Unraveling the *GENE*esis of Autism Spectrum Disorders (ASD)

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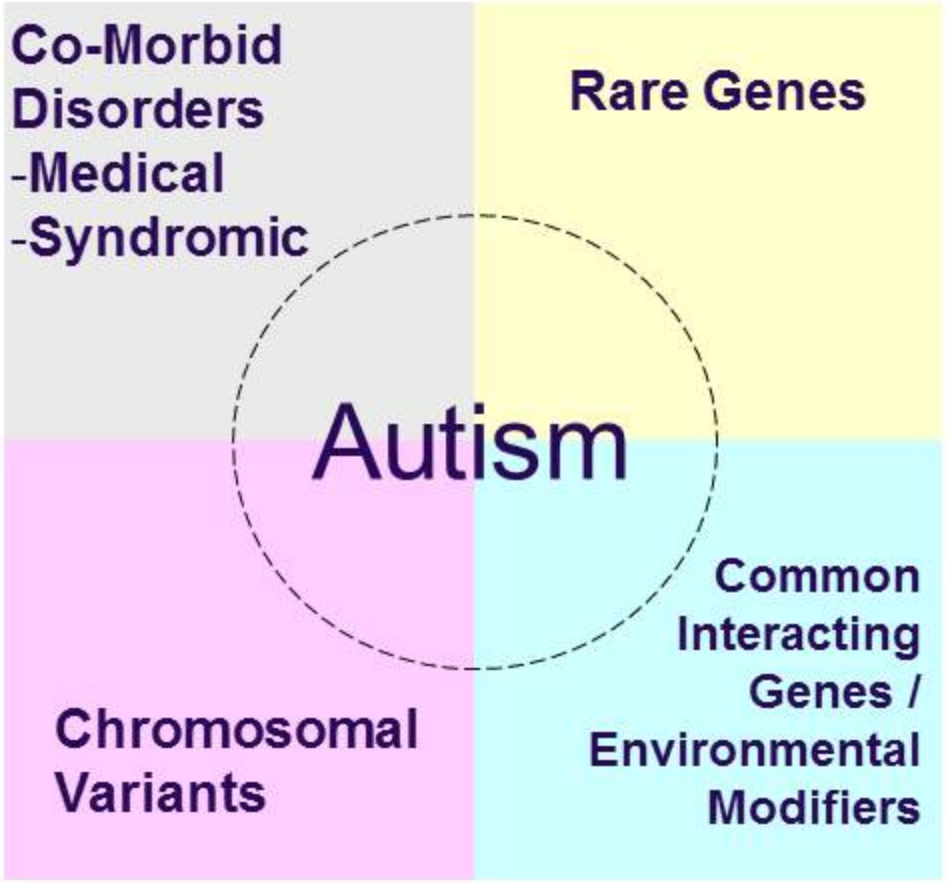
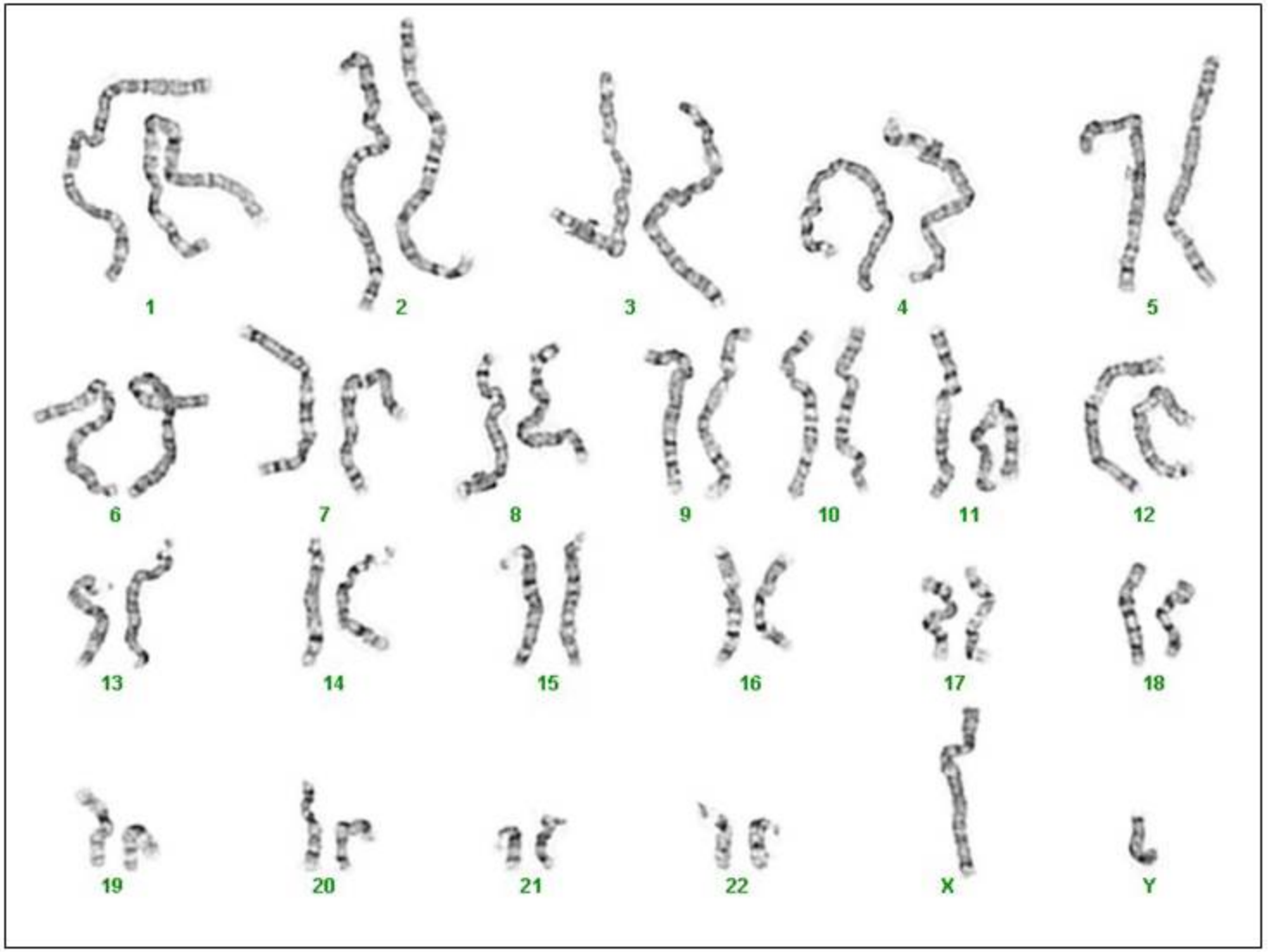
ASD Genetics



