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Health Research



Being Proactive for Children with Autism



***Autism SPECTRUM Interdisciplinary
REsearch (ASPIRE) Program;***

www.autismresearch.ca



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Autism Spectrum
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Aspiring to Reduce Health Vulnerabilities Through Improved Recognition and Management of The Autism Spectrum Disorders (ASDs)



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CHILD
& FAMILY
RESEARCH
INSTITUTE





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The Impact of ASDs

★ “When autism first grabbed hold of my life, I was unprepared, overwhelmed and frightened. I looked at all the healthy, perfect children of the world and felt cheated, depressed, angry and isolated as a parent. I cried. I blamed. I pretended that everything would be just fine. But, in reality, I knew my life was altered, never to be the same again.”

★ From A Mother’s Eyes. A View of Autism (Coppola)

aspire

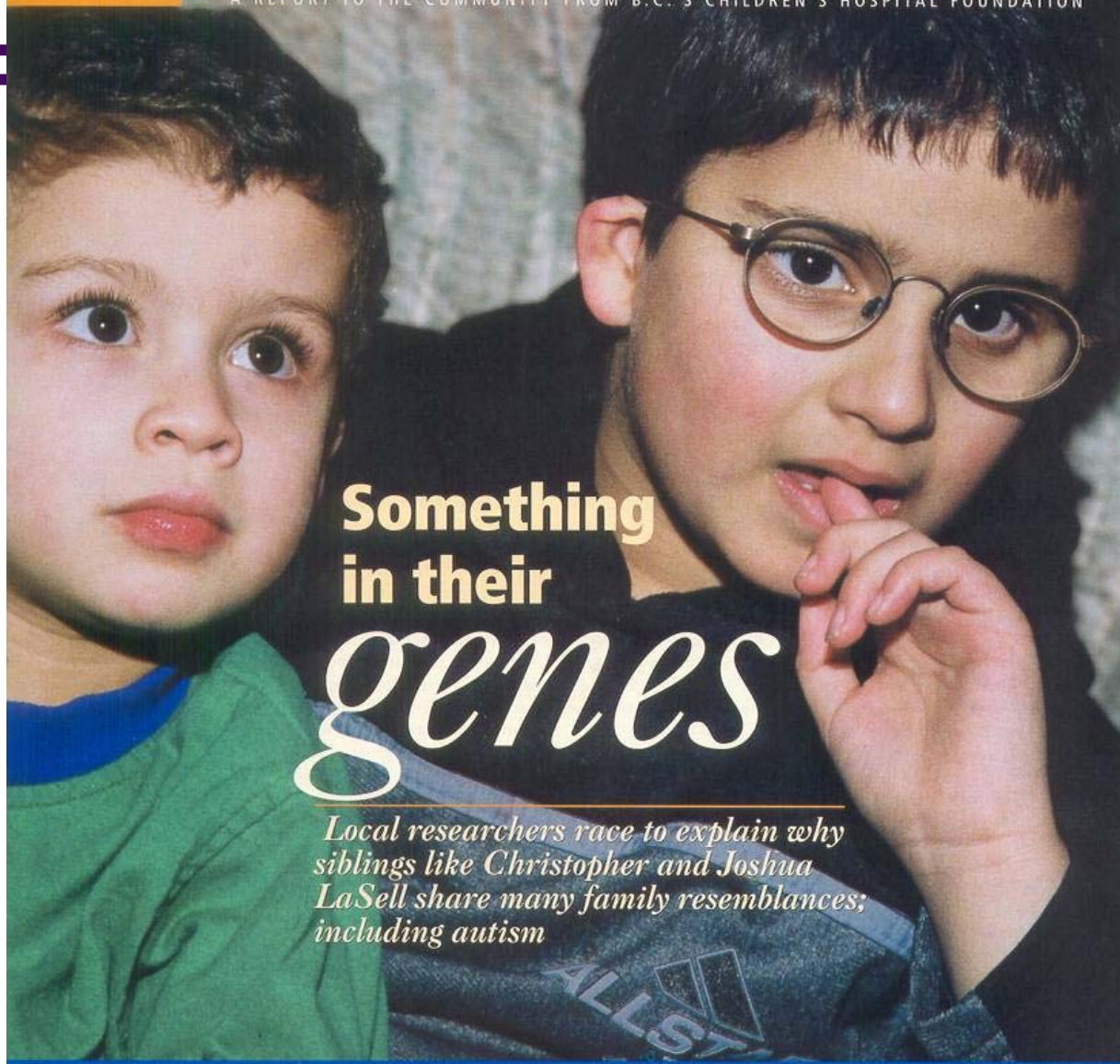
SPRING 2003



speaking of children

A REPORT TO THE COMMUNITY FROM B.C.'S CHILDREN'S HOSPITAL FOUNDATION

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Something in their *genes*

Local researchers race to explain why siblings like Christopher and Joshua LaSell share many family resemblances; including autism



Public Health Importance of Autism

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The Autism Spectrum Disorders

- **Autistic disorder**- due to a triad of deficits in:
 - (1) social interaction
 - (2) communication
 - (3) restricted & stereotypic behaviors
- **Pervasive developmental disorder not otherwise specified**

(PDD-NOS) autistic behavior not fulfilling the criteria of other disorders on the spectrum
- **Asperger's syndrome** – nonretarded, clumsy children with normal speech, deficient sociability and narrow range of interests

The Spectrum of Autism

- ★ Presents with a variable spectrum of severity in many different forms
- ★ The diagnosis is given when an individual displays a number of characteristic behaviors

The Incidence of Autism

- ★ 1/2000 – 1/2500 20 years ago
- ★ 1/1000 10 years ago
- ★ 1/160-1/250 now!
- ★ Male: female ratio = 4:1
- ★ No racial, ethnic, social predisposition



Incidence of ASDs

Autism Society of Canada

- ★ ASC - ↑ frequency of 150% over the last 5 years
- ★ 50-70% have co-morbid intellectual disability (ID).
- ★ ASDs are the most common childhood developmental disorder.
- ★ In Canada there are an estimated 195,000 persons living with an ASD.
- ★ ↑ of 3000/year

Incidence of ASDs

- ★ These are life-long disabilities with an onset of symptoms in early childhood.
- ★ Often, affected children are not diagnosed until they are 3 years of age or older, despite
- ★ Indications reveal that the earlier intervention is initiated, the better the outcome.

