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RECENT ADVANCES IN THE GENETICS OF AUTISM SPECTRUM DISORDERS
A Minireview

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Introduction

Autism is a severe neuropsychiatric pervasive developmental disorder with an early childhood onset. The condition is recognised in pre-school-age children but it is a life-long disorder. Its clinical characterisation includes impairments in social interactions, communication or language abnormalities and restricted repetitive or stereotyped behaviour (American Psychiatric Association, 2000). The repetitive behaviour consists of repetition of words and phrases in a stereotyped way and movements of the limbs and body. These stereotypical movements may not be specific for autism because they also occur in patients with dementia, in particular, frontotemporal dementia (Mendez *et al.*, 2005). The communication deficit persists in children with autism (Wray *et al.*, 2005) and hence early diagnosis of language development in autism is important. Impairment in social interactions could be due to a deficit in spatial focusing of auditory attention (Teder-Salejarvi *et al.*, 2005). In adolescence, cognitive ability and social interaction skills may improve in some cases (McGovern and Sigman, 2005). The risk of developing autism has been consistently found to be associated with infantile microcephaly, different kinds of social impairments (Wing, 1997) and accelerated head growth in early development (Bolton *et al.*, 2001; Dementieva *et al.*, 2005). The clinical characteristics of the disorder closely overlap with other related conditions such as Asperger syndrome and atypical autism and hence autism is classified under a broad domain of pervasive developmental disorders. Although there is some similarity between autism and Asperger syndrome, they differ in their natural history, age of onset and sleep problems (Simpson, 2003; Polimeni *et al.*, 2005). There are considerable variations in clinical presentation and severity of impairment in autism among affected individuals even within the same family. A variety of early developmental delays have been currently used to diagnose the autistic condition.

Previous studies have reported a lower

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incidence rate of approximately 4-10 per 10,000 individuals for autism (Smalley *et al.*, 1988; Gillberg and Wing, 1999). However, recently it has been found that the incidence of autism is continuously rising with time (Rutter 2005). For instance, in a recent study using the International Statistical Classification of Diseases, the cumulative incidence of childhood autism in Japan is 27.2 per 10,000 (Honda *et al.*, 2005). Similarly, according to the Danish population-based study, the incidence rate and prevalence of childhood autism in children younger than 10 years is 2 per 10,000 (Lauritsen *et al.*, 2004) and in Western Australia the incidence in children 4 years of age is 5.5 per 10,000 (Williams *et al.*, 2005). In the United States, a population-based study reported that the prevalence of autism spectrum disorders is 10-60 individuals per 10,000. (Newschaffer *et al.*, 2005; Barbaresi *et al.*, 2005; Chakrabarti and Fombonne, 2001; Yeargin-Allsopp *et al.*, 2003). These values, when taken into consideration, suggest that autism may not be as rare a disease as previously thought. The recent increase in prevalence or the variability among different studies could be due to methodological variations, differences in diagnostic criteria, types of measurements and geographical differences involving environmental factors.

