Review

Autism and mental retardation: the genetic relationship and contribution

M.A.F. El-Hazmi[1]

SUMMARY Autism, a neurodevelopmental disorder first described in 1943, is reviewed. The signs and symptoms of the disorder are described together with the etiological factors. The evidence for a genetic etiology of autism and its association with other genetic disorders are discussed. Possible candidate genes for autism are described.

Introduction

Autism is a neurodevelopmental disorder and is considered one of the most disabling features for neurological, emotional and intellectual development [*1,2*]. First described by Leo Kanner in 1943, it was considered to be a rare disorder, but in recent years with more elaborate diagnostic procedures, autism is reported to affect 2–10 in 10 000 children in the general population, with boys comprising almost 75% of all autistic children [*3*]. Despite the different prevalence rates in boys and girls, no link to the sex chromosomes has been reported [*4,5*]. Almost 80% of affected children develop signs and symptoms of autism during the first year of life, while the rest develop the full-blown disease by the time they reach the third year of life [*2,4,5*]. Although the etiological factors have not yet been specifically identified, a genetic involvement is implicated. This paper investigates the complex nature of the genetic etiology of autism.

Major signs and symptoms of autism

Individuals with autism have difficulty with communication, social behaviour and perception of the environment [*2–11*]. Autistic children spend much of their time in repetitive and apparently pointless activities, which absorb them to the extent that everything else surrounding them is ignored. The lack of communication, interest in their surroundings and normal play development, and the limited response to love and affection are among the early signs of autism.

Severe deficits are obvious in the behavioural domains of social interaction and language and communication play. Other deficits are manifested as stereotypes and by a persistent, narrow range of interest and activities.

The unpredictability of daily activities is a source of tremendous anxiety in these patients. They often do not communicate easily and some do not speak at all. They

[1]*Department of Medical Biochemistry and WHO Collaborating Centre for Haemoglobinopathies, Thalassaemias and Enzymopathies, College of Medicine and King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia. E-mail: mohsen@ksu.edu.sa.*

have difficulty in making sense of their environment and have unusual responses to touch, pain and temperature. Autism presents a spectrum of neurological and neuropsychological phenotypes, including cognitive characteristics, poor performance on tests and stereotyped behaviours (Box 1). Nonetheless, autistic children are generally healthy and have normal life expectancy.

Etiological factors

The causative factors in autism are biological in nature and involve the brain. However, the definitive underlying disorder(s) in autism has not yet been discovered. It is believed that a combination of various factors contribute to the development of autism [*12–17*]. These include genetic factors, viral infections, prenatal complications and postnatal defects (Box 2). It is well established that autism is an oligogenetic defect and multifactorial with contribution from environmental factors.

Box 1 **Symptoms of autism [*2–11*] stimuli**

Unresponsiveness to people
Lack of attachment to parents or caretakers
Rigid or flaccid tone while being held
Little or no interest in human contact
Impaired speech or language onset in childhood
Meaningless repetition of words or phrases
Bizarre or repetitive behaviour patterns, such as uncontrollable head banging, screaming fits or arm flapping
Self-destructive behaviours
Great diseases from minor changes in the environment
Overreaction or underreaction to sensory stimuli
Delayed mental and social activities

Evidence for genetic etiology

Genes located in 3–5 interacting loci play a role in the development of autism. In some subsets of families, autism has been shown to have monogenetic etiology [*17*]. However, extensive studies on families and twins have shown that autism is a complex genetic disorder, caused by the interactive effects of several genes [*12,14*]. The recurrent risk is almost 60–160 times more among siblings of an affected sibling, in contrast with the siblings of unaffected siblings in the general population. In addition, a high rate of concordance (approximately 60%), a high heritability and paternal and maternal penetrance are well established. Another interesting finding is that there is a very wide variation in signs and symptoms, intelligence and language among autistic individuals. These and other observations have led to the suggestion that autistic individuals have different combinations of contributing genes.

