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ScienceDirect
Metabolism Clinical and Experimental 57 (Suppl 2) (2008) S40–S43
Metabolism
Clinical and Experimental
www.metabolismjournal.com

# Autism, a brain developmental disorder: some new pathopysiologic and genetics findings

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**Abstract**

Autism is a severe neurodevelopmental disorder that is typically diagnosed by 3 years of age. Core symptoms of autism include profound deficits in social interaction and communication, restricted interests, stereotyped responses, and other repetitive patterns of behavior. Other abnormalities include mental retardation and comorbid epilepsy. These symptoms underscore the consequences of genetic inheritance for brain function and behavior. The etiology of autism may involve an interaction between genetic susceptibility (mediated by multiple genes) and environmental factors influencing brain development.


## 1. Introduction

There is increasing evidence that abnormalities in brain development either predispose to or directly cause certain neuropsychiatric disorders. Although it is not surprising that childhood disorders, such as autism, are caused by neurodevelopmental abnormalities, disorders that display their most characteristic symptoms during or after adolescence also may be influenced by developmental abnormalities that occurred in utero. Thus, there is a compelling rationale for behavioral scientists and clinicians to understand the basic mechanisms that regulate assembly of the brain because this information may be key to understanding the etiology and perhaps the treatment of major neuropsychiatric disorders.

Investigating the interplay between genes and the social environment in relation to the onset, course, and outcomes of psychopathology is being increasingly widened to incorporate lessons from neuroscience [1,2].

## 2. Autism

Autism is a neurodevelopmental syndrome with markedly high heritability. The diagnostic indicators of autism are core behavioral symptoms rather than definitive neuropathologic markers. Etiology is thought to involve complex, multigenic interactions and possible environmental contributions.

Improved clinical tests are enabling us to classify autism spectrum disorders (ASDs) with greater precision and diagnose them at earlier ages. This raises the possibility of earlier and potentially more effective therapeutic interventions. To fully capitalize on this opportunity, however, will require better understanding of the neurobiological changes underlying this devastating group of developmental disorders.

The heterogeneity and clinical variability of autism has prompted some researchers to use the term *autisms* instead of autism [3]. Epidemiologic studies suggest incidence rates of autistic disorder of 2 to 5 cases per 10 000 individuals [4].

The current diagnosis of ASD is based on behavioral history and behavioral assessments. These disorders represent a collection of pervasive developmental neurogenetic conditions that alter socialization and communication, and they are generally apparent by 3 years of age. Autistic disorder (also called “classic” autism) is the prototypical pervasive developmental disorder. There are 5 ASDs described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* of the American Psychiatric Association [4]: (*a*) autistic disorder; (*b*) Asperger syndrome; (*c*) pervasive developmental disorder—not otherwise specified; (*d*) childhood disintegrative disorder; and (*e*) Rett syndrome. Currently, significant debate exists

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doi:10.1016/j.metabol.2008.07.005

about the perceived marked increase in the incidence of these conditions.

According to the World Health Organization *International Classification of Diseases, 10th Revision*, Chapter V: Diagnostic Criteria for Autism [5], the condition can be divided into childhood autism and atypical autism (F84.0 and F84.1). The characteristics of childhood (typical) autism have been described above. In atypical autism, abnormal or impaired development is evident at or after the age of 3 years. With respect to symptoms, the criteria for diagnosing atypical autism are more flexible than those used for the typical form. For example, in the atypical form, it is unnecessary to meet the criteria for a number of areas of abnormality.

## 3. Neurobiology

The social, language, and behavioral problems that occur with autism suggest that the syndrome affects a functionally diverse and widely distributed set of neural systems. At the same time, however, the pattern of brain abnormality appears discrete because autism spares many perceptual and cognitive systems. For example, autism is not incompatible with normative intelligence or even superior visual perceptual and other neuropsychological skills and talents. Although the full syndrome likely involves insults to multiple systems, it remains possible that the initial insult is localized, branching off into more pervasive impairments because of the highly interdependent nature of early neurodevelopmental processes.

According to Geschwind and Levitt [3], recent genetic findings, coupled with emerging anatomical and functional imaging studies, suggest a potential unifying model in which higher-order association areas of the brain that normally connect to the frontal lobe are partially disconnected during development. This concept of developmental disconnection can accommodate the specific neurobehavioral features that are observed in autism, their emergence during development, and the heterogeneity of autism etiology, behaviors, and cognition.

