10,000+ Genomes Done: Where to go now?

Stephen W. Scherer, PhD, DSc, FRSC
Director, McLaughlin Centre and
The Centre for Applied Genomics
The Hospital for Sick Children
University of Toronto, Canada

Why perform research in ASD?

1. Truth will be found in science
2. Earlier detection of ASD and related conditions can benefit health outcomes
3. Better understanding of the causes of autism will benefit medical management
4. Individualized approaches may be the way forward in ASD
5. Understand human development (cognition, speech, behavior)

GENETIC RESEARCH

Solving puzzle of son's autism soothes family

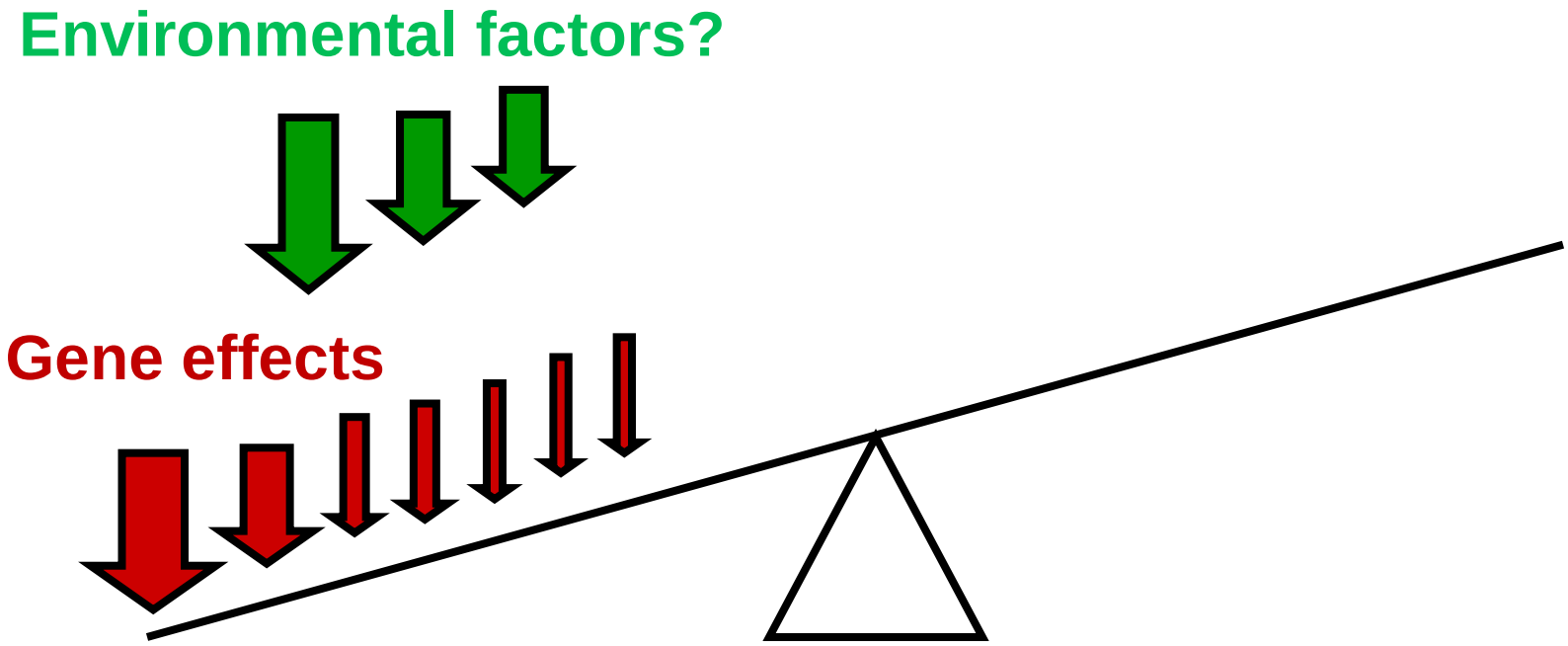
Study reveals DNA clue to cause of condition

MEGAN OGILVIE

Lisa Bond and son Joshua, 11, enjoy their nightly routine of bedtime play at their Stouffville home. The family is one of only four in Canada that know their child's autism is due to a genetic error, discovered by Sick Kids researchers.

del(16p11.2)
AJHG 2008; *Nature* 2011)

Genetic "architecture" in autism



- **Diagnosis:** Mutations in single genes can be sufficient to cause ASD
- >100 'high impact' ASD genes; potentially 1,000 common variants
- **Treatment:** Early intervention can help tip the balance; new therapeutics?