ASD Genetics

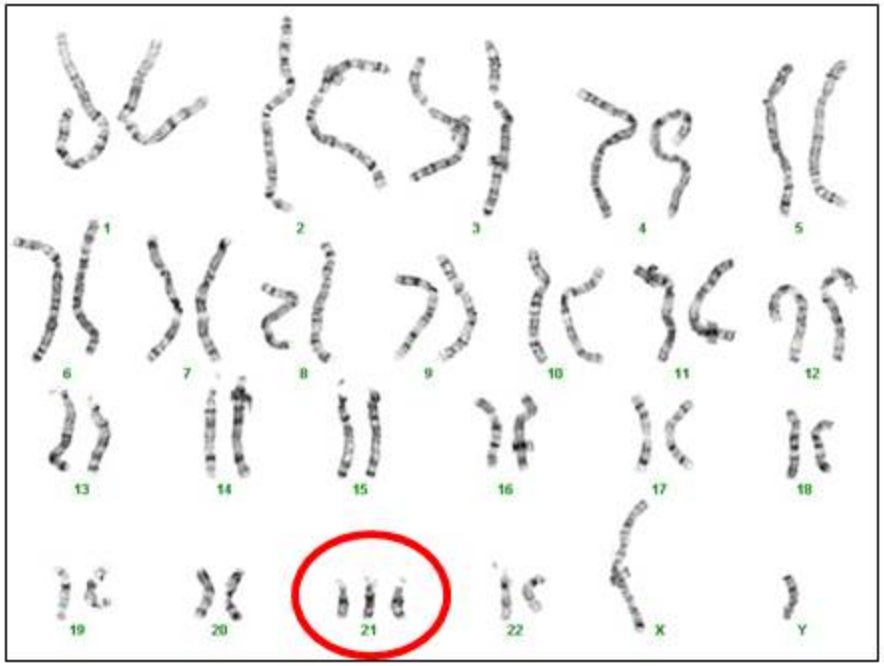
Chromosomal: **Peripheral blood karyotype**	Cytogenetic changes are one of the most frequently identified causes of autism with a diagnostic yield of between 4-28% abnormality rate in individuals with ASDs depending on co-existing clinical features (i.e; ID)

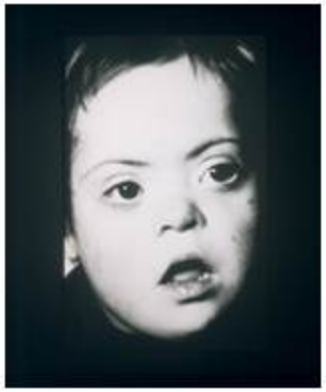
Cytogenetic Analysis



Cytogenetic Analysis

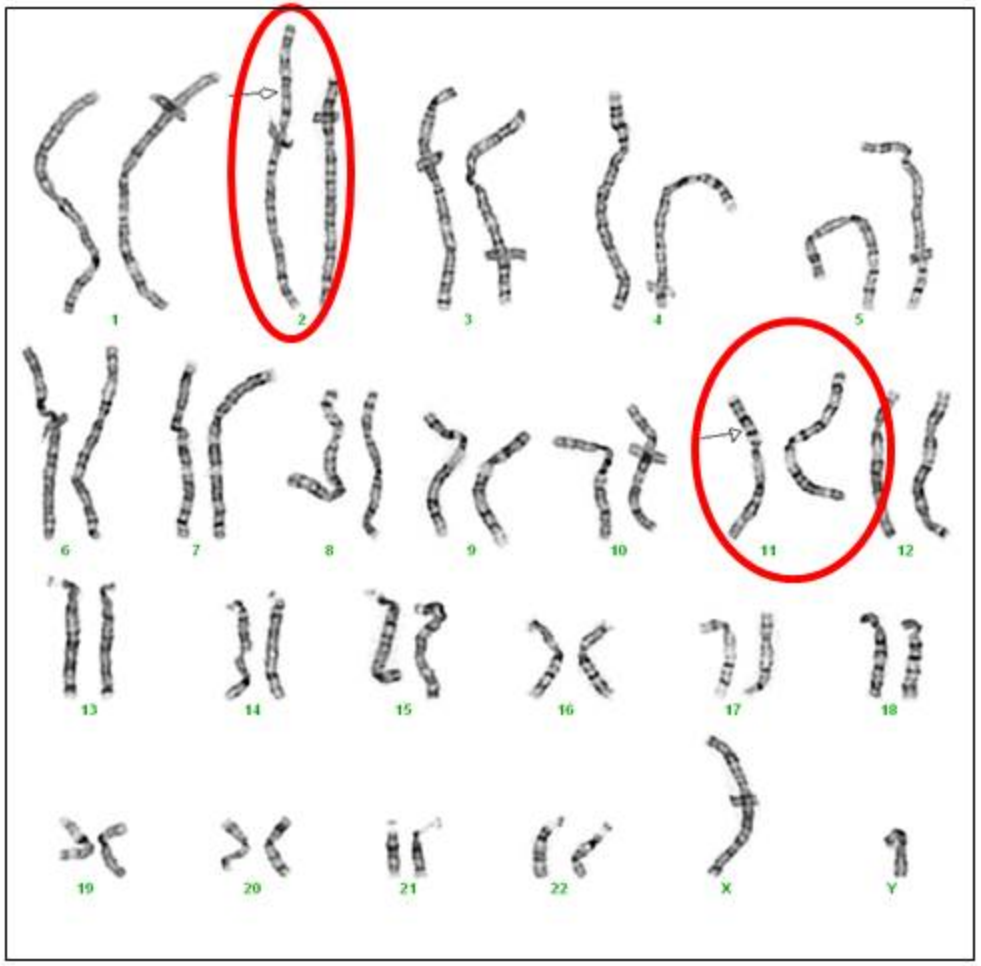
Most common whole chromosome ***numerical anomaly*** with ASDs is Trisomy 21 (Down Syndrome)





