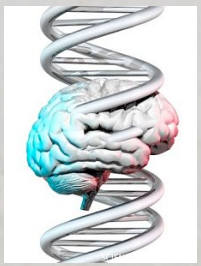
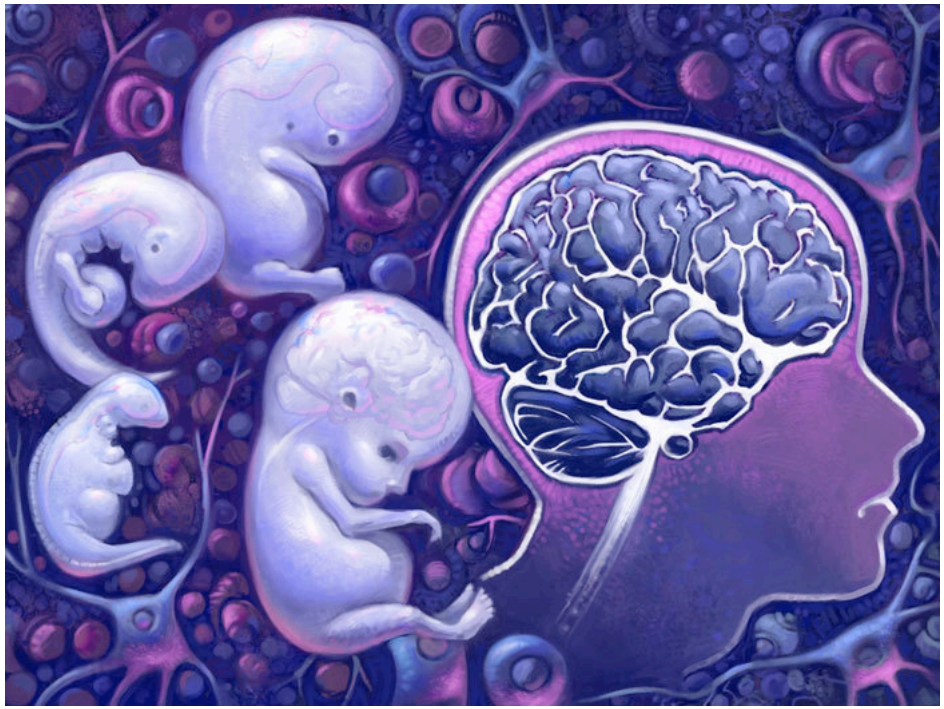
Understanding Neurodevelopment – Challenges and Aspirations in Child and Adolescent Mental Health

15th ESCAP Conference
Dublin 2013

Prof Louise Gallagher
TCD



Why do we need to understand typical and atypical neurodevelopment?



Will understanding neurobiology lead to improvements in diagnosis, treatment, prevention, quality of life?

Neurodevelopmental disorders

- Communication disorders
- Learning disorders
- Autism
- Chronic tic disorders
- ADHD
- Schizophrenia
- Psychosis

Categorical diagnoses in DSM 5

Deficits - language, social cognition, attention, sensory-motor functioning

What have we learned about atypical neurodevelopment?

- Example from Rett Syndrome
- Autism Spectrum Disorders
- Converging neurobiology of neurodevelopmental disorders
- Challenges to integrating understanding neurodevelopment
- Aspirations for the future of neurodevelopmental research

Rett Syndrome

- Early onset neurodevelopmental disorder
- Similarities to ASD
- Predominantly girls
- Well defined syndrome – 4 clear stages of progression:
  1. Stagnation
  2. Regression (6-18 months)
  3. Seizure development
  4. Late motor deterioration

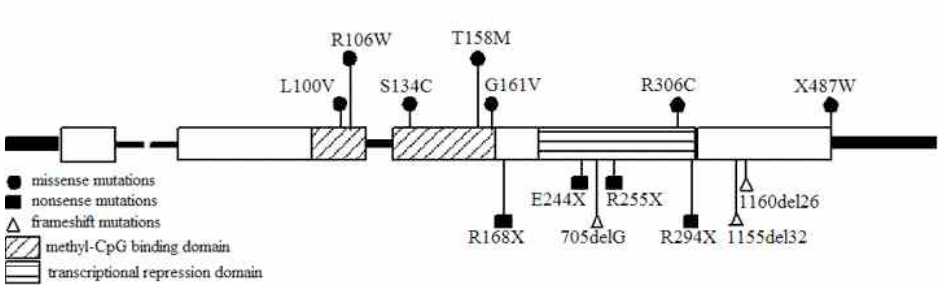
Rett Syndrome – A Rare Neurodevelopmental Syndrome with a Genetic Aetiology

Andreas Rett, 1966

- Physical phenotype
  - Small hands and feet
  - Deceleration of head growth (→ microcephaly)
- Behavioural phenotype
  - social withdrawal,
  - repetitive hand movements,
  - avoidance of eye contact
  - lack of social/emotional reciprocity
  - Impaired nonverbal behaviors
  - Breathholding
- Physical phenotype
  - GI disturbances
  - Seizures
  - Sensory disturbances

Discovery of a gene for Rett

- MECP2 (xq28) – de novo or germline mutations
- CDKL5, FOXG1 ~ 10% cases
- Duplication of MECP2 in males
- MECP2 – Methyl-CpG binding protein – 3 binding domains



Zoghbi et al, 1999

Rett syndrome – phenotypic differences

Phenotypes Associated with *MECP2* Mutations in Human Females

Characteristic	Phenotype for		
	Classic RTT[a]	Mild RTT Variants[b]	Severe RTT Variants[c]
Age at onset	Onset between 6–18 mo	Later onset	Congenital onset
Head/body size	Small head, body	May have small head, body	Small head, body
Seizures	Seizures		Early seizure onset
Speech	Loss of speech	Speech is preserved	
Motor function	Motor deficiencies	Usually ambulatory	Hypotonia, motor deficiencies
Hand use	Stereotypical hand motions	Retain hand use	
Social Interactions	Autistic features		
Intelligence	Mental retardation	Mild or no mental retardation	Mental retardation
Spinal curvature	Scoliosis and/or kyphosis		Scoliosis and/or kyphosis
Respiration	Breathing dysfunction		Breathing dysfunction

[a] Null alleles or severe inactivating mutations, balanced XCI.

[b] Hypomorphic alleles (late truncations) with balanced XCI or null alleles with favorably skewed XCI. (Very late truncations and some missense mutations, such as A140V and Q406X, result in no phenotype in females even when XCI is balanced. These same mutations do, however, produce phenotypes in males.)

[c] Null alleles or severe inactivating mutations, possibly due to unfavorably skewed XCI.

From Shahbazian and Zoghbi, 2002

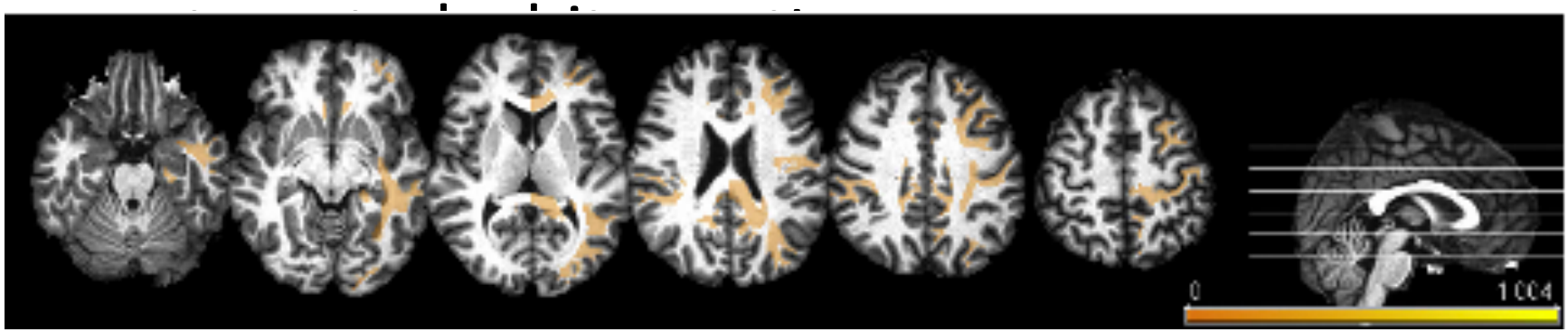
Rett syndrome - Neurochemistry

- **Pontine noradrenergic deficits**
  - ⬇ NA functioning, NA excitability in locus coeruleus
  - ⬇ TH mRNA expression in mouse models (-/- male and -/+ female)
  - ⬇ TH expressing neurons and density of dendritic arborizations – immature neurons
  - Implicated in both respiratory and cognitive dysfunctions

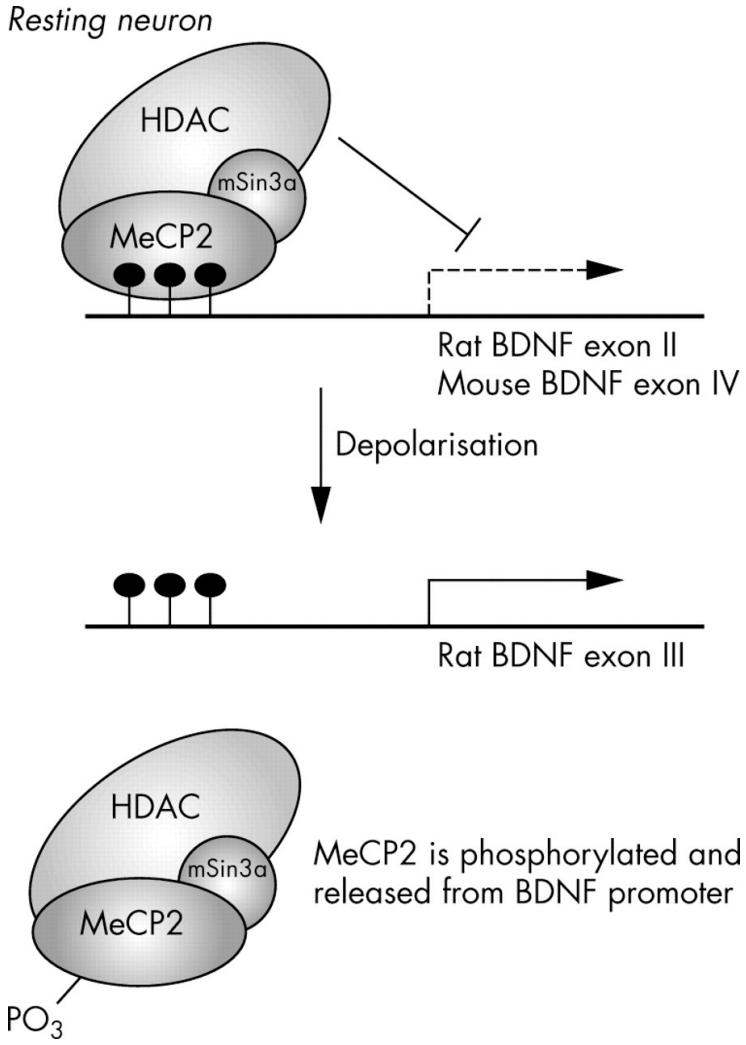
- **Midbrain dopaminergic disturbances**
  - Nigrostriatal dopaminergic deficits – hypothesised to underpin motor abnormalities
  - ⬇ TH immunoreactivity in caudate-putamen om -/- mouse model
  - ⬇ DA – midbrain and striatal regions – PM animal studies -/- model
  - Changes remain static but behavioural phenotype and deficits progress
  - Oral L-DOPA administered to mouse model ---- amelioration in some motor deficits

