What do we know about the genetics of autism?

Santhosh Girirajan
Pennsylvania State University, University Park

National Autism Conference
August 3, 2015

Outline of the talk

- Principles and applications of genetics
  - Detecting genetic variants: implications for genetic testing
- Genetics of autism
  - Chromosomal disorders and copy-number variants
  - Base pair changes (exome sequencing)
- Sex differences in autism

Objectives of the talk

- Obtain a basic understanding of types of genetic variants and how to detect them
- Understand the implications of genetic variants
- Understand how CNVs and SNVs disrupt genes
- Understand the complexity associated with autism – heterogeneity of autism

What will not be discussed in this talk?

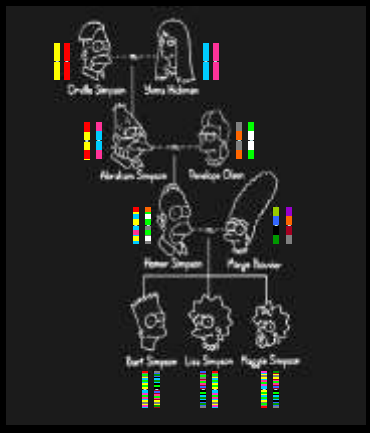
- About how autism was determined to have a genetic basis
- Syndromic forms of autism – Fragile X, Tuberous sclerosis etc
- Details of each of the CNVs or genes identified to be associated with autism
- Mouse models, stem cell models, whole genome sequencing, genome wide association studies

However, you can contact me (anytime) requesting

- Details on any specific aspect of the talk
- Details on any aspect of genetics or any of the above
- About my research interests

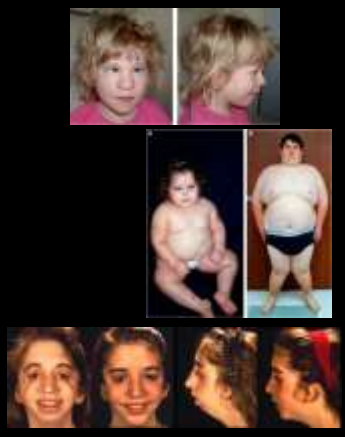
Contact: Santhosh Girirajan, Email: sxg47@psu.edu

Human genetics and genomics



Why do we have our father's nose and mother's eyes?

Human traits

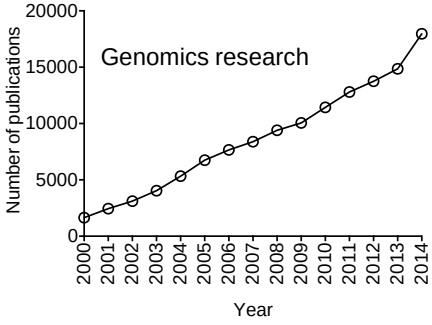


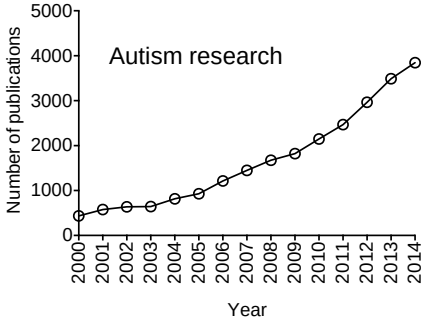
Developmental problems

Images courtesy: pinterest.com, sikids.com; Cassidy et al, EJHG; wiki.ggc.edu

Research in genomics and autism

Number of research papers in PubMed with the term "genomics" or "autism" from years 2000 to 2015

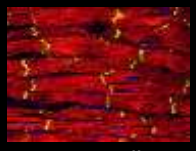




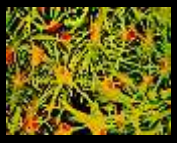
Major reasons for these increases:

- Advent and utility of high throughput technologies for understanding the nature of the genome in natural variation and disease
- Increased awareness and development of more sensitive tests for detecting autism
- High heterogeneity of autism – multiple genes implicated

Human biology and genetics



Heart cells

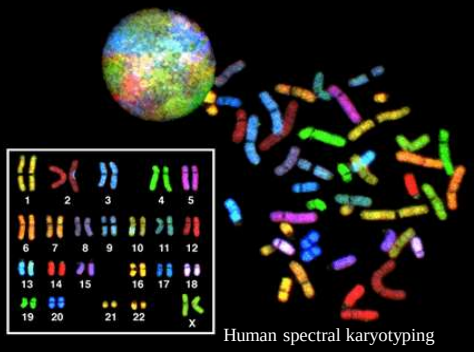


Nerve cells

Bone cells

Fat cells

Cells, chromosomes, and DNA

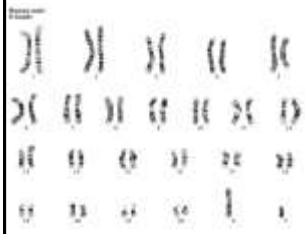


Human spectral karyotyping

- Genetics is the science of heredity and variation
- Genomics is the study of genomes

Chromosomes, DNA and genes

Human chromosomes



An excerpt from the human genome

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GTAAGCAAGGCTGTGTGGGCATGGGACCCGCCAAGCCATGCAAGGGATATAATCTCCTGGTGTGCCGCTT
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CTTCCCTTGGCTAGGAAAGGGAAATCCCCCGACCACTTGTGCTGCTTCCCAGATGAGGTGACACCCTGCC
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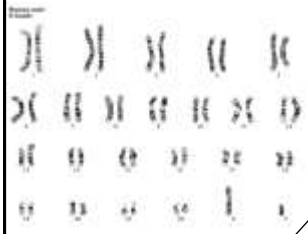
Chromosomes, DNA and genes

Human chromosomes



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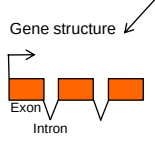
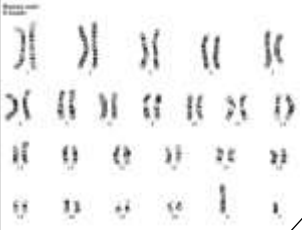


- Classically, DNA sequences coding for proteins are called genes

www.pathology.washington.edu; www.expasy.org

Chromosomes, DNA and genes

Human chromosomes



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GTTTGCCTGAGTGTCACCAGTGGAGGCTGCAGAACAGCAAATATTGCTGCCTGATCCTTCTTCTGGAAGC
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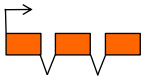
Gene structure



Messenger RNA

Amino acids

Met	Trp	Phe	Trp	Glu
ATG	TGG	TTT	TGG	CAG

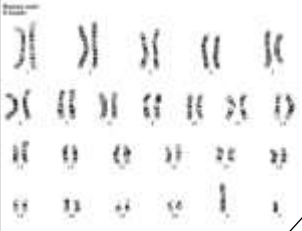
Protein

- Classically, DNA sequences coding for proteins are called genes
- There are approximately 22,000 annotated genes in the human genome

www.pathology.washington.edu; www.expasy.org

Chromosomes, DNA and genes

Human chromosomes



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GTTTGCCTGAGTGTCACCAGTGGAGGCTGCAGAACAGCAAATATTGCTGCCTGATCCTTCTTCTGGAAGC
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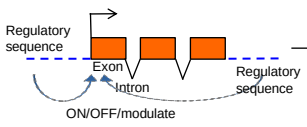
Gene structure



