

Neurogenetic Basis of Autism and Epilepsy



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Disclosures

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History

- 1943 - Leo Kanner
- 1944 - Hans Asperger



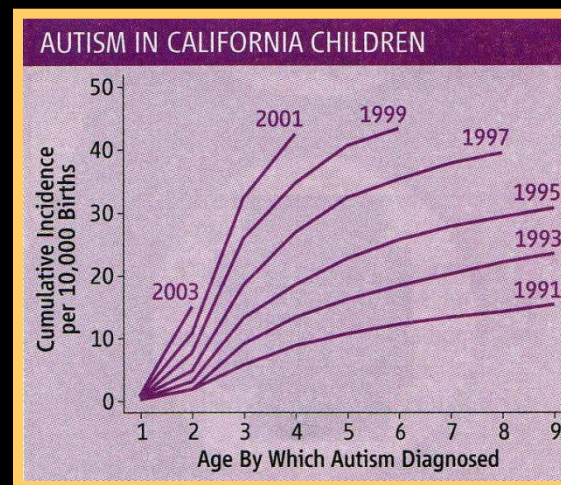
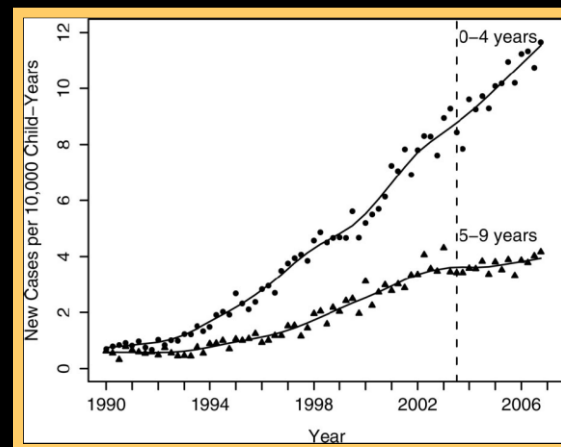
Kanner L (1943) *Nerv Child* 2:217–250.

Asperger H (1944) “Autistic psychopathy” in childhood (translated and annotated).
In: Frith U (ed) (1991) *Autism and Asperger syndrome*. Cambridge University Press, Cambridge UK, pp 37–92.

Epidemiology

- Prevalence – 9.0 per 1000 age 8.
- Male:female ratio – 4.5:1
- 1 in 110 children (1:80 to 1:240)

Chakrabarti S, Fombonne E. *Am J Psychiatry*. 2005;162:1133–1141.
Fombonne E *J Clin Psychiatry*. 2005;66(suppl 10):3– 8.
Centers for Disease Control and Prevention. *MMWR Morbid Mortal Wkly Rep*. 2006;55:481– 486.
Hertz-Picciotto I, Delwiche L. *Epidemiology* 2009;20: 84–90.
Holden C. *Science* 2009; 323: 565.
Rice C, et al. *MMWR Surveill Summ*. 2009;58(10):1-20.



Diagnostic Criteria

- Qualitative impairment in **social interaction**.
- Qualitative impairments in **communication**.
- Restricted **repetitive and stereotyped** patterns of behavior, interests, and activities.
- Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: social interaction, language as used in social communication, or symbolic or imaginative play.
- Not Rett or Childhood Disintegrative Disorder
Childhood.