Early Diagnosis and Autism

Research efforts must be geared toward developing **earlier diagnostic criteria** that identify children at risk in infancy - for maximal benefit of ABA

Genetics and Autism

- ★ **ASDs are highly genetic** – evidence from sibling, twin & family studies
- ★ **Recurrence Risk:**
 - 6-10% Autistic Disorder
 - 25 - 30% broader phenotype

Genetics and Autism

- ★ **Increased Risk to Siblings**

- ★ **Twin Studies**

 - **Concordance rates**

 - **Monozygotic - 92%**

 - **Dizygotic - 10%**

ASDs are heterogeneous

The heterogeneity within the autism diagnosis (based on variable behavioral indices) obscures the genetic basis of the disorder and impedes our ability to develop effective treatments.



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Finding Genes for ASDs

- ★ Because ASDs are very heterogeneous – *We need methods of separating individuals into subgroups based on behaviour and other discrete clinical findings.*



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Relevance of Genetics

Advances in **genetics and clinical phenotyping ASD** are essential for more accurate and early diagnosis, prognosis, prevention and the provision and timing of “best-fit” services.



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ASPIRE TEAM

- ★ **CIHR, MSFHR, CFRI-funded** –
Interdisciplinary Health Research Team
- ★ **> 60** clinician and basic science
investigators and parent advisory
committee
- ★ **Goal:** to develop methods for very early
identification of children at risk



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ASPIRE Action Plan

★ Genetics Study

- Research Registry - online research
- Repository DNA from families with ASD
- Genetic Subgrouping - Genomic Microarray, Molecular Testing & Comprehensive Clinical Assessment Protocol
 - Medical
 - Behavioral
 - Psychometric
 - Morphologic

Complex Genetic Etiology for ASDs

- ★ ASDs have a complex genetic etiology involving multiple genes and environmental factors
- ★ Alleles (normal gene variants in the population) may have subtle/no phenotypic effects;
- ★ In combination, they lead to the extreme phenotype of AD
- ★ Different combinations of alleles might produce different phenotypes

Co-Morbidities Provide Clues Toward ASD Cause

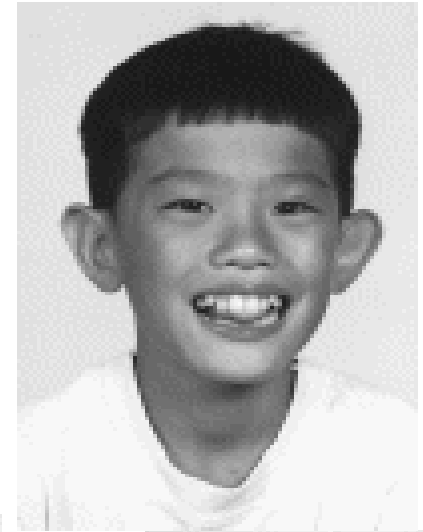
- 15-37% of cases co-occur with another co-morbid medical disorder (epilepsy (30%), ID (70%), psychiatric illness, autoimmune disorders most common)

Known Genetic Subtypes of the ASDs

An autism spectrum disorder co-occurs with a known genetic (chromosomal, single gene or syndromic) disorder in up to 14% of cases

Known Genetic Subtypes of the ASDs

Fragile X
syndrome
(FXS) (30%
on the ASD
spectrum;
FXS is seen in
7-8% of ASD
populations)



Known Genetic Subtypes of the ASDs

Untreated
Phenylketonuria
(PKU) (30% with
ASD)



Known Genetic Subtypes of the ASDs

Most Common Genetic Co-Morbidities

Fragile X syndrome (30% on the ASD spectrum; FXS is seen in 7-8% of ASD populations)

Untreated Phenylketonuria (PKU) (30% with ASD features)

Tuberous sclerosis (25% have an ASD)

Mitochondrial Dysfunction (up to 7%)

Down Syndrome (2% of ASD cases; 5-7% prevalence of ASD in DS cases)

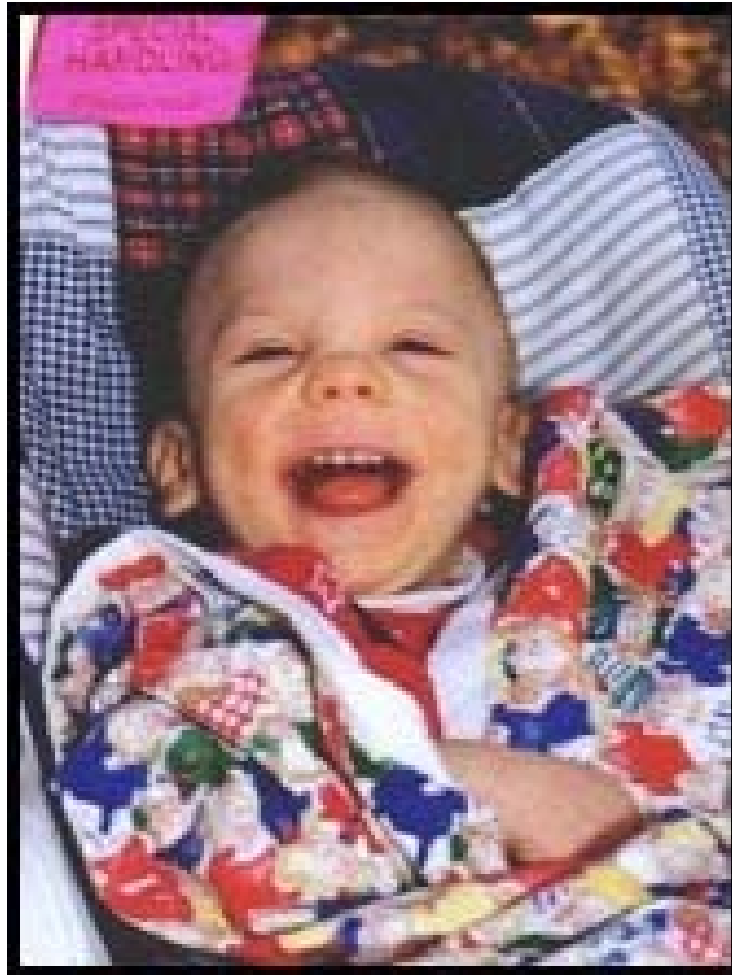
15q11-13 duplications (1-4% ASD cases)

Known Genetic Syndromes and the ASDs

- Smith-Magenis
- Angelman syndrome
- 22q13 deletion
- ARX mutations
- PTEN mutations
- Adenylsuccinate lyase deficiency
- San Filippo syndrome
- Aarskog syndrome
- Marfan syndrome
- Hypomelanosis of Ito
- Joubert syndrome
- Moebius syndrome
- CHARGE syndrome
- Smith-Lemli-Opitz syndrome
- Cornelia De Lange syndrome
- Soto syndrome
- Cohen syndrome
- Williams syndrome