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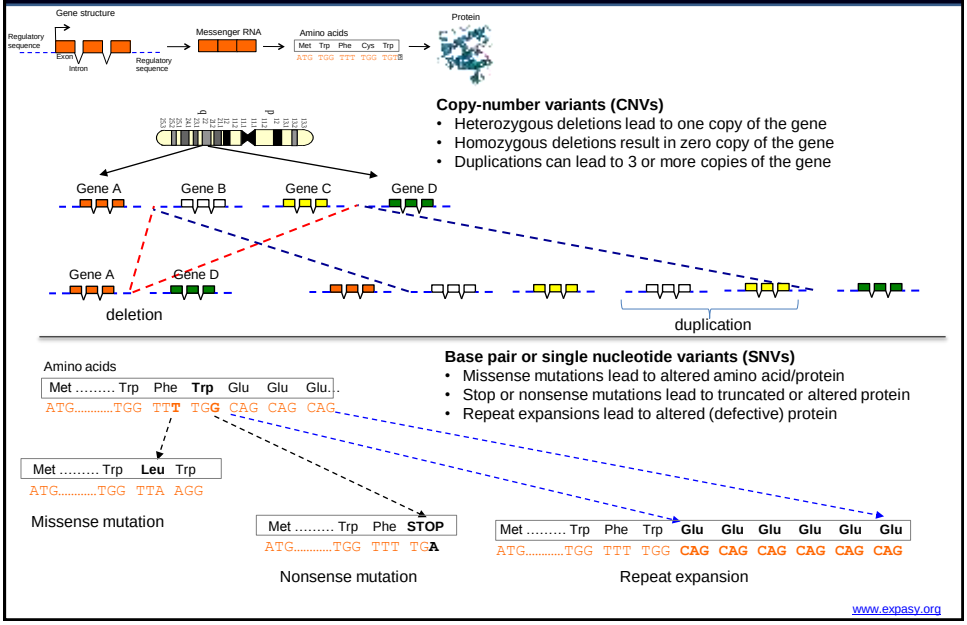
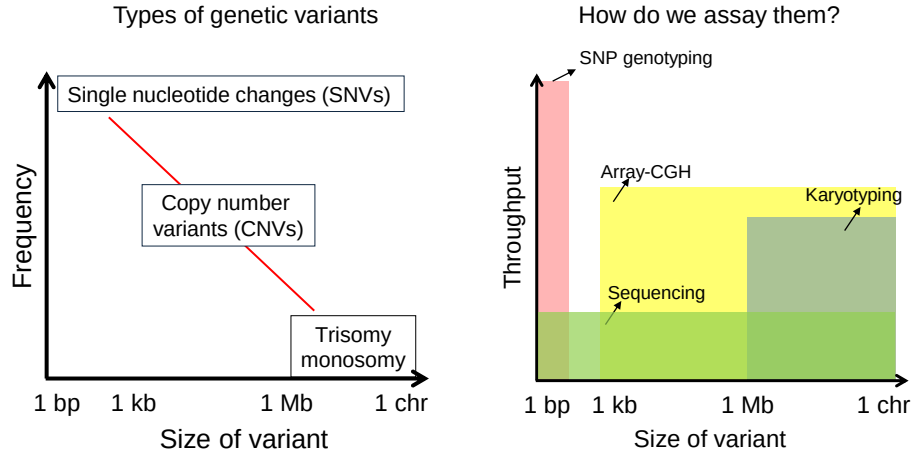
- Any disruption (or altered expression) of genes leads to human variation or disease

www.pathology.washington.edu; www.expasy.org

Genetic variants and gene disruptions

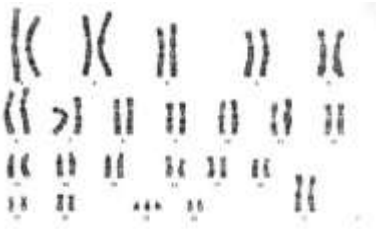


Genetic variants and assays

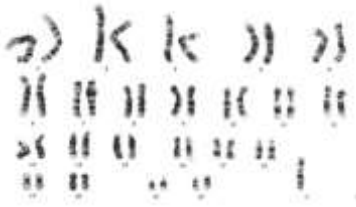


Karyotyping: for detecting cytogenetic (chromosomal) changes

- Chromosomal banding in metaphase (cell division) – Q, Giemsa, C, R, silver nitrate
  - Banding patterns are reflective of regional differences in base pair composition and other functional characteristics
- Chromosomal banding was adopted as a clinical tool for karyotyping in the clinic from the 1960s – amniocentesis for chromosomal abnormalities
  - Down syndrome (Lejeune, 1958)
  - Turner syndrome and Klinefelter syndrome (1959)



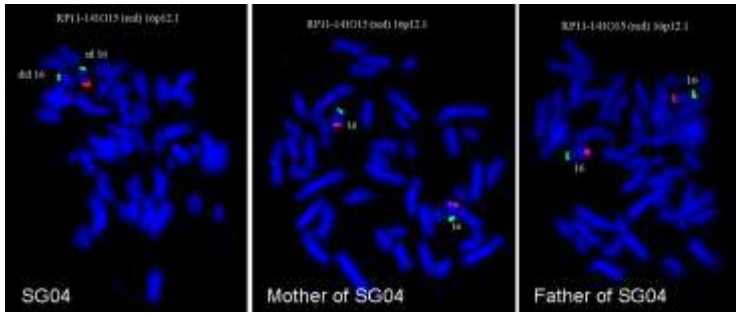
Down syndrome



Turner syndrome

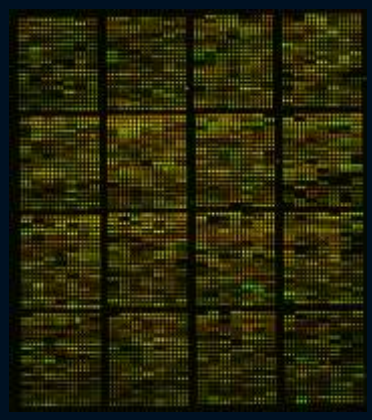
Fluorescent *in situ* hybridization (FISH)

- The idea that complementary DNA sequences can hybridize to probes to query specific DNA segments
  - For cytogenetic localization of DNA sequences
- FISH helped identification of chromosomal deletions and duplications
  - Prader-Willi/Angelman syndrome (15q13.1 deletion)
  - 15q11.2q13.1 duplication
  - Smith-Magenis syndrome (17p11.2 deletion)



Girirajan et al, Nature Genetics, 2010

Array comparative genomic hybridization



Normal Human DNA Sample

Array of BACs/Oligos

Hybridization

Disease individual DNA Sample

Cy3 Channel

Cy5 Channel

Merge

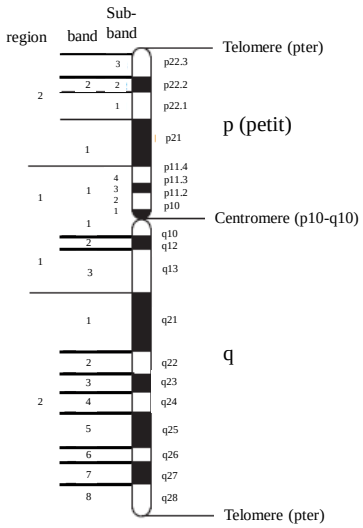
Targeted array

BACs/oligos

TEL

dist: >50 kb<5 Mb
95% identity, 10 kb

Chromosomal address of the genetic lesion



Dup(15q11.2-q13.1)

5.6 Mbp

Dup(14q32.13-q32.2)

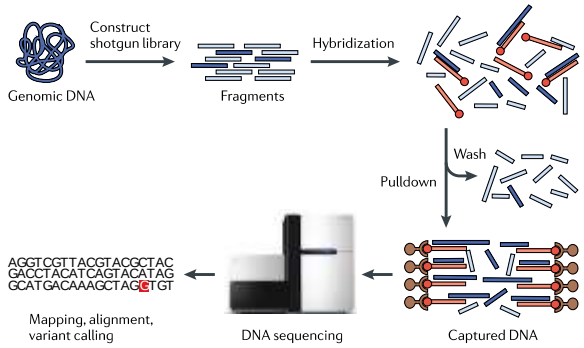
848 kbp

Del (5q15-q23.3)

35 Mbp

Girirajan, Nature Genet, 2010

Exome sequencing for identifying base pair variants



- A technique to sequence all protein-coding regions (exons) of the human genome to identify mutations
- Has been replacing or is complementary to standard karyotyping and array CGH as a diagnostic tool in clinical laboratories
- High throughput but will generate large sizes of data files for analysis (more so for whole genome sequencing)

Bamshad et al, NRG, 2011

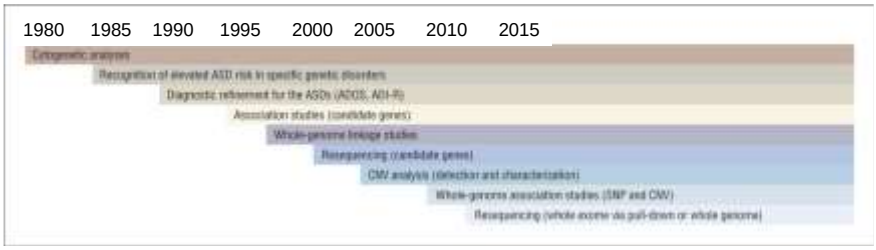
Summary: Principles and applications of genetics

