Unraveling the Mystery of Autism:
From Genotyping and Phenotyping to Prospective Identification and Prevention

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Program Overview

Autism and the related pervasive developmental disorders (autism spectrum disorders or ASDs) are characterized by impairments in social interaction, verbal & non-verbal communication and repetitive behaviours. It is a devastating group of conditions, with variable degrees of impairment, affecting between 1/250 and 1/500 individuals. The diagnosis is often difficult to make and there is no specific treatment, although intensive behavioural interventions in early childhood can have a remarkable impact on the development of social skills and language in children who might otherwise not play with other children or even speak legible words. Parents are often at a loss as to how to help their children, particularly since reciprocal interactions are so impaired. The impact on the family can best be understood through the words of families with children with autism:

"We have not been dealing with autism for a chronologically long time; our son is not quite 11 years old, but we already feel a lifetime has been lost" Peter Miles

"As we look back on life with our boys we realize that our issues started many years ago...had our doctor only known more about ASDs it would have been so much easier. We had so many questions for which he had no answers, no encouraging words or helpful tips. He made no suggestions as to who might know what to do or how to help us. He simply patted us on the back and told us to "give them time…they are boys…let them mature…don't compare them to your nieces and nephews". And the clock ticked away…the days…the months …and the years with frustration on all sides."
Victoria & Harry McArthur

Early Intensive Behavioural Intervention (EIBI) is almost like a miracle for many children with ASD: before treatment, there is often no language but only severe behaviour problems, likely because of the inability of these children to communicate their needs and to understand others. With EIBI, 75% of children with autism have language, and improve dramatically in social skills, and stereotypic behaviours decrease. These are the core symptoms of autism, and yet with appropriate intervention – about 20-40 hours per week for two years prior to age 6 – many children are integrated into a normal school system. The toll, however, is high – these children do not have a normal childhood, and it is a very costly program for parents (both in terms of time and money) – especially since government funded programs, that were recently instituted in most provinces, are inadequately funded and there are insufficient trained personnel to carry out the treatment. Moreover, research is needed to assess the effects of continued IBI beyond 6 years, including the effects on older children and adults. In all likelihood, there is benefit of IBI at all ages.

Most researchers believe that the earlier treatment is initiated, the better the outcome. Ideally, one would like to begin treatment, in a naturalistic manner, soon after birth. The question is: how do we identify those infants at risk for developing autism before there are clear symptoms?

PROGRAM OVERVIEW (continued from Page 1)

The ultimate aim of our Research Program is to develop methods enabling the identification of infants at risk for ASD prior to the development of any symptoms and intervening to prevent debilitating aspects of the autistic syndromes.

To do this, we have 4 major research goals:

• **To establish a Research Registry** with ~5000 families providing information on different aspects of ASD enabling subgrouping of families

• **To identify Genes involved in susceptibility to ASDs**, to develop screening methods to identify persons at high risk for ASDs

• **To carry out a Prospective Study of ASDs** to identify the earliest signs of atypical development heralding an ASD, and an **Intervention/Prevention Study** aimed at preventing the development of overt ASD symptoms

• **To undertake an Epidemiological Study of ASDs in Canada**, to determine the incidence and prevalence of these conditions and identify etiologic factors

RESEARCH REGISTRY

Project Leader: Jeanette Holden

Families from all over North America and elsewhere are invited to participate and it is expected that we will recruit approximately 5000 families to help us understand ASDs.

It is clear that not all cases of autism are the same, and that there are likely many subgroups of ASDs, each with specific behavioural and clinical features. The distinction among these subgroups may be subtle, and therefore not easily recognized – except with detailed assessments of a variety of behavioural and physical features. Clearly, if there are 20 different subgroups, each representing 2-10% of cases, a very large number of families need to be assessed to identify common features.