MSSNG – Using open science to deepen the understanding of autism

AUTISM SPEAKS
It's time to listen.

SickKids
THE HOSPITAL FOR SICK CHILDREN

verily

DNASTACK

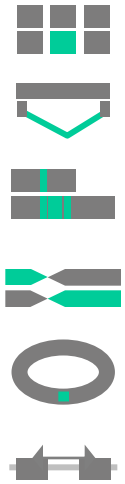
Google

Private-Public partnership to improve understanding and treatment of autism

>10,000 whole genome sequences and deep phenotype data from families with autism

Data made freely available through open-access web-based portal (~200 institutions users in 17 countries)

Genome sequencing provides detection of *all* genetic variation



	Sanger	Targeted NGS	PCR	FISH	Karyotype	CMA	WES	WGS
SNVs & Indels	✓	✓	✓				✓	✓
CNVs			✓	✓		✓	limited	✓
Repeat Expansions			✓					✓
Structural Variants				✓	✓		limited	✓
Mitochondrial	✓	✓					✓	✓
Paralogues (e.g. SMN1/2)	✓	✓						✓

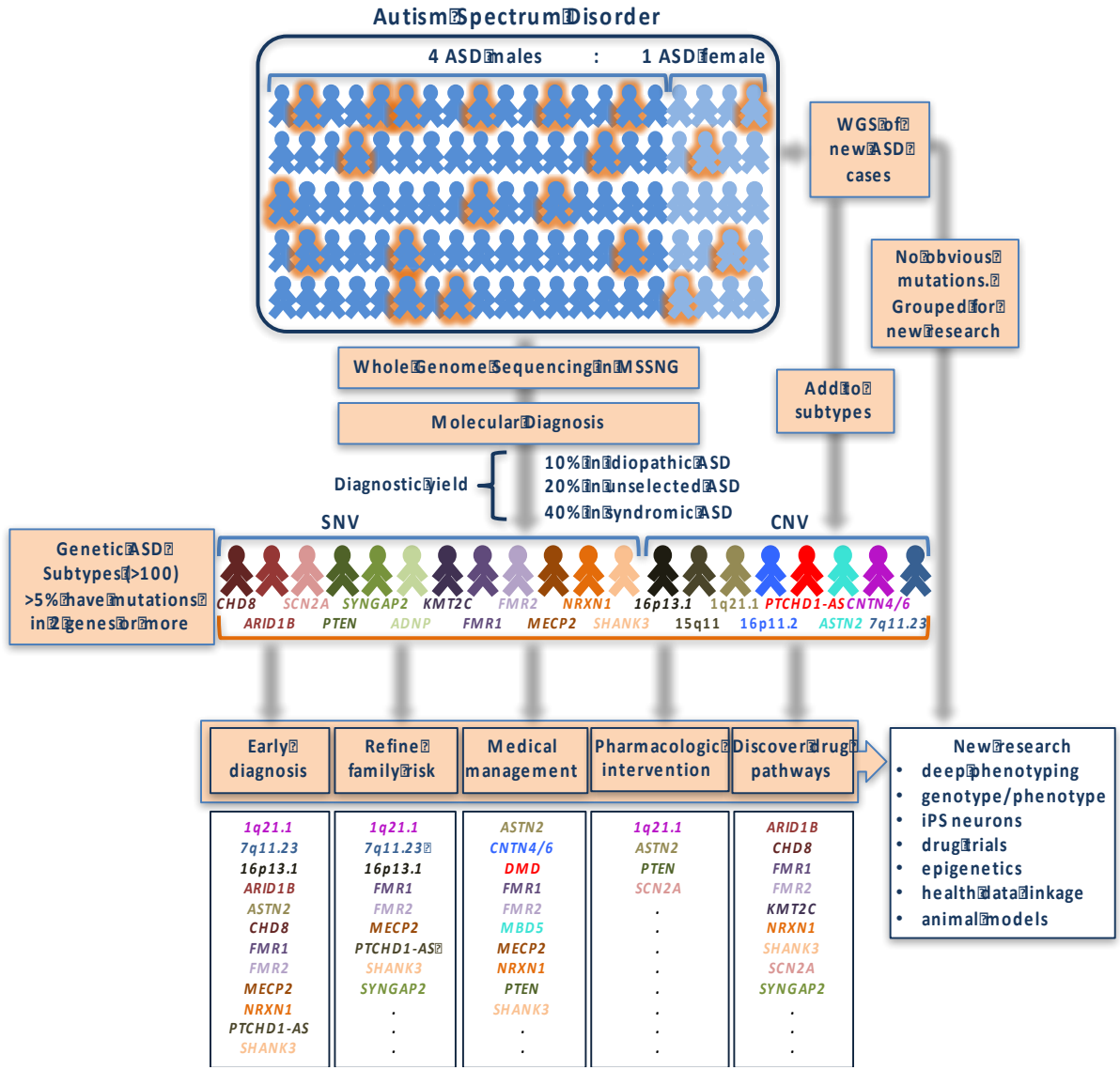
1. Unlike other methods, WGS robustly captures **all** common variant types
2. WGS captures CNVs with greater resolution than chromosomal microarrays (CMAs)
3. WGS captures variants in exomes with greater accuracy than Whole Exome Sequencing (WES)