Association of autism with other genetic disorders

The autism syndrome is often associated with a number of other genetic disorders. These include fragile X syndrome, tuberous sclerosis, Rett syndrome, epilepsy, Asperger syndrome and Down syndrome [*13 23*]. In an extensive study of almost 34 800 children in which intelligence quotient (IQ) was measured, the proportion of children affected with autism in groups of different IQs was calculated [*24*]. The study showed that among 44 children with

Box 2 **Causes of autism** [*12–17*]

Prenatal factors
Intrauterine rubella, tuberous sclerosis, disorders such as Cornelia de Lange syndrome, chromosomal abnormalities such as fragile X syndrome, Angelman syndrome and Down syndrome (occasionally), and brain abnormalities such as hydrocephalus

Perinatal factors
Perinatal difficulties have little causative role in autism

Postnatal factors
Untreated phenylketonuria, infantile spasms, herpes simplex encephalitis and a focal brain lesion (very rare) such as a neoplasm

an IQ range of 0–19, 86% of the children had autism. Among 96 children with an IQ range of 20–49, 42% had autism, while among 700 children with an IQ range of 50–69, 3% had autism. Among the 34 100 children with IQs of 70 and above, only 0.013% had autism. This study revealed a close correlation between autism and mental retardation.

Mental retardation is due to several etiological factors which include some purely genetic factors such as phenylketonuria. The most frequent chromosomal abnormality associated with autism is fragile X syndrome in that 2%–5% of autistic children also have fragile X syndrome. At least 15% of males with fragile X syndrome fulfil the criteria for infantile autism. Austistic abnormalities also occur frequently with tuberous sclerosis, Prader–Willi syndrome, Asperger syndrome, Rett syndrome, Angelman syndrome and epilepsy [*13–23*]. Several studies have documented that approximately 30% of children with autism have epilepsy and other genetic disorders characterized by autistic abnormalities such as Smith–Lemli–Opitz syndrome [*25*], FG syndrome [*26*] and reduced adenosine deaminase activity [*27*]. It has been shown that the genes for Prader–Willi syndrome/Angelman syndrome and fragile X syndrome are homologous, with genetic imprinting and unstable trinucleotide repeats causing mental retardation, autism and aggression [*17–23*]. Many patients with Angelman syndrome have autistic disorders, mental retardation and epilepsy [*18*].

Box 3 **Genes and gene loci in autism** [*13,17–23*]

Gene(s) on chromosomes
Chromosome 15: maternal effect
Chromosome 7 (hotspots): paternal effect
Chromosome 13: maternal effect
Chromosomes 4, 7, 10, 16, 19, 22: possible candidates revealed by analysis of genetic markers

Single genes
Serotonin transporter gene
γ-aminobutyric acid receptor gene
c-Harvey-ras-1 (HRAS1) gene
Human leukocyte antigen (HLA) haplotypes
Human homeobox gene (HOX)

Candidate genes for autism

An extensive genomic search has been undertaken within families with one or more autistic children to identify susceptibility genes contributing to the development of autism. These studies include chromosomal analyses, linkage studies and molecular investigations [*28*]. Autistic individuals, however, rarely have offspring and, therefore, multigenerational pedigrees are extremely rare. The most frequently used approach is to conduct molecular genetic studies using an affected sib-pair approach, wherein multiplex families with primary autism are investigated. Genetic models based on twin and family studies suggest that autism is an "oligogene defect," i.e. it results from the interactive effect of several genes. In addition, since the variation in severity of clinical presentation of autism suggests the combination and interaction of the genes that produce autism, genotype–phenotype correlations have been studied. A few subsets of familial monogenic inheritance have been demonstrated. It is believed, however, that any number of genes expressed in the central nervous system during fetal life and in the first 2 postnatal years could be candidates for causing autism (Box 3).