Rett – brain structure

- Global brain atrophy – frontal, occipital and dorsal parietal
- Structural neuroimaging - ↓ FA in left peripheral white matter areas - middle temporal, middle occipital, pre-cuneus and



Oishi et al, 2013


Resting neuron
HDAC
mSin3a
MeCP2
Rat BDNF exon II
Mouse BDNF exon IV
Depolarisation
Rat BDNF exon III
HDAC
mSin3a
MeCP2
PO3
MeCP2 is phosphorylated and
released from BDNF promoter

Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice

Daniela Tropea[a,1], Emanuela Giacometti[b,1], Nathan R. Wilson[a,1], Caroline Beard[b], Cortina McCurry[a], Dong Dong Fu[b], Ruth Flannery[b], Rudolf Jaenisch[b,c,2], and Mriganka Sur[a,2]

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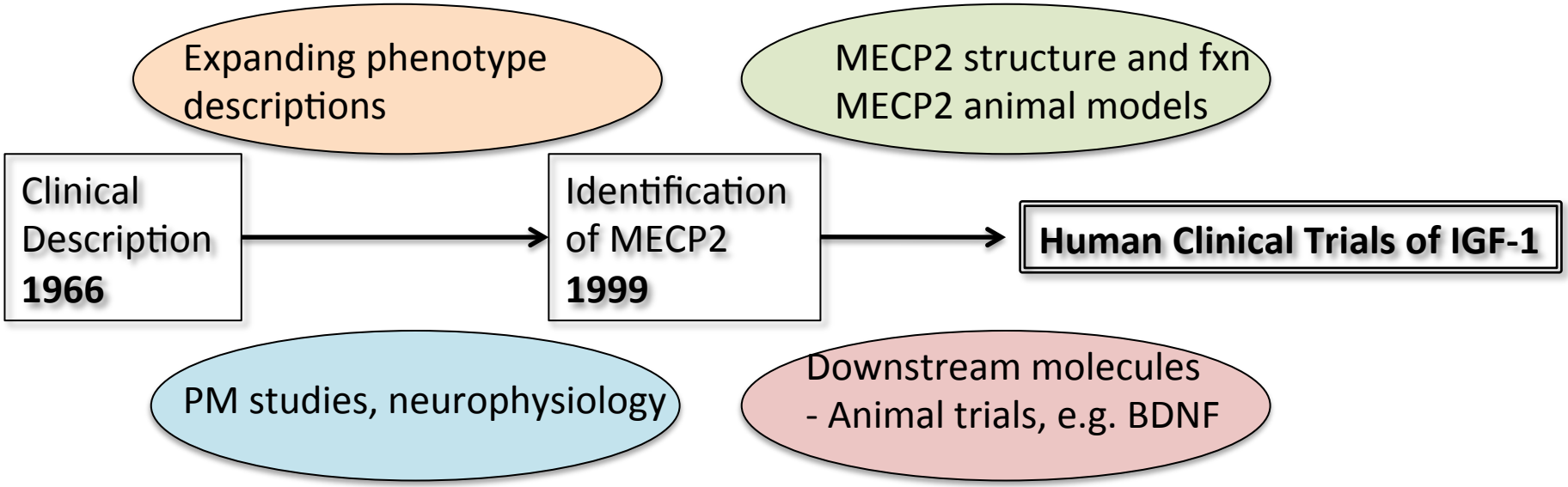
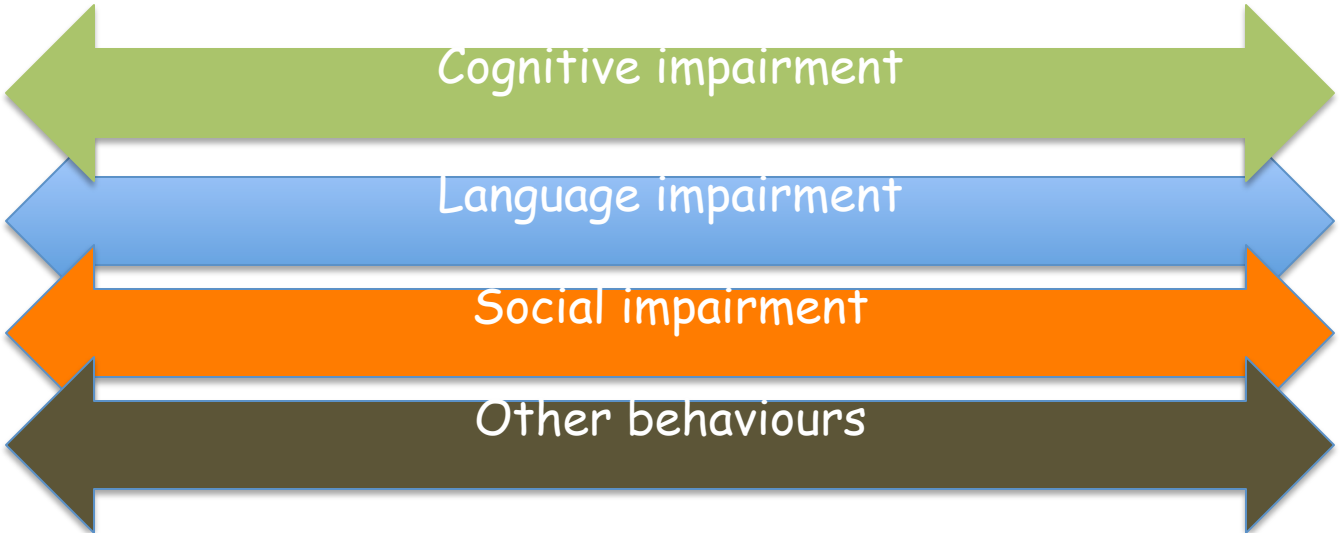
Contributed by Rudolf Jaenisch, December 11, 2008 (sent for review November 9, 2008)

Rate of progress towards potential treatments for Rett Syndrome



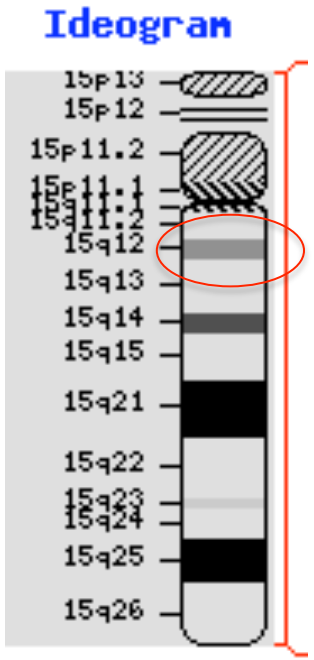
Autistic Spectrum Disorders



Autism Genetics

Higher rates of autism in MZ twins compared with DZ twins

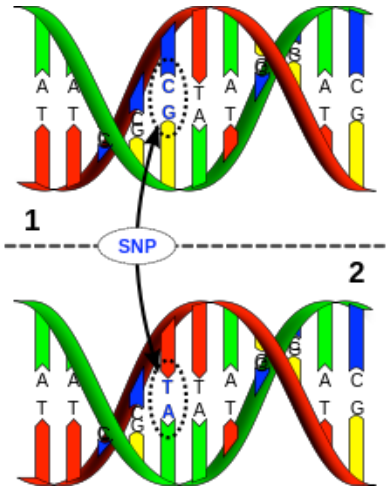
Higher rates of autism in first-degree family members



Chromosomal anomalies known to cause autism

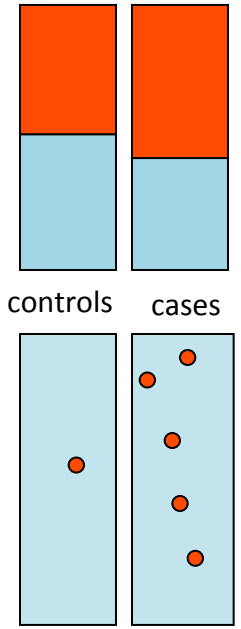
Genetic risk factors

Changes in coding sequence



Common – Greater frequency in population with a trait compared with controls, mild increase in the odds of having a trait

Rare – Very low frequency – Significantly increase the odds of having a trait



Changes in chromosome structure

Amplification Copy Number 6

1 Copy Duplication Copy Number 3

Normal Copy Number 2

1 Copy Deletion Copy Number 1

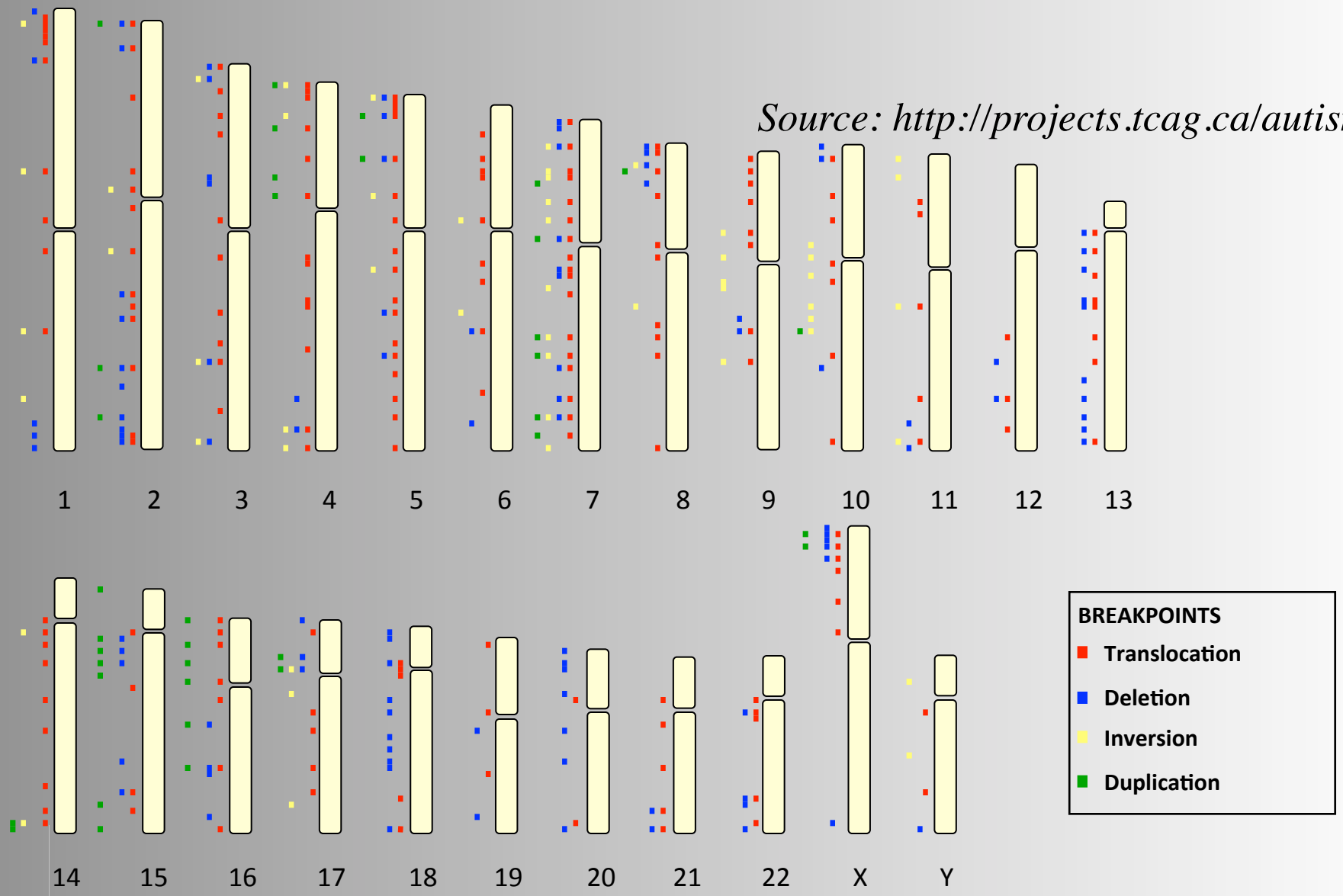
2 Copy Deletion Copy Number 0

Identifying the genetic risk factors in ASD

- Given a heritable component, how have we *attempted* to discover the genetic risk loci underpinning the family and heritability data?