”The best exome is the genome”

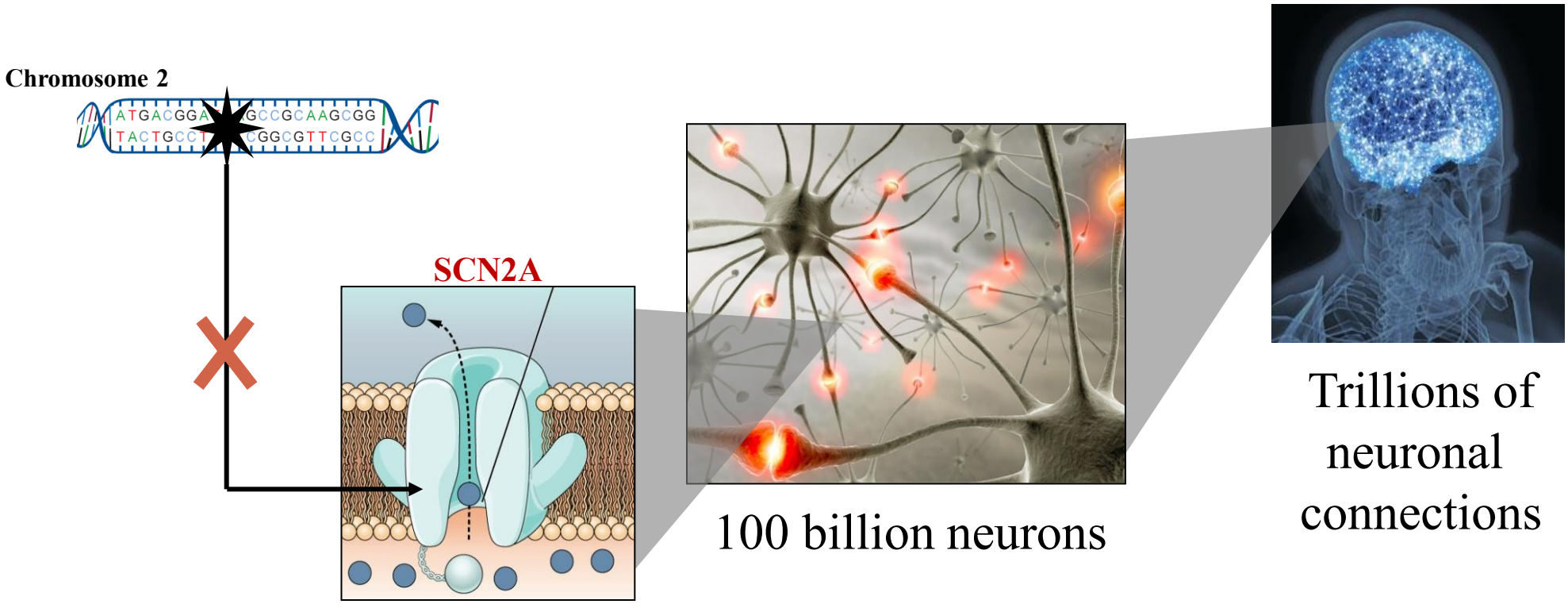
4. WGS is technologically simpler than WES, with faster turnaround time
5. WGS covers the ~98% ”non-coding” DNA for detection of new types of mutations (e.g., enhancers, non-coding RNAs) **and things we don’t know about yet**.