Cytogenetic Analysis

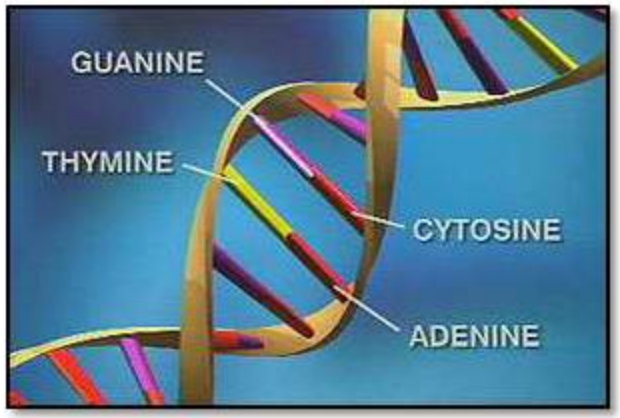
- **Structural anomalies**
- **e.g., translocations**
- **t(2;11)(p13.3;p13)**
- **Breakpoint location is important –may disrupt one or more genes linked with ASDs**



Submicroscopic anomalies

- **Small abnormalities may not be seen even with high band level resolution -> FISH**

- **FISH: Fluorescence in situ Hybridization**

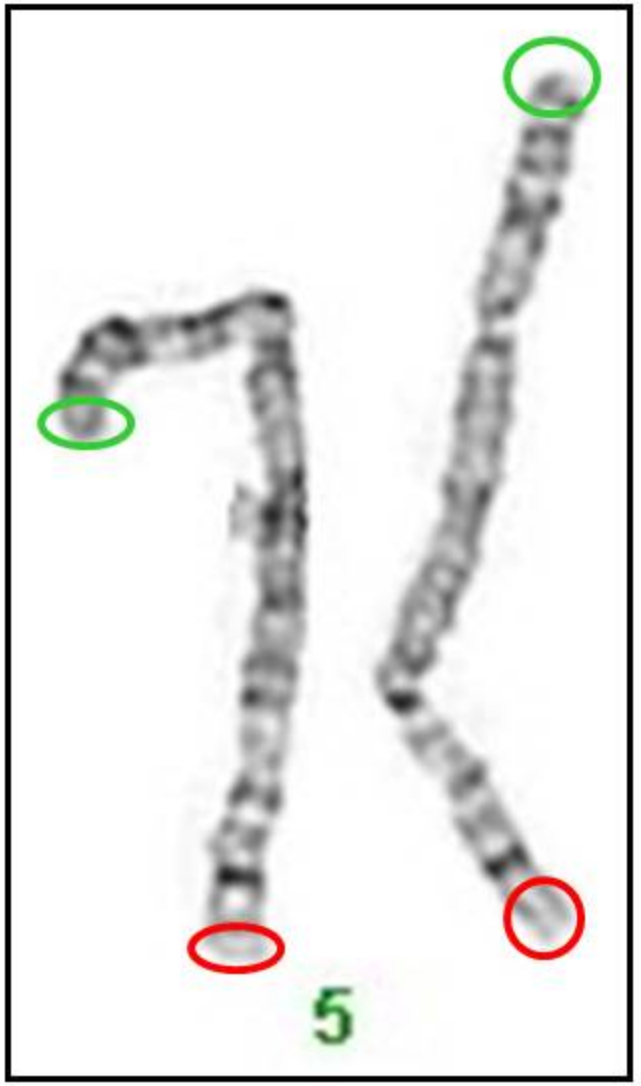


Subtelomeric FISH

Gene rich ends = telomeres

50% of all structural anomalies involve the telomeres

3-6% of individuals with ID reported to have a subtelomeric abnormality

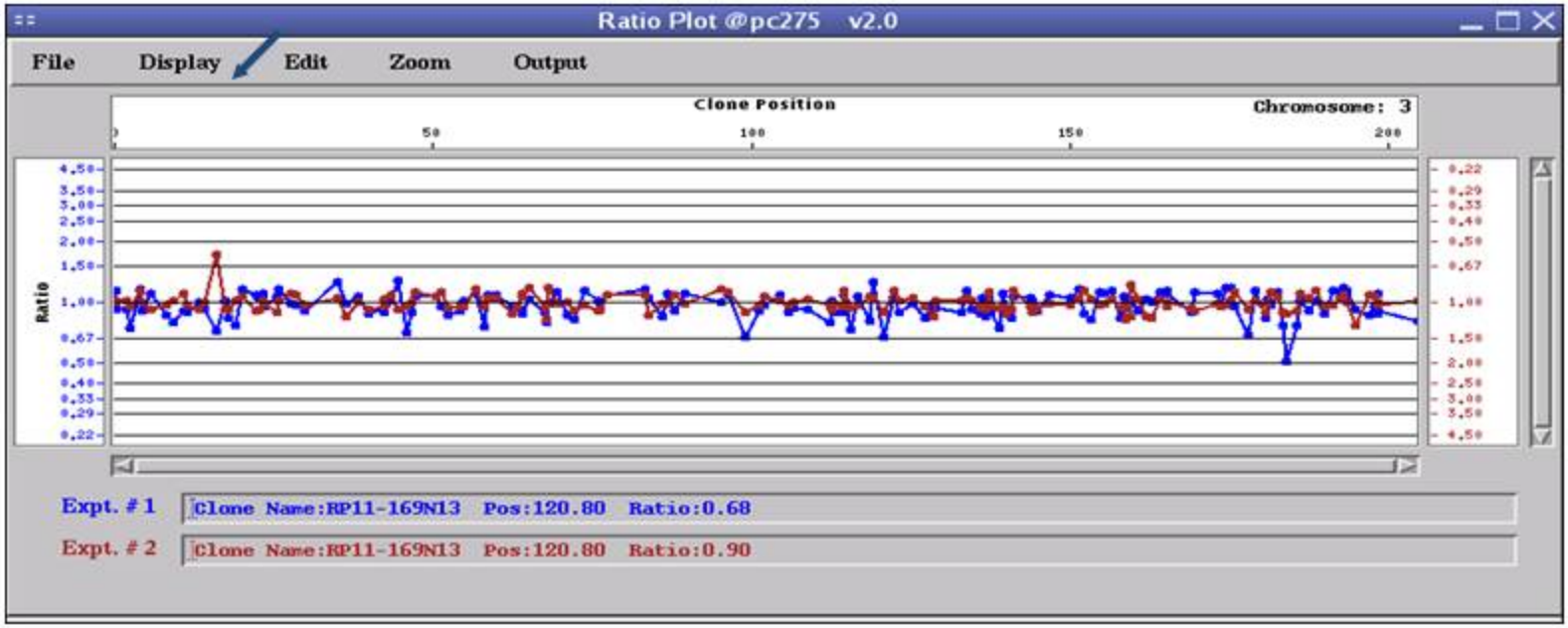


CNVs in ASD

The co-occurrence of autism with submicroscopic chromosomal abnormalities, such as microduplications and microdeletions, is significant and useful for localizing candidate gene regions for autism.