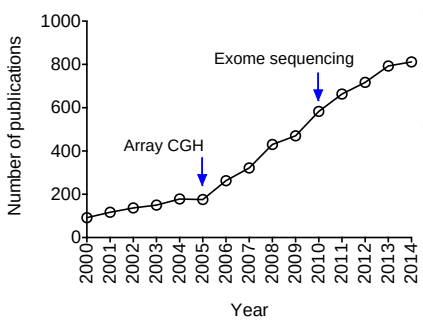
- Basic genetics: chromosome, DNA, gene
- Types of mutations: CNVs, SNVs, repeat expansions
- Genetic techniques to identify variants
  - Karyotyping
  - FISH
  - Array CGH
  - Exome sequencing

Further reading

- Trask, Trends in Genetics, 1991
- Emmanuel and Saitta, Nature Review Genetics, 2004
- Trask, Nature Review Genetics, 2002
- Alkan et al, Nature Reviews Genetics, 2012
- Shendure and Ji, Nature Biotechnology, 2008

Advances in the genetic studies of autism



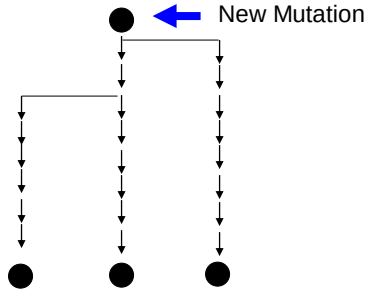


- Number of research papers in PubMed with the term “genomics” AND “autism” from years 2000 to 2015
- With reducing costs of genomic technologies, discovery of genes and genomic regions contributing to autism is increasing

Abrahams and Geschwind, JAMA Neurology, 2010

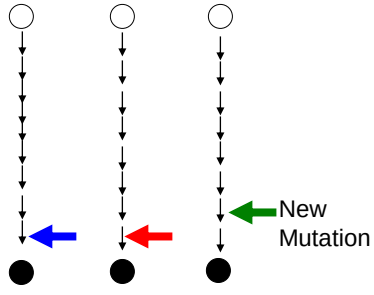
Genetic models to identify causes of autism

A) Common Disease Common Variant



- New mutation occurs 1000s of generations ago, the mutation carrying block becomes common in the population because identity by descent

B) Common Disease Rare Variant Model



- New mutation frequency is high and occurs in immediate generation(s), individually rare mutations but collectively contribute significantly because multiple genes lead to disease

Slide courtesy: Evan Eichler

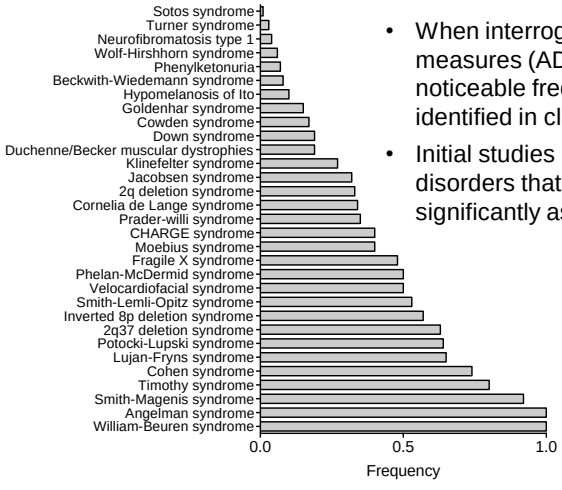
Linkage and association studies of autism

- Using linkage studies (looking at shared blocks of DNA common in all affected individuals within a large family - chromosome 7q35 (containing *CNTNAP2*) and 20p13 have been implicated
- Genome wide association studies (GWAS) for common variants identified a handful of loci including genes on 5p14.1 (*CDH9* and *CDH10*), 5p15.31 (*SEMA5A* and *TAS2R1*), and 7q35 (within *CNTNAP2*)
- The contribution of common variants to risks of small effect (Odds ratio <3) is still being explored with larger sample sizes

Please refer to Chen *et al*, Ann Review of Pathology, 2015; Geschwind and State, Lancet, 2015, Geschwind, Ann Rev Medicine, 2009, Gaugler et al, Nat Genetics, 2014.

Genetic syndromes associated with autism

- Although not specific to autism, these disorders include Fragile X syndrome (1-2% of individuals with autism), Tuberous sclerosis (~1%), Timothy syndrome (<1%), and Rett syndrome (~0.5%)

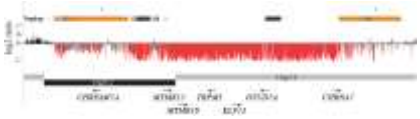


- When interrogated using standardized measures (ADI(R), ADOS, SCQ, SRS) noticeable frequency of autism was identified in classical genetic syndromes
- Initial studies identified several syndromic disorders that were later identified to be significantly associated with autism features

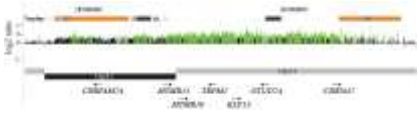
Polyak et al, AJMG, 2015

Rare copy number variants (CNVs)

- Frequency of <0.1% to <1% in the general population
- Contributes to a range of human disorders including autism, intellectual disability, and schizophrenia
- CNVs contain functionally-relevant genes
  - Haploinsufficiency or triploinsufficiency



Deletion



Duplication

Genomic disorders with typical syndromic features

Intellectual disability, craniofacial features, sleep disturbance, obesity, self-injurious behaviors

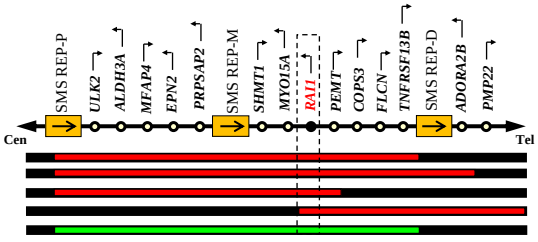
Smith-Magenis syndrome

Intellectual disability, growth retardation, ADHD, autism

Potocki-Lupski syndrome

Girirajan, PhD Thesis, 2008

17p11.2 deletion or mutations in *RAI1*



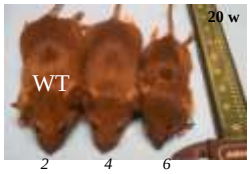
17p11.2 duplication

Reduced *Rai1*

Copies

Obesity
Hypoactivity
Craniofacial defects

Overexpressing *Rai1*

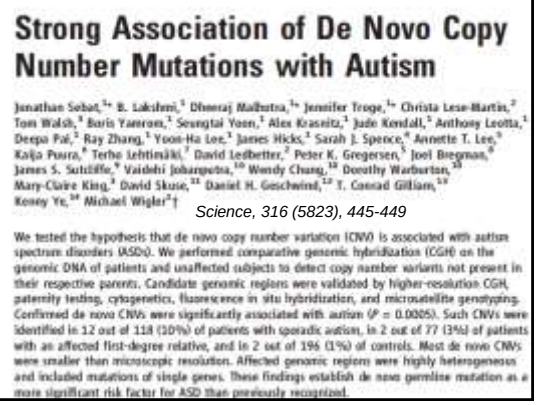


Growth retardation
Hyperactivity
Abnormal social behavior

Rare copy-number variants in autism

- Duplications on chromosome 15q11.2q13.1 was one of the first locus to be implicated in autism
  - Children that inherited the duplication from the mother showed features of autism (Cook et al, 1997, AJHG), while paternally inherited duplications did not show autism features
  - This duplication accounts for ~1.5% of children with autism

- In 2007, using DNA microarrays, Sebat and colleagues performed a genome-wide search for CNVs in autism
- They found that 10% of individuals carrying a large (>500,000 base pairs) of deletions or duplications that occurred *de novo* (i.e. not inherited from a parent).
- This study lead to a watershed in autism genetics with multiple CNVs being discovered for autism risk