Modified from J. Belmont, R. Taft, D. Bentley, Illumina

ASD is a collection of rare disorders/conditions that clinically group together

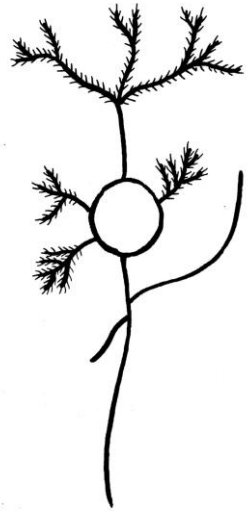


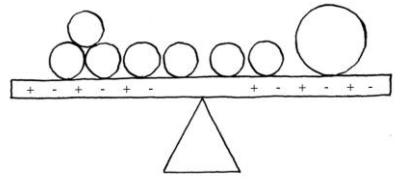
Alterations affect ASD genes/proteins that regulate and maintain neuronal synapse action



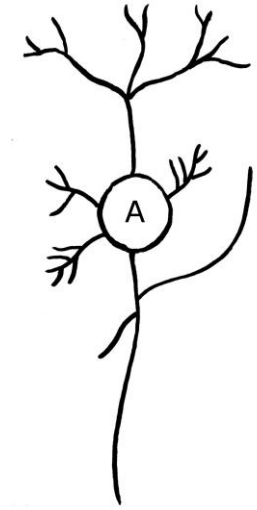
Genes like CHD8, NRXN1, SHANK3, ARID1B, SCN2A make critical proteins for brain cell function

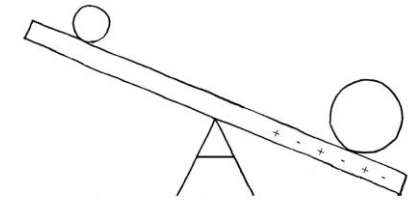
Genes/mutations affect neurons/people in different ways



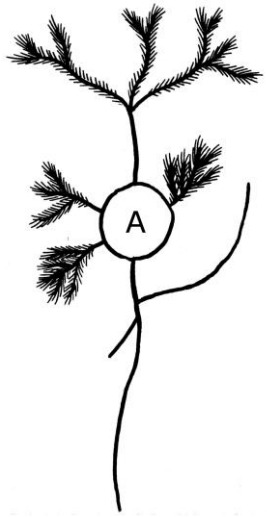


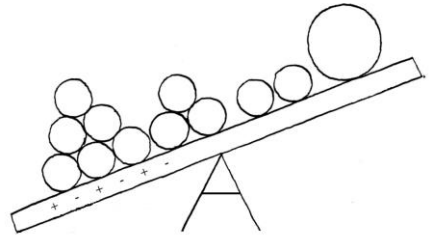
Neurotypical
NRXN1$^{+/+}$
SHANK2$^{+/+}$
PTCHD1AS$^{+/Y}$