Chromosomal Microarray Screening

- for sub-microscopic chromosomal changes:
Copy Number Variants (CNVs)



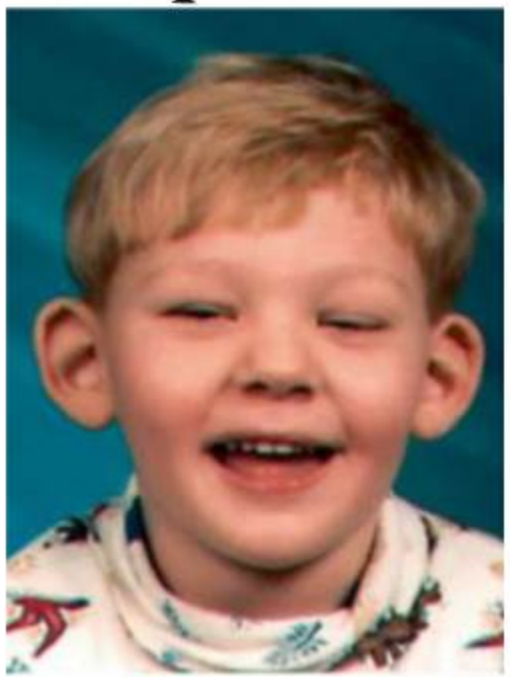
Genetic Syndromes & Chromosomal Variants/Genes Linked with ASDs

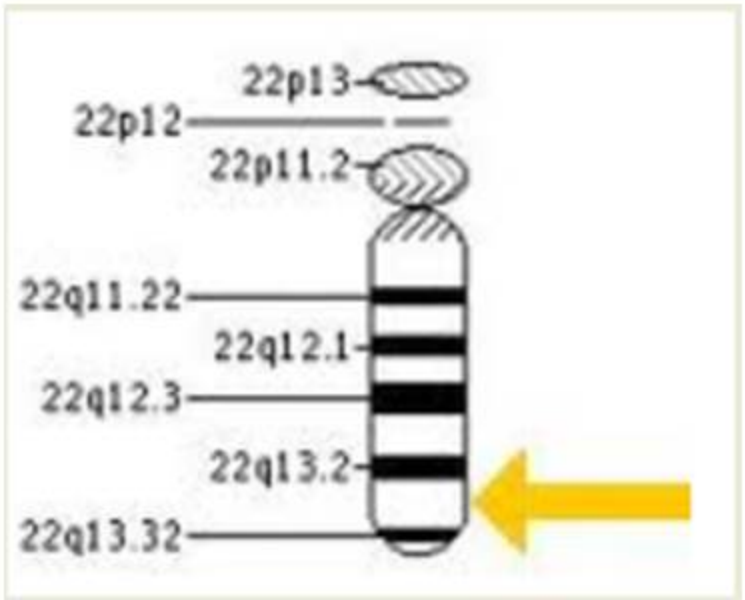
Chromosomal Aneuploidy & Microdeletions/Microduplications	Estimated frequency (%) of ASDs in the disorder	Estimated frequency (%) of the disorder in ASDs
15q11-q13 duplication	80-100	1- 4
Angelman syndrome (mat del 15q11 or paternal uniparental disomy; *UBE3A*)	80-100	1
Smith-Magenis (del 17p11; *RAII*)	80-100	<<1
22q11 deletion syndrome	20-47	~1
Charge syndrome (del 8q12; *CHD7*)	28-40	NA
2q37 deletion syndrome	24-35	1
Prader-Willi syndrome (pat del 15q11 or maternal uniparental disomy; *UBE3A*)	25	NA
Down syndrome (trisomy 21)	5-10	2
22q13 deletion syndrome (*SHANK3*)	1-10	1-2