Malfunction of nearly every neural system in the brain has been proposed at some point as the cause of autism. Theories typically derive from beliefs about the most salient behavioral and psychological features of the disorder. On the other hand, those who focus on the emotional deficits and their role in social difficulties often highlight the limbic system in the pathogenesis of autism. Currently, there is a growing body of research data to support roles for selected aspects of the temporal and frontal lobes and portions of the amygdala in the pathobiology of autism [6].

Kanner's [7] original description of autism noted that many of the patients had enlarged heads. Although this observation was confirmed subsequently by others [8,9], it did not receive much attention until postmortem and MRI studies began to confirm that the brain is enlarged in autism [10]. However, it is not yet understood whether all brain regions and systems are equally enlarged in autism.

Functional magnetic resonance imaging (fMRI) studies suggest that the dorsomedial prefrontal cortex (PFC) is a critical substrate for social cognition; that is, for thinking about others' thoughts, feelings, and intentions [6]. In addition, the ventromedial PFC has been implicated in processing normal affect [11]. The orbital and medial PFC have dense reciprocal connections with medical temporal areas, forming a system for regulating emotional processes. A positron emission tomography study, for instance, has reported reduced dopaminergic activity in the medial PFC of autistic subjects [12].

People with autism often find bodily contacts to be aversive, thereby limiting what they can learn from others during social interactions. The amygdala is an important area of the brain, among others, for integrating the internal milieu with the social ambiance. Individuals with autism consistently demonstrate dysregulation of amygdalar function. Diverse regions of the amygdala, which contain neuropeptides, figure in the appraisal systems that underlie behavioral approach and avoidance responses [13].

Animal models suggest that developmental abnormalities in the amygdala may play a particularly important role in the development of autistic symptoms. For example, bilateral damage of the amygdala shortly after birth in monkeys can produce patterns of behavior similar to those of autism, such as social isolation, lack of eye contact, impaired facial expression, and motor stereotypes [14]. Creation of similar lesions in adult monkeys fails to reproduce these behaviors. The early postnatal lesions do not immediately produce autistic characteristics; rather, these characteristics emerge with age and experience, suggesting a role for faulty early social and emotional learning. Furthermore, monkeys with early lesions in the amygdala and surrounding entorhinal cortex go on to develop abnormalities of the frontal cortex in adulthood [15,16], showing how an isolated deficit can have more widespread neurofunctional implications through its influence on brain development.

Based on clinical studies, Prado and Eberhart [17] link the molecular pathways altered in autism to the neurodevelopmental and clinical changes that characterize the disease. They also focus on signaling molecules such as neurotrophin, Reelin, phosphatase and tensin homolog (PTEN) and hepatocyte growth factor, neurotransmitters such as serotonin and glutamate, and synaptic proteins such as neurexin, SHANK, and neuroligin. They also discuss evidence implicating oxidative stress, neuroglial activation, and neuroimmunity in autism.

Hughes [18] conducted a clinical and electroencephalographic study on autistic children and found 46% to have seizures. A relatively high proportion of this cohort (20%) also exhibited epileptiform discharges but without associated clinical seizures. Because such discharges have always been viewed as focal events, and the clinical seizures as requiring a spread of abnormal electrical activity over the brain, the

inference from these data was that children with autism may have a deficiency of corticocortical fibers. Since that time, many MRI and fMRI studies have been published confirming that one of the principal findings in this devastating condition is *underconnectivity*. Specific findings include thinning of the corpus callosum and reduced connectivity, especially with the frontal areas and the fusiform facial area. Other studies involving positron emission tomography scans, magnetoencephalography, and perception have added to the evidence of underconnectivity. One final point is that the initial overgrowth of white matter in the first 2 years of life in autistic children is followed later by arrested growth, resulting in aberrant connectivity. In addition, impaired myelination of white matter is likely to be significant in the etiology of autism.

## 4. Genetic origins

Accumulating evidence indicates that autism is a genetic disorder with complex inheritance. Twin studies show a 60% to 91% concordance rate in monozygotic twins, depending on whether a narrow or broad phenotype is considered [19]. In contrast, concordance was not observed in dizygotic twins [19]. The sibling recurrence rate has been estimated to be 4.5% [20]. The pattern of relative risk in autism is consistent with multiplicative inheritance, with multiple gene variants converging to lead to the phenotype.