Chromosome 15

Strong evidence from several studies points towards the involvement of one or more loci on the long (q) arm of chromosome 15 near the centromere in the etiology of autism [*29,30*]. This region is a well known hotspot for duplications and deletions leading to genetic abnormalities, including Prader–Willi syndrome and Angelman syndrome [*31*]. In this region, a long duplication is associated with an almost 50% risk of autism. The genes for the receptor of γ-amino butyric acid (GABA), a major inhibitory neurotransmitter, are also located in this region. GABA receptors are located on the nerve cells and the genes for these receptors are considered possible candidates for autism as they are also associated with seizure and anxiety. Other studies have identified three markers between the GABA receptor genes and the centromere which appear as positive markers for autism. In addition, microrearrangements in the 15q region have been identified in some autistic families [*32*]. *PTPN9*, a gene involved in the control of cell growth and development of the brain, is also located on chromosome 15 and may also be involved in the development of autism. In addition, there is a maternal imprinting effect on the inheritance of chromosome 15 defects [*33–36*].

Chromosomes 7 and 13

Genomic screening of families with autism has resulted in the discovery of a number of hotspots on chromosome 7 that have links to autism. This region is believed to be expressed in the brain during development and contains a number of genes involved in brain development and function. Furthermore, in this region of chromosome 7, there are implications of some form of specific speech and language impairment and autism [*37*]. There is also a paternal imprinting effect on the inheritance of chromosome 7 defects.

Using over 400 genetic markers, chromosome 13 has been screened. Positive linkage to autism has been identified on chromosome 13, which has a maternal imprinting effect [*38*]. Recently an autistic individual was identified carrying a translocation of chromosomes 7 and 13 [*39*].

Other chromosomes

Using genetic markers on regions of the following chromosomes, it appears that there is a positive linkage to autism on chromosomes 4, 10, 16, 19 and 22 and on the X-chromosome [*40–46*]. Further studies are continuing to confirm the associations and to identify the specific susceptibility loci on these chromosomes.

Single genes linked to autism

From molecular genetic studies of sibling pairs in families with two or more autistic siblings, several genes appear to be linked, either strongly or moderately, to autism [*28,45*]. Initial suggestions that genes on the X-chromosome may be linked, thus resulting in the sex difference in autism prevalence, have been ruled out [*28*].

Two small population-based studies have reported an association between autism and an allele on the c-Harvey-ras (*HRAS*) gene on 11p [*47*]. A gene designated *PTPN9* on chromosome 15, which is involved in the control of cell growth and differentiation, and another designated *SLP1*, which is expressed in the brain, have been suggested as plausible candidates for involvement in the abnormal brain development that may underlie autism. In addition, the *HOXA1* gene, one of a large group of genes involved in determining the pattern of brain development in the early embryo, has also been implicated, since variants of *HOXA1* have been found at a higher frequency in autistic children than in normal controls.

Serotonin, an excitory neurotransmitter, occurs at a higher level in autistic patients. It requires a transporter to be removed from the synaptic cleft after performing its function. Any defect in the transporter will alter the concentration of serotonin in the synapse and consequently alter brain function. Some studies have shown an association between autism and the serotonin transporter gene on 17q and an extended human lymphocyte antigen haplotype B44-SC30-DR4 on 6p in a small sample.

Conclusion

The genetics of autism is still in its infancy and a great deal has yet to be learned from family and twin studies about the causative factors and about susceptibility genes. The co-existence of autism with mental retardation and with other genetic defects points to a major genetic contribution to the development of autism.

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Disorders of childhood and adolescence

Mental and behavioural disorders are common during childhood and adolescence. An estimated 10%–20% of children have one or more mental or behavioural problems. Many disorders commonly found amongst adults (e.g. depression) can begin during childhood. There are two broad categories specific to childhood and adolescence: Disorders of psychological development, e.g. dyslexia or autism; and behavioural and emotional disorders, e.g. attention deficit/hyperactivitiy disorders (ADHD) or conduct disorders. Child and adolescent disorders require a continuum of care over time linking settings such as families, schools, hospitals and outpatient facilities.

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