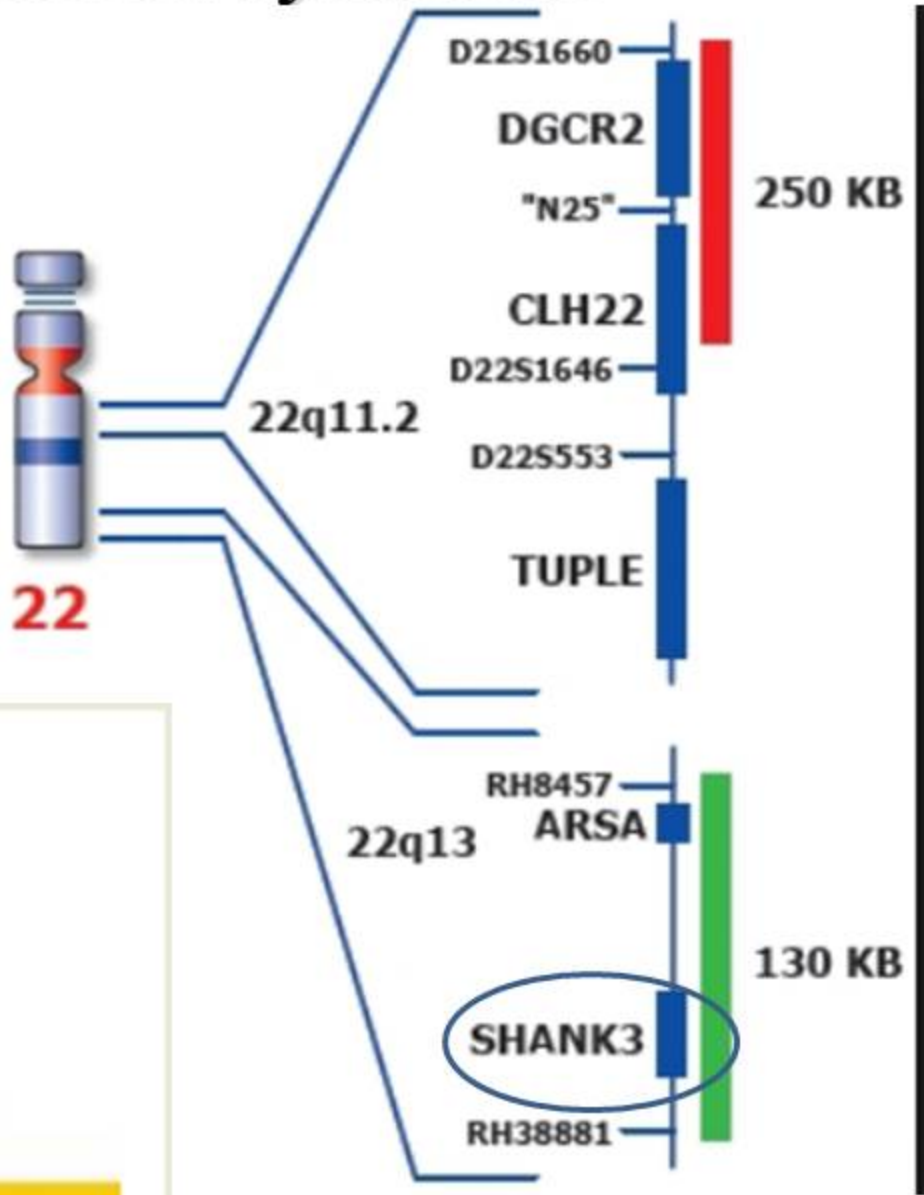
Learning Objectives

- To recognize the variable and complex genetic contributors to the Autism Spectrum Disorders (ASDs).
- To understand the clinical manifestations of ASDs– behavioural, developmental, medical and syndromic.
- To understand the concept of clinical *phenomics and subtyping* to lessen the degree of heterogeneity intrinsic to genetic studies.
- To become familiar with the clinical, cytogenetic and molecular genetic approaches to the study of the ASDs and relevance toward improved management and care of persons with ASDs and their families.

Autism 22q13 Microdeletion Syndrome

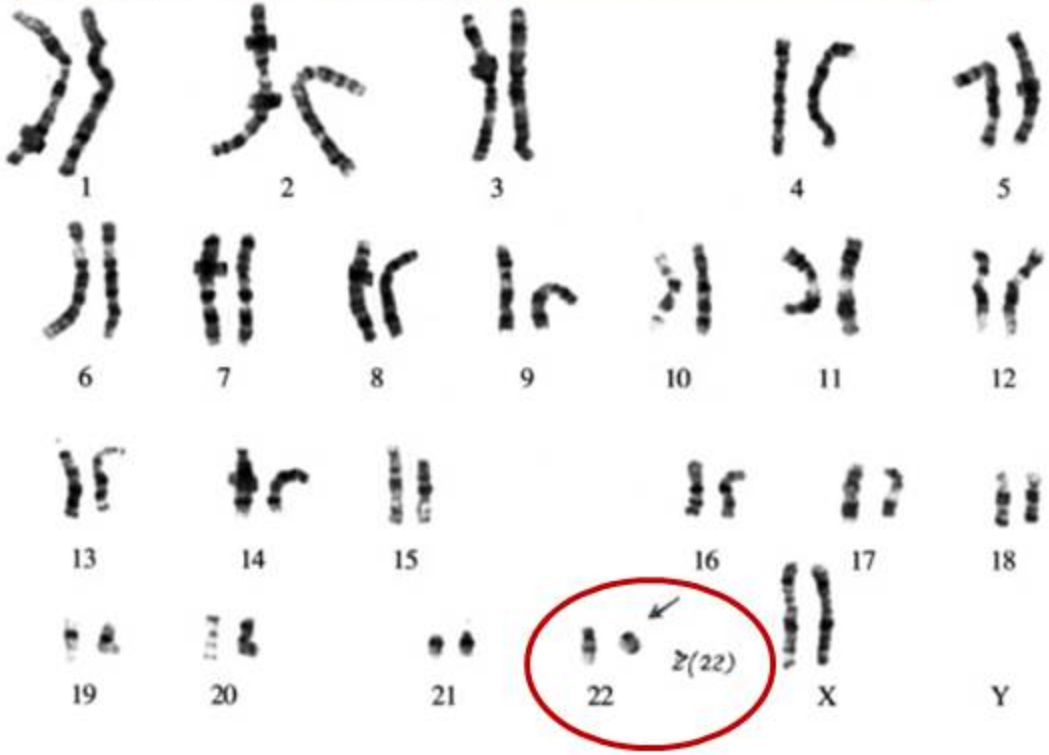






22q13.3 Micro-deletion Syndrome

- 22q13.3 deletion syndrome
  - Subtle phenotype
  - Mild to severe global developmental delay
  - Absent or delayed speech
  - Generalized low muscle tone
  - Minor anomalies: narrow head shape, eye and ear anomalies, relatively large hands, dysplastic toe nails
  - Autism



7q11.2 Microdeletion & ASDs: Williams-Beuren Syndrome

Features: Structural heart defects, elfin face, mental and statural deficiency, characteristic dentition, and infantile hypercalcemia. Contiguous gene deletion on 7q11.2.

Microduplication 7q11 & ASDS

Features: Contiguous gene duplication on 7q11.2. Autistic Disorder; Severe expressive language delay, mutism, oral motor apraxia, Minor congenital anomalies

J Autism Dev Disord
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ORIGINAL PAPER

Association of *GTF2i* in the Williams-Beuren Syndrome Critical Region with Autism Spectrum Disorders

Patrick Malenfant · Xudong Liu · Melissa L. Hudson · Ying Qiao · Monica Hrynchak · Noémie Riendeau · M. Jeannette Hildebrand · Ira L. Cohen · Albert E. Chudley · Cynthia Forster-Gibson · Elizabeth C. R. Mickelson · Evica Rajcan-Separovic · M. E. Suzanne Lewis · Jeanette J. A. Holden

Other Syndromes & ASD
Sotos Syndrome

Features: rapid growth, ID. High-arched palate, prominent jaw. Large stature with birth length at 90th - 97th centiles. Bone age is advanced in most . Caused by mutations in NSD1 on 5q35.

