Introduction

Autism is a behaviorally defined syndrome. Core characteristics include abnormal social interactions, abnormal communication both verbal and non-verbal, repetitive and stereotypical behaviors, and an onset before 3 years of age. Males are affected by autism approximately 4 times more frequently than females indicating a sex-associated susceptibility. Based on DSM-IV criteria, subtypes of autism spectrum disorders (ASD) are grouped together and recognized as autism, Asperger disorder, Rett syndrome, childhood disintegrative disorder (CDD) and Pervasive Developmental Disorder-not otherwise specified (PDD-NOS). The prevalence of ASDs is currently considered to be approximately 4-6 per 1000 people. Increased rates are being noted throughout the world, based on a number of different epidemiological studies.
A recent study from England, reported a prevalence of 63 cases of ASD per 10,000 (about 17 per 10,000 with autism and about 46 per 10,000 with other PDDs). These numbers represent a 10-fold increase in prevalence rates compared with the often-cited older figures of 3 to 4 cases per 10,000. The new statistics indicate that about 1 in every 160 children may have a form of autism. The developmental course varies in different affected individuals, with regression noted in approximately one third and seizures in approximately one third. Whether autism should be regarded as a single condition with a highly variable severity (ASD) or a grouping of specific disorders is unclear, but heterogeneous etiologies appear likely.

Genetics of Autism

Genetics undoubtedly plays a strong role. The heritability of autism is high since the monozygotic twin concordance rate is high (60-95%), while the sibling and dizygotic rate is relatively low (3-6%), but still relatively higher than the general population prevalence. The significant sibling risk versus the rapid decline in risk for cousins and distant relatives argues for a multifactorial basis and for multiple susceptibility genes to be present. Current models range from 3 major interacting loci to more than 15 genes, each with minor effects.

Some studies have shown a wide range of subclinical forms of the disorder in the family members and relative of affected probands. Among relative, increased frequencies of speech disorder, and unusual personality characteristics, such as aloofness, shyness and eccentricity have been found. Prevalence of major affective disorders, such as depression, among parents of autistic children may help to distinguish subtypes, as per Dr. Ira Cohen.

Genome wide linkage studies of families with multiplex autism have been undertaken to help in mapping genes related to autism. Various studies have found positive evidence for linkage on chromosome 1, 2q, 7q, 9, 13, 15q, 16p, 17q, 19, 22, and X. Although no specific gene has yet been identified, a number of candidates are being investigated. The most intensively studies regions are on chromosomes 2q, 7q, and 15q. One promising gene on chromosome 7q is a gene for speech-language disorder 1 (SPCH1), which has been found to be due to mutations in the gene FOXP2 that is mutated in certain families with a monogenetic hereditary disorder of speech. Also on Chromosome 7 is another candidate gene, RELN, which encodes a protein involved in neuronal migration during brain development.
Other classes of candidate genes include neurotransmitter receptors and homeobox genes.

At IBR, we discovered that a significant proportion of autistic individuals have the Fragile X Syndrome. Since it appears the missing fragile X gene protein functions to repress or modulate the expression of a limited set of other genes, a similar mechanism may hold for classical autism. Several other distinct genetic diseases have been associated with autism, including tuberous sclerosis, phenylketonuria and neurofibromatosis. Several environmental agents, such as prenatal exposure to German measles, Thalidomide and possibly Valproate, have been associated with autism and could reflect a genetic susceptibility as well.

One interesting study has reported significantly elevated brain neurotrophins and neuropeptides in blood samples from newborns who were later diagnosed with autism and mental retardation (Nelson et al, 1991). Although this important study has yet to be replicated, for technical reasons, such neuroactive peptides (VIP, BDNF, NT4/5, CGRP) could have important roles in early development of the brain, and their imbalance could reflect an underlying genetically determined abnormality leading to autism.

Conclusions

Autism has a strong heritability. This implies that genetics plays a major role in the etiology of autism. Current research is directed at identifying the genes and pathways involved in autism. This information will be needed to develop rational ways to successfully treat this severe neuro-behavioral disorder that exerts a devastating toll on children, families, society and the system!