The first autism disease genes

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The autistic disorder was first described, more than sixty years ago, by Dr. Leo Kanner of the Johns Hopkins Hospital (USA), who created the new label 'early infantile autism'. At the same time an Austrian scientist, Dr. Hans Asperger, described a milder form of the disorder that became known as Asperger Syndrome, characterised by higher cognitive abilities and more normal language function. Today, both disorders are classified in the continuum of 'Pervasive Developmental Disorders' (PDD), more often referred to as Autism Spectrum Disorders (ASD).

The prevalence of (classic) autism in the general population is about 15-20 in 10.000, while all Autism Spectrum Disorders (ASD) affect about 60 in 10.000 children. Males are affected four times more often than females. In approximately 10% of cases, autism is associated with a recognized cause, such as Fragile X Syndrome, Tuberous Sclerosis or diverse chromosomal abnormalities (mean observed rates between 5-10%), but in a vast majority of cases, no known causes are associated with autism.

All of these neurodevelopmental disorders are characterized by varying deficits in communication skills, social interactions, and restricted, repetitive and stereotyped patterns of interests and activities. Problems that may accompany these disorders are sensory distortion, mental retardation or seizures. Disease onset occurs during the first three years of life. Although early intervention has considerable impact on reducing symptoms and increasing a child´s ability to learn new skills, it is estimated that only 50% of children are diagnosed before the age of 3 years.

Most children with ASD respond well to behavioural management and highly structured, specialized programs in educational settings. Other therapeutic interventions comprise medications to treat behavioural problems such as aggression, self-injury, or severe tantrums.

Warning signs for Autism Spectrum Disorders such as social symptoms, communication deficits and repetitive behaviours should be considered sufficient reason to have a child evaluated by specialized professionals. The earlier the disorder is diagnosed, the sooner the child can be helped through treatment interventions.

Advances in autism research: genetic influences

Research into the causes, diagnosis, and the treatment of ASD has advanced interactively. Imaging studies have shown that many major brain structures are implicated in autism. Other research is focusing on the role of neurotransmitters such as serotonin, dopamine, and epinephrine. The past decade has been marked by an increased interest in the genetic basis of autism, and recent developments point to genetic factors playing a prominent role in the causes for ASD.

The role of gene mutations in autism

Twin and family studies have suggested an underlying genetic vulnerability to ASD. The estimated prevalence of autism in siblings is 5-10%. A higher recurrence risk in families with autistic subjects (45-times greater than the prevalence in the general population) and higher concordance for autism among monozygotic (60-90%) than dizygotic (0-10%) twins argue for a genetic predisposition to idiopathic

autism. These data are interpreted as showing that liability to autism is in large part due to oligogenic inheritance in which a combination of multiple – possibly interacting – susceptibility alleles results in autism. A series of multiple independent whole genome scans and chromosomal abnormality studies have pointed out several candidate regions on chromosomes 2q, 7q, 6q, 15q and sex chromosomes. These regions possess candidate genes that have been screened for mutations or association with autism. In a European multicentre project called PARIS (Paris Autism Sib-pair International Study; coordinated by C. Gillberg & M. Leboyer) a large number of multiply affected families were identified, and several mutations of genes encoding proteins implicated in the process of synapse formation (synaptogenesis) have been described.

Autism and synapse formation (synaptogenesis)

In 2003 two new highly conserved members of the human neuroligin family – HNL4, located at Xp22.3 – were characterized (Jamain et al, 2003). A crucial factor in synapse formation, neuroligins are cell adhesion molecules that can trigger the formation of presynaptic structures in non-neuronal cells. The rare mutations of the neuroligins (1%) are associated with autism spectrum conditions. Another step forward in this compelling neurobiological story was the identification of a de novo frame-shift mutation in the X-linked HNL4 gene in two brothers, one with autism and the other with Asperger Syndrome. Since autism and Asperger Syndrome are overly represented in males, mutations in these genes may influence the process of synaptogenesis, and consequently may predispose males to Autism Spectrum Disorders.

In 2007, mutations of another gene encoding SHANK3 were reported (Durand et al, 2007). This gene regulates the structural organization of dendritic spines in neurons and is a binding partner of neuroligins, previously found to be mutated in autism and Asperger Syndrome.

Surprisingly, a mutation of a single copy of SHANK3 at chromosome 22q13 is sufficient to induce language impairment, learning disabilities and/or social communication disorders associated with Autism Spectrum Disorders. Frequency of SHANK3 variants is very low even among autism patients and nearly absent in the general population. These results have thus shed light on one synaptic pathway sensitive to gene dosage and associated to Autism Spectrum Disorders.

In a large international study with a sample of 1.168 multiplex families, another exciting discovery led to the detection of sub-microscopic chromosomal abnormalities (Autism Genome Project, 2007): Copy Number Variant analysis (CNV) highlighted the role of a gene encoding neurexin, which is a tightly linked protein to neuroligin, implicated in synapse formation for glutamate neurons. This revealed a hemizygous deletion of coding exon for neurexin gene for a pair of affected siblings. Accumulating evidence thus points out that neurexin/neuroligin/Shank3 (NLGN3/4, SHANK3, NRXN1) genes are related to autism risk, establishing a direct proof of the association of autism with synaptic abnormalities. Neurexin induces glutamate postsynaptic differentiation in contacting dendrites, while neuroligins induce presynaptic differentiation in glutamate axons. The neurexin-neuroligin link thus appears to be fundamental for glutamatergic synapse formation. Furthermore, aberrant glutamate function is often cited as a cause for autism.

By influencing the process of synapse formation for glutamate neurons, gene mutations predispose individuals to Autism Spectrum Disorders.

Autism and circadian rhythms

Another approach in research of the genetics of autism implies the

melatonin pathway. Melatonin is produced in the dark by the pineal gland and is a key regulator of circadian and seasonal rhythms. A low melatonin level was reported in individuals with Autism Spectrum Disorders, but the underlying cause of this deficit was unknown. In several individuals with Autism Spectrum Disorders, deletions of the ASMT-gene were found. This gene, located on the pseudo-autosomal region 1 of the sex chromosomes, encodes the last enzyme of melatonin synthesis. Biochemical analyses performed on blood platelets and/or cultured cells revealed a highly significant decrease in AMST activity and melatonin level in individuals with Autism Spectrum Disorders (Melke et al., 2008).

Recent research indicates that a low melatonin level, caused by a primary deficit in gene activity (AMST), is a risk factor for Autism Spectrum Disorders, and highlights the crucial role of melatonin in human cognition and behaviour.

Clinical implications

-- These findings stress the importance of further research into genetic abnormalities in autism to obtain a better understanding of the underlying disease mechanisms. However, several questions such as correlations between genotypes and phenotypes including cognition and brain imaging studies still remain to be investigated.

-- Research to unravel autism requires multidisciplinary approaches involving psychiatrists, psychologists, geneticists and brain imaging specialists.

-- Autistic patients require a broad workout taking into account psychiatric, somatic, cognitive, social and professional issues;

furthermore they should be invited to participate in various research projects, ranging from fundamental research to more applied projects on the development of new therapeutic strategies. In view of these requirements the French Ministry of Research has established in 2007 the foundation Fondation FondaMental with the aim to intensify research in this field and to offer high-functioning autistic subjects optimal treatment and care in specialized expert centers.

References

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