Strong Association of De Novo Copy Number Mutations with Autism

Jonathan Sebat,[1*] B. Lakshmi,[1] Dheeraj Malhotra,[1*] Jennifer Troge,[1*] Christa Lese-Martin,[2] Tom Walsh,[3] Boris Yamrom,[1] Seungtai Yoon,[1] Alex Krasnitz,[1] Jude Kendall,[1] Anthony Leotta,[1] Deepa Pai,[1] Ray Zhang,[1] Yoon-Ha Lee,[1] James Hicks,[1] Sarah J. Spence,[4] Annette T. Lee,[5] Kaija Puura,[6] Terhe Lehtimäki,[7] David Ledbetter,[5] Peter K. Gregersen,[5] Joel Bregman,[8] James S. Sutcliffe,[9] Vaidehi Jobanputra,[10] Wendy Chung,[11] Dorothy Warburton,[12] Mary-Claire King,[3] David Skuse,[13] Daniel H. Geschwind,[14] T. Conrad Gilliam,[15] Kenny Ye,[16] Michael Wigler[1]†

Science, 316 (5823), 445-449

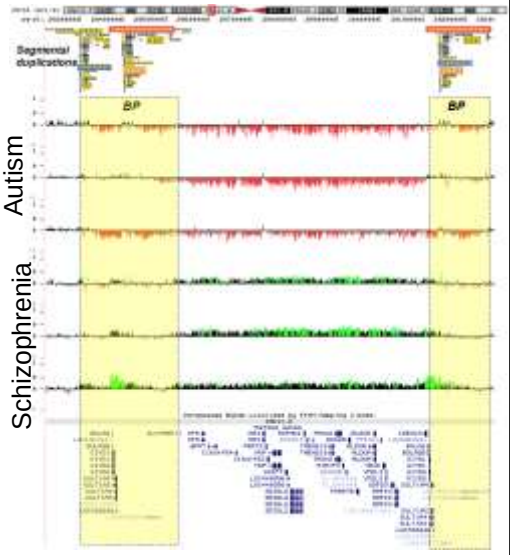
We tested the hypothesis that de novo copy number variation (CNV) is associated with autism spectrum disorders (ASDs). We performed comparative genomic hybridization (CGH) on the genomic DNA of patients and unaffected subjects to detect copy number variants not present in their respective parents. Candidate genomic regions were validated by higher-resolution CGH, paternity testing, cytogenetics, fluorescence in situ hybridization, and microsatellite genotyping. Confirmed de novo CNVs were significantly associated with autism ($P = 0.0005$). Such CNVs were identified in 12 out of 118 (10%) of patients with sporadic autism, in 2 out of 77 (3%) of patients with an affected first-degree relative, and in 2 out of 196 (1%) of controls. Most de novo CNVs were smaller than microscopic resolution. Affected genomic regions were highly heterogeneous and included mutations of single genes. These findings establish de novo germline mutation as a more significant risk factor for ASD than previously recognized.

A list of rare CNVs in autism

- 15q13.1 duplication – *Cook, AJHG, 1997;Thomas, AJHG, 1998*
- 22q13 deletion – *Phelan, 1997; Moesner, AJHG, 2007*
- 16p11.2 deletion – *Sebat, Science, 2004, Weiss, NEJM, 2008, Kumar, HMG, 2008*
- 16p13.11 deletion – *Ullman, Hum Mut, 2007; Hannes, JMG, 2009*
- 17q12 deletion – *Mefford, AJHG, 2007, Moreno-De-Luca et al, AJHG, 2010*
- 15q13.3 deletion – *Sharp, Nat Genet, 2008*
- 1q21.1 deletion – *Mefford, NEJM, 2008*
- 7q11.23 duplication – *Sanders, Neuron, 2011*

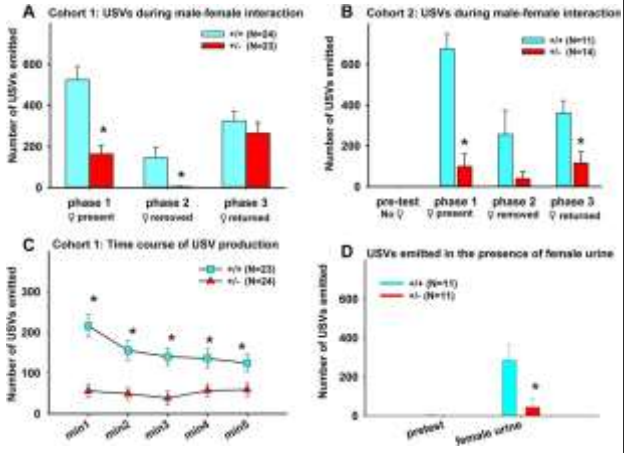
16p11.2 deletion as an example

- Weiss et al and Kumar et al identified 16p11.2 deletions and duplications in individuals with autism
- The 16p11.2 deletion specifically accounts for 1% of cases with autism – associated with macrocephaly
- It is known (Courchesne et al, JAMA, 2003) that autism is associated with macrocephaly
- McCarthy et al detected an enrichment for 16p11.2 duplications in individuals with schizophrenia
- Reciprocal deletion/duplication CNVs associated with opposing phenotypes



16p11.2 deletion mice show social behavior defects

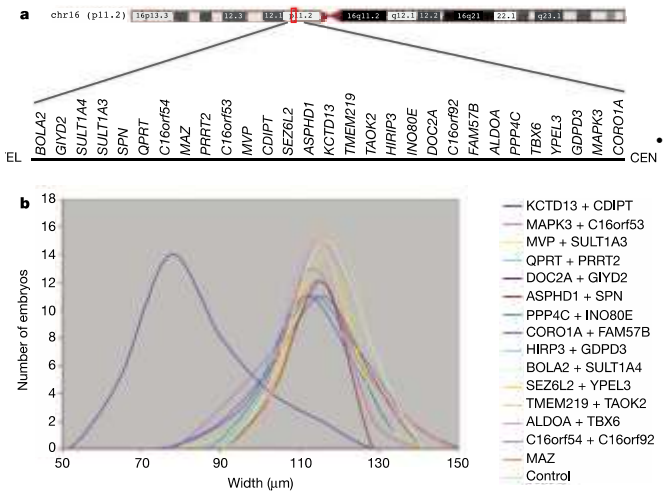
- Ultrasonic vocalizations (USVs) were tested in young adult male 16p11.2 deletion mice during a novel three-phase male–female social interaction test.
- This test detects vocalizations emitted by a male in the presence of an estrous female, how the male changes its calling when the female is suddenly absent, and the extent to which calls resume when the female returns.
- Fewer vocalizations were detected in 16p11.2 deletion males.



Yang et al, Autism Research, 2015

Identifying phenotype-specific genes within CNV regions – 16p11.2

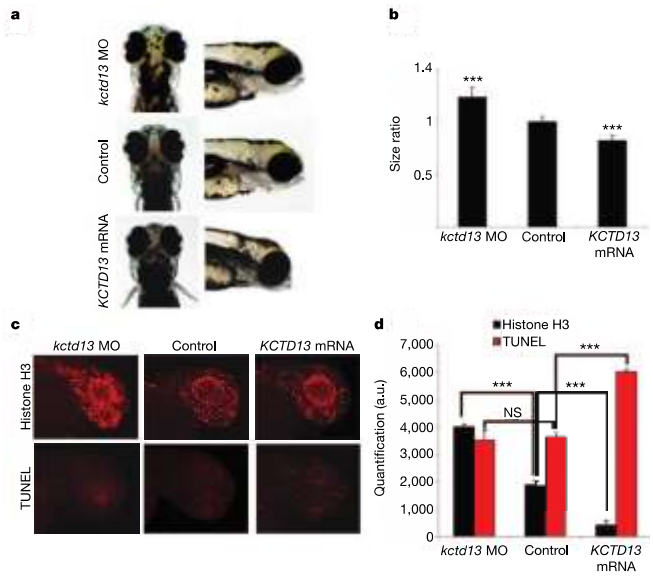
- Golzio et al modeled duplication and deletion of individual genes in zebrafish



- They performed systematic overexpression and downregulation of pairs of genes within the CNV
- Observed microcephaly and macrocephaly phenotype with *KCTD13*