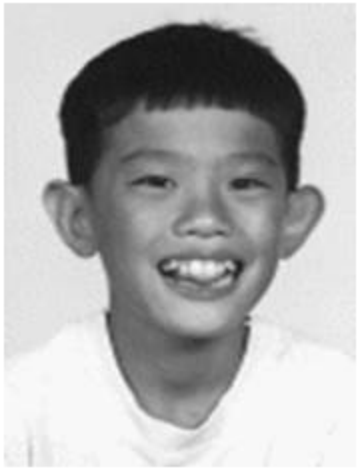
Genetic Syndromes & Single Genes Linked with ASDs

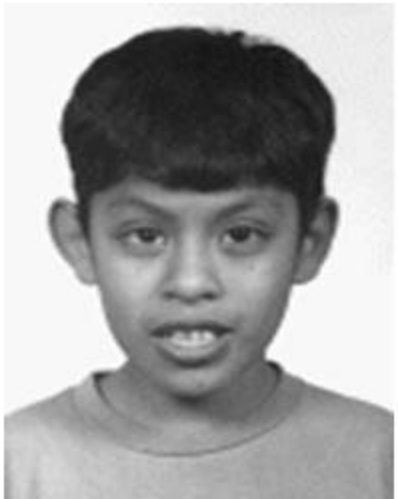
Genetic Syndrome/Single Gene Disorders	Estimated frequency (%) of ASDs in the disorder	Estimated frequency (%) of the disorder in ASDs
Rett syndrome (*MECP2*)	80-100	>5
Adenylsuccinate lyase	80-100	NA
Smith-Lemli-Opitz syndrome	50-86	NA
Tuberous Sclerosis (chromosome 9q34 or chromosome 16p13 mutation)	25-60	1-4
Fragile X Syndrome *(FMR1)*	20-30	7-10
De Lange syndrome *(NIPBL)*	36	NA
Phenylketonuria (untreated)	30	NA
Hypomelanosis of Ito	10	NA
Neurofibromatosis type 1 (*NF1)*	4	~1
DMD/BMD	3-4	<1
Sanfilippo syndrome	3	<1

FRAGILE X

Features:

Large ears, narrow face, prominent jaw, difficulty with fine and gross motor skills, hyper-sensitivities, hand mannerisms, easily distracted, hyperactive, difficulty with changes in routine, mild to profound ID.





Phenylketonuria (PKU)

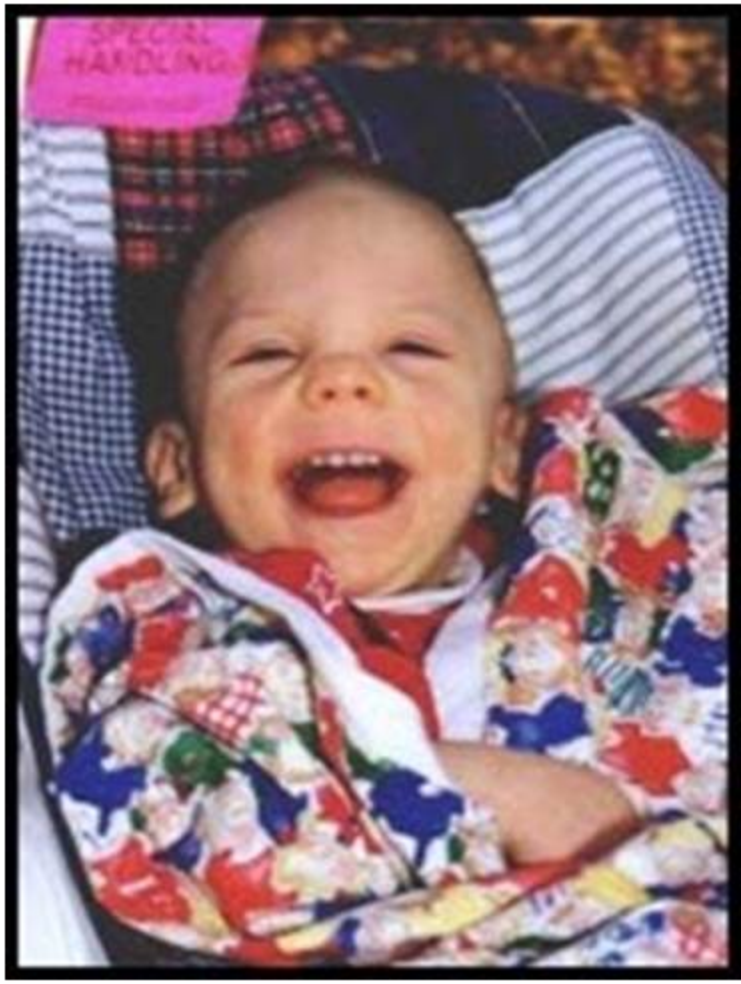
Features:

- fair features (1:11,000).
- Missing phenylalanine hydroxylase (recessive)
- Failure to break down phenylalanine
- Build up of this amino acid→ toxic
- Results in severe ID
- 30% have autistic symptoms

(From The National PKU Website)

Other Syndromes & ASD: Smith-Lemli-Opitz Syndrome

Features: ID of variable degree and severe behavior abnormalities. The physical abnormalities range from minor facial anomalies to lethal malformations of the central nervous system, heart, kidneys, and other organs. Caused by deficiency 7-dehydrocholesterol reductase, (DHCR7) on 11q12-q13.