Coexisting Diagnoses

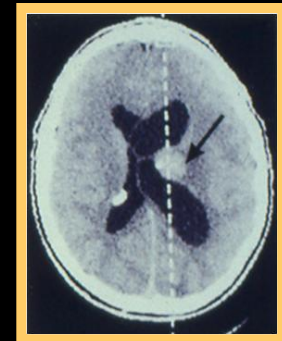
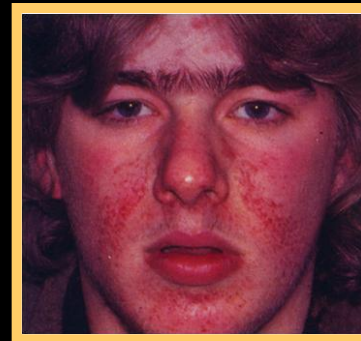
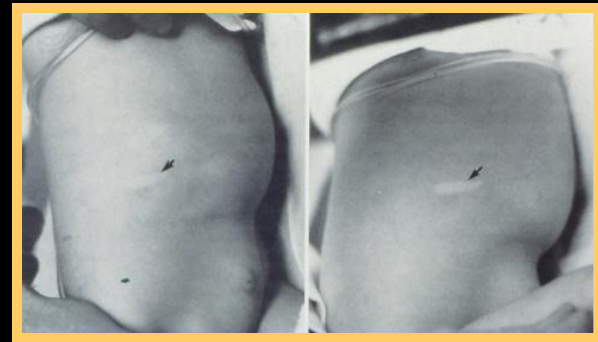
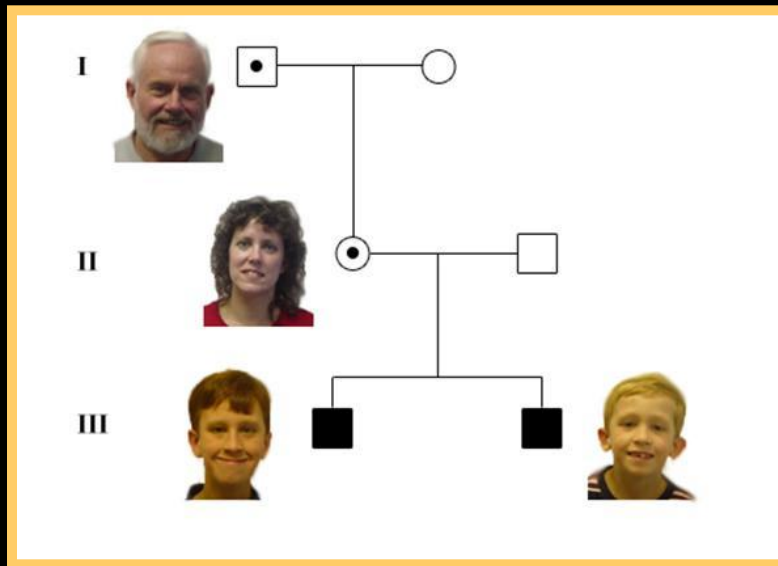
- Seizures (25%) (6%-40%)
- Mental Retardation (28%) (26%-30%)
- Repetitive behaviors (OCD/stereotypies)
- Hyperactivity (ADHD)
- Aggression / self-injury (Intermittent explosive disorder)
- Sleep dysfunction (RLS/dyssomnia)
- Mood disorders (anxiety, depression, bipolar)

Heterogeneous

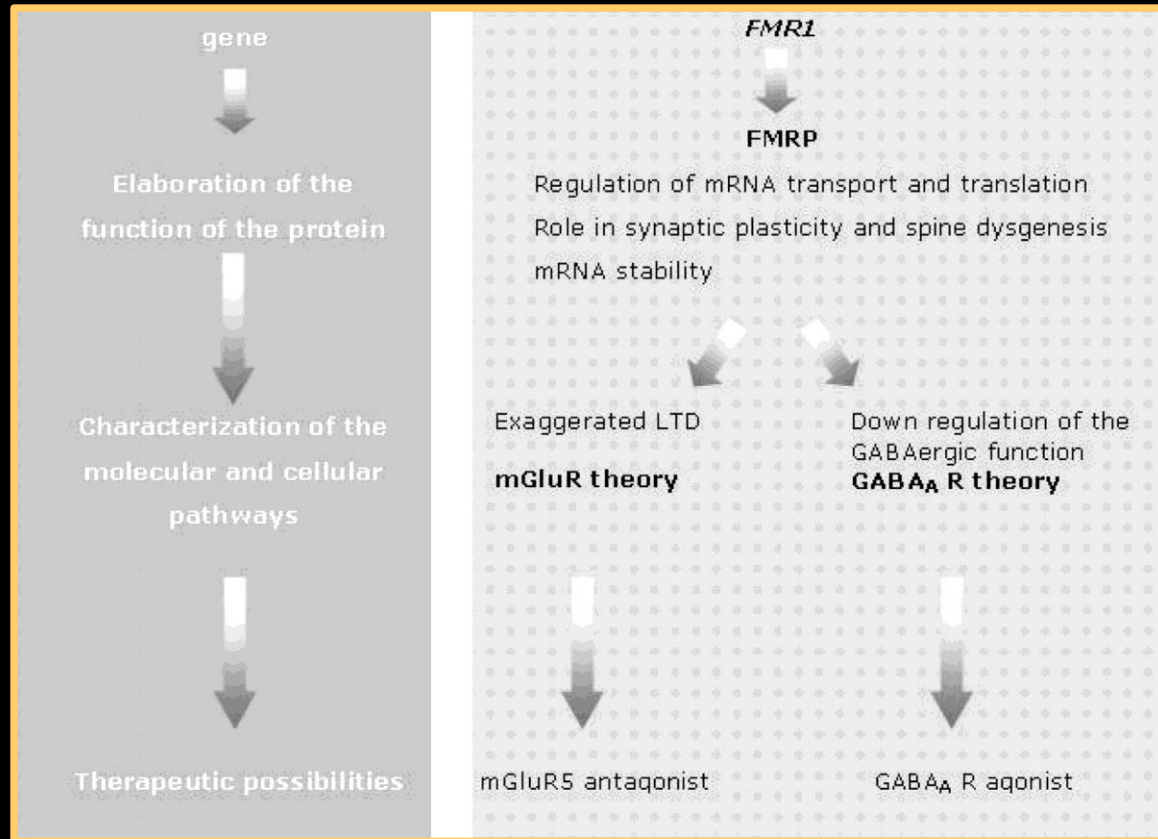
- Isolated ASD: multiple biological vulnerabilities underlie autism: 85%-90%
- Broader ASD Phenotype: 1/3 of first degree relatives
- Syndromal ASD: multiple diseases have a higher incidence of autism: 10%-15%

