variety of analysis types including linkage, association, allele sharing, transmission disequilibrium, subset analysis using SNPs, coding polymorphisms, and specific mutations

1. Pro = study supporting candidate gene assignment
2. Con = study not supporting candidate gene assignment

Multifactorial Inheritance

The heritability estimate of autistic disorder, calculated from recurrence risk data and monozygotic (MZ):dizygotic (DZ) twin concordance data, is more than 90%. Many have considered idiopathic autism to be a "multifactorial" disorder based on: (1) this high heritability, (2) the failure to identify major autism genes, (3) the 4:1 male-to-female sex ratio, and (4) sibling recurrence risk of approximately 4% [Ritvo et al 1989, Bolton et al 1994].

The multifactorial threshold model predicts that the more frequently affected sex (male) has a lower recurrence risk than the less frequently affected sex (female) and that the less often affected sex (female) is more severely affected. Recent studies indicate that autism does not follow this model: (1) Sibs of male and female probands with idiopathic autism have the same risk of developing autism [Jones et al 1996, Miles et al 2004], (2) the proportion of relatives with a mild subclinical autism phenotype is not increased when the proband is female [Pickles et al 2000]; (3) when analyses are limited to probands with essential autism, females have less severe autistic symptoms than males, particularly in categories of social interactions, pretend play, repetitive activities, and preoccupation with parts of objects [Miles et al 2004].

The presence of evidence that does not support the multifactorial threshold model does not eliminate the possibility that many genes are involved in autism, but rather suggests that the overriding impediment to understanding the inheritance of autism is genetic heterogeneity.

Evaluation Strategy

In addition to behavioral diagnostic testing, all individuals with autism should have a complete medical

evaluation designed both to elucidate diagnostic possibilities and to identify medical issues that affect development and behavior of nonverbal children. This basic evaluation should be expanded if history and physical examination raise concerns about metabolic, medical, or neurologic conditions.

Family history. A three-generation pedigree should be obtained with attention to behavioral diagnoses. Relatives with behaviors that are possible manifestations of autism may be examined directly or their records reviewed. Language, social, and psychiatric disorders, including alcoholism, occur more often in relatives, including sibs, of clearly autistic probands, particularly those with essential autism [Fombonne et al 1997, Bolton et al 1998, Piven & Palmer 1999, Pickles et al 2000, Miles et al 2003].

Clinical examination. Physical examination should include the following:

- Measurement of height, weight, and occipito-frontal circumference (OFC) to look for evidence of (1) microcephaly and growth retardation which suggest various chromosome disorders and monogenic syndromes; or (2) macrocephaly associated with Sotos syndrome.
- A complete dysmorphology examination
- An examination of the skin (including Woods lamp examination) evidence of tuberous sclerosis complex and neurofibromatosis type 1.

Testing. At the time of initial evaluation, the following are appropriate:

- High-resolution chromosome analysis; consideration of chromosomal microarray analysis or targeted FISH studies if the individual has complex autism or a family history suggestive of a chromosome disorder
- Metabolic testing. (1) The utility of a metabolic evaluation, including quantitative plasma amino acids; urine organic acids; plasma concentration of lactate, pyruvate, creatine kinase; serum concentration of uric acid; and CBC is of limited benefit for the majority of patients. (2) Further studies are needed to determine the prevalence of mitochondrial respiratory chain disorders in autism, especially those with recurrent setbacks, hypotonia, and failure to thrive.
- Electroencephalogram, especially if there is a history of regression
- MRI. The brain MRI helps in the classification of essential and complex autism in individuals with idiopathic autism; however, its use is controversial because of the expense and need for sedation by an anesthesiologist.

Molecular genetic testing

***FMR1*.** At the time of initial evaluation, it is appropriate to perform molecular genetic testing for fragile X syndrome.

Currently, no other molecular tests are known to diagnose significant proportions of individuals with idiopathic autism. The following mutations have been reported in isolated cases:

- ***NLGN4*.** Jamain et al (2003) identified a nonsense mutation in *NLGN4* in two brothers with autism and Asperger syndrome, both without mental retardation. Subsequently, Laumonnier et al (2004) identified a two-base-pair deletion in *NLGN4* in 12 affected members of a French family with X-linked mental retardation, some of whom were also autistic.
- ***NLGN3*.** Jamain et al (2003) identified a C-to-T transition in the *NLGN3* gene, in two brothers, one with autism and the other with Asperger syndrome. The mutation was inherited from the mother and was absent in 200 controls.

  Note: Subsequent studies failed to find mutations in either *NLGN3* or *NLGN4* in probands with autism [Vincent et al 2004, Talebizadeh et al 2004, Ylisaukko-Oja et al 2005]. Although current evidence indicates that mutations in *NLGN4* or *NLGN3* represent rare singe-gene causes of autism, their analysis could be considered for families with autism with evidence of X-linked inheritance.