Known Genetic Subtypes of ASDs

Most Common Genetic Co-Morbidities:

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

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

Tuberous sclerosis (25% have an ASD)

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

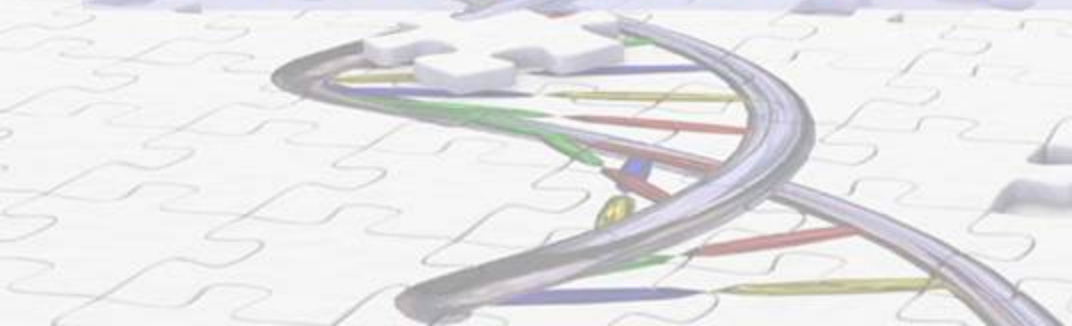
Untreated Phenylketonuria (PKU) (30% with ASD features)

Mitochondrial Dysfunction (up to 7%)


SPRING 2003
Children's Hospital Foundation
speaking of
children
A REPORT TO THE COMMUNITY FROM B.C.'S CHILDREN'S HOSPITAL FOUNDATION
Something in their genes
Local researchers race to explain why siblings like Christopher and Joshua LaSell share many family resemblances; including autism

Intersecting Gene Pathways & ASDs

- Multiple genes linked through common genetic pathways – interruption leads to ASD predisposition. Evidence shows strong support for **disruption of synaptic homeostasis** as a risk factor for autism.
- e.g. ***TSC1, TSC2, NF1* and *PTEN*** gene activation of the *mTOR/PI3K* pathway affecting cellular/synaptic growth rate
- ***NRXN/NLGN/SHANK*** pathway disruption of synaptogenesis and balance between excitatory and inhibitory neurotransmission
- Mutations in ***IL1RAPL1*** – mislocalization of post-synaptic density protein in organization of NMDA receptors, ion channels and other signaling proteins at the post-synapse.



Complex Genetic Bases for ASDs

- Many ASD genes/chromosomal syndromes, CNVs, point mutations – these account for only 10-20% of cases collectively, and individually <2%.
- Proposed 80-90% of pathogenic genetic associations have yet to be identified.
- **Identifying disease genes requires a better definition of the disorders.**
- *Subgroups* sharing a genetic etiology represent more cases
- **But how to identify these?**
- **Using behavioural phenotypes alone to restrict heterogeneity is problematic**
- Diverse neurobehavioural/cognitive phenotypes such as ASD, Asperger or ID may be caused by identical mutations (e.g. in *NLGN4*).

Deep Phenomics as Clues to Autism Cause and Outcome

How to Define ASD Subtypes: The Relevance of MCAs

- Most studies have focused on cognition, general language impairment and/or other core behavioural symptoms – but could also reflect common subtle patterns of minor congenital anomalies (MCAs)
- Clinical and dysmorphic features are more stable and reliable for screening for genes related to a complex phenotype.
- The presence of multiple MCAs distinguishes children who are at increased risk for both major malformations and behavioural disorders.

MCAs as Clues to ASD Cause and Outcome

- **20% of children with autism have changes in physical phenotype**
- **Up to 40% are diagnosed with a genetic syndrome**
- **Current standard of care for ASD evaluation includes a clinical genetics assessment (American College of Medical Geneticists, 2008)**

MCAs as Clues to ASD Cause and Outcome

Minor Congenital Anomalies (MCAs)

In ASD, minor physical variants are found:

- webbing of the toes
- changes in shape/position of the eyes and ears
- large or small head size

The presence of MCAs in autism has been suggested to be related to the shared genetic risk of developing autism (Miles and Hillman, 2005).

May be related to a specific genetic subgroup that could serve as stable biomarkers for early screening.

→ clues to genes, environmental factors and developmental processes causing autistic behaviours.

MCAs as Clues to ASD Cause and Outcome

These MCAs often occur as *clusters of symptoms* (i.e., show patterns), suggesting syndromic relationships to each other and to ASD.

Further validated when identified consistently in association with genetic biomarkers for syndromes associated with ASD behaviours (e.g., Fragile X and other examples).

MCAs as Biomarkers for ASDs

Walker (1977) used the Waldrop scoring scale for 16 anomalies. The mean minor anomaly score of 5.76 for children with autism was >> than the control group score of 3.53 – *suggests organicity.*

Links et al. (1980) – children with autism had > anomalies than their siblings - those with higher anomaly scores had lower IQs, and spent more time in the hospital.

MCAs as Biomarkers for ASDs

Rodier et al. (1996, 2002) - physical phenotypic features could identify children whose autism was due to mutations in the embryologically important homeobox genes involving development of the brain stem and face.

Environmental teratogens, such as *valproic acid* and *thalidomide*, may produce teratogenic phenocopies by influencing the same early developmental pathways.

"The Autisms" – Diagnostic Challenges

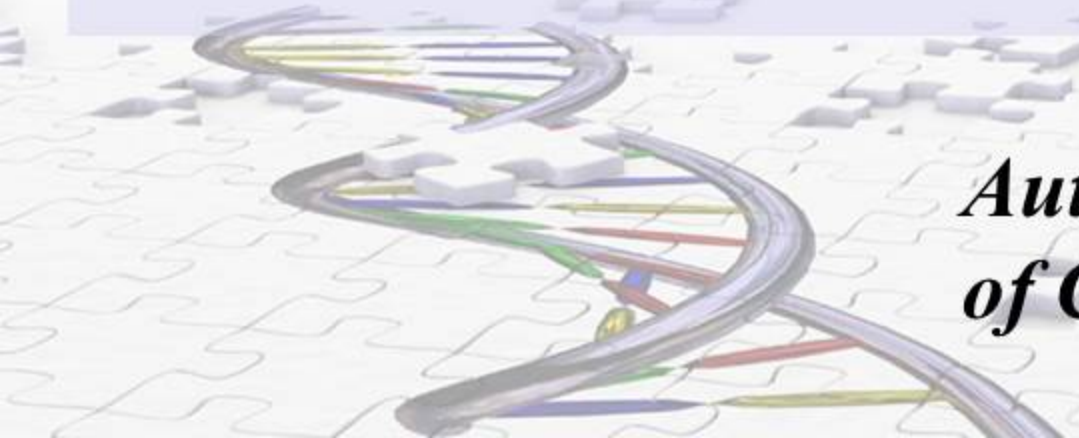
- **Early treatment can make a difference**
- **Diagnosis of autism: typically > age 3yrs**
- **The diagnosis of autism is complex and does not imply etiology.**
- **ASD diagnosis is derived from presence of a *highly variable* constellation of behavioural and developmental *symptoms* ranging from mild to severe.**
- **<u>Due to a triad of deficits in:</u>**
  (1) social interaction (2) communication (3) restricted & stereotypic behaviors

There is no single cause of autism.