Syndromal ASD

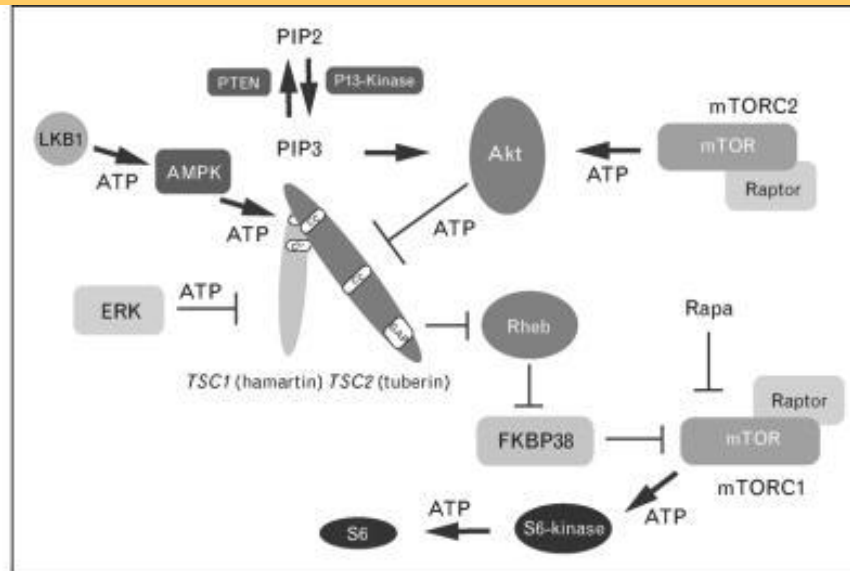
- Fragile X syndrome (2%-5%)
- Tuberous Sclerosis (1%-4%)