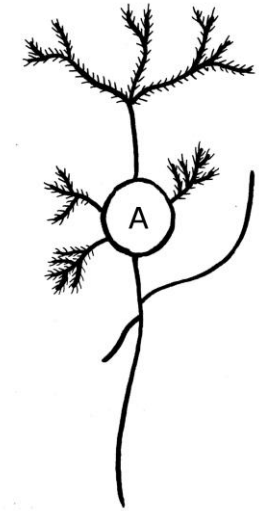


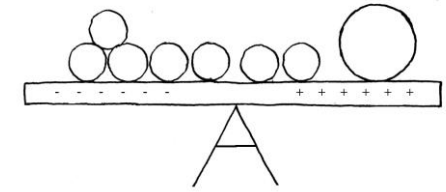
NRXN1$^{+/-}$





SHANK2$^{+/-}$





PTCHD1AS$^{-/Y}$

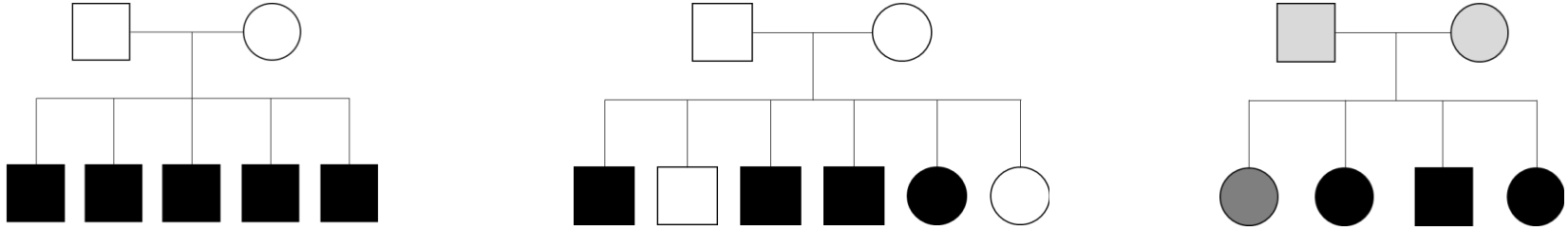
Where to go now?

Like any good scientist…

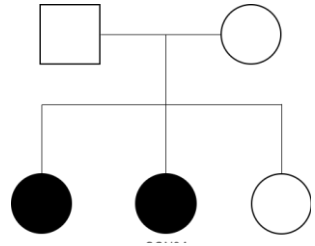
Follow our nose!

Sequence interesting families from around the world (including from clinical trials)

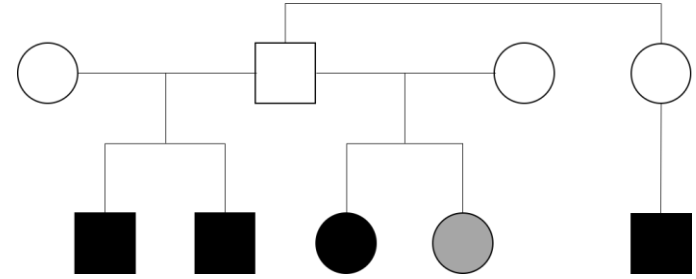
a: Multiple affected siblings



b: Multiple affected females



c: One father with **multiple** affected half-sibling offspring



Washington Post, Sept. 15th, 2019

The Washington Post

Prices may vary in areas outside metropolitan Washington.

K RE V1

Partly sunny 86/69 • Tomorrow: Partly sunny 91/68 C12

Democracy Dies in Darkness

SUNDAY, SEPTEMBER 15, 2019

The autistic children of Donor H898

BY ARIANA EUNJUNG CHA

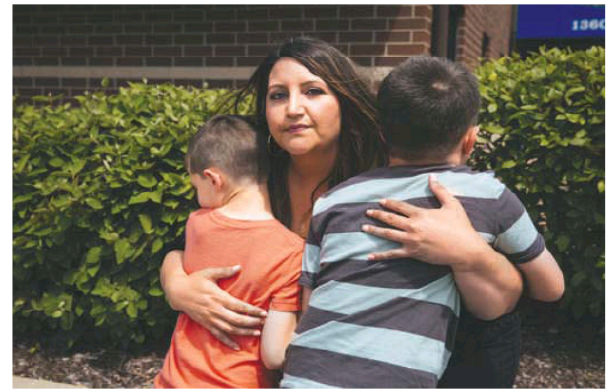
At least a dozen diagnosed as being on the spectrum were conceived with his sperm, spurring scrutiny and a suit

BARTLETT, ILL. — Danielle Rizzo's son is screaming. He is planted in the middle of the lobby of his elementary school, clinging to rainbow-colored blocks as she gently explains that she is here — off schedule, in the middle of the day — to take him to a doctor's appointment. But the first-grader is not listening.

"Happy Meal," he repeats over and over again. "Happy Meal!"

His little brother, who is also going to the appointment, is nearby, not moving. Rizzo is relieved that the two of them are not melting down at the same time, which happens all too often, and firmly guides them out the door.

Rizzo's children, ages 7 and 6, were at the center of one of the most ethically complex legal cases in the modern-day fertility industry. Three years ago, while researching treatment options for her sons, Rizzo says she made an extraordinary discovery: The boys are part of an autism cluster involving at least a dozen children scattered across the United States, Canada and Europe, all conceived with sperm from the same donor. Many of the children have secondary diagnoses of ADHD, dyslexia, mood disorders, epilepsy and other developmental and learning disabilities.