Other Syndromes & ASD

Smith-Lemli-Opitz Syndrome



Other Syndromes & ASD

Cornelia de Lange Syndrome



Other Syndromes & ASD

Sotos Syndrome



Other Syndromes & ASD

Williams-Beuren Syndrome

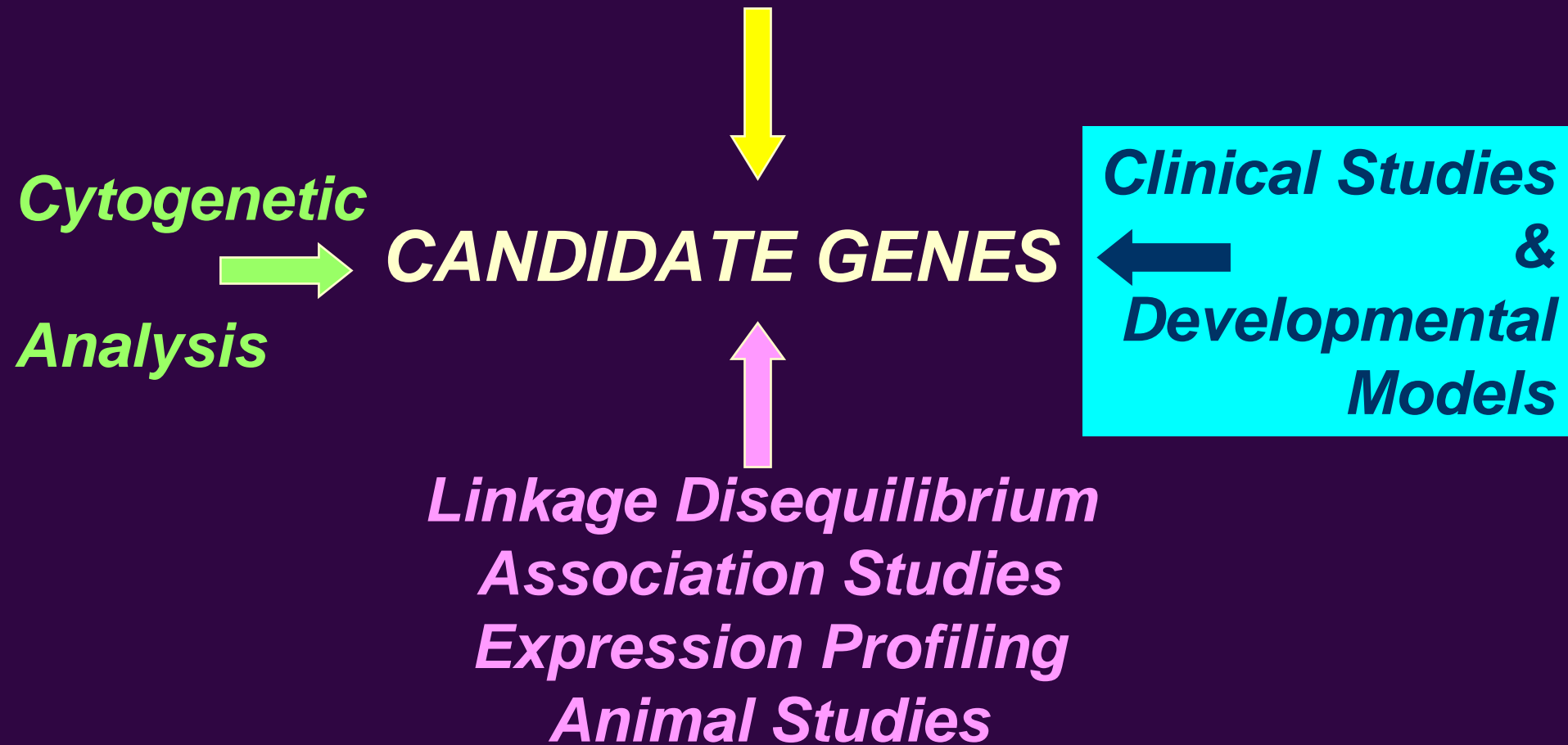


Clinical Phenotyping

Novel instruments beyond behavioural indices are needed to define **genetically homogeneous subgroups** and determine if specific clinical profiles are associated with specific genetic profiles

Strategies for Identifying Autism Genes

Whole Genome Screens



ASD Dysmorphology

In ASD, minor malformations are found:

- hypertelorism
- syndactyly of the toes
- anomalies of the mouth and ears
- abnormal ear shape/position
- macrocephaly.
- May serve as biomarkers to separate subsets of subjects for genetic studies

Clinical Studies: Dysmorphology

- ★ Can we find some shared physical characteristics among the families in each genetic subgroup
- **AIM:** → Define phenotypes associated with specific genetic SUBTYPES
- Most phenotyping studies have focussed on cognition and core behavioural diagnostic symptoms only

Value of a Clinical Morphology Examination in Autism

★ Children with autism and abnormal features on physical examination were 10-fold more likely to have an identifiable genetic condition and were twice as likely to have structurally abnormal brain MRIs

Value of a Clinical Morphology Examination in Autism

- 20% of children with autism clearly have an abnormal physical phenotype
- In addition, up to 14% are diagnosed with a genetic syndrome associated with autism (dup 15q11, 22q11 or 22q13 deletion syndrome, Sotos, Tuberous sclerosis, karyotypic anomaly)

Value of a Clinical Morphology Examination in Autism

★ Phenotypically normal vs abnormal subgroups of children with autism (essential vs. complex) are causally different and may serve to identify underlying autism susceptibility genes

The quest for genetically predictive biomarkers for the ASDs

- For all outcome measures, individuals with complex autism do less well, being twice as likely to have