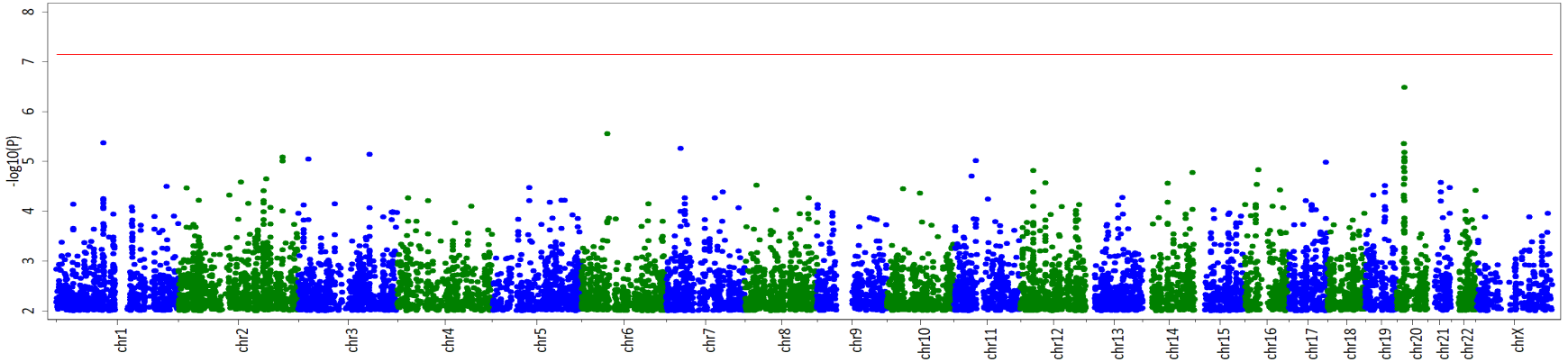
1. Gross chromosomal anomalies (Syndromal autism)
2. Linkage
3. Association
4. Structural variation
5. Sequence variation

Cytogenetically-visible breakpoints in autism



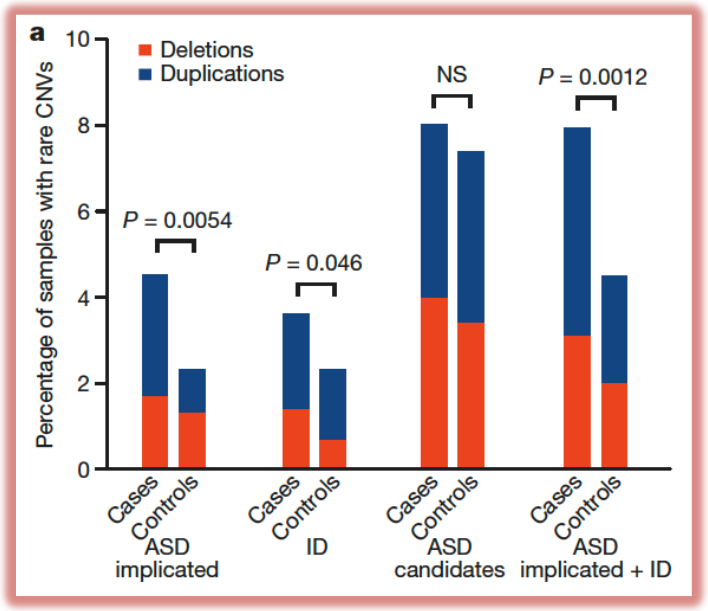
Genome-wide Association Studies: Major Findings

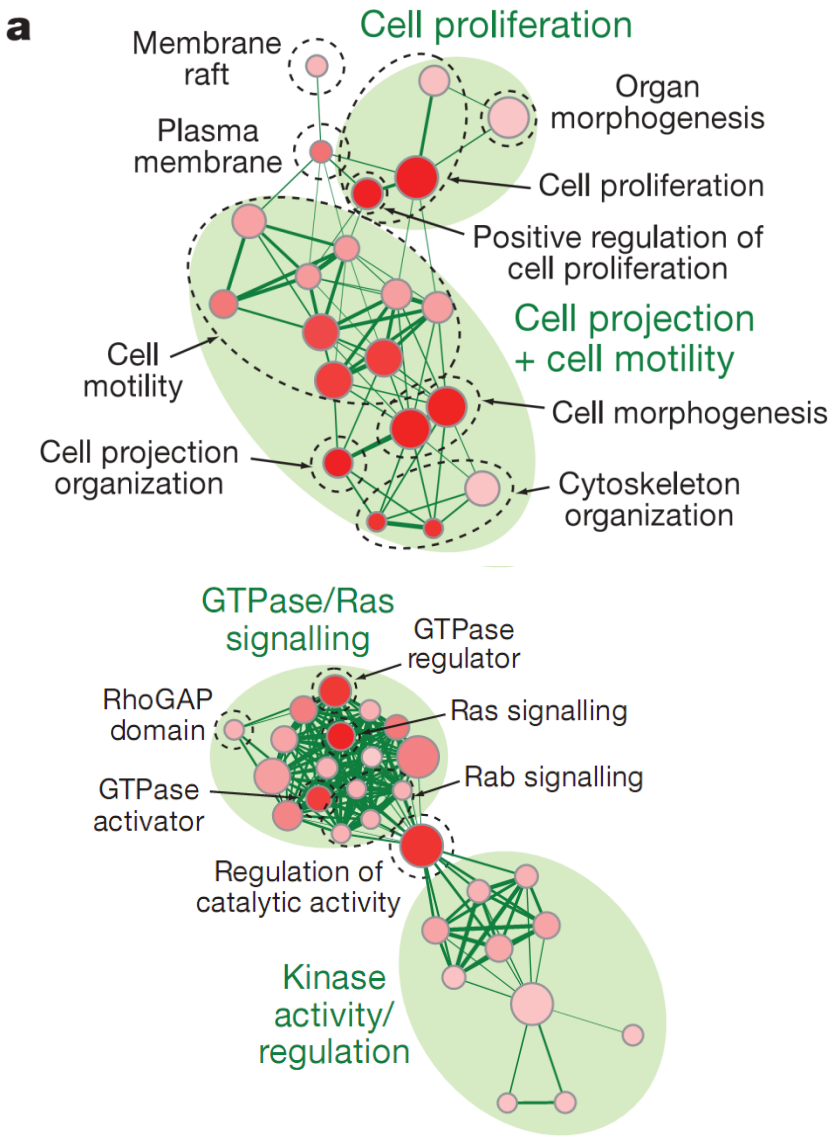
Manuscript	Sample Size	Array Size	Major Findings
Wang et al., 2009	>900	500K	CDH9/CDH10
Weiss et al., 2009	>800	500K	TAS2R1/ SEMA5A
Anney et al., 2010	>1300	1M	MACROD2
Devlin, Anney., in prep	+1000	1M	
PGC., in prep	>5000	>1M	



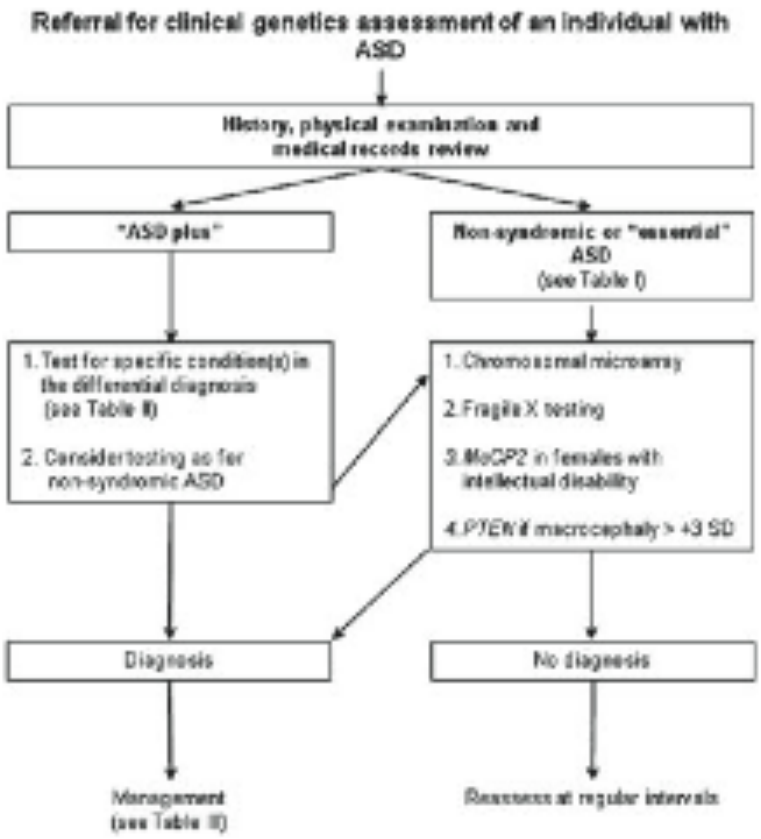
Published in final edited form as:
Nature. 2010 July 15; 466(7304): 368–372. doi:10.1038/nature09146.