TAYLOR GLASCOCK FOR THE WASHINGTON POST

Danielle Rizzo with her boys, ages 6 and 7, in Streamwood, Ill. After finding out her sons were part of an autism cluster, she sued the sperm bank and its parent company.

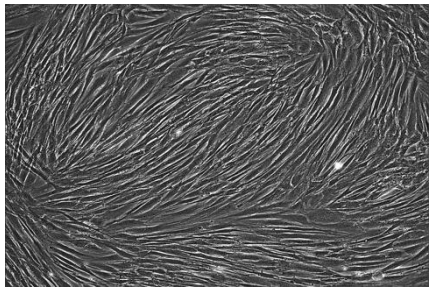
The phenomenon is believed to be unprecedented and has attracted the attention of some of the world's foremost experts in the genetics of autism, who have been gathering blood and spit samples from the families.

Autism, which affects an estimated 1 of 59 children in the United States, is a "spectrum disorder" characterized by difficulties navigating social situations and restricted or repetitive behavior. Some people who have it never speak and need daily care, while others, like actress Daryl

SEE CHILDREN ON A10

Generation of personalized neurons by cellular reprogramming

Fibroblasts from skin biopsy (46;XY) (del)(*PTCHD1*)



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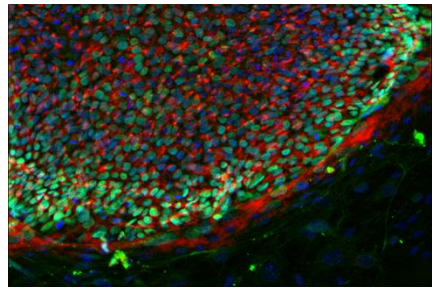
Induced pluripotent stem cells



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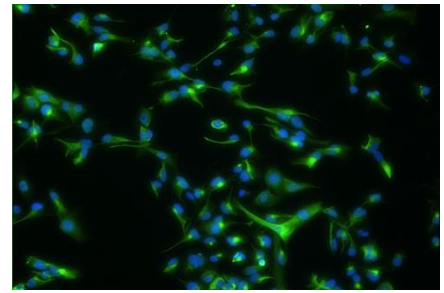
Neuronal precursor cells



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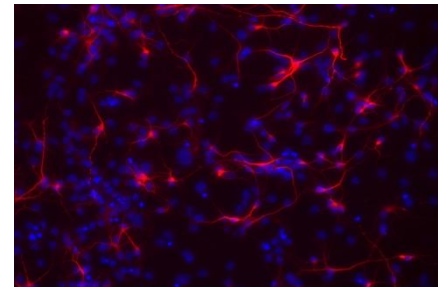
Neurons