Golzio et al, Nature, 2011

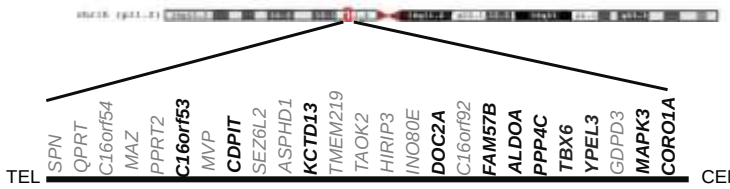
A gene for neuroanatomical features in 16p11.2 CNVs

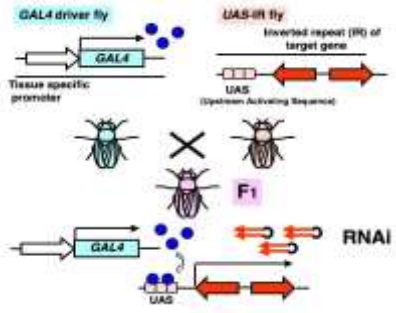


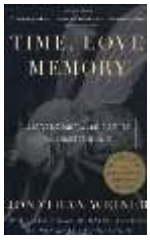
- Increased proliferation (increased phospho-histone 3) or apoptosis (TUNEL) observed with deletion or duplication of *KCTD13*

Golzio et al, Nature, 2011

Using *Drosophila* to assess function of genes within rare CNV regions







- Daughterless-Gal4 : Ubiquitous
- GMR-Gal4 : Eye Specific
- Elav-Gal4 : Nervous system specific
- C5-Gal4 and MS1096-Gal4: Wing

Shoko Nishihara, (2012). **Heritable and inducible RNAi knockdown system in *Drosophila***. Retrieved 20,8,2013 , from http://jcggdb.jp/GlycoPOD/protocolShow.action?nodeId=t32.

http://commons.wikimedia.org/wiki/File:Drosophila-drawing.svg

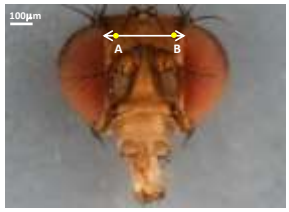
Ubiquitous knockdown of 16p11.2 genes

	Da-Gal4 at 25°C				
Gene Name	**Larval Lethality**	**Pupal Lethality**	**Wing Defects**	**Eye morphology defects**	**No gross Defects**
PPP4C					
ALDOA					
CORO1A					
MAPK3					
TBX6					
FAM57B					
C16ORF53					
CDIPT					
KCTD13					
DOC2A					
YPEL3					
	Early development		**Adult development**		

- > 80% of flies showing phenotype
- < 20% of flies showing phenotype
- < 10% of flies showing phenotype
- 0% of flies showing phenotype

Role in early development:
ALDOA, *PPP4C, CORO1A, TBX6 and MAPK3.*

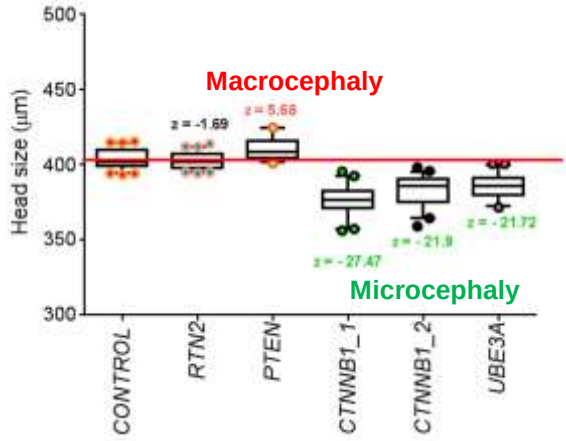
Head phenotypes of 16p11.2 genes



Negative control:
RTN2 - Reticulon

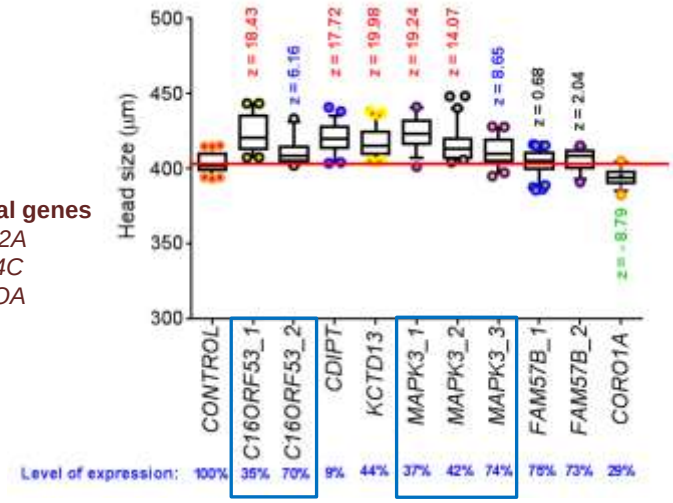
Macrocephaly:
PTEN - Phosphatase and tensin ortholog

Microcephaly:
CTNNB1 – Beta catenin 1
UBE3A – Ubiquitin protein ligase 3A



Head phenotypes of 16p11.2 genes

Lethal genes
DOC2A
PPP4C
ALDOA

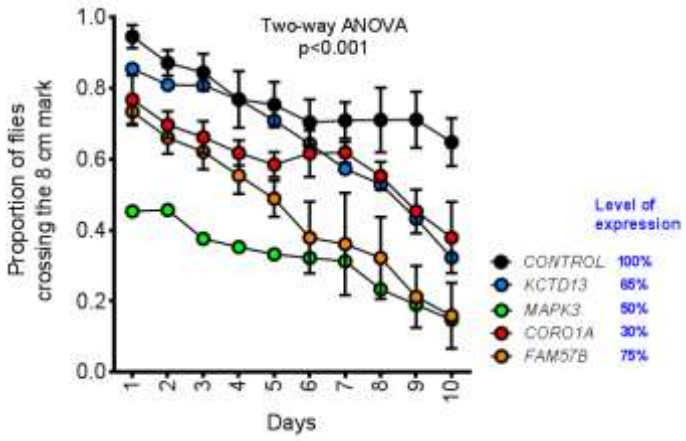


Macrocephaly
C16ORF53
CDIPT
KCTD13
MAPK3

Microcephaly
CORO1A

Dosage dependent severity
C16ORF53
MAPK3

Motor defects of 16p11.2 genes



Potential contributors to motor function :
MAPK3, FAM57B, CORO1A and KCTD13.

Challenges in understanding the molecular mechanisms of autism

- Genetic heterogeneity: Hundreds of genes and genomic regions have been identified as conferring risks for autism
- Phenotypic heterogeneity: variable in severity and frequency of comorbid features
  - Associated with comorbidity of nosologically distinct phenotypes
    - Intellectual disability (68%)
    - Epilepsy (40%)
    - Behavioral and 'emotional' disturbance (30%)

Polyak et al, AJMG, 2015

Common molecular etiology for "distinct" neurodevelopmental phenotypes

15q13.3 deletion
- Mental retardation (Sharp, Nat Genet, 2008)
- Epilepsy (Helbig, Nat Genet, 2009)
- Schizophrenia (Stefansson, Nature, 2008)
- Aggressive behavior (Shachar, JMG, 2009)
- Autism (Pagnamenta, EJHG, 2008)

1q21.1 deletion
- Autism (Szatmari, Nature Genet, 2008)
- Glioblastomas (Veeriah, Nature, 2009)
- Schizophrenia (Stefansson, Nature, 2008)
- Mental retardation (Mefford, NEJM, 2008)
- Heart defect (Greenway, Nat Genet, 2009)
- Cataracts (Mefford, NEJM, 2008)

16p11.2 deletion
- Autism (Weiss, NEJM, 2008)
- Obesity (Walters, Nature, 2010)
- Mental retardation (Rosenfeld, JNDD, 2010)