Functional Impact of Global Rare Copy Number Variation in Autism Spectrum Disorder





Implications for diagnosis

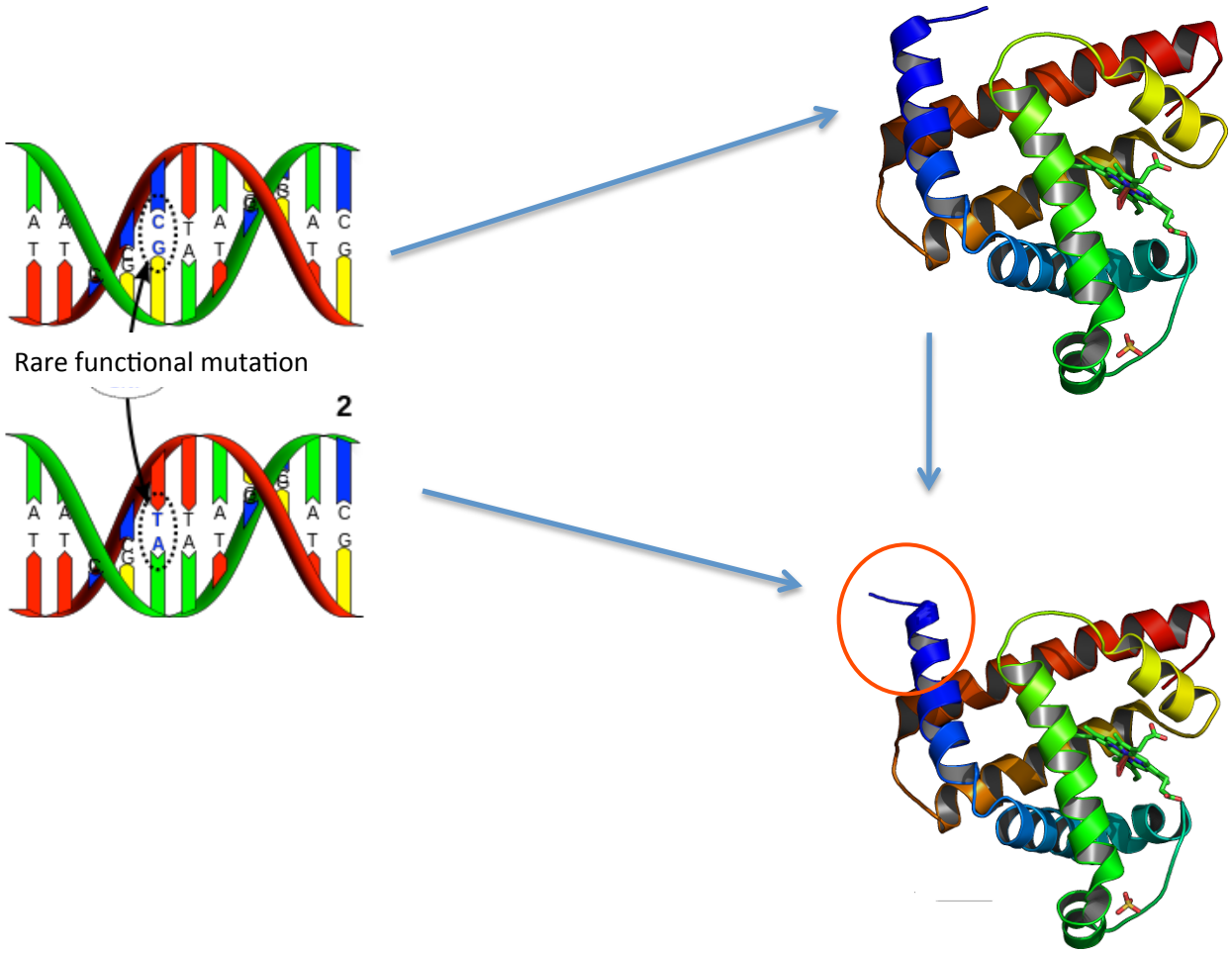


- Specific genetic aetiology in up to 15%
- Single gene disorders - Fragile X syndrome, Rett syndrome, TS, PTEN mutations
- Microscopic – Trisomy 15q, sex ch aneuploidy, lg deletions, duplications
- Submicroscopic → CNV at 16p11.2, 15q11-13, 22q11.2, Rare 'de novo' CNV

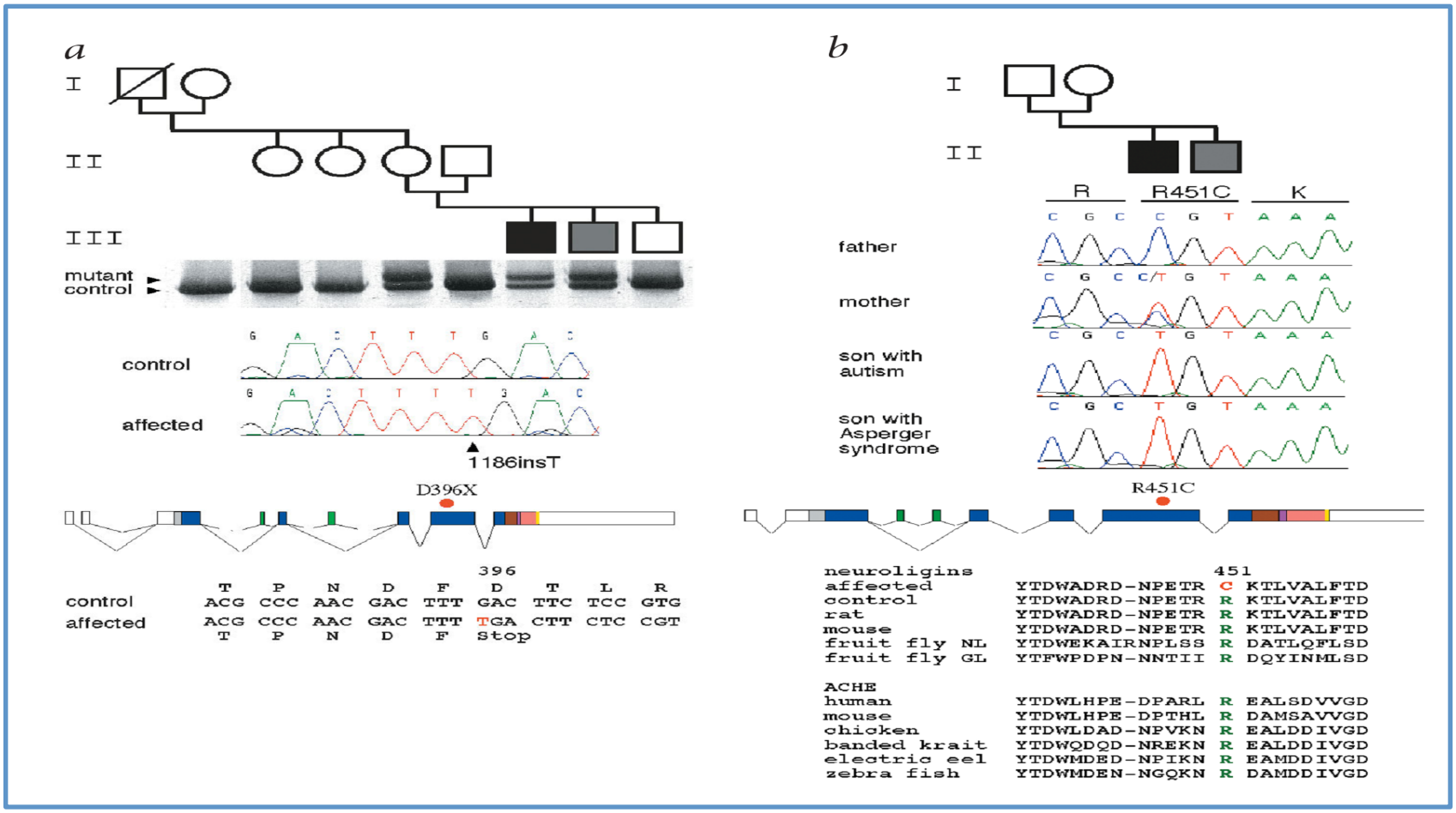
- 'ASD plus' → syndromic or 'complex'
- Non-syndromic → non-syndromic, healthy, normal growth, no major congenital abnormalities