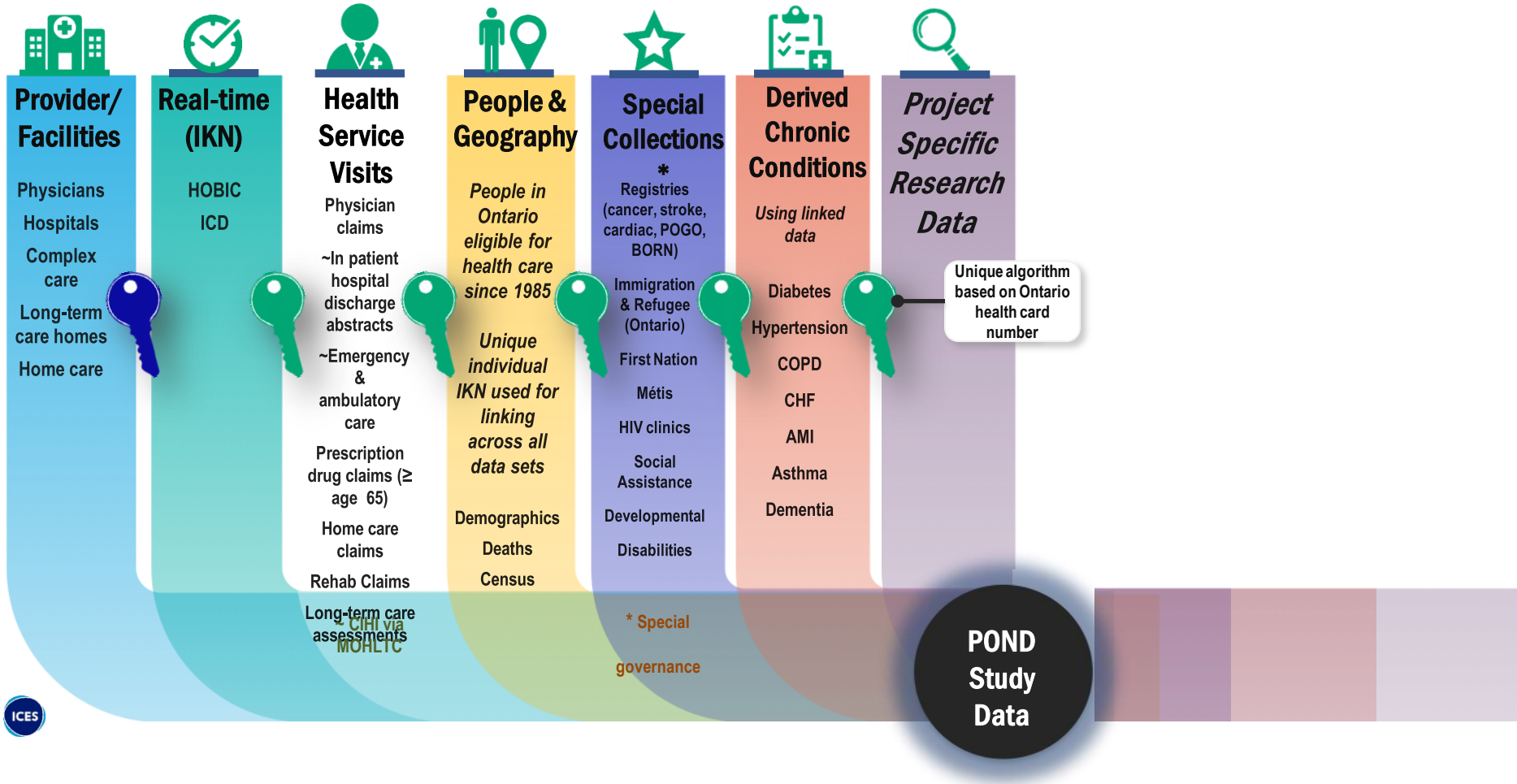
1. Study neuronal development in ASD
2. Test effect of novel medicines in a human system

Courtesy of Joel Ross and James Ellis, SickKids
Karun Singh, McMaster University

Best way to find the Environmental Factors: Link to Health/Admin. databases

Core data repository: coded and linkable (Ontario)

