

## **A Genetic Study of Autism/PDD; Molecular and Family Studies**

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Autism and the related pervasive developmental disorders (PDD) represent one of the most disabling conditions of childhood in terms of prevalence, morbidity, outcome and economic cost. Although the etiology of this disorder has been studied for many years, little of clinical relevance has been uncovered. It seems clear that genetic factors are important in the etiology of autism/PDD and raise the hope that molecular biological approaches may eventually shed light on the real cause of autism/PDD.

The objective of this study is to investigate the genetic etiology of autism/PDD by focussing on families with at least two affected children. These families most likely represent pure genetic cases of autism/PDD and a close analysis of such families may reveal clinical features associated with such an etiology. In this way, the genetic-biochemical defect causing autism/PDD may be better understood and may lead to more rational treatment approaches.

#### ***Prevalence and Classification***

Autism is a developmental disability characterized by impairments in reciprocal social interaction, in verbal and nonverbal communication and a pattern of repetitive, stereotypic activities. Autism represents one end of the spectrum of conditions called the Pervasive Developmental Disorders (PDD) that share clinical features but differ on natural history, number of symptoms, or patterns of behaviours. Autism represents the most extreme form of PDD and occurs in 4-10/10000 children with four affected males to every affected female. DSM-IV has specified several new subtypes of PDD other than autism. Atypical autism refers to individuals with some autistic behaviours but not enough to qualify for a diagnosis of autism. Asperger disorder is another less severe form of PDD than autism characterized by an absence of clinically significant language and cognitive delay. Both these subtypes are said to be more common than autism. Other more rare forms of PDD include Rett syndrome and disintegrative disorder of childhood. Thus overall the prevalence of PDD in young children may be as high as 0.5%, in line with recent comments that the number of PDD children coming to clinical attention may be increasing.

#### ***The Role of Genes in Autism/PDD***

The evidence that genetic factors play a role in the etiology of autism is fairly clear. Six major reviews of sibling, twin and family studies have all concluded that a genetic etiology exists for many cases of autism/PDD. For example, the risk of autism to siblings of children with autism is between 2% and 8% or between 50 and 200 times the general population rate. Four twin studies have reported that the concordance rate for autism is much higher among identical twins than non-identical twins indicating that the basis of the family clustering is genetic.

It is also clear that other forms of PDD run in the families of children with autism. For example, the co-twins of an identical twin with autism can have atypical autism or Asperger syndrome, and the risk of Asperger syndrome and atypical autism in the non-twin siblings of individuals with autism is 2.8%. Another type of impairment that has recently been reported to occur in first degree relatives is a lesser variant of PDD characterized by similar impairments in reciprocal social interaction, communication and interests but not enough to merit a diagnosis of PDD. For example, a recent family history study found that roughly 20% of siblings of children with autism have social or communication impairments or a restricted pattern of interests compared with 3% of siblings of Down syndrome controls. These results indicate that the genes for autism also confer susceptibility to milder manifestations of PDD, even some which fall below threshold for diagnosis.

The mechanism for this large variation in clinical expression is unknown. Obstetrical complications have been suggested

as contributing to severity among genetically susceptible individuals. In fact, the present study has found that affected siblings within a family are very similarly affected in terms of IQ and severity of impairment. This suggests that genetic factors, are probably responsible for the variation in clinical expression among PDD children.

### ***The Present Investigation***

*The Genetics of Autism/PDD; Family and Molecular Studies* has been ongoing for the last 12 years. We were funded in 2002 for another five years. The overall objective of this research program is to identify and map genes important in the etiology of autism/PDD.

The current sample consists of 180 families with at least two affected individuals (multiplex, MPX), 57 families with an affected male (male simplex, male-SPX), 28 families with an affected female (female simplex, female-SPX) and 23 families who have adopted a child with autism/PDD or contain a step-parent of a child with autism/PDD. Both the male and female SPX families have at least one full unaffected sibling to attempt to distinguish these families from MPX families. The goal is to collect 200 MPX families from across Canada over the course of the study.

An extensive test battery of assessments is conducted on the affected individuals to confirm the diagnosis of autism/PDD. Clinical features that may be relevant to genetic subgroups are also measured through psychometric assessments and adaptive behaviour. The results of the clinical and psychometric assessments are compiled and reviewed by three raters to determine a best estimate diagnosis for each affected individual. Blood is taken from the parents, affected and unaffected siblings and maternal and paternal grandparents (if possible) for genetic analysis.

Clinical information is being gathered and evaluated by Dr. Szatmari's research team at the Offord Centre for Child Studies, Hamilton Health Sciences, Faculty of Health Science, McMaster University. The analysis of the blood is being conducted by Dr. Steven Scherer at the Hospital for Sick Children in Toronto. Dr. M.B. Jones of Pennsylvania State University is a statistical consultant for the study. Dr. Susan Bryson of the IWK Health Centre in Halifax, NS, Dr. Wendy Roberts of The Hospital for Sick Children, Dr. William Mahoney, Dr. Lonnie Zwaigenbaum, and Dr. Jeremy Goldberg of Chedoke-McMaster Hospitals form the diagnostic committee and are also involved with analysis of the clinical data. Dr. L. Tuff of McMaster University supervises the psychometric testing as well being involved in the clinical data analysis. Christina Strawbridge is our psychometrist. Bev DaSilva is our administrative assistant. Kim Gumbley is our blood technician. The study is coordinated by Ann Thompson.

Families participating in the study are kept informed of the study's progress through an annual newsletter which provides an update on the study as well as information and services available to assist families who have a child or children with autism/PDD. The CIHR grant has also provided funding for one conference per year for families with a child or children with autism/PDD. In the past, these conferences have provided an opportunity for the parents to come together and discuss the unique challenges posed by children with autism/PDD.

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**We are currently enrolling families with two or more individuals affected with Autism/PDD (siblings, cousins, or any other extended relative pairs).**

**The principal investigator of the study is Dr. Peter Szatmari  
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