Fragile X Syndrome



Tuberous Sclerosis Complex



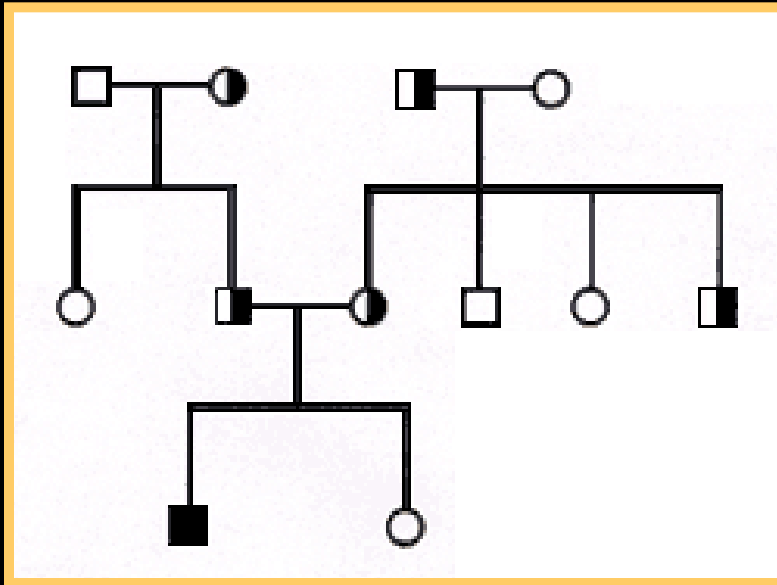
A complex series of phosphorylation events and other protein interactions regulate hamartin/tuberin and activity of the mTOR kinase. Initial growth factor binding to transmembrane receptors (not shown) activates PI-3 kinase resulting in increased production of PIP3 with AKT activation that directly phosphorylates and inhibits tuberin. ERK can also phosphorylate and inactivate tuberin. In contrast, AMPK phosphorylation at distinct amino acid residues serves to activate tuberin. Loss of the *TSC1* or *TSC2* genes leads to constitutive activation of mTOR within mTORC1 with greatly increased levels of phosphorylated ribosomal S6 kinase and phosphorylated ribosomal S6. Rapamycin inhibits mTOR activity within mTORC1 to restore inhibition of this kinase and downstream components within this signaling pathway. ATP indicates phosphorylation events. AKT (proto-oncogene also known as PKB); AMPK, AMP-activated protein kinase; ERK, extracellular signal-regulated kinases; FKBP38, FK506-binding protein 38; LKB1, Peutz-Jeghers syndrome kinase; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; PI-3, phosphoinositide 3; PIP2, phosphatidylinositol bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKB, protein kinase B; PTEN, phosphatase and tensin homolog; Rapa, rapamycin; Raptor, regulatory-associated protein of mTOR, Rictor, rapamycin-insensitive companion of mTOR; Rheb, Ras homolog enriched in brain; *TSC1*, (hamartin); tuberous sclerosis complex gene 1; *TSC2*, (tuberin) tuberous sclerosis complex gene 2. \longrightarrow , activates; \longleftarrow , inhibits.

Non-syndromal ASD



- **Epistatic models**
(interaction between genes)
- **Epigenetic factors**
(heritable changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence)