A diagnosis of an ASD is really a description of the commonality of the behavioural symptoms, rather than their common etiology.

The Health Problem & Importance to Canada

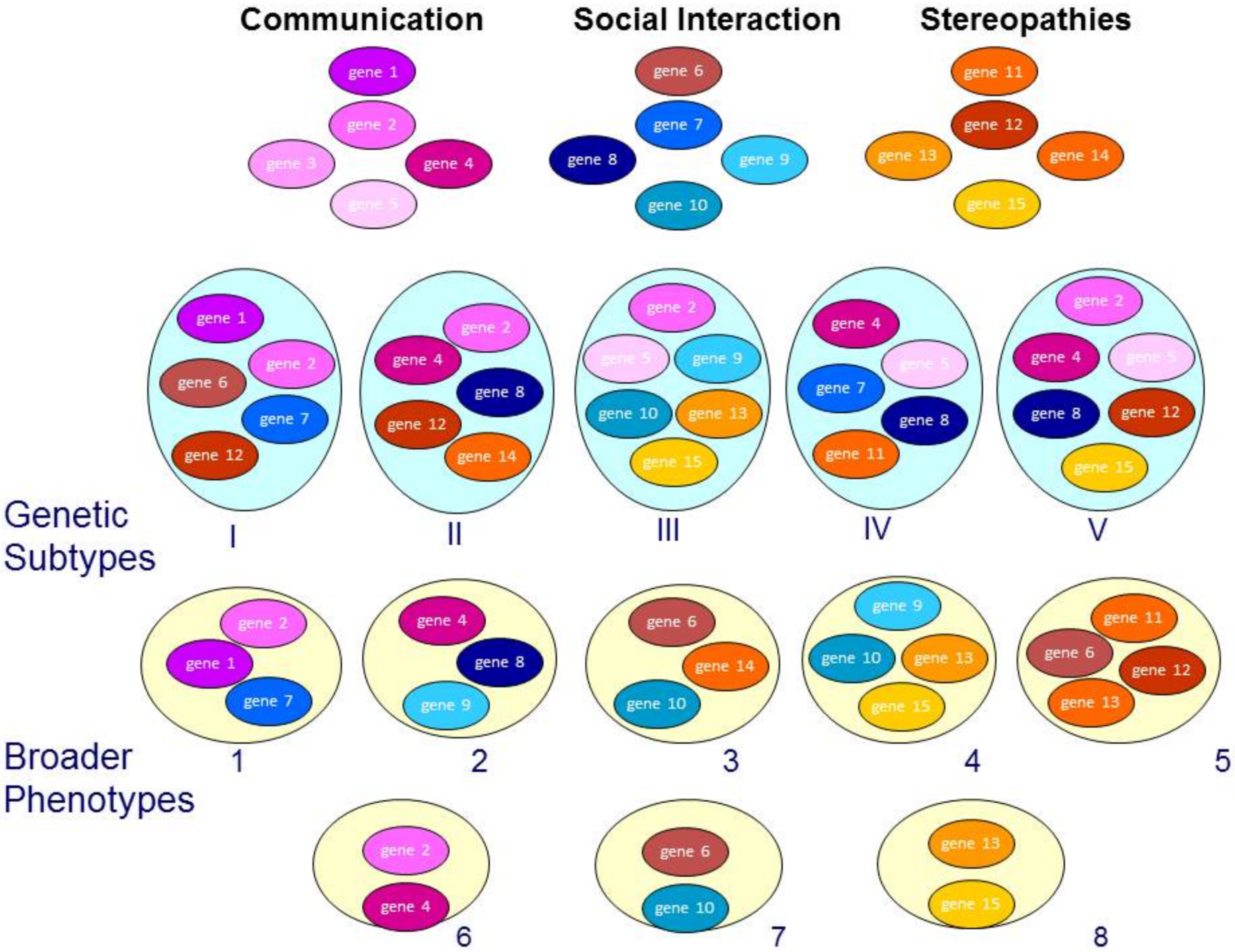
- ASC -↑ frequency > 150% over the last 5 years
- ASDs are the most common childhood developmental disorder; 1/88 children
- In Canada there are an estimated 400,000 persons living with an ASD.
- ↑ of 5000/year
- Found throughout the world in families of all racial, ethnic and social backgrounds
- The educational, health and social service cost per affected individual is ~$1.5-3.5 million.



Autism Society of Canada

Genetic Evidence for ASDs

- **Most heritable neurodevelopmental disorder. Sibling risk 19%.**
- Evidence from twin and family studies indicate a **heritability of up to 92%.**
- Neuroanatomical and neuroimaging studies, showing abnormalities stemming from atypical neuro-developmental processes occurring during the first and second trimesters of pregnancy.
- No consensus on how heterogeneous nor how many genes are involved.
- **This heterogeneity confounds genetic studies.**


Communication
Social Interaction
Stereopathies
gene 1
gene 2
gene 3
gene 4
gene 5
gene 6
gene 7
gene 8
gene 9
gene 10
gene 11
gene 12
gene 13
gene 14
gene 15
Genetic Subtypes
I
II
III
IV
V
Broader Phenotypes
1
2
3
4
5
6
7
8

Complex Genetic Bases for ASDs

- Current research methods reflect the proposed nature of genetic contribution
- **The "common disease-*common* variant" hypothesis** assumes that many ASDs arise from common variants in a small number of genes. **Linkage and GWAS**
- The **"common disease-*rare* variant" hypothesis** aims to identify genes or gene regions in a small number of individuals and assume there are many different genes involved and a portion can be detected using **Cytogenetic, copy number variant microarray approaches**
- **Genomic sequencing** of candidate genes from CNVs, multiple and single incidence family trios allow studies in large groups of individuals to identify mutations that account for similar cases.