- ***PTEN*.** In a study of 18 individuals with autism spectrum disorders and macrocephaly (HC = +2.5 to +8 SD), Butler et al (2005) identified three with mutations in the coding region of *PTEN*. Two had no features of Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome (see *PTEN* Tumor Hamartoma Syndrome); one boy had pigmented macules on the glans penis. *PTEN* sequencing is clinically available and may be considered in an autistic individual with significant macrocephaly.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Secondary autism. Five to ten percent of individuals with autism have a single-gene or chromosomal disorder as the underlying etiology. Genetic counseling for these families is based on information relevant to the primary diagnosis. Supernumerary isodicentric 15q chromosomes are *de novo* occurrences. Duplication of proximal 15q may result from segregation of a parental chromosome translocation or a maternally derived interstitial 15q duplication.

Mode of Inheritance

The mode of inheritance for idiopathic autism is unknown.

Risk to Family Members — Idiopathic Autism

Parents of a proband. No data are available on the risk to parents of a proband of having idiopathic autism; however, parents are more likely to exhibit mild autistic phenotypes, such as social awkwardness, and a variety of psychiatric disorders including alcoholism, depression, obsessive-compulsive disorder, and panic and anxiety disorders [DeLong & Dwyer 1988, Smalley et al 1995, Piven & Palmer 1999, Miles et al 2003]. Cederlund & Gillberg (2004) reported that 70% of probands with idiopathic autism studied had a first- or second-degree relative with autistic symptoms, and that 15% had fathers with Asperger syndrome.

Sibs of a proband

- The empiric aggregate risk to sibs of individuals with idiopathic autism is 4% for autism and an additional 4-6% risk for milder symptoms, including language, social, and psychiatric disorders [Jorde et al 1991, Bolton et al 1994, Miles et al 2005]. For families with two or more affected children, the recurrence risk approaches 35% [Ritvo et al 1989]. No recurrence risk data are available for families who have one autistic child plus another child or relative with mild autistic symptoms. Therefore, the amount of weight to put on mild autistic symptoms in siblings, parents, and other relatives when estimating recurrence risk for families is unknown.
- **Essential idiopathic autism**
    - Male sibs (brothers) of a proband with essential autism have a 7% risk for autism and an additional 7% risk for milder autism spectrum symptoms.
    - Female sibs (sisters) of a proband with essential autism have a 1% risk for autism. The risk for milder autism spectrum disorder is unknown.
- **Complex idiopathic autism.** The recurrence risk to sibs of a proband with complex autism is 1% for autism and an additional 2% for a milder autism spectrum symptoms.

Offspring of a proband. No data are available.

Related Genetic Counseling Issues

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal testing for autism is not available.

Management

Treatment of Manifestations

Optimally, an autism intervention program utilizes an experienced team of medical, behavioral, and educational specialists. Working with an established team is easiest for families; however, many physicians and families have successfully pieced together programs that work well. Early diagnosis and early intensive behavioral therapy are essential to an optimal outcome. The National Research Council publication *Educating Children with Autism* (2001) provides a comprehensive review and is available online. Also available is an evaluation of single-subject studies to determine which educational practices meet the criteria of "evidence-based practice" [Odom et al 2003].

The goals of treatment are to promote functional conversational language and social interactions while mitigating repetitive, self-stimulatory behaviors, tantrums, aggression, and self-injurious behaviors. A number of alternative therapies either do not have scientific evidence of efficacy (multivitamins and minerals, hug therapy) or have been refuted in double blind studies (administration of secretin, facilitated communication, auditory training).

Three categories of therapy exist:

Behavioral and Educational Therapy

The programs for which empirical evidence of efficacy exists have used structured behavioral and educational approaches to teach children to comprehend and use language, attend to their environment, imitate others, interact socially, and play appropriately with toys. Features include a functional approach to behavior problems and predictable and routine classroom and home arrangements with planned transitions between activities and environments. Validated intensive intervention with individualized one-on-one instruction averages 25 hours per week of classroom instruction, with a minimum of 15 hours per week. All successful programs have a parent training component. (See Iovannone et al 2003 for a synthesis.)

Intensive early-intervention programs can be classified by the extent to which teaching is contextualized. At one end of the spectrum are intensive, rigidly structured, decontextualized, adult-directed, one-on-one interventions that use the principles of Applied Behavior Analysis (ABA) [McEachin et al 1993]. Debate exists about the appropriateness and ultimate success of taching social and language skills in a rote manner. However, ABA programs that use a discrete-trial training format are supported by the most published data. A recent study comparing an intensive behavioral intervention program to two classroom-based "eclectic" programs showed stronger results for the behavioral intervention [Howard et al 2005]. The principles of ABA have also been applied in "contemporary" ABA [Prizant et al 2000] programs in which instruction is embedded in home and classroom routines and the interaction is either shared or child directed [Hancock & Kaiser 2002]. On the other end of the spectrum are developmental social-pragmatic interventions, the best known of which is the Developmental, Individual-Difference, Relationship-Based model (DIR) [Greenspan & Wieder 2000]. The DIR model is based on the premise that adults must engage children with autism through the affective system. The underlying emotional processes are strengthened and children with autism become able to interact with people, language, and ideas in increasingly complex ways. However, the only published data by Greenspan & Wieder (2000) was a retrospective chart review.