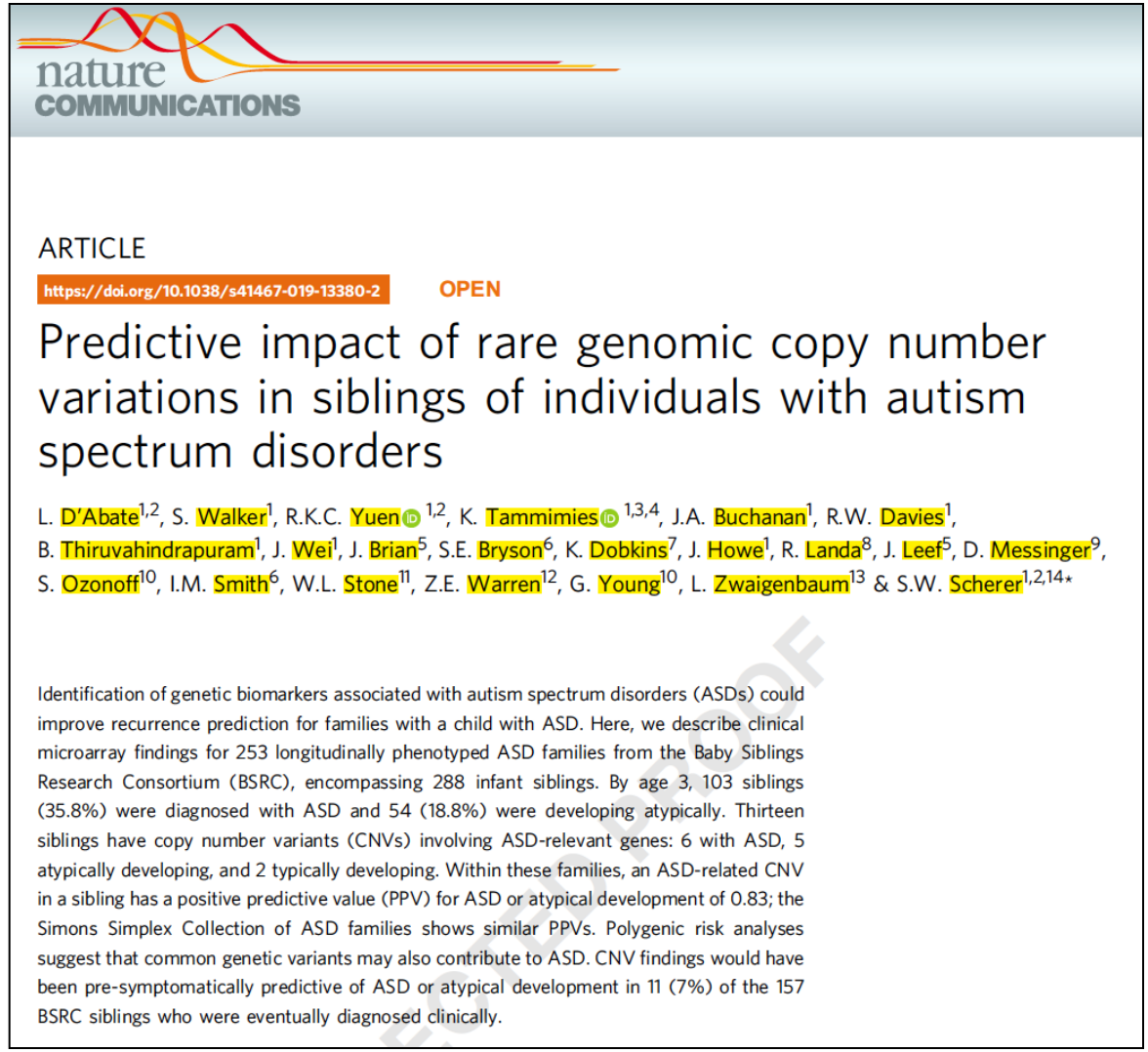
667 have consented to linkage using their Ontario Health Card Number



Jennifer Brooks, Public Health and Policy/ICES, University of Toronto

10 years of research to learn something we already knew!

Where to go?



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-13380-2 OPEN

Predictive impact of rare genomic copy number variations in siblings of individuals with autism spectrum disorders

L. D'Abate[1,2], S. Walker[1], R.K.C. Yuen[1,2], K. Tammimies[1,3,4], J.A. Buchanan[1], R.W. Davies[1], B. Thiruvahindrapuram[1], J. Wei[1], J. Brian[5], S.E. Bryson[6], K. Dobkins[7], J. Howe[1], R. Landa[8], J. Leef[5], D. Messinger[9], S. Ozonoff[10], I.M. Smith[6], W.L. Stone[11], Z.E. Warren[12], G. Young[10], L. Zwaigenbaum[13] & S.W. Scherer[1,2,14]*

Identification of genetic biomarkers associated with autism spectrum disorders (ASDs) could improve recurrence prediction for families with a child with ASD. Here, we describe clinical microarray findings for 253 longitudinally phenotyped ASD families from the Baby Siblings Research Consortium (BSRC), encompassing 288 infant siblings. By age 3, 103 siblings (35.8%) were diagnosed with ASD and 54 (18.8%) were developing atypically. Thirteen siblings have copy number variants (CNVs) involving ASD-relevant genes: 6 with ASD, 5 atypically developing, and 2 typically developing. Within these families, an ASD-related CNV in a sibling has a positive predictive value (PPV) for ASD or atypical development of 0.83; the Simons Simplex Collection of ASD families shows similar PPVs. Polygenic risk analyses suggest that common genetic variants may also contribute to ASD. CNV findings would have been pre-symptomatically predictive of ASD or atypical development in 11 (7%) of the 157 BSRC siblings who were eventually diagnosed clinically.

FOR PROOF