Several candidate gene studies have been conducted on the basis of limited knowledge of neuropharmacology in autism, developmental neuropathologic abnormalities, or chromosomal anomalies. Autism spectrum disorder is considered to be a complex multifactorial disorder involving many genes. It shows a striking difference in male-female ratio, estimated at 4-10:1. It has become a consensus that chromosomal analysis is important in any child who presents with ASD because approximately 5% to 14% of these patients have a known genetic disorder of chromosomal abnormality. Cytogenetic abnormalities have included deletions involving 7q, 22q13, 2q37, 18q, Xp, and sex chromosome aneuplodies (47, XYY and 45, X/46, XY mosaicism) [21,22]. The 4 most common associations include fragile X syndrome, tuberous sclerosis, 15q duplications, and untreated phenyketonuria.

Several susceptibility loci that can contribute to the ASD phenotype have been identified and catalogued in the Online Mendelian Inheritance in Man (OMIM) database (http://www.ncbi.nlm.nih.gov/sites/entrez), which supports a complex, heterogeneous, and multilocus etiology.

The use of array comparative genomic hybridization or chromosomal microarray has revealed that a myriad of de novo copy number variations (also called structural variations, or deletions and duplications of genomic regions) are significantly associated with autism. Sebat and associates [23] reported that microscopic copy number variations were identified in 10% of patients with sporadic autism, 3% of patients with an affected first-degree relative, and 1% of controls. These genomic regions were highly heterogeneous and included mutations of single genes. Sebat et al concluded that de novo germline mutation is a very significant risk factor for ASD. Jacquemont and associates [24] found detectable abnormalities in a much higher percentage of patients (8/29) with ASD (27.6%).

Recent studies have supported the role of a multitude of genes/pathways in ASD, which include clock genes [25], PRKCB1 gene (protein kinase C-$\beta$ gene) [26], CNTN4 (contactin 4) [27], CNTCAP2 (contactin associated protein-like 2 gene, a member of the neurexin family) [28], immune genes [29], STK39 gene (serine/threonine protein kinase 39) [30], MAOA gene (monoamine oxidase A) [31], CSMD3 gene (CUB and Sushi multiple domains3, a candidate gene for autism) [32], genes controlling affiliative behavior [33], DRD1 (dopamine D1 receptor) [34], neurexin 1 [35], SLC25A12 (solute carrier family 25, member 12) [36], JARID1C gene (jumonji AT-rich interactive domain 1C) [37], and Pax6 (paired box gene 6) [38]. Most of those findings will need replication, but they may also give rise to new insights into neuronal circuits relevant to, and etiological hypotheses to explain, these disorders. The rapid advance of technology in the genetics of ASD is likely to bring more insights into the etiology of autism, that, in the near future, may help clarify pathophysiologic mechanisms that contribute to the susceptibility to ASD.

Recent studies have also led to the identification of several autism susceptibility genes and an increased appreciation of the contribution of de novo and inherited copy number variation. Promising strategies are also being applied to identify common genetic risk variants. Systems biology approaches, including array-based expression profiling, are poised to provide additional insights into this group of disorders, in which heterogeneity, both genetic and phenotypic, is emerging as a dominant theme [39].

## 5. Conclusions

New investigative and diagnostic technologies such as fMRI, positron emission tomography, array comparative genomic hybridization and chromosomal microarray, have greatly enhanced our understanding of the neurobiology of autism. Use of these methods has generated several heuristic hypotheses to explain the abnormalities of certain brain regions that occur in early neurodevelopment—among them the concept that, in autism, during the brain assembly process, higher-order association areas of the brain that normally connect to the frontal lobe are partly disconnected [3].

Although recent progress has narrowed the search for genes of major effect, many basic questions remain. Examples include the following: are the genes interacting in an additive or a multiplicative manner? Why do the deficits or abnormalities of autism appear to cluster? To what extent will individual deficits be found to occur on a continuum with normal behavior?

Alternative approaches may be needed to find genetic risk factors in autism. Simply increasing subject numbers or using more closely spaced markers may not be fruitful. A more refined approach may be needed in association and linkage studies to characterize specific components of the phenotype (ie, examination of specific traits, behavioral components, or endophenotypes). This approach will likely benefit from the use of quantitative measures such as neuropsychological (eg, face recognition), neurophysiological (eg, event-related potentials, functional imaging measures), and biological measures (eg, platelet serotonin). Use of these approaches to examine the genetic determinants of autism is just beginning.

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