Carter and Scherer, 2013

Rare sequence variants

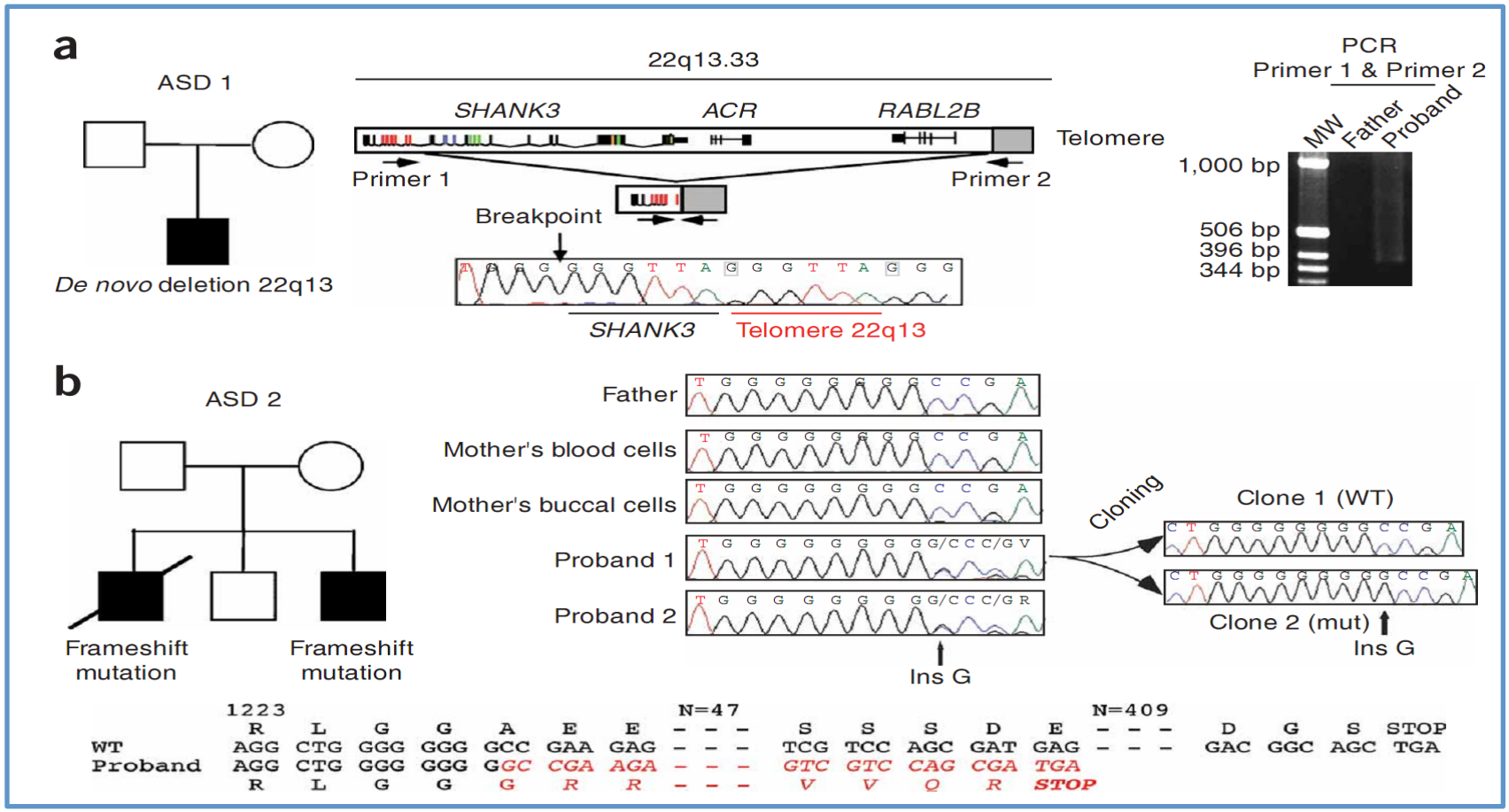


Family-based re-sequencing of NLGN3 and NLGN4



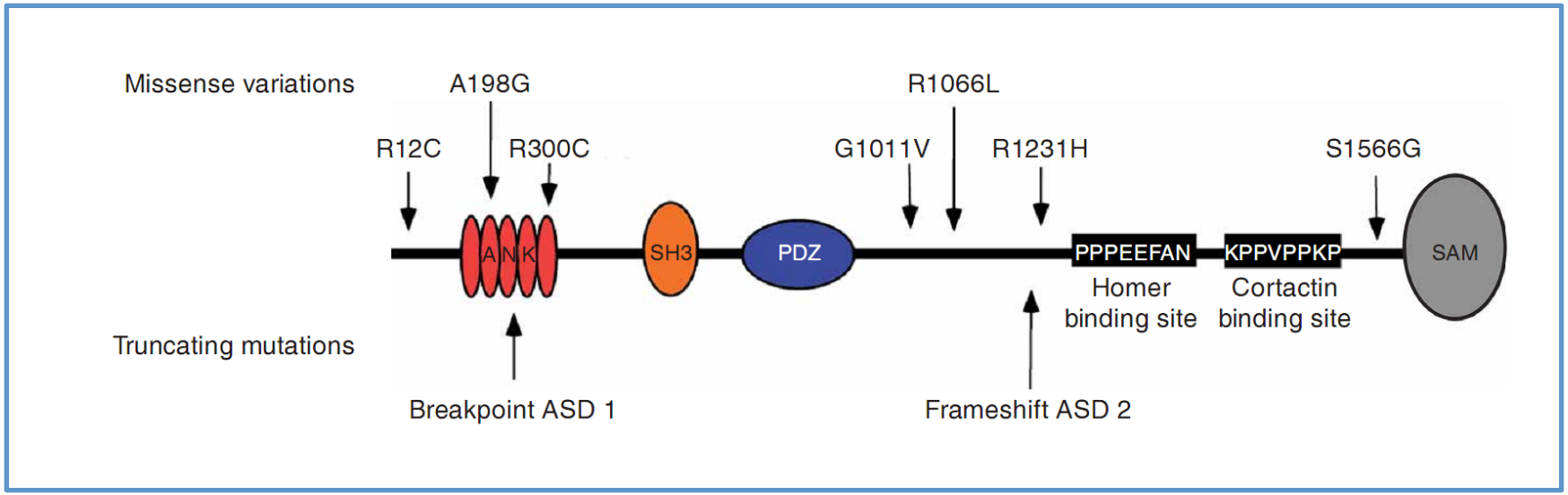
- Jamain et al., 2003, Nature Genetics

Family-based re-sequencing of SHANK3



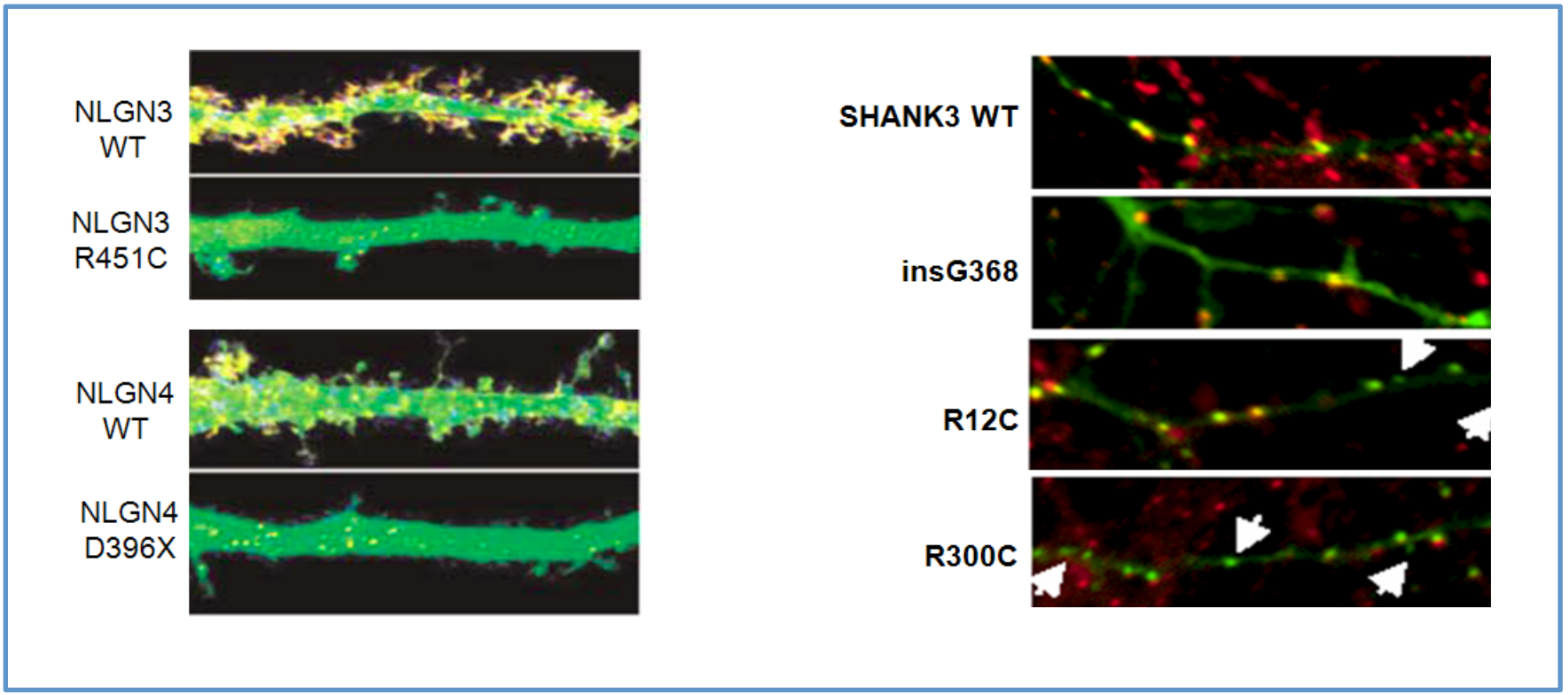
- Durand et al., 2007 Nature Genetics

Family-based re-sequencing of SHANK3



- Durand et al., 2007 Nature Genetics

Functional implications of Mutation



Impact on Synapse validation

- Chih et al., Hum. Mol. Genetics, 2004

Impact on Neuronal wiring?