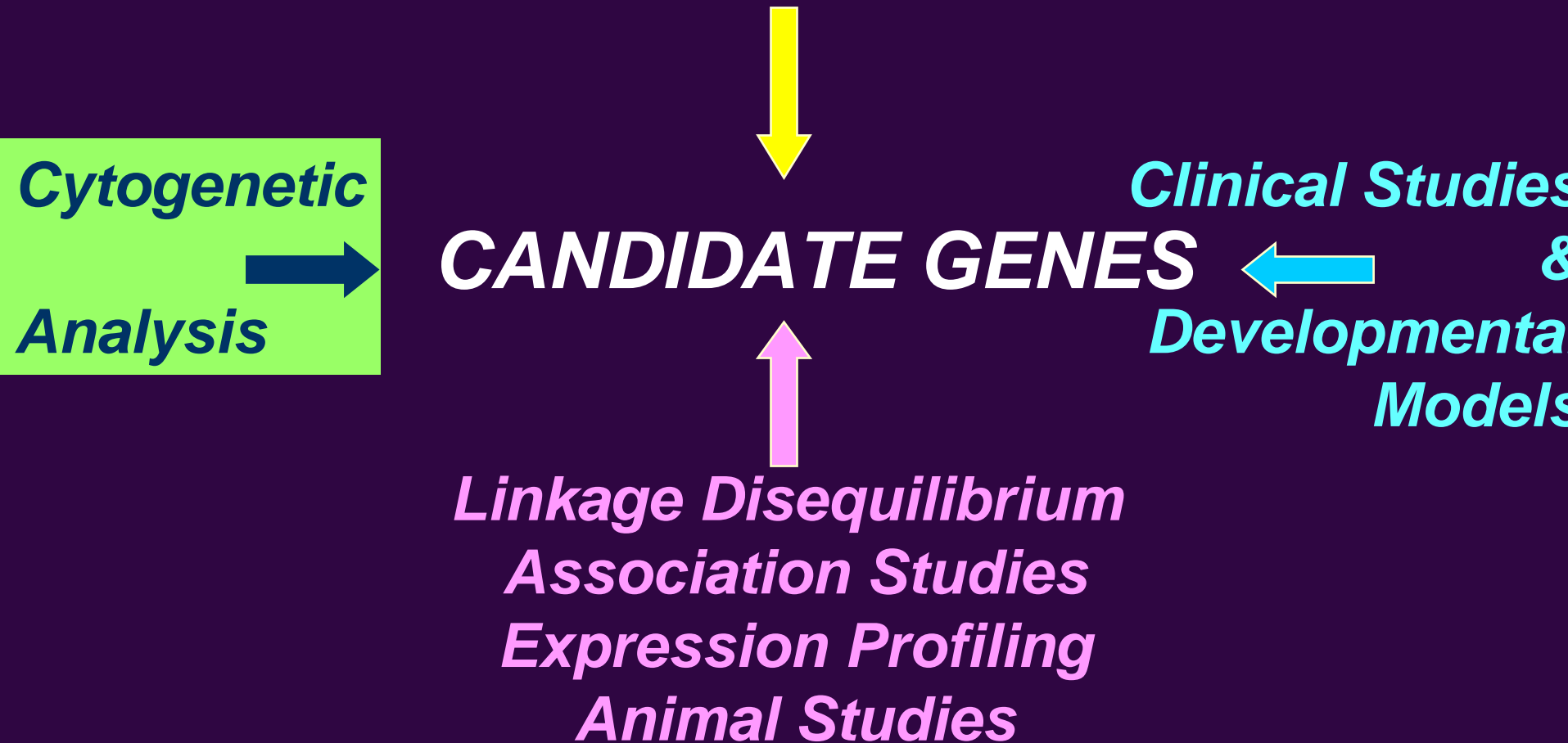
- IQ/DQ scores < 55
- Seizures
- Abnormal brain structure

Dysmorphology - 86% positive predictive value of poor outcome

Microcephaly – 100% PPV of a poor outcome

Strategies for Identifying Autism Genes

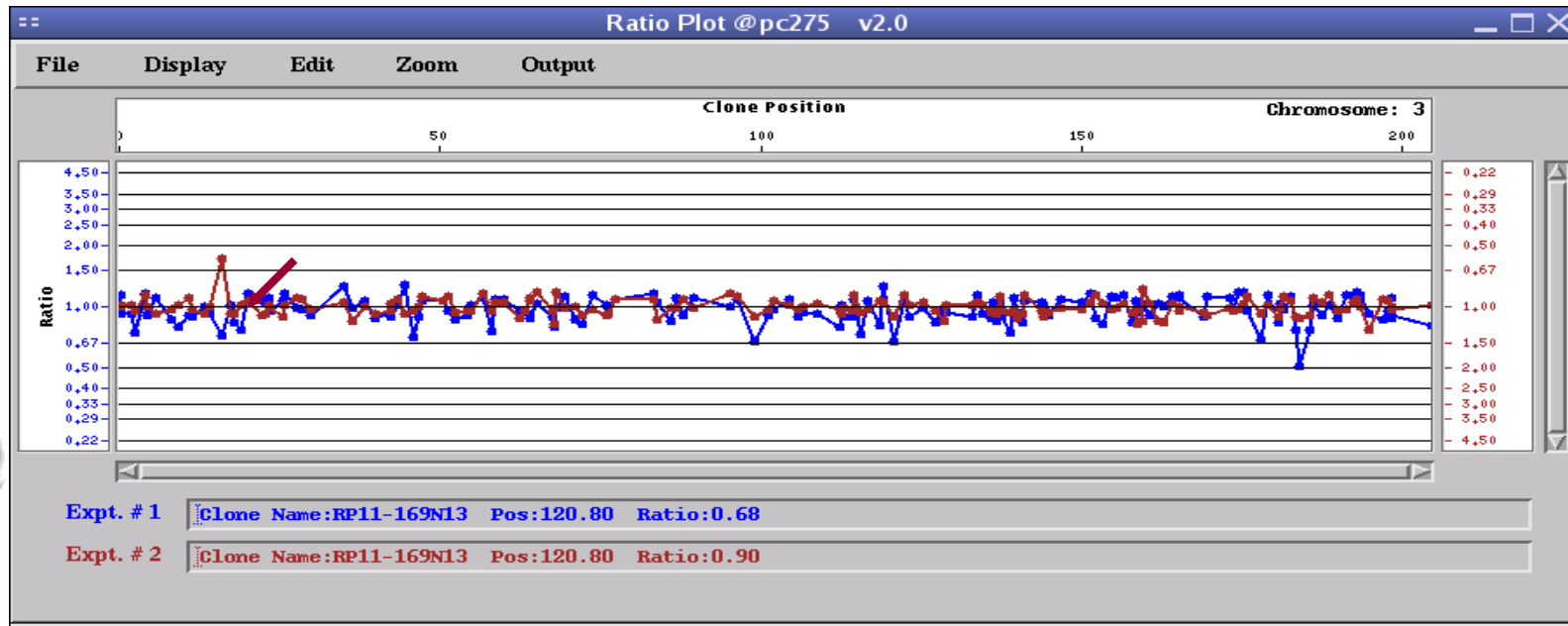
Whole Genome Screens





Screening for sub-microscopic chromosomal abnormalities

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**Microarray-Comparative Genomic
Hybridization (Array-CGH) 1 Mb resolution**



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Microarray Rationale

The reported estimates of **the rate of chromosome anomalies in autism range from 5-48%**, depending on whether subjects with cognitive delay and/or physical anomalies are included.



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Microarray Rationale

- ★ Chromosomal anomalies may be relatively common and clinically important markers for identifying underlying causes of, and susceptibility loci for ASDs.