We have therefore established a Research Registry – where families with one or more individuals with an ASD can participate in on-line research projects. The latter are mainly questionnaire-based and are directed at examining several aspects of the ASD-phenotype. Information from a large number of families will help us to understand, for example, whether and how gluten-free diets have been helpful; patterns of sleep disturbance in children with ASD and successful treatments for these problems; extent and nature of gastrointestinal disturbances; social interaction styles; etc

Families from all over North America and elsewhere are invited to participate in this research. We also hope to do genetic studies on these families and will be collecting cheek swab samples to isolate DNA. ***Stay tuned for information on collecting cheek swabs in the very near future.***

Some studies currently on-line or in development:

* Sleep Disorders Survey : deals with issues such as length of sleep, difficult sleep issues, behaviours during sleep or at bedtime

* Gastrointestinal Disorders: questions about gastrointestinal functioning and dietary habits

* Handedness Survey: examines hand preference among individuals with ASD and their families

* Social Subtypes: deals with social interaction subtypes

* Autism Spectrum Quotient: asks about the "broader phenotype" (i.e., having some autistic characteristics) in family members.

IDENTIFYING CULPRIT GENES & DEFINING GENETIC SUBGROUPS

Project Leaders: Jeanette Holden, Maurice Feldman and Suzanne Lewis

PURPOSES: To identify genes important in the etiology of ASDs and to characterize genetic subgroups using a variety of clinical and behavioural phenotyping methods.

IDENTIFYING CULPRIT GENES

Sibling, twin and family studies recognize a genetic etiology for many cases of autism, and the heritability is ~80-90%. We are using four approaches to identify culprit genes in 200 new multiplex families we are recruiting.

1) **DNA Studies:** Two general approaches we are using include:

Genome Scan: Full genome scans can identify chromosome regions with possible candidate genes The new families will be studied to determine whether they show linkage to any of the regions indicated in other studies.

Candidate Gene Testing: This approach involves testing genes that may be involved in some of the behavioural characteristics seen in individuals with ASD. We have used this approach to identify possible culprit genes in 125 of 180 families we currently have samples for, and have identified 10 genes in 5 pathways/biological systems for further study.

2) **Cytogenetics:** Spectral karyotyping (SKY) and telomeric FISH are used to detect small chromosome rearrangements within the chromosomes, as well as at the ends of the chromosomes.

3) **Biochemical Studies:** Levels of various neurotransmitters and amino acids are being measured in blood – for correlations with variations in genes coding for these molecules, or involved in their synthesis.

DEFINING PHENOTYPIC SUBGROUPS

A broad range of clinical and behavioural assessments are being done on the 200 multiplex families recruited through our Regional Teams, to subgroup families with similar phenotypes. Such subgrouping will help to identify the many genes involved in ASD. As a complement, families are being divided according to "genetic subgroups" to identify phenotypic similarities.

Family History: a detailed family history is taken to determine what other conditions are present in different families; previous findings have shown an increased prevalence of conditions such as depression, autoimmune disorders, etc. in *some* families with ASD.

Dysmorphology: Some children/adults with autism seem to resemble one-another, suggesting that there are different "autistic syndromes". Defining these features requires careful and detailed measurements of facial features. Clinical geneticists in our team use standardized anthropometric measurements to look for subtle differences and similarities in families. 2D photos and 3D scanning will complement direct measurements to identify different phenotypic syndromes.

Core Autistic Features: All affected children are assessed using the ADI-R and ADOS, as well as the PDDBI to determine degree of ASD behaviours.

DEFINING PHENOTYPIC SUBGROUPS (continued from Page 3)

Communication: Children with ASD appear to have difficulties with multimodal communication – this will be assessed using specific tests as well as equipment designed to determine what modalities are being used by children with ASD.

Theory of Mind: Children with ASD often have difficulties understanding what another person knows, thinks or feels. This will be assessed in affected children and family members, to determine whether this is part of the "broader phenotype" in some families.

Lying and Deception: Some children with ASD are very poor "liars", and this may reflect different genetic predispositions.

THE INFANTS AT RISK FOR AUTISM (TIARA) PROGRAM

Project Leaders: Maurice Feldman, Becky Ward, Jeanette Holden

Although there is no cure for autism, Early Intensive Behavioural Intervention can dramatically affect language development and enhance social interaction; the earlier intervention is introduced, the better the outcome. Currently, diagnosis can be made by ~12-18 months of age; however, in practice this is rare and most children are only identified between 2-4 years for the more severe forms of ASD, including classical autistic disorder . Milder forms, such as Asperger syndrome, are often not diagnosed until school age or later.