- Durand et al. Nature Genetics 2007

Courtesy of Thomas Bourgeron. INSERM, Paris

Emerging models of synaptic proteins

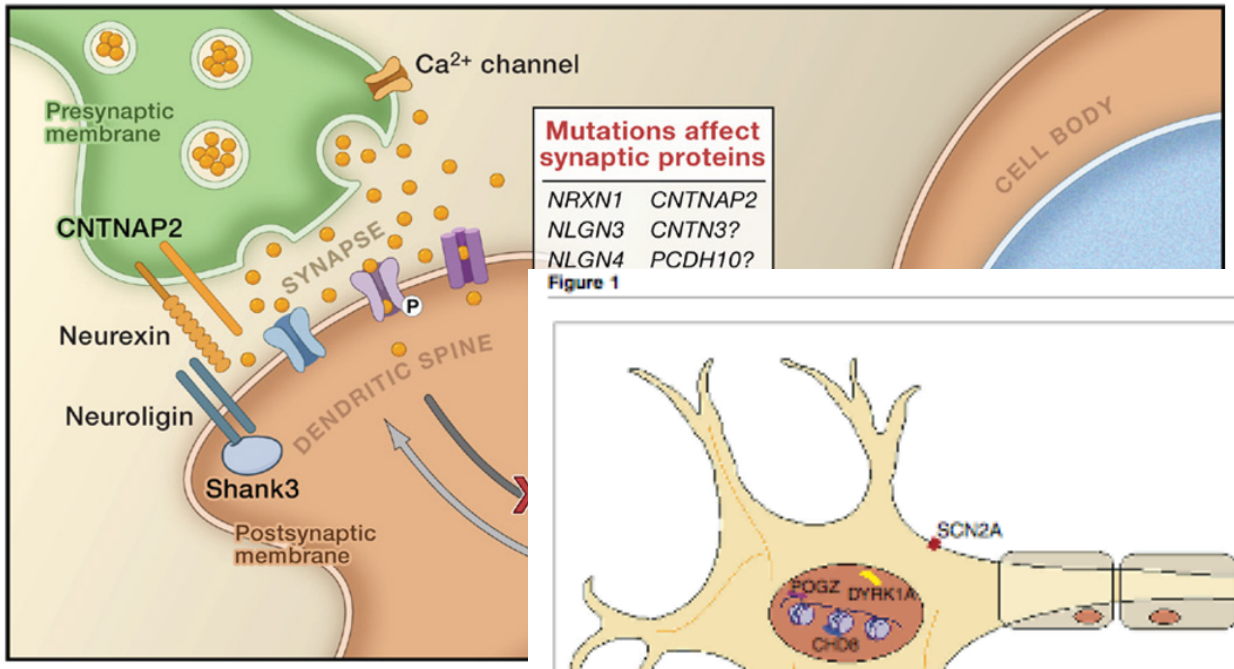
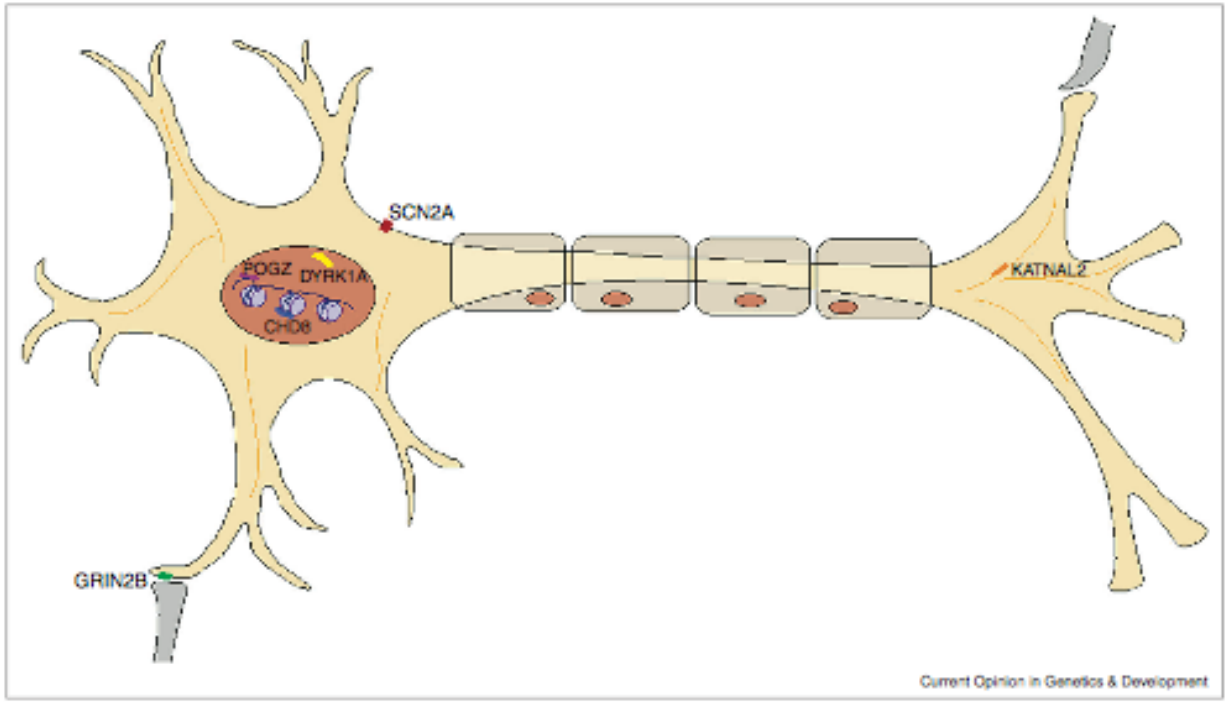
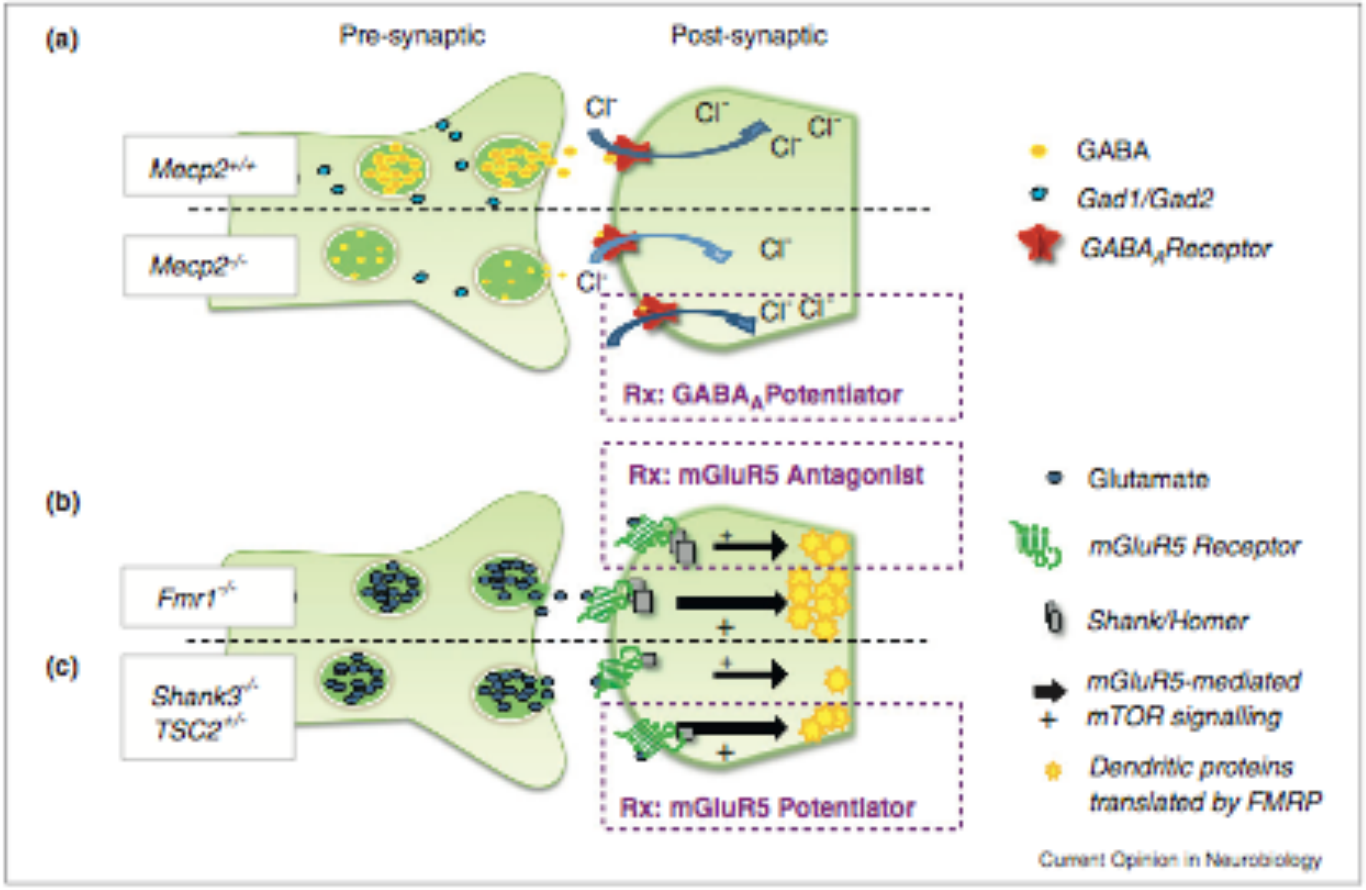


Figure 1



Cellular localization, within a representative neuron, of proteins implicated in recent whole exome studies and accompanying follow-up sequencing. Implicated functions include chromatin remodeling/transcriptional regulation (CHD8), DNA binding/mitotic activity (POGZ), nuclear kinase activity (DYRK1A), microtubule binding/severing (KATNAL2), glutamate receptor (GRIN2B), and voltage-gated sodium channel (SCN2A) [EntrezGene].

Animal models of neurodevelopmental disorders and therapeutics



Challenges to integrating what we have learned

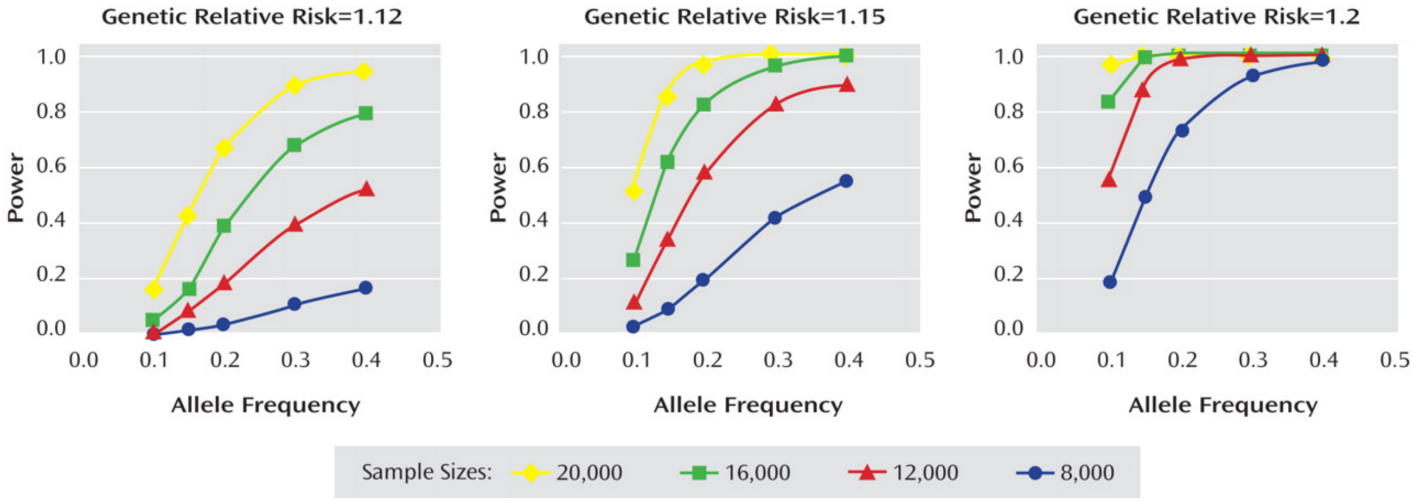
- Genetics - Replication and further discovery will require 10s of 1000s of samples
- Imaging the brain provides correlational findings that are difficult to integrate with genetic data
- Overlapping neurobiology between disorders – is there any specificity to symptoms?
- Brain is an inaccessible organ. Inadequate model systems – neuroblastoma cells/ mouse models

THE AMERICAN JOURNAL OF PSYCHIATRY

psychiatryonline

From: Genomewide Association Studies: History, Rationale, and Prospects for Psychiatric Disorders

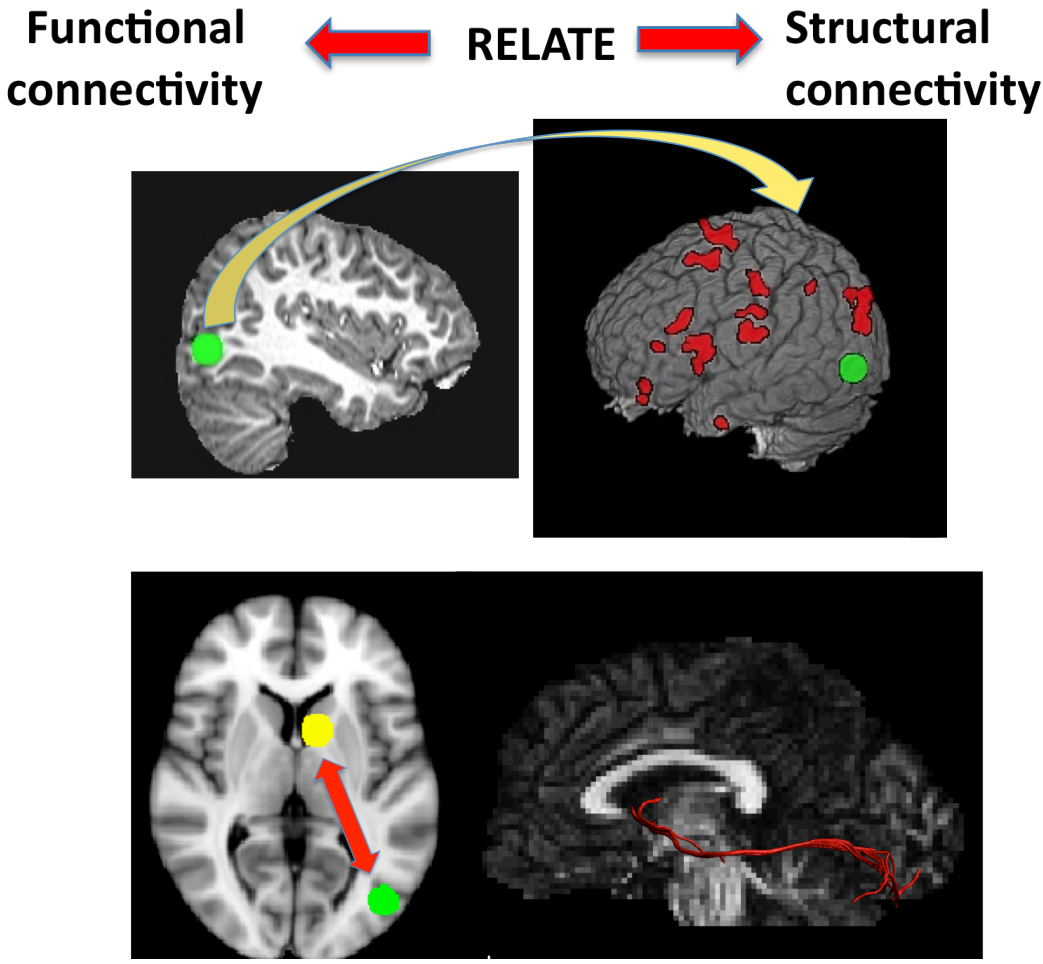
Am J Psychiatry. 2009;166(5):540-556. doi:10.1176/appi.ajp.2008.08091354