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Autism, CGH-arrays and Molecular Assessments of Microdeletions & Microduplications

By including individuals with **dysmorphic features and ID** the likelihood of identifying submicroscopic changes and related ASD culprit genes may be higher



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Study Design

ADI-R Diagnosis of Autism

Initial Clinical Investigation

1 Clinical & Dysmorphology Assessments

- ✧ Prenatal birth and medical histories
- ✧ Family history
- ✧ Physical exam
- ✧ Anthropometry exam
- ✧ 2-D imaging
- ✧ 3-D imaging (in some cases)

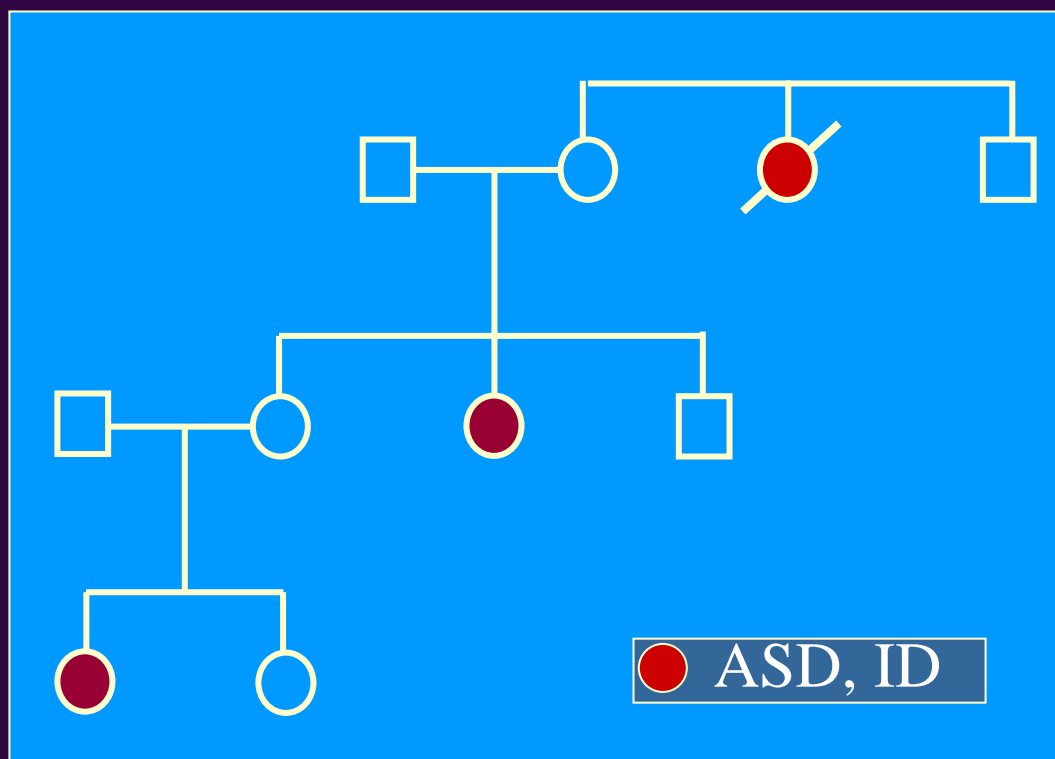
2 Cytogenetic Analysis

- ✧ Karyotype
- ✧ Fragile X
- ✧ Dup15q11-q13
- ✧ Del 22q11-q13
- ✧ Subtelomeric FISH
- ✧ **Microarray CGH**

Case Study

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★ 3 generation family with history of autism, and ID.





Proband

7.5 years

- > Diagnosed with high functioning autism at age 6
 - > Mild intellectual disability (ID)
 - > Normal Karyotype, 46, XX at 500-550 band level resolution (BLR)
-

- > Height, weight and head circumference at the 75th %
- > Down-slanting palpebral fissures
- > Prominent supraorbital ridges with deep set eyes
- > Broad and high nasal root and bridge
- > High arched palate and pointed chin



***The proband's
maternal aunt***

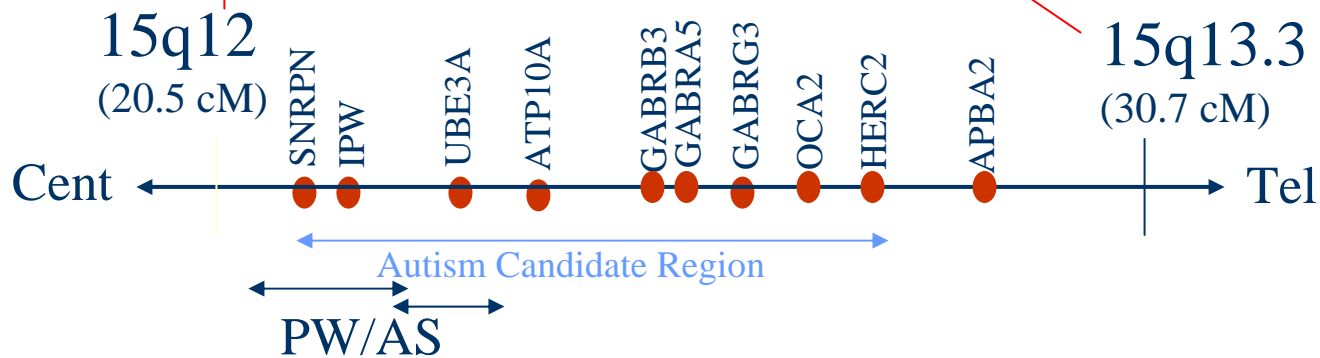
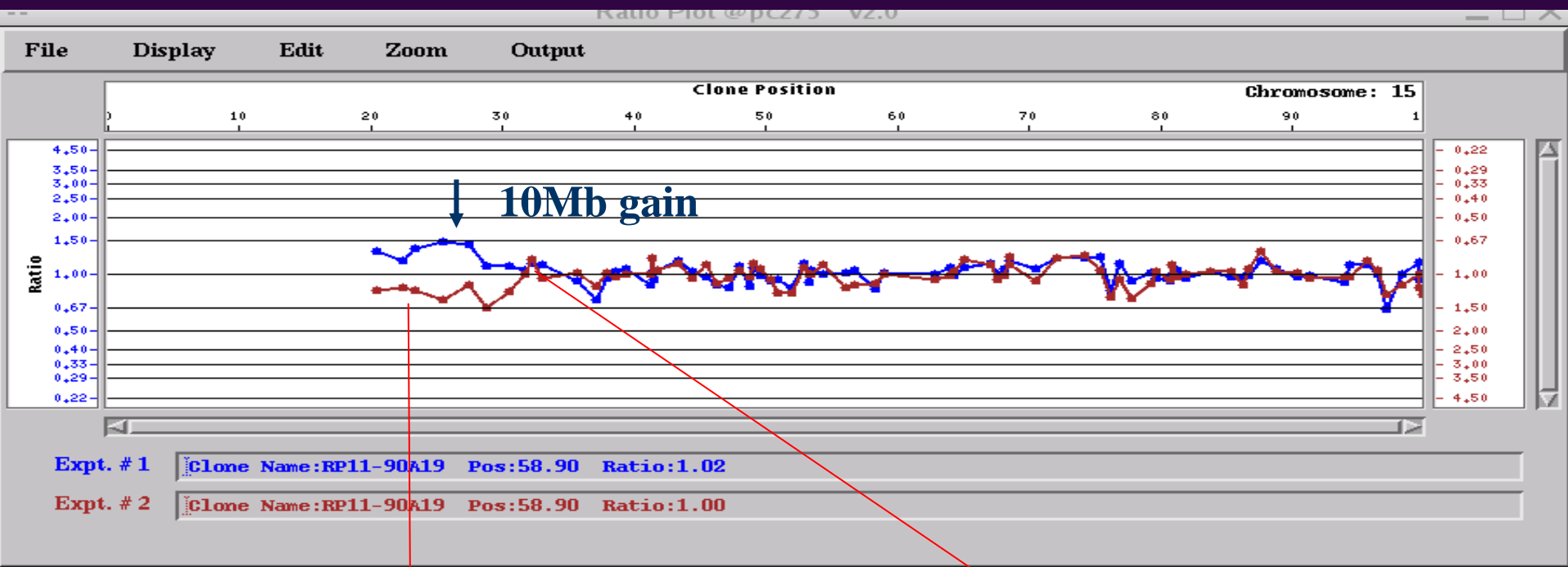