Neuropathology

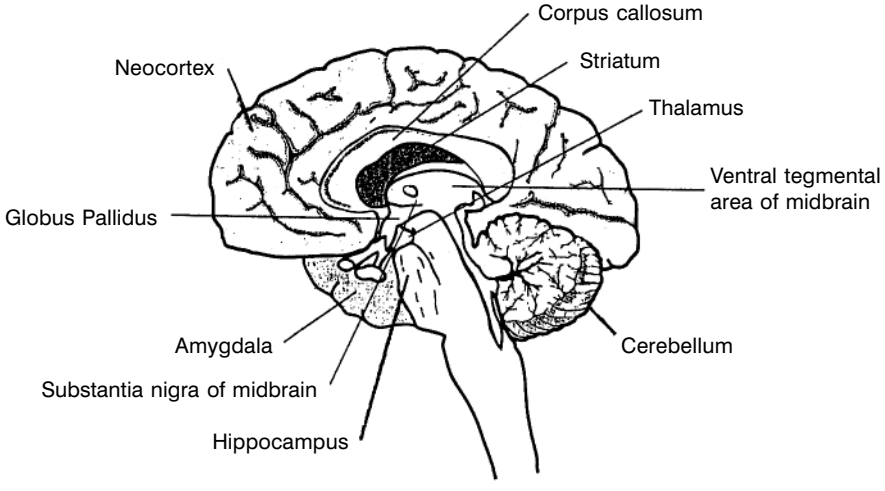
The finding that maternal exposure to the teratogenic agents thalidomide and misoprostol can cause autism spectrum disorders (Miller *et al.*, 2004; 2005; Miyazaki *et al.*, 2005) implicated that errors in early embryonic brain development may be responsible for autism (Miller *et al.*, 2004). These errors include ophthalmological anomalies (Miller *et al.*, 2005), a variety of systemic malformations, disruption of early serotonergic neuronal development, cranial nerve palsies and ear malformations. This pathophysiolgy could be due to an early developmental failure of the amygdala-fusiform system, visual perceptual area of the ventral temporal pathway or other parts of the brain (Schultz, 2005). In accordance with this notion, several abnormalities such as abnormal cortical serotonin synthesis (Chandana *et al.*, 2005), decrease in tracer alpha-methyl- tryptophan (AMT) in the left cortical region and cerebral folate deficiency have been reported. These errors may contribute to the developmental delay in autism through various mechanisms (Moretti *et al.*, 2005). In animal models, an increase in serotonin activity also was observed during brain development. Additionally, the neuropeptides oxytocin and vasopressin may be involved in brain disregulation in autism. These hormones excite different neuronal populations in the amygdala (Croonenberghs *et al.*, 2005; Huber *et al.*, 2005; Scott and Deneris, 2005; Whitaker-Azmitia, 2005; Lim *et al.*, 2005) and hence may cause different clinical characteristics of autism. The neuronal involvement in autism is further supported by the observation that the antiepileptic drug valproate causes a variety of malformations such as an increase in neural tube defects, developmental delays, autism, limb defects, cardiovascular abnormalities and endocrinological disorders (Alsdorf and Wyszynski 2005). These results strongly suggest that disregulation of the brain may be the major cause of autism.

There is no single region of the brain that has been identified as being associated with autism. However, there are several key brain structures that have been implicated in social cognition deficit in autism. These include the amygdala (FIGURE 1), the superior temporal sulcus

region and the fusiform gyrus (Pelphrey *et al.,* 2004). Additionally, behavioural imaging and postmortem studies have shown the signs of structural mal-development of frontal lobe, cerebellum, limbic system and related inferior olive - a precerebellar structure (FIGURE 1). There is also evidence for the localised enlargement of the frontal cortex in autism (Carper and Courchesne, 2005). In the limbic system, the hippocampus, amygdala and entorhinal cortex have shown an increase in packing density and small cell size. In the cerebellum, Purkinje cells are significantly reduced which again indicates the abnormal brain development. This is consistent with experiments involving primates in which early hippocampal damage produced stereotypes and loss of social affiliation (Bauman and Kemper 2005). The inferior olive neurons are relatively disrupted in autism. These neurons generate rhythmical oscillation in membrane potential. When these olive neurons are impaired they are perhaps unable to rapidly process sequences of cues for the development of normal language skills (Welsh et al., 2005). Based on these as well as other observations it was hypothesised that an imbalance between excitation and inhibition in key neuronal systems might cause autism (Cline, 2005).

The relationship between repetitive behaviour and associated clinical features in autism is complex. However, repetitive behaviour or circling is one of the defining features of autism. In animal models, the induction of circling may be determined by the GABAergic substantia nigra reticulata and dopaminergic substantia nigra compacta (Gabriels *et al.*, 2005; Velisek *et al.*, 2005). Similarly, there may be a localised dysfunction of the temporal lobe (Bachevalier, 1994), hippocampal formation, reduced white matter volume in corpus callosum (FIGURE 1) and right hemisphere and other widely distributed abnormalities of neuronal organisation and connectivity in the brain (Minshew *et al.*, 2004; Polleux and Lauder, 2004). Because the various regions of the brain are shown to be involved in autism, it is pos-

FIGURE 1
A schematic illustration of the locations of the brain regions that are implicated in autism disorder. The figure shows the location of amygdala, hippocampus, cerebellum and corpus callosum



sible that a specific neurological dysfunction can produce a characteristic symptom. For instance, the substantia nigra may be involved in one such symptom as circling behaviour and oxytocin and vasopressin in amygdala and abnormal synthesis of serotonin in the cortical region may determine other characteristic features of autism (Zwaigenbaum *et al.*, 2005). In spite of this, a specific cognitive deficit in autism has not been found (Carvajal-Molina *et al.,* 2005) and there are no universally accepted changes in brain structure, cell composition and clinical or biomarkers for autism (Beauregard *et al.*, 1995; Bauman, 1996; Zilbovicius *et al.*, 2000; Waiter *et al.*, 2005).