- Large clinical databases
- International samples
- Reduction in phenotype definition – increase phenocopies

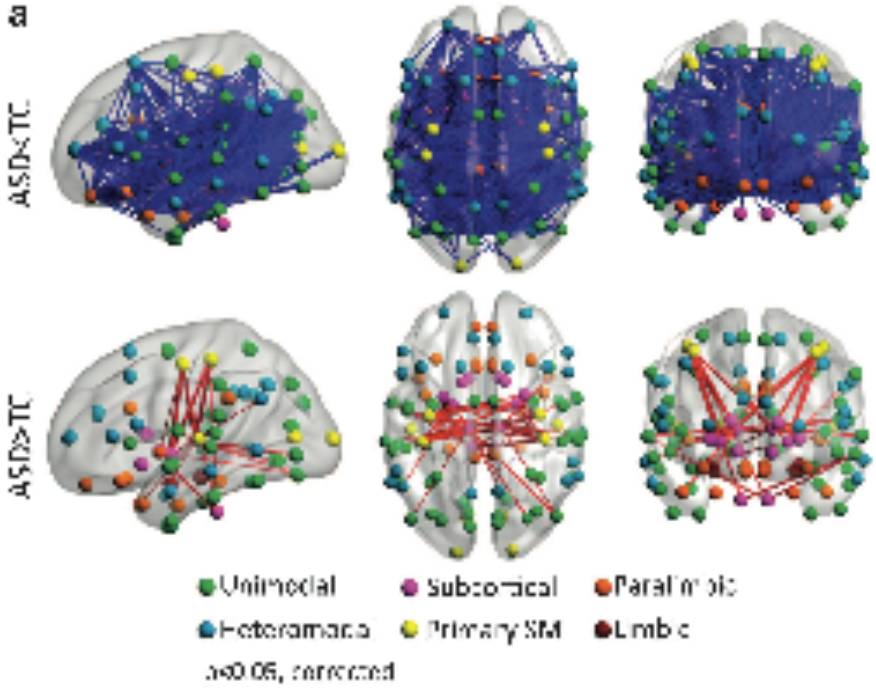
Evidence for altered brain connectivity in autism

- Long range hypoconnectivity
- Short range hyperconnectivity
- Resting state - hypoconnectivity



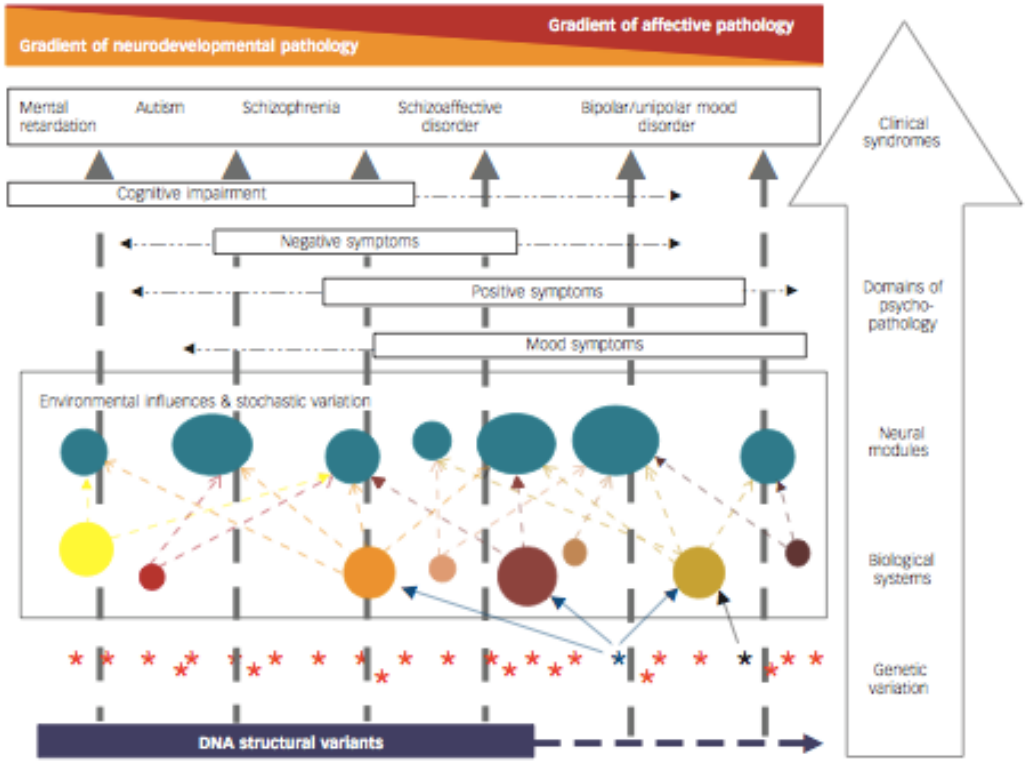
McGrath et al

Resting state hypoconnectivity



Di Martino et al, 2013

- ↓ cortico-cortical iFC – esp paralimbic and unimodal association areas (FG, STG)
- ↓ lobar connecitivity – esp temporal
- ↑ Connectivity sub-cortical regions –primary parietal sensorimotor regions
- Alterations in interhemispheric connectivity
- Suggestive of maturational abnormalities in ASD



Craddock and Owen, 2010

ID/ ASD

Asperger syn ADHD Tics

Psychoses

Prenatal/ infancy

Early-mid childhood

Adolescence/ early adulthood

Normal brain development

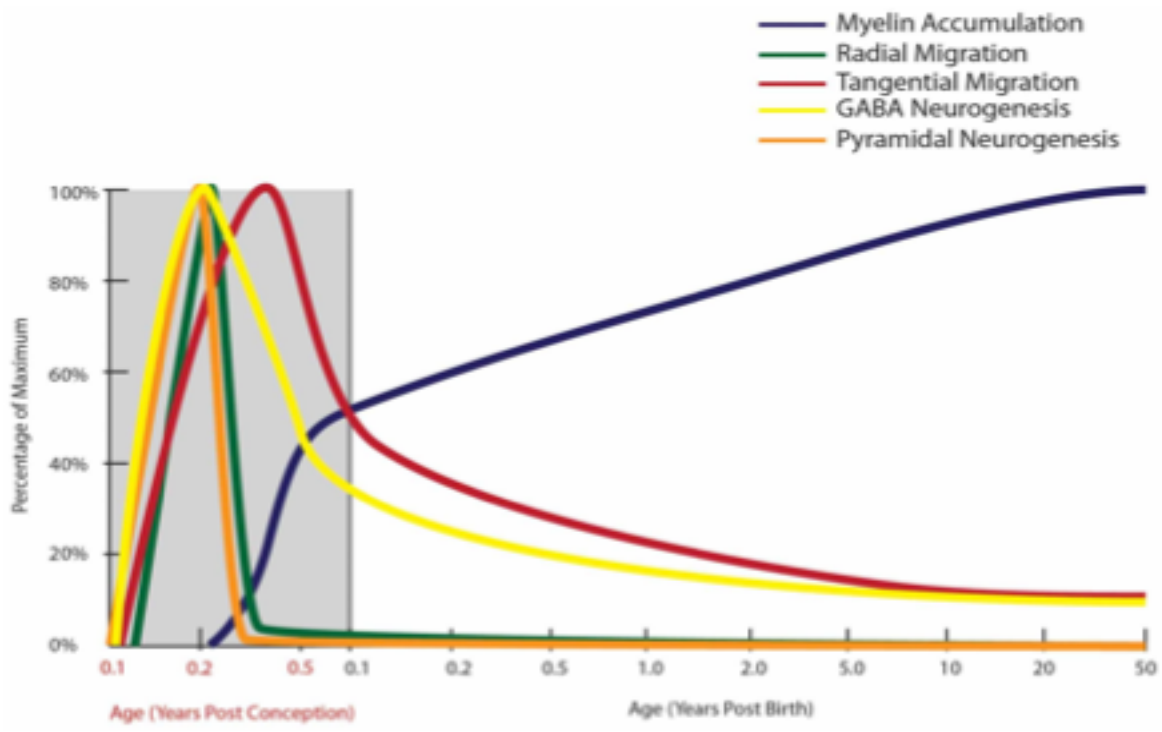


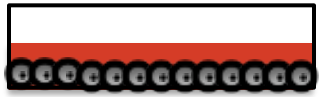
FIGURE 2 | Normal developmental trajectory of neurogenesis, neuronal migration, and myelination in the human. Neurogenesis and the subsequent migration of neurons to the cortex begin within a few weeks of gestation in the human (Zecevic et al., 2011). Pyramidal neurogenesis and migration of these cells to the cortex occurs by radial migration and is completed by mid-gestation (Nadarajah and Parnavelas, 2002), while genesis and migration of GABAergic interneurons continues into early post-natal life, with emerging evidence based on the presence of molecular markers of immature neurons suggesting that this process continues into adulthood in primates (Gould et al., 1999, 2001; Bernier et al., 2002; Fung et al., 2011a; Wang et al., 2011). Prefrontal myelination occurs predominantly in early post-natal life, still increasing through adolescence before reaching adult levels (Kang et al., 2011).

Induced pluripotent stem cells (iPS cells)

adult cell

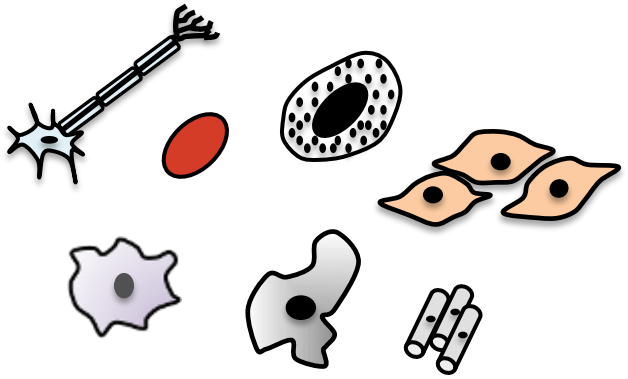
'genetic reprogramming'
= add certain genes to the cell

induced pluripotent stem (iPS) cell
behaves like an embryonic stem cell



culture iPS cells in the lab

differentiation



all possible types of specialized cells

Advantage: no need for embryos!