38 years

- > Diagnosed with an autism spectrum disorder at age 28
- > IQ estimated at 35-50 at age 5
- Seizure disorder
- > Normal Karyotype 46,XX at 500-550 BLR

-
- > Height at 5th%, weight at the 50th % and OFC at the 25-50th%
 - > Broad and high nasal root
 - > Down-slanting palpebral fissures and coarse facial features
 - > mandibular hypoplasia with retrognathia and pointed chin

Array CGH Findings

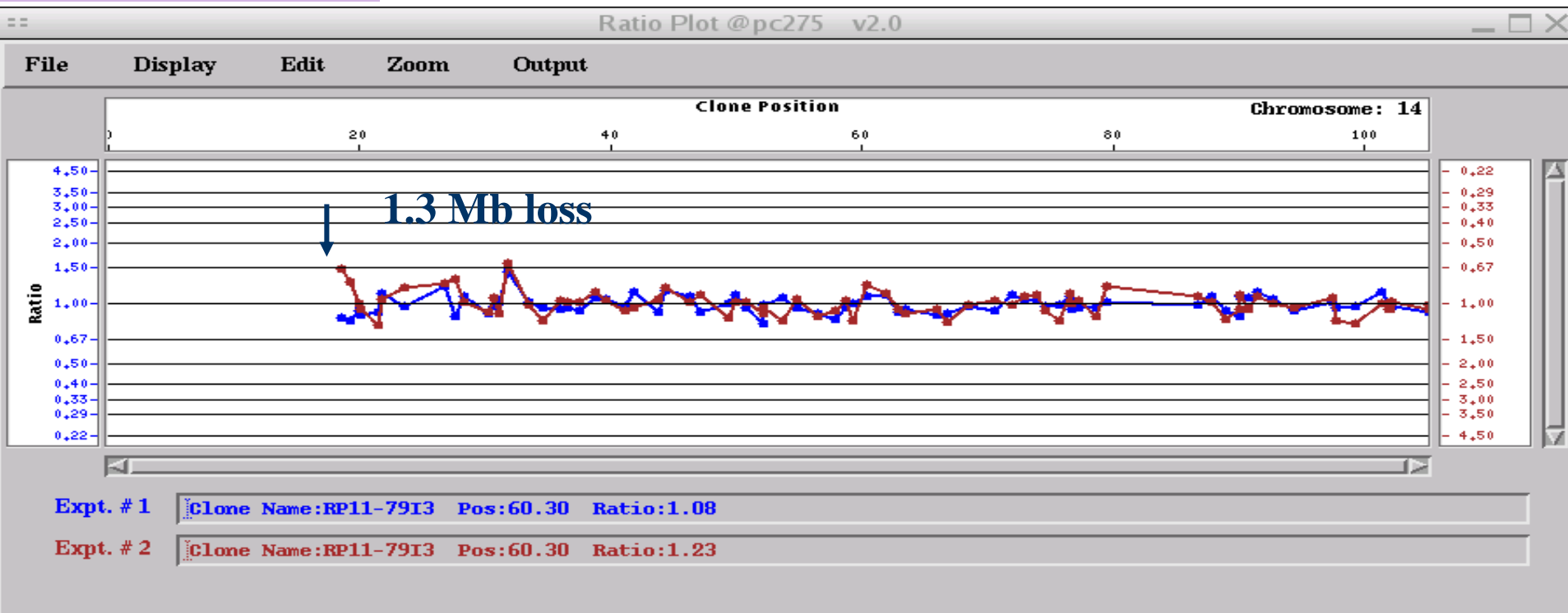


7 clone gain of proximal 15q including the PW/AS critical region



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Array CGH Findings



2 clone loss of proximal 14q corresponding to
14q11.2