Chromosomal abnormalities

Autism is a complex multi-factorial developmental disorder with a strong genetic component. Cytogenetic studies reveal that approximately 1.7 to 4.8% of individuals with autism have chromosomal abnormalities (Reddy, 2005). A variety of structural abnormalities (TABLE I) including duplication, inversion, deletion and translocation have been reported (reviewed in Shastry, 2003). The most common abnormality is the duplication of the proximal region of the long arm of chromosome 15 (i.e. 15q). For instance, a partial duplication of chromosome 15 that involves the Prader-Willi/Angelman syndrome critical region (15q11-q13) has been found in three cases of autism. Similarly, a paternally derived interstitial duplication in the same critical region (15q11-q13) was also found in a female patient (Veltman *et al.,* 2005). This suggests that in some cases, genomic imprinting may be involved in autism (Simie and Turk, 2004; Samaco *et al.,* 2005). When pathology is considered, patients with interstitial deletions in chromosome 12 exhibit mental retardation and developmental delay while patients with deletion in chromosome 18 show communication problems and mental retardation. Similarly, inversion in chromosome 17 is associated with developmental delay. Although in some cases deletion ranged from 5 to 260 Kb and patients exhibited a varying degree of intellectual impairments, there is no clustering of break points involved and deletions are scattered throughout the genome. Interestingly, in a population-based study, a minority of cases of autism have been found to be associated with mitochondrial dysfunction (Oliveira *et al.,*

TABLE I
A partial list of cytogenetic abnormalities associated with autism

Deletion at marker D7S630	Deletion at marker D7S517
Deletion at marker D8S264	Partial duplication of 7p
Interstitial duplication of proximal 15q	Deletion in 2q, 3q, 18q and Xp
del (12)(p11.2 q21.2)	del (13)(q13.2 q14.1)
inv (10)(p11.2 q21.2)	inv (17)(q2 q25)
t(7; 13)(q31.3; q21)	t(5; 7)(q14; q32)
t(1; 14)(q25; q31.2)	

del = deletion; inv = inversion; t = translocation

2005). Therefore, it could be a mitochondrial disorder as well. However, it requires further investigation. The above studies taken together suggest that autism is a polygenic disorder.

Linkage analysis

The genetic aetiology of autism remains elusive both at the cellular and molecular levels. While the existing genetic data do not strongly support any one mode of inheritance, twin and family studies endorse a multi-locus aetiology. For instance, multiple studies reported that identical (monozygotic) twins are 60-90% concordant for autism (Folstein and Rutter 1977; Ritvo *et al.*, 1985; Steffenburg *et al.*, 1989; Bailey *et al.*, 1995; Folstein and Rutter, 1997). On the other hand, nonidentical (dizygotic) twins and siblings have a much lower (0 – 20%) concordance rate (August and Stewart, 1981; Bolton *et al.*, 1994; Lauritsen and Ewald, 2001). When a broader phenotype of autism was included, the concordance rate was increased to 92% and 10% for monozygotic and dizygotic twins respectively (Folstein and Rutter, 1977). Additionally, prevalence of autism is found to be 3 to 4 fold higher in males than in females (Folstein and Rosen-Sheidley, 2001) and the reason for this is unknown. However, this may suggest that sex-specific factors might be involved in its development. In accordance with this notion, evidence for sex-limited and parent of origin specific effects in the aetiology of autism have been reported (Lamb *et al.*, 2005). Interestingly, a male specific region of linkage on chromosome 17q was also recently reported in the autism spectrum disorder (Stone et al., 2004). It is not surprising that such a sex-specific effect may exist because it is already known that male and female brains develop and function differently. In addition, there may be microscopic structural differences between male and female brains (Wisniewski, 1998; Wrase *et al.*, 2003).