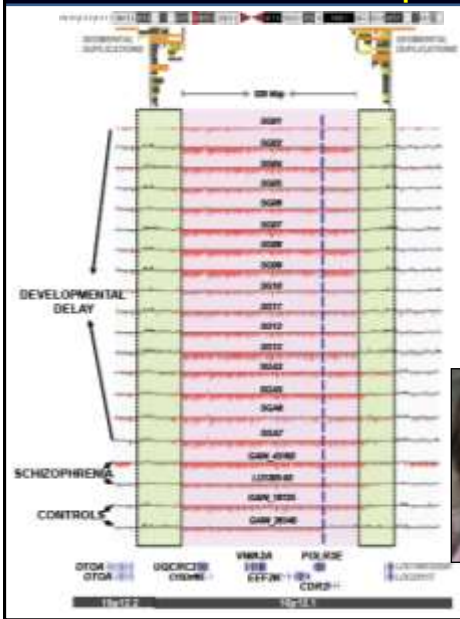
- Also seen in unaffected parents
- Challenge in diagnosis and management

Comorbid features confound diagnosis

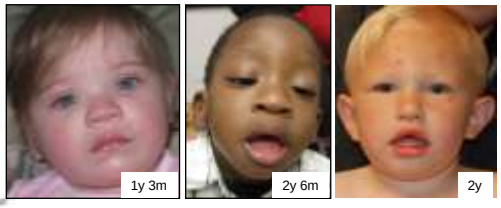
- Comorbid phenotypes confer severity and variability
- Depends on age and genetic background
- This can confound diagnosis and prevalence estimates (see Polyak et al, AJMG, 2015).

http://www.proprofs.com

The 16p12.1 deletion as a paradigm for complex genetics



- Mostly inherited (95%)
- Carrier parents show neuropsychiatric features
  - Variable features within family
- Enrichment (25%) for large CNV (>500kb) second hits in probands
- Clinical features more distinct or severe than that associated with second hit



Girirajan et al. Nat Genet, 2010

A second-site (two-hit) model for 16p12.1 deletion

carrier parents

First hit

16p12.1 microdeletion

High penetrance
Variable expressivity
Subclinical manifestations
Learning disabilities
Psychiatric issues

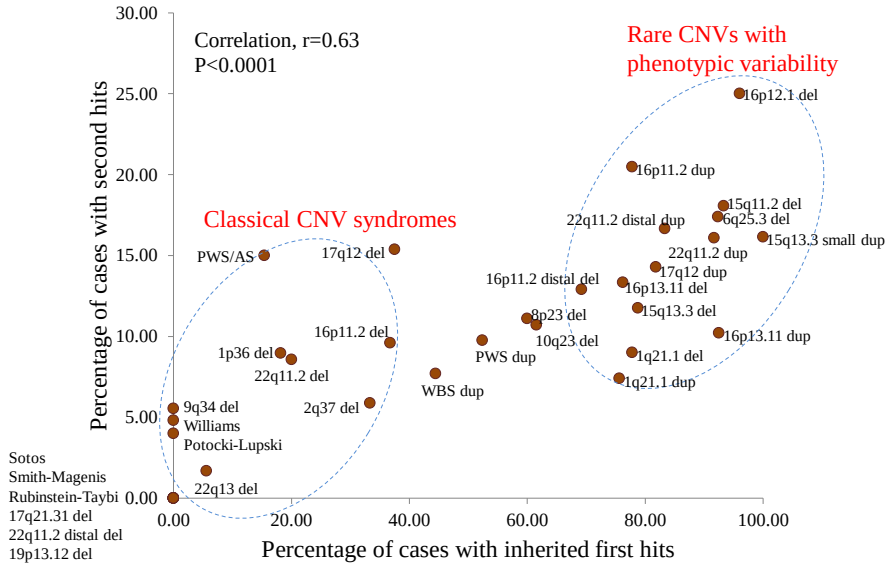
Second-site hit

Large CNV
Single gene mutation
Epigenetic factors
Environmental factors

probands

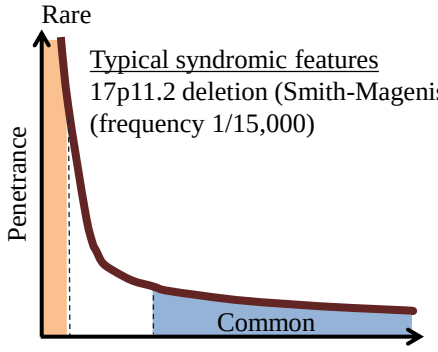
Overt phenotypes
Severe cognitive delay
Craniofacial dysmorphology
Cardiac defects

Second-site hits frequent in CNVs with variable features



Girirajan et al, New Engl J Med, 2012

Summary: Rare CNVs in human neurodevelopmental disorders



Typical syndromic features
17p11.2 deletion (Smith-Magenis)
(frequency 1/15,000)

Variable phenotypes
16p12.1 deletion (1/~2000)

Necessary and sufficient

Haploinsufficiency

Reduced *Rai1*

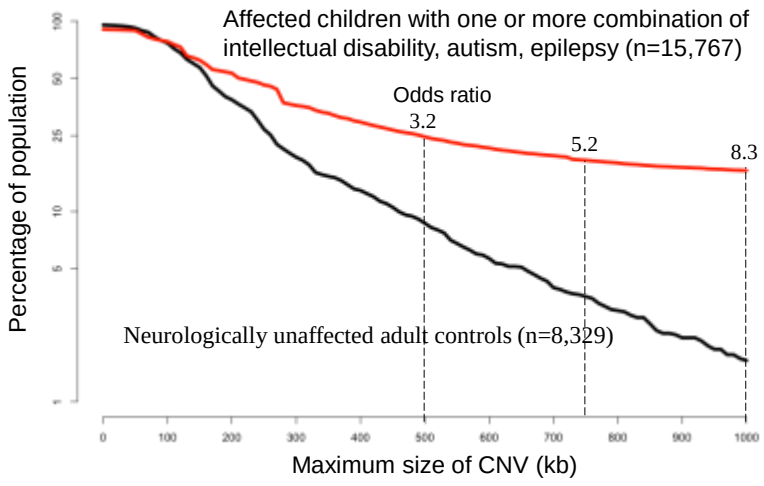
Triplosensitivity

Overexpressing *Rai1*

Necessary but not sufficient

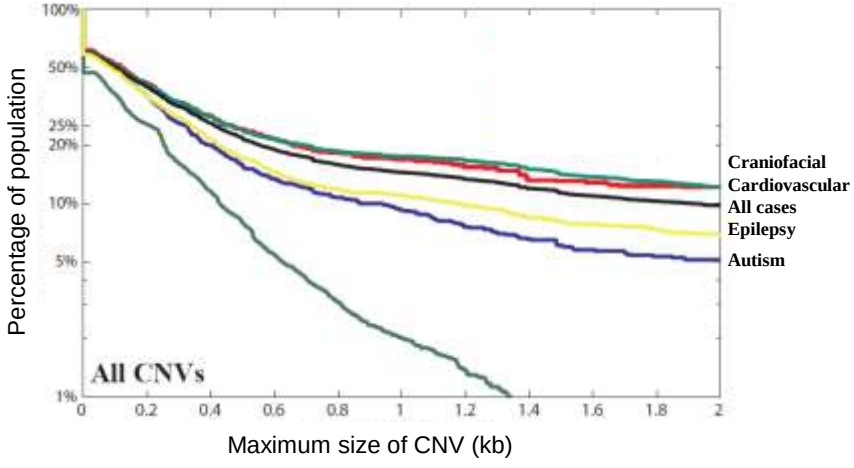
- Contributes towards a continuum of phenotypes in neurodevelopmental disorders
- Other factors play a role in phenotypic heterogeneity and comorbidity