Research to date suggests that the earlier intervention starts, the better the outcome. The challenge: to identify infants at risk before 1 year of age.

PURPOSE: To develop a procedure to identify infants at high risk for developing ASD, together with an intervention protocol that addresses problem behaviours and developmental problems associated with ASD. The expectation is that initiating treatment at a very early age will result in a reduction or elimination of overt symptoms of AD, providing these children with language and social skills that will enable them to interact and be integrated with their peers and others.

Hypothesis: Information on the development of an infant at risk for ASD, combined with family information and genetics, will predict those infants at highest risk for ASD.

Strategy:

Siblings of individuals with ASD have a 6% risk for ASD and a further >20% risk for ASD-symptoms (i.e., significant impairment in verbal *or* non-verbal communication, *or* social interactions, *or* restricted interests). The task is to determine which families constitute this very high risk group. Therefore, we will

1) examine development and monitor duration of concerning behaviours in 400 infants who have an older sibling with ASD and 100 not-at-risk infants from 6 months to 3 years; and 2) determine what familial factors, including genetic, contribute to increased risk for recurrence.

TIARA SCREENING PROGRAM

To be completed on the at-risk and not-at-risk infants**:**

- **Parent Observation Checklist**
- **Optional Journal or Calendar** to track significant events
- **Videotape (instructional video in preparation)** every 3 months to assess:
  * Infant Behavioural Summarized Evaluation and Childhood Autism Rating Scale infant behaviours
  * Still-Face effect
  * Preverbal speech perception
  * Maternal sensitivity & Infant attachment
  * Contingent Responsiveness
  * Hand preference test.
- **Monthly Phone Interview**
- **Optional infant Event Related Potentials** (Kansas – J Hill Karrer)
- **Take photographs:** once a year
- **Parenting Stress Index:** every 6 months (both parents)
- **Diagnostic Assessment:** as needed

Regular monitoring by phone and through submission of the above will help us identify infants who may be developing atypically.

TIARA PREVENTION-INTERVENTION PROGRAM

When infants are identified whose development and behaviour are concerning, they will be randomly assigned to a current practice group or to the TIARA experimental protocol. There are two components to the latter: **promotion and redirection**

The TIARA Program is being designed to **promote** optimal development and **redirect** behaviours. Parents will be provided brief manuals and videotapes that focus on promoting communication, social and play development using natural language and behavioural strategies and which redirect actions to develop positive behaviours.

EPIDEMIOLOGY OF ASDs IN CANADA

Project Director : Hélène Ouellette-Kuntz

Purposes:

•**To establish a National Epidemiologic Database for the Study of Autism in Canada (NEDSAC)** with anonymous information on children with ASD to 14 years of age, in various regions.

•**To estimate the prevalence and incidence of ASDs in Canada.**

•**To examine geographic and/or secular variations in rates.**

The findings will be important for service planning, tracking incidence rates and identifying possible clusters.

Methods:

Anonymous information about cases of ASD is collected from agencies and schools in different regions of Canada, including BC, Alberta, Manitoba, Southeastern Ontario, and PEI (see map – dark blue shaded areas are currently included in catchment area).

EPIDEMIOLOGY OF ASDs IN CANADA (continued from Page 5)

First Five Data Collection Regions:

- **Southeastern Ontario:** The NEDSAC coordinating center is at Queen's University; the catchment area is the surrounding 6 counties.
- **PEI:** within the Department of Health and Social Services.
- **Manitoba:** at St. Amant Centre, partnering with Children's Special Services Program (Dept. Family Services).
- **Alberta:** at the University of Calgary/Alberta Children's Hospital; catchment area is the region served by the Calgary Regional Health Authority.
- **BC:** at the University of British Columbia/BC Children's & Women's Hospital; surveying all of BC and the Yukon.