These monozygotic and dizygotic concordance rates indicate that both genetic and environmental factors contribute to the risk of developing autism. Although previously it was reported that measles, mumps and rubella (MMR) vaccination might cause autism, recently it was found that there is no such association (Taylor et al., 1999) indicating that MMR vaccine is not an environmental risk factor for autism. The higher concordant rate (90%) in monozygotic twins and the marked difference between the mono- and dizygotic concordance rate suggest that autism is highly heritable and the genetic basis is complex. It is likely that multiple genes contribute to autism susceptibility in an interactive manner, but the exact number of contributing genes and their modes of inheritance are not known. However, ten genome wide linkage studies have shown suggestive evidence for linkage on 17 of the 22 autosomes and at various locations on the X-chromosome (Barrett *et al.*, 1999; Philippe *et al.*, 1999; Risch *et al.*, 1999; Buxbaum *et al.*, 2001; Liu *et al.*, 2001; McCauley *et al.*, 2005; Santangelo and Tsatsanis, 2005). These chromosomal regions may contain one or more susceptibility genes and these may determine one or all of the clinical characteristics of autism. However, it should be noted that several of these analyses reported only moderate positive signals on several chromosomes and only a few regions appear to be consistent across studies (Folstein and Rosen-Sheidley, 2001; Yonan *et al.*, 2003). The most consistent finding, to date, has been on chromosome 2q, 7q, 15q and 17q11-q22 (Cantor *et al.*, 2005; Santangelo and

Tsatsanis 2005) with a possibility of chromosome 1 (Badner and Gershon, 2002; Bartlett et al., 2005a). It is still not clear whether these are the major susceptibility loci for autism or other loci also influence the disorder. One of the reasons for inconsistency in linkage could be due to locus heterogeneity or sample size or both.

These linkage studies and the drop in the concordance rate between monozygotic and dizygotic twins suggest that a single gene is not responsible for disease expression and the genetic aetiology of autism is heterogeneous (different family has different genes). It is a polygenic disorder (an individual may carry more than one defective gene) with epigenetic influences (Folstein and Rosen-Sheidley, 2001) and with allelic heterogeneity (different variants in the same gene). Different genetic factors may be associated with different characteristic features of autism such as poor social interactions, communication and repetitive behaviour. Evidence that thalidomide induces embryopathy and less than 100% concordance rate among monozygotic twins also suggests the involvement of environmental factors. In addition, social and emotional factors may also play a role in autism (Simpson, 2003; Santangelo and Tsatsanis, 2005). Thus, it appears that autism is a syndrome with a strong genetic component.

Candidate gene analysis

When linkage analysis was extended to identify autism susceptibility candidate genes, most of the results are either conflicting with the other studies or resulted in frustration. Many genes which are known for their role in brain functions did not show association with the condition (TABLE II). However, serotonin transporter intron-2 polymorphism (Mulder *et al.,* 2005), Reelin (reeler mutant mouse has cerebral cortex malformation), tryptophan hydroxylase (Bartlett *et al.*, 2005b; Coon *et al.*, 2005), neuroligins 3 and neuroligins 4 (Jamain *et al.,* 2003) and genes mapping to chromosome 7q (Bonora *et al.*, 2005) have been found to have some role in autism. The region on 7q35 may contain a gene that may be related to the variability in spoken language (Alarcon *et al.*, 2005), but these findings have to be replicated by other studies. In a sub-population of autistic patients, increased blood levels of 5-hydroxy tryptamine (5-HT) have been repeatedly observed. Therefore, it is possible that disrupted developmental control of 5-HT production in autistic children could result in hyperserotonaemia and this may have a role in specific aspects of the behaviour (Chugani *et al.*, 1999; Leboyer *et al.*, 1999). Similarly, neuroligins are needed for the formation of morphologically well- differentiated synapses and they mediate excitatory and inhibitory synapse formation. They carry out this function by binding to neurexin. Mutations in these genes may affect cell adhesion molecules located at the synapse and impair its cell surface transport (Chubykin *et al.*, 2005; Levinson *et al.*, 2005). In the same way, Reelin may also act as a terminal signal for neurons at the end of their migration pathway and the reduced amount of reelin mRNA in the frontal and cerebellar area may suggest an impairment in the reelin signalling system in autism (Fatemi *et al.*, 2005). Although these studies have given a wealth of information, research to date on the genetics of autism has not uncovered a major susceptibility locus (there may not be any such locus) despite considerable efforts. In addition, only a few candidate genes have been shown to display specific mutations that segregate with autism but these are

TABLE II
A partial list of genes that are unlikely associated with autism[a]

Hox A1 and Hox B1	Dopamine receptors D2 and D5
Reelin	Monoamine oxidase A and B
DLX6	Brain derived neurotrophic factor
FOXP2	Neural cell adhesion molecule
DOPA decarboxylase	Genes in 800 Kb region of 7q32
Proenkephalin	Methyl-CpG-binding protein 2
Tyrosine hydroxylase	Catechole-O-methyltransferase
Dopamine D4 exon III (DRD4)	Prodynorphine
WNT-2	Piccolo gene
CPA1 and CPA5	