Global assessment of rare and common CNV load



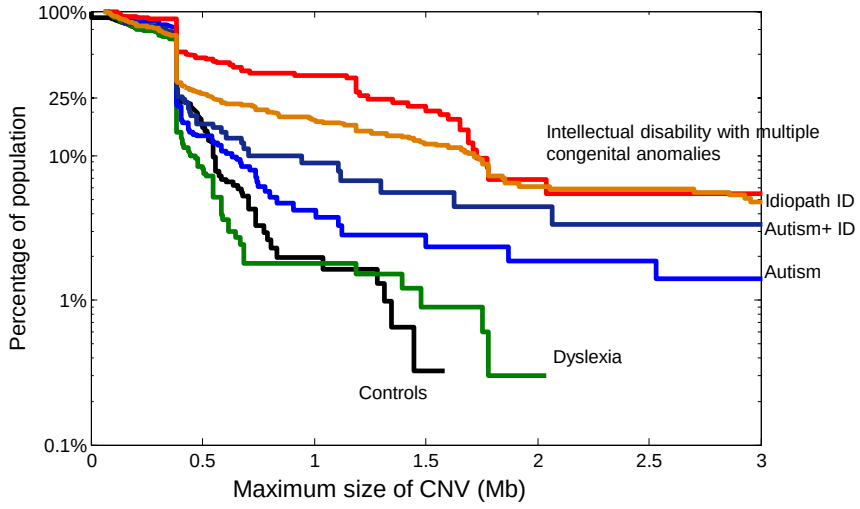
Cooper, Coe*, Girirajan*, et al, Nat Genet, 2011*

CNV load correlates with severity of features



Cooper, Coe*, Girirajan*, et al, Nat Genet, 2011*

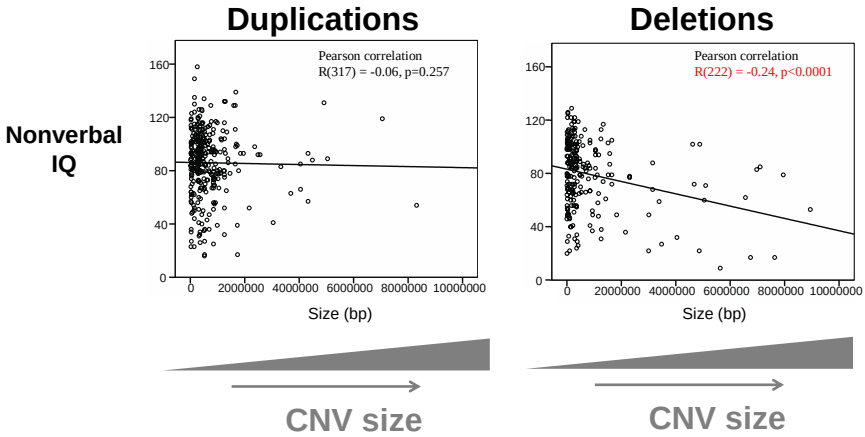
CNV load correlates with a range of neurodevelopmental disorders



Girirajan et al, PLoS Genetics, 2011

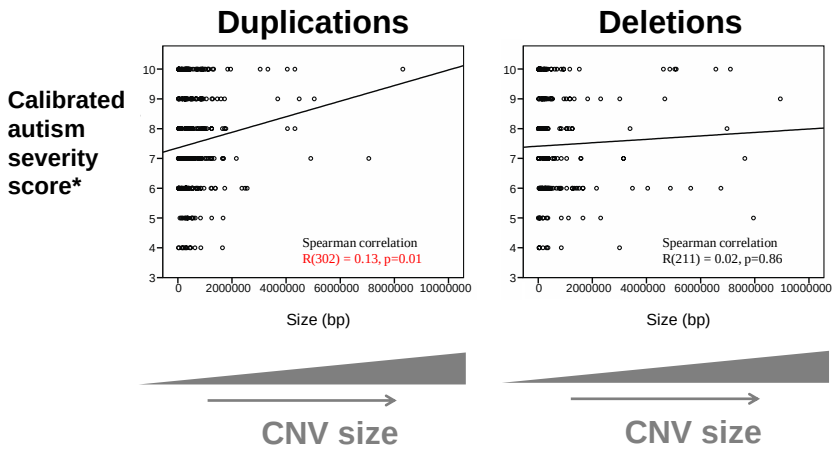
Deletion size associates with intellectual disability severity in autism cohort

2,588 samples analyzed from Simons Simplex Collection



Girirajan*, Dennis* et al, Am J Hum Genet, 2013

Duplication size correlates with autism severity



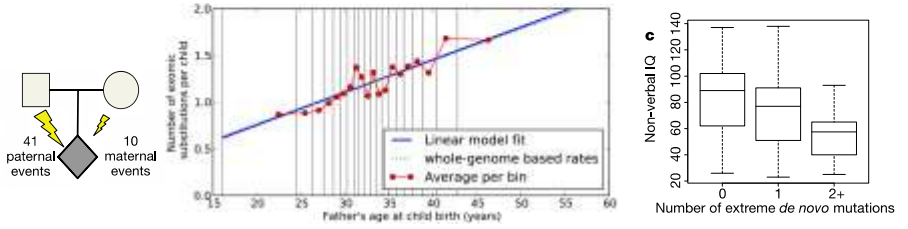
*Age-normalized ADOS score: measures deficits in social communication and repetitive/restricted interests/behaviors

Girirajan*, Dennis* et al, Am J Hum Genet, 2013

Exome sequencing in autism

Exome sequencing has revolutionized disease gene discovery. Several themes have emerged from these studies

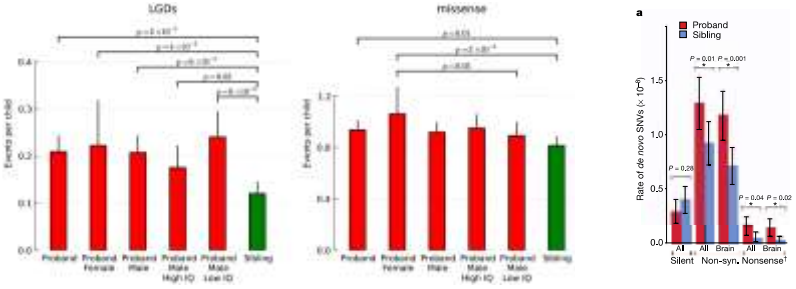
1. Increased paternal age contributes to a higher risk for autism and related disorders
2. Decreased non-verbal IQ is significantly associated with an increasing number of mutational events



O'Roak et al, 2010, 2012, Iossifov et al, 2014, Sanders et al, 2012

Exome sequencing in autism

3. Gene disruptive mutations are more likely to affect Fragile X pathways, chromatin modifiers, embryonic developmental and postsynaptic density proteins
4. Females and males with low IQ require a higher mutational burden than males for manifestation of the phenotype
5. The rate of mutations is significantly higher in probands compared to the siblings



O'Roak et al, 2010, 2012, Iossifov et al, 2014, Sanders et al, 2012

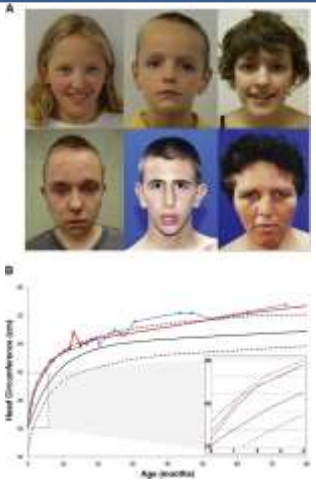
Identification of an autism subtype: *CHD8* mutations

Disruptive *CHD8* Mutations Define a Subtype of Autism Early in Development

Raphael Bernier,[1,19] Christelle Golzio,[2,19] Bo Xiong,[3,19] Holly A. Stessman,[3,19] Bradley P. Coe,[3,19] Osnat Penn,[3] Kali Witherspoon,[3] Jennifer Gerdts,[3] Carl Baker,[3] Anneke T. Vulto-van Silfhout,[4] Janneke H. Schuurs-Hoeijmakers,[4] Marco Fichera,[5,6] Paolo Bosco,[7] Serafino Buono,[7] Antonino Alberti,[7] Pinella Failla,[8] Hilde Peeters,[7,9] Jean Steyaert,[9,9,10] Lisenka E.L.M. Vissers,[4] Ludmila Francescatto,[3] Heather C. Mefford,[11] Jill A. Rosenfeld,[12] Trygve Bakken,[13] Brian J. O'Roak,[14] Matthew Pawlus,[15] Randall Moon,[15,16] Jay Shendure,[3] David G. Amaral,[17] Ed Lein,[18] Julia Rankin,[17] Corrado Romano,[5] Bert B.A. de Vries,[4] Nicholas Katsanis,[2] and Evan E. Eichler[3,16,*]