EuroStemCell

REMEDI

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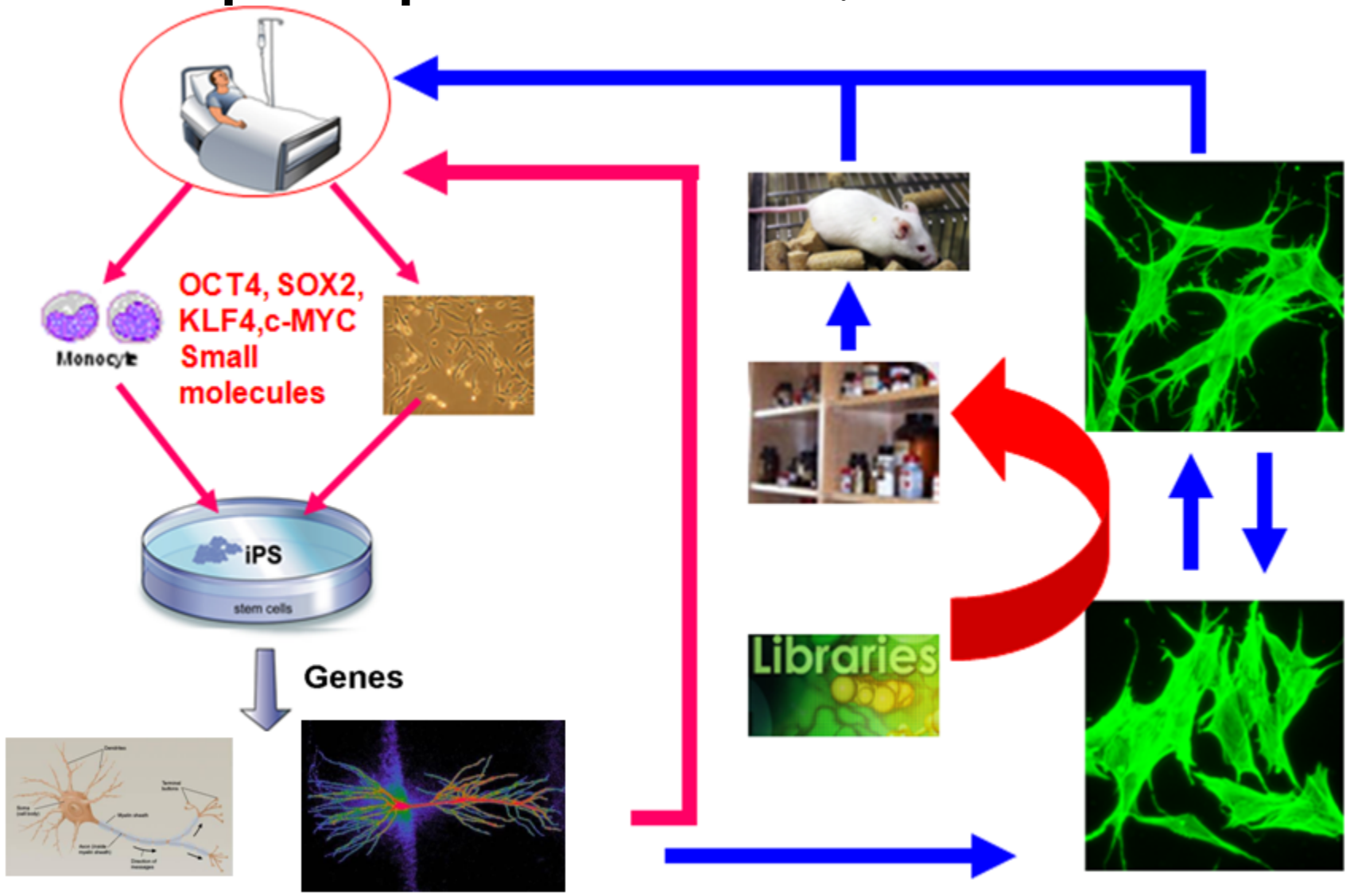
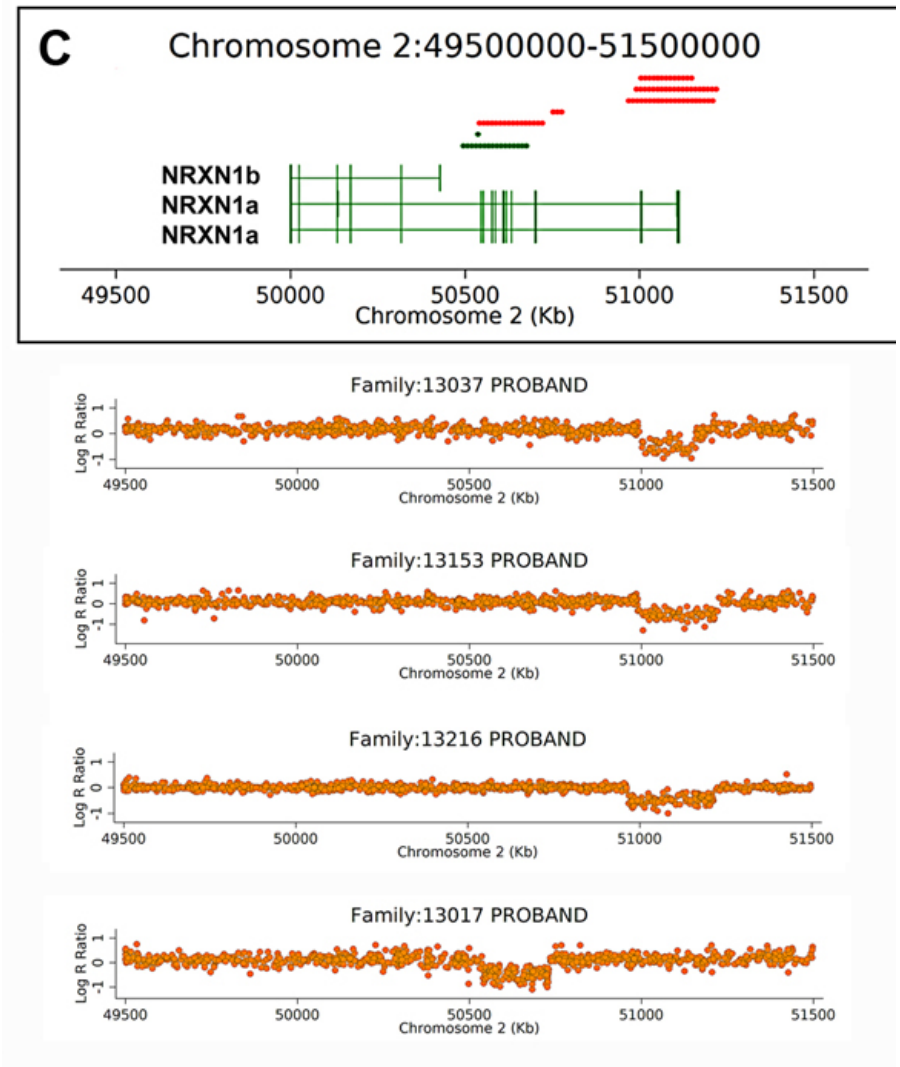
MRC Medical Research Council

Future directions – Induced pluripotent stem cells

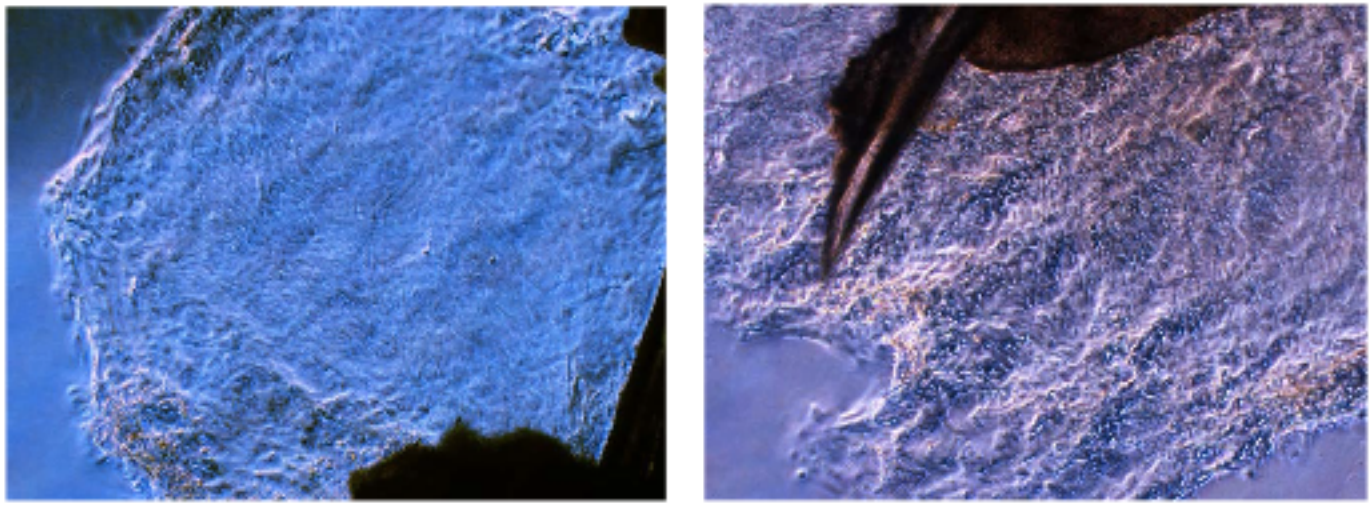


Disruption of Neurexin 1 gene in Irish Families



Stem cells – Neurexin 1 deletion

ASD biopsy



Indepth phenotyping patients:

- Neurocognitive
- Neuroimaging
- Physical
- Behavioural

Cell line phenotyping:

- Electrophysiology
- Molecular – test molecular compounds
- Morphology

Summary

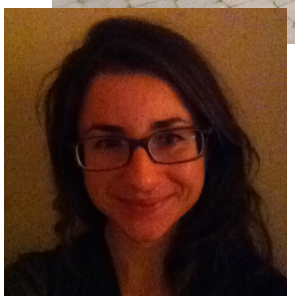
- Genetics research has not been in vain! – Emerging neurobiology of neurodevelopmental disorders
- Genetic diagnosis is a reality for a small number of individuals with ASD
- Convergence between the emerging neurobiology and changes observed in functional and structural neuroimaging
- Potential new technologies to interrogate brain function and possibly aid the development of new therapies
- Caution! – we still need to understand the role of development and the relationship between perturbations in the neurobiology and symptoms
- Dimensional approach to symptoms – may aid our understanding of the co-occurrence of symptoms between disorders but we need to figure out why the symptoms are different too!

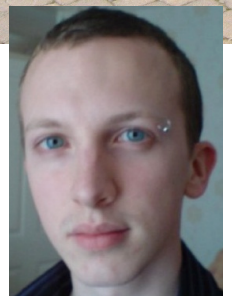
“Genes and family may determine the foundation of the house but time and place determine its form”

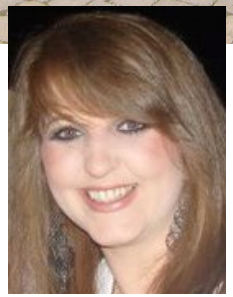
(Jerome Kagan)

THE MEATH FOUNDATION

Supported by
wellcome trust







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