[a] = detailed references can be found in Shastry, 2003; DLX5 and Piccolo = genes in chromosome 7q21-q22; FOXP2 = one of the genes in chromosome 7q31; CAP1 and CAP5 = members of the carboxypeptidase gene family located at chromosome 7q32; Hox A1 and Hox B1 = homeobox genes; WNT-2 = secreted cystein-rich glycoprotein

yet to be replicated. Those genes which are responsible for controlling the early patterning of specific neuronal subpopulations and their regulation during development are also likely to be involved in autism.

Summary

Autism is a complex behaviourally defined childhood developmental disorder without an established aetiology. Currently a variety of early developmental delay and regressions in behaviour have been used to diagnose the condition. The social and behavioural deficits are the hallmarks of autism. Autistic spectrum disorders have profound effects on the lives of patients and their families. It is a syndrome with a strong genetic component and has a heritability value of about 90%. However, the transmission pattern does not follow any one mode of inheritance. Although many regions of the brain are shown to be involved in autism there are no universally accepted changes in the brain structure. Despite considerable efforts to identify chromosomal regions and genes, no disease genes have been identified which can account for major portions of autism disorder. The positive association studies of some candidate genes still need to be replicated by others. There are no physical tests that can be of diagnostic value or drugs that can produce major benefits for autistic disorders. Behavioural therapy, environmental management and structured education may be the most effective way to help the affected children. Additionally, antipsychotic medication may have some limited effects to reduce the level of physical aggression. In the future, investigation of genetic and environmental factors may help provide better diagnosis and treatment.

Glossary

Amygdala
Portion of the limbic system that functions to add emotional overtones to memories.

Association
Groups of anomalies that occur together more often than chance.

Autosomes
Any chromosome other than the X or Y chromosomes

Candidate gene
A gene mapped to a region known to be linked to a specific disease.

Cerebellum
Part of the brain located posterior to the medulla oblongata.

Chromosome
Genetic material complexed with RNA and proteins to form a thread like structure.

Corpus Callosum
A mass of white matter within the brain.

Cytogenetics
The study of chromosome structure.

Deletion
The loss of chromosomal material.

Dizygotic
The product of fertilization of two separate eggs by two separate sperms, resulting in non-identical twin pairs.

Dopamine
Transmitter liberated by neurons in some autonomic ganglia and in the central nervous system.

Duplication
A chromosomal aberration in which the segment of the chromosome is repeated.

GABA
Gamma aminobutyric acid, an inhibitory neurotransmitter.

Gene
The fundamental physical unit of heredity.

Genome
The complete set of genes in an organism.

Genotype
Genetic make-up of an individual

Hippocampus
A region of the brain involved in learning, generation of emotions and memory.

Idiopathic
A disease or condition for which causes are unknown.

Insertions
The addition of DNA sequence.

Interstitial deletion
Deletion that removes part of the interior of the chromosome.

Inversion
A chromosomal aberration in which the order of a chromosomal segment has been reversed.

Karyotype
The chromosomal complement of a cell or an individual.

Killobase pairs
A unit of measurement used in genetics to denote 1000 bases of DNA

Linkage
Describes two loci that are located close enough on the same chromosome.

Mitochondria
The cells power house generating energy.

Monogenic
Controlled by only one gene.

Monozygotic
Arising from a single fertilized egg, resulting in genetically identical twins.

Mutation
The process that produces an alteration in DNA or chromosome structure.

Oxytocin
Hormone secreted from posterior pituitary.

Polygenic
Controlled by more than one gene.

Polymorphism
The existence of two or more genetically determined forms in a population.

Reelin (relin)
A large extra-cellular matrix protein gene involved in neuronal migration.

Rubella
German measles.

Serotonin
5-hydroxytryptamine (5HT), a neurotransmitter.

Sex chromosome
X or Y-chromosomes determining gender.

Teratogenic
Capable of producing abnormal development of a foetus.

Transmitter
Chemical substance liberated by a presynaptic nerve terminal.

Translocation
A chromosomal mutation associated with the transfer of a chromosomal segment from one chromosome to another.

Vasopressin
Peptide hormone secreted by hypothalamus

White matter
Part of the central nervous system appearing white.

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