Patient	12714.p1	13986.p1	Nij023486	APP_09580 – 100	11654.p1	13844.p1	14016.p1	Troina2659	12991.p1	12752.p1	Troina2037	Nij – 010878	14233.p1	14406.p1	Nij07 – 06546	Observed N (% of Sample)
Sex	M	M	F	M	F	M	M	M	M	F	F	M	M	M	M	
Age at testing (years)	4	5	15	6	12	8	8	13	16	4	41	11	16	13	17	
Macrocephaly	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	12 (80%)
Prominent supraorbital ridge	u	u	+	–	+	u	+	+	+	u	+	–	u	u	+	7/9 (78%)
Hypertelorism	u	u	+	+	+	u	+	–	+	u	+	–	u	u	–	6/9 (67%)
Down-slanted palpebral fissures	u	u	+	–	+	u	+	+	–	u	+	–	u	u	+	6/9 (67%)
Flat feet	u	u	–	–	–	u	–	–	+	u	–	–	u	u	+	2/9 (22%)
Tall	+	+	+	+	+	+	+	+	–	u	–	+	+	+	+	12/14 (86%)
Overweight	–	–		–	–	–	–	–	–	u	+	+	–	+	–	3/14 (21%)
ASD	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	13 (87%)
Intellectual disability	–	+	+	+	+	+	–	+	+	–	+	–	+	–	–	9 (60%)
Attentional problems	–	–	+	+	+	–	–	–	+	+	+	+	+	+	–	9 (60%)
Anxiety problems	+	–	–	–	–	–	+	–	+	+	–	–	–	–	–	4 (27%)
Seizures	–	–	–	–	+	–	+	–	+	–	–	–	–	–	–	3 (20%)
Regression	+	–	+	+	+	+	–	+	–	–	–	–	+	–	–	7 (47%)
GI problems	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	12 (80%)
Sleep problems	–	+	+	+	+	–	+	–	+	+	–	–	+	+	+	10 (67%)
C section	–	–	–	–	+	–	–	+	+	+	–	–	–	–	+	5 (33%)
Birth induction/ augmentation	+	+	–	–	+	–	+	–	+	–	–	–	–	+	–	6 (40%)

+, present; –, absent; u, unknown. Detailed phenotypic data are outlined for each patient in the above domains in Table S5. Where a denominator is indicated, unknown values were excluded from the percent of sample calculation.



Bernier et al, Cell, 2014

Summary: Genetics of autism

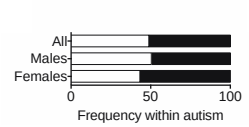
- Syndromic autism, genome-wide association studies, linkage
- Rare CNVs
- Syndromic CNVs (Smith-Magenis syndrome)
- CNVs associated with autism
- Example of 16p11.2 deletion (~1% of autism)
  - 16p11.2 mouse models
  - 16p11.2 zebrafish models
  - 16p11.2 fly models
- Heterogeneity of autism
- 16p12.1 deletion as
  - Multiple genetic hits and comorbid features
- Exome sequencing
  - Identifying subtypes of autism

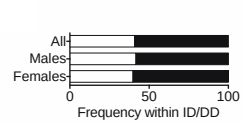
Sex differences in autism and intellectual disability

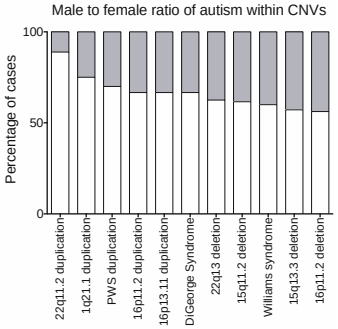
- There is a documented sex bias in autism with a diagnosis skewed towards males than females (4:1 ratio for autism and 2:1 for intellectual disability)
- Recently a female protective genetic model has been proposed where females require a higher genetic load compared to males to manifest autism
- We tested various factors affecting the genetic and phenotypic heterogeneity associated with autism
  - Frequency of comorbid features
  - Male to female ratio for specific rare CNVs
  - Burden of copy-number variants
  - Frequency of family history of neurodevelopmental features

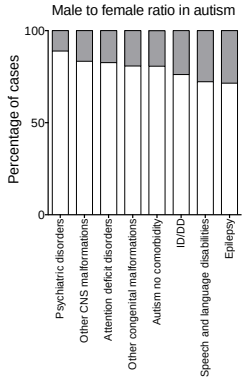
Sex differences in autism and intellectual disability

- Frequency of comorbid features
- Male to female ratio for specific comorbid features and specific CNVs

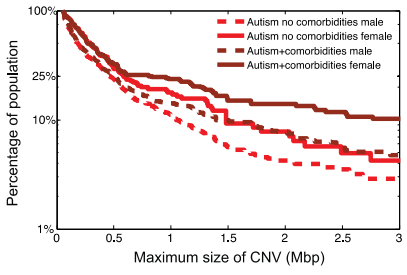


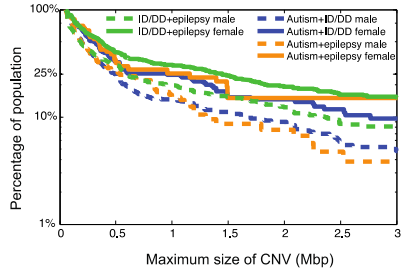






CNV load is higher in females than males with autism

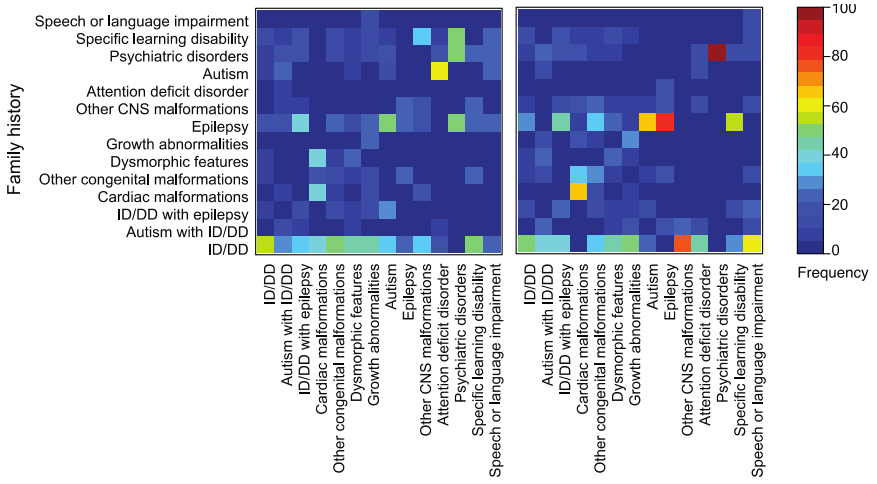




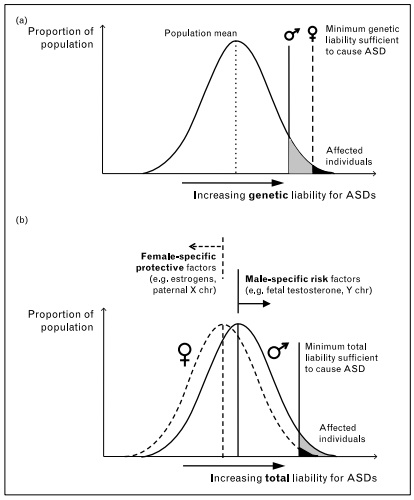
- Higher CNV load in females compared to males for autism, intellectual disability and ASD co-occurring with ID or epilepsy
- Epilepsy in autism is significantly associated with intellectual disability
  - Individuals with autism manifesting with epilepsy are more likely than those without epilepsy to have intellectual disability

Polyak et al, unpublished

Females require a higher genetic load in the background than males



A genetic liability model for autism



Werling et al, 2014, Reich et al, 1975

Conclusions

- Autism is a heterogeneous disorder ranging in severity and variability of associated features
- Recent technological advances have greatly improved our understanding of the molecular etiology of autism
- Genetic heterogeneity is extensive and will generate a large set of candidate genes as diagnostic markers and for therapies
- Detailed genetic and iterative phenotypic evaluations will help identify subtypes of autism
- Functional evaluation of the identified genes in model systems are important to map the molecular basis of autism and to devise targeted therapies
- There is an increasing need for multidisciplinary collaborative team of teachers, clinicians, parents, and researchers for addressing the challenges associated with autism

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