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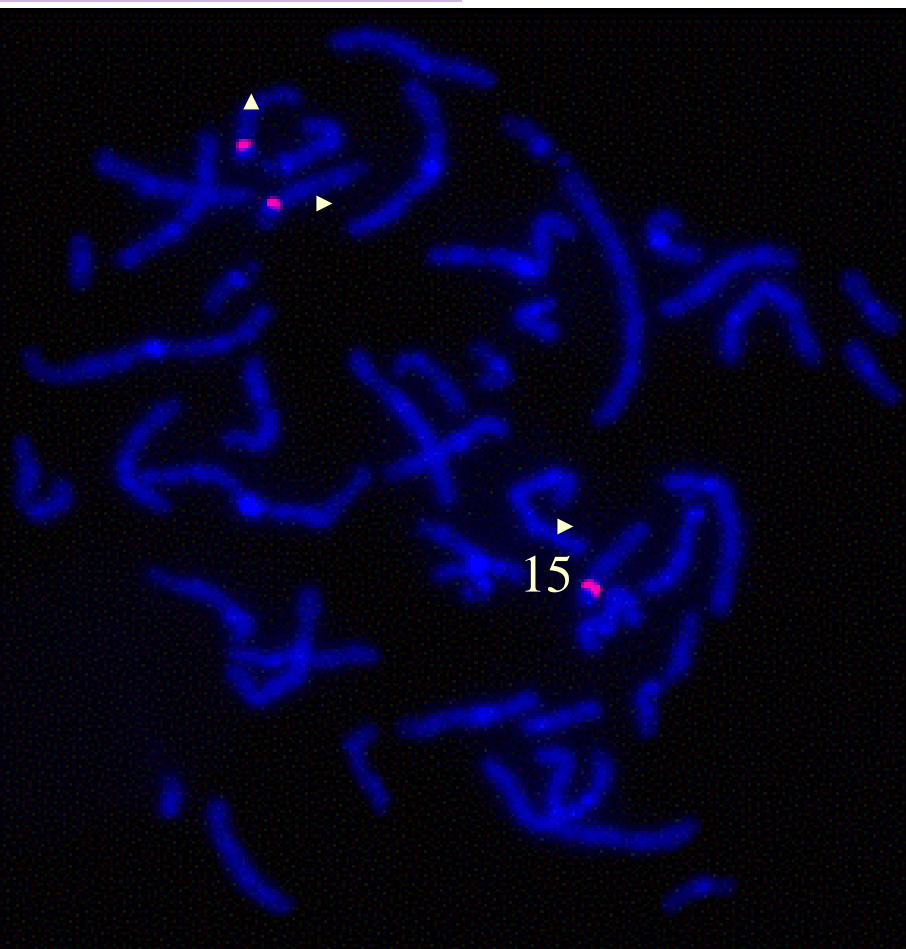
Expectations Based on Array Findings

- 1) Gain of proximal 15q is due to an interstitial duplication seen in 1-4% of cases of ASDs
- 2) Loss of 14q is due to a pericentromeric polymorphism

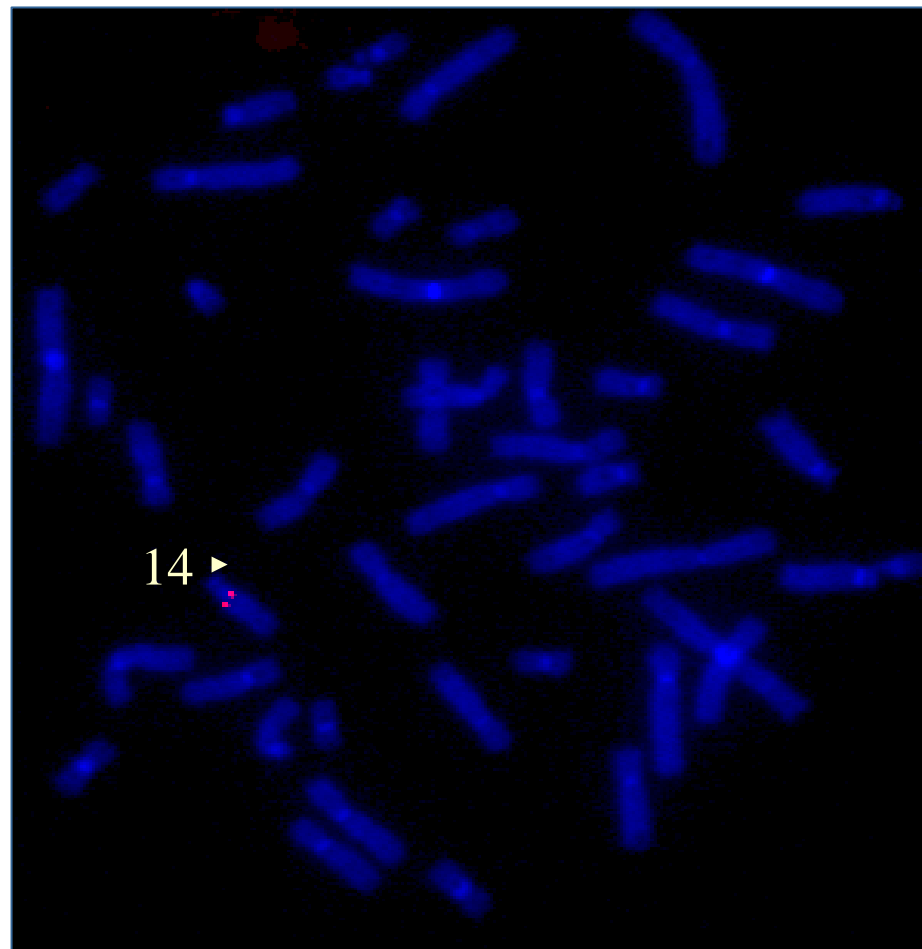


FISH Confirmation in Proband

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Chromosome 15 gain



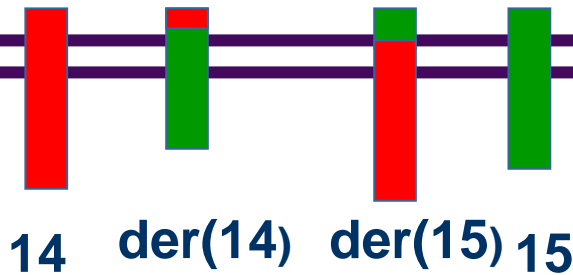
Chromosome 14 loss



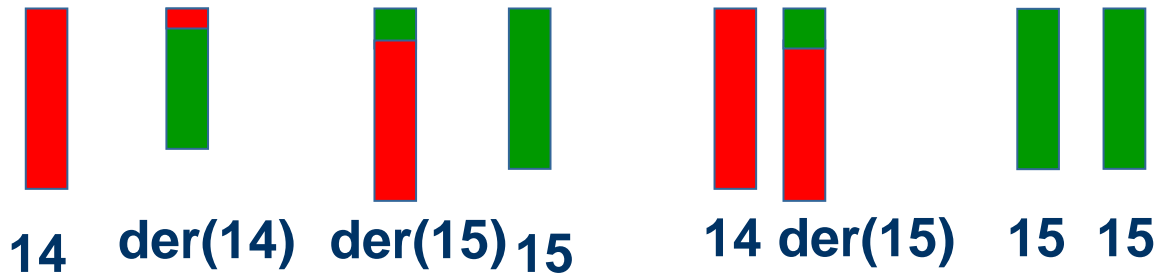
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Proposed Mechanism for the Gain of 15q and Loss of 14q