Canadian Pediatrics Surveillance Program (CPSP) Initiative:

- LOI (approved in principle) for incidence study of ASDs <48 months of age.
- Reporting via pediatricians and child psychiatrists.
- Determine frequency and nature of regressive autism, as well as identify co-morbidities.
- Areas showing significant variations in reports of ASDs will be further investigated.

MODEL SYSTEMS

Cell Model System to Assess Gene Variations

Thomas A. Grigliatti

Specific Aims:

To determine whether variations in genes found associated with ASD affect the function of the biochemical pathways in which they play a key role.

Method: Construct insect cell lines with human genes in the biochemical pathways, comparing function using different gene variants.

A Mouse Model for Autism

Elizabeth M. Simpson

Hypothesis: Mouse genetic models displaying autistic behavioural phenotypes can be developed and used to reveal the mechanisms underlying ASD.

Specific Aims:

* Develop tests to assess ASD phenotype
* Do QTL mapping for behavioural phenotypes
* Assess ASD phenotype in transgenic & knockout mice bred to test the "Maternal Effect Model"

PARENT ADVISORY GROUP

Group Composition

•Co-Chaired by Dr. Becky Ward and Anita Acheson

•Group meets once every two months

•12 parents (representing a full range of ASDs and ages) from the Ottawa area and other regions of Ontario and Quebec; one professional; one adult with ASD

•Most members are very well versed in current autism research. Majority of parents have done extensive home programming to supplement available services. Most have tried multiple treatment strategies.

•Range of additional expertise among parents: i.e. nurse, chemist, Master's student, computer scientist, etc.

Parents offer the unique opportunity of sharing their direct experiences with autism; This group provides a forum for parents and researchers to share their respective expertise

Activities

•Review draft questionnaires and pamphlets for feedback

•Review current ASD-CARC research projects

•Discuss ideas for ASD research

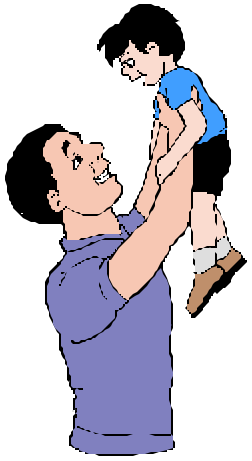
•Discuss recruitment ideas and strategies

•Suggest means for improving parent participation in studies and on web-site

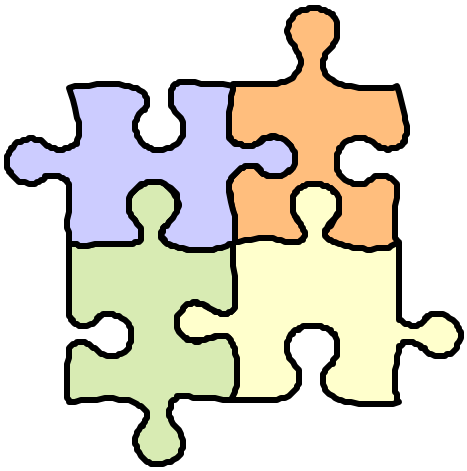
•Review parent videotapes of children and discuss coding criteria

•Discuss possible "subtyping" in autism

•Created private e-mail group for sharing information between meetings



ANNUAL ASD/CARC MEETING



2nd annual Team and Project Leaders Meeting

February 8-10, 2002

This annual meeting allows us to review our progress and make plans for new studies in the next years.

ASD/CARC

(Autism Spectrum Disorders Canadian American Research Consortium)

TEAM MEMBERS

Eastern Ontario (Kingston) Regional Team
Jeanette J.A. Holden, PhD - ASD/CARC Program Director
Maurice Feldman, PhD - Regional Team Co-leader
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Kevin Munhall, PhD - Communication
Doug Munoz, PhD - Eyetracking
Kevin Parker, PhD - Statistics
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Graeme Smith, MD, PhD - Clinical Phenotyping
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Deborah Dewey, PhD - Regional Team Co-Leader
Debra Busic - Regional Project Coordinator
Suzanne Hala, Ph.D - Behavioural Phenotyping

Major Funding By:

CIHR-IHRT Program Grant #RT-43820

Ontario Mental Health Foundation Grant

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