Many children with autism require visual supports in the classroom and at home to learn to use language. One widely used communication intervention that capitalizes on the visual strengths of children with autism is the Picture Exchange Communication System (PECS) [Bondy & Frost 1994]. In the PECS system, children are taught to select pictures of desired objects or activities as a way of requesting access to the object or activity. PECS has been used successfully with children from three to six years old with cognitive skills ranging from severe mental retardation to normal [Schwartz et al 1998]. Although inexpensive, implementation initially requires two adults. Another communication intervention is the Visually Cued Instruction and Schedules program [Courchesne et al 1990, as cited in Dalrymple 1995], which uses graphic clues as an instructional or environmental prompt to aid language comprehension and communication, organizational skills, and improved self management. Visual Schedules provide pictures to help children identify the sequence of daily activities. Visually cued instruction has been used successfully with children with autism with a minimum age of three to six years and with IQs ranging from severe mental retardation to normal. Materials can be teacher-made and are inexpensive.

Another promising intervention is Social Stories [Gray & Garand 1993]. The purpose of a Social Story is to increase appropriate behavior by explaining social situations in ways that are understandable to the student and decrease problem behavior. The assumption is that much problem behavior is caused by a lack of understanding of what is expected or what is going to happen; social stories build understanding, allowing the student to behave appropriately. Social stories are inexpensive to create and take much less time and expertise to implement than other interventions and have been used successfully with children with autsim. For a review see Kuoch & Mirenda (2003).

Medication. The use of medications has increased as newer medications, especially the atypical antipsychotics, which affect both the serotonin and dopamine systems, and serotonin re-uptake inhibitors (SRIs), which modulate the serotonin system, have been studied in children. In 1997, the National Institute of Mental Health formed the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network to investigate the safety and efficacy of drugs for treating the behaviors associated with autism. Reports from that consortium have provided authoritative reviews of the pharmacotherapy of autism [McDougle et al 2000, Scahill et al 2001, McDougle et al 2005]. The conclusions:

- No medications are autism specific. Medications should be selected to ameliorate a specific symptom such as poor sleep, aggressive or self-injurious behavior, and repetitive or stereotypic behaviors that interfere with learning and social interactions [Bodfish 2004, McDougle et al 2005].
- A medication that alleviates one maladaptive behavior, such as aggression or hyperactivity, may have no effect on core autistic symptoms.
- Marked differences exist in the efficacy and side effects of drugs in adults vs children.
- Affected individuals may respond differently to the same medication [Gordon 2000; McDougle, Scahill et al 2000]. The response to a medication may reflect genetic differences between individuals, the waxing and waning of the behaviors over time, the progression of the disorder, and/or placebo effect.
- Medication management should be integrated into a family-centered, multi-modal behavioral and educational program.

Medical management. Although most children with autism are healthy, evidence is mounting that medical disorders have a significant affect on behaviors, level of functioning and response to educational therapies. Sensory issues including a blunted pain response, inability to tell others when then are uncomfortable, and poor tolerance of medical evaluations can lead to suboptimal medical care. Emerging areas of research include gastrointestinal, feeding, sleep, metabolic, and pain disorders [Linday 2001, Bradley et al 2004, Polimeni et al 2005]. Anecdotal evidence of severe gastroesophogeal reflux causing intractable insomnia and self-injurious behaviors are compelling and indicate that physicians need to have a high index of suspicion, especially with unexplained behavioral exacerbations, and to provide the same level of medical intervention as in typically developing children.

Targeted Therapies

Sensory integration (SI) is the organization and processing of sensory information for specific functional

use. Proponents of sensory integration therapy view the aberrant behavior of children with autism as an attempt to establish an internal state of equilibrium. Scientific theory exists for this view, but little empiric data support its use. Nevertheless, caregivers at home and in the classroom report decreased hyperactivity, inattention, and self-stimulation following SI therapy. Although the program should be designed by an occupational therapist with training in sensory integration, many of the techniques, including brushing, use of weighted vests, swinging, and jumping are easily adapted to home and school use.

Social skills interventions are designed to teach young children to engage in age-appropriate social interactions with their typically developing peers. Results vary [Goldstein & Cisar 1992, Goldstein et al 1992, Sainato et al 1992, Shearer et al 1996, Zanolli et al 1996]. Classroom-based programs show greater generalization of improved behaviors than non-classroom-based programs. Strategies are being developed and tested to increase generalization and to limit the amount of teacher prompting needed to sustain the social interactions.

Alternative Therapies

A number of alternative therapies either do not have scientific evidence of efficacy (e.g., multivitamins and minerals, heavy metal chelation, casein free/gluten free diets) or scientific evidence in double blind studies has refuted efficacy (e.g., secretin, facilitated communication, auditory training).

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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