**Grandmother
(Balanced t(14;15) carrier)**

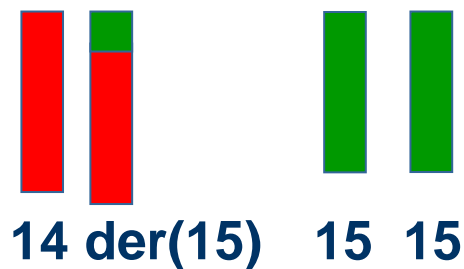


**Mother
(Translocation carrier)**



Maternal Aunt (autism)

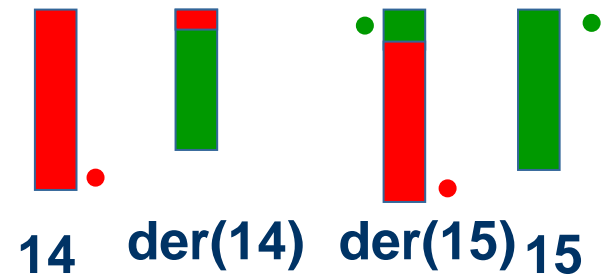
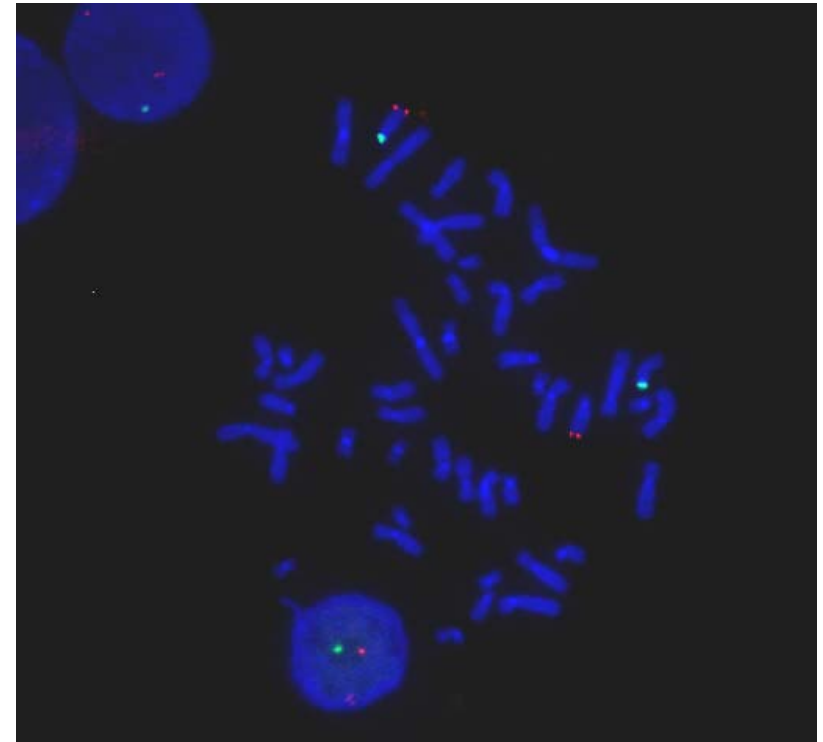
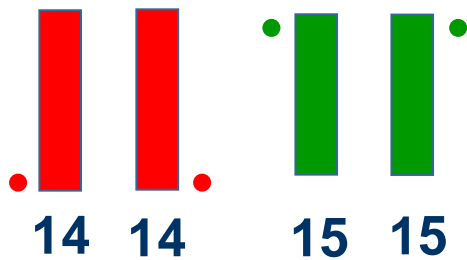
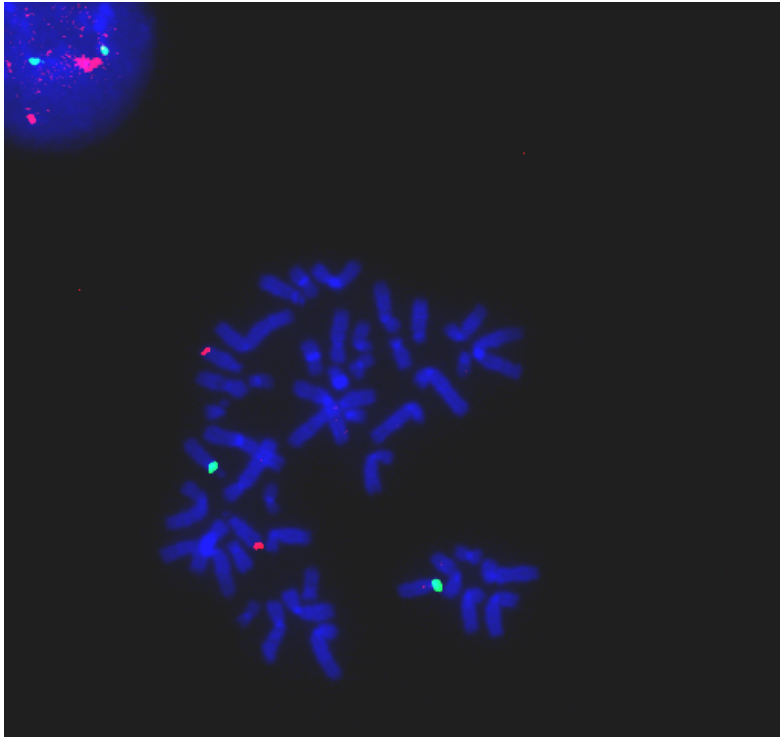
**Proband
(autism)**





Confirmation of Balanced Translocation in the Carriers

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Case Study Conclusions

- ★ Report of a novel mechanism leading to recurrence of proximal 15q gain and autism that would otherwise have gone unrecognized from routine clinical testing.
- ★ Proximal 15q gain may occur as a result of cryptic balanced translocations



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Case Study Conclusions

- ✧ **Array-CGH** is an important tool for revealing cryptic submicroscopic chromosomal changes that may help identify the underlying etiology of autism and ID.
- ✧ **Clinical profiling (behavioural AND physical)** is a crucial approach when searching for autism susceptibility genes.



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ASD-Array Long-term Objectives

- ❖ Description of New ASD Syndromes and Culprit Genes
- ❖ Screening of larger ASD populations for recurrence to determine clinical sequelae relevant to providing improved anticipatory care and “best fit” health and educational services across the lifespan



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How Society Needs to Respond...

Need to Support:

- ★ Evidence-based research to improve
 - Early diagnosis
 - Effective treatments
 - Adequate family supports
 - The condition of autism through understanding it's causes, how and why it manifests and what treatments work and to whom are they best suited



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How Society Needs to Respond...

- ★ **Need to Support:**
- ★ The building of capacity in ASD Research
- ★ Opportunities for Multidisciplinary Networking in ASD Research
- ★ Opportunities to Increase Training Capacity of Future Researchers and Professionals Skilled in the Provision of ASD Services



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