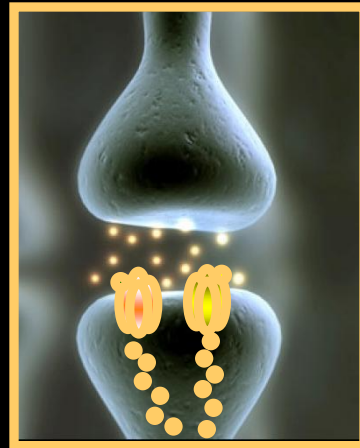
Inheritable



- MZ twins – 70% to 90% concordance
- Recurrence risk in siblings – 2%-8%

Hypothesis

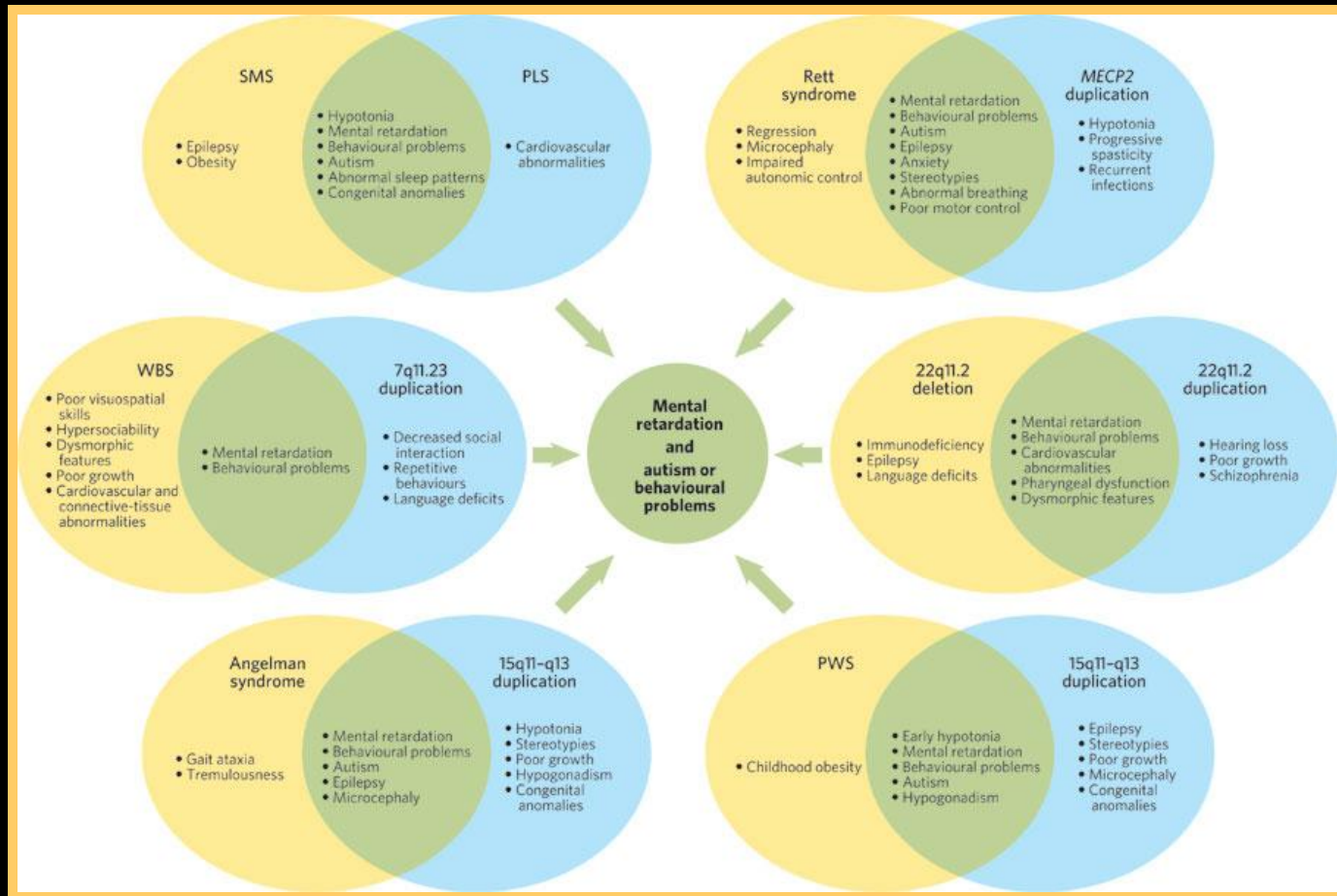
Defective function of neuronal proteins critical for early brain development



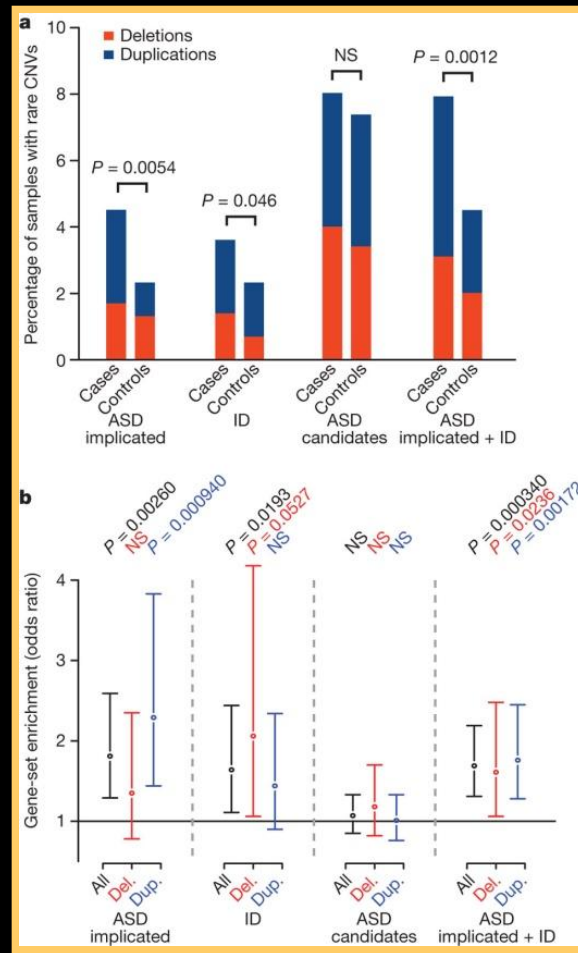
Abnormal dendritic architecture and functional synapse

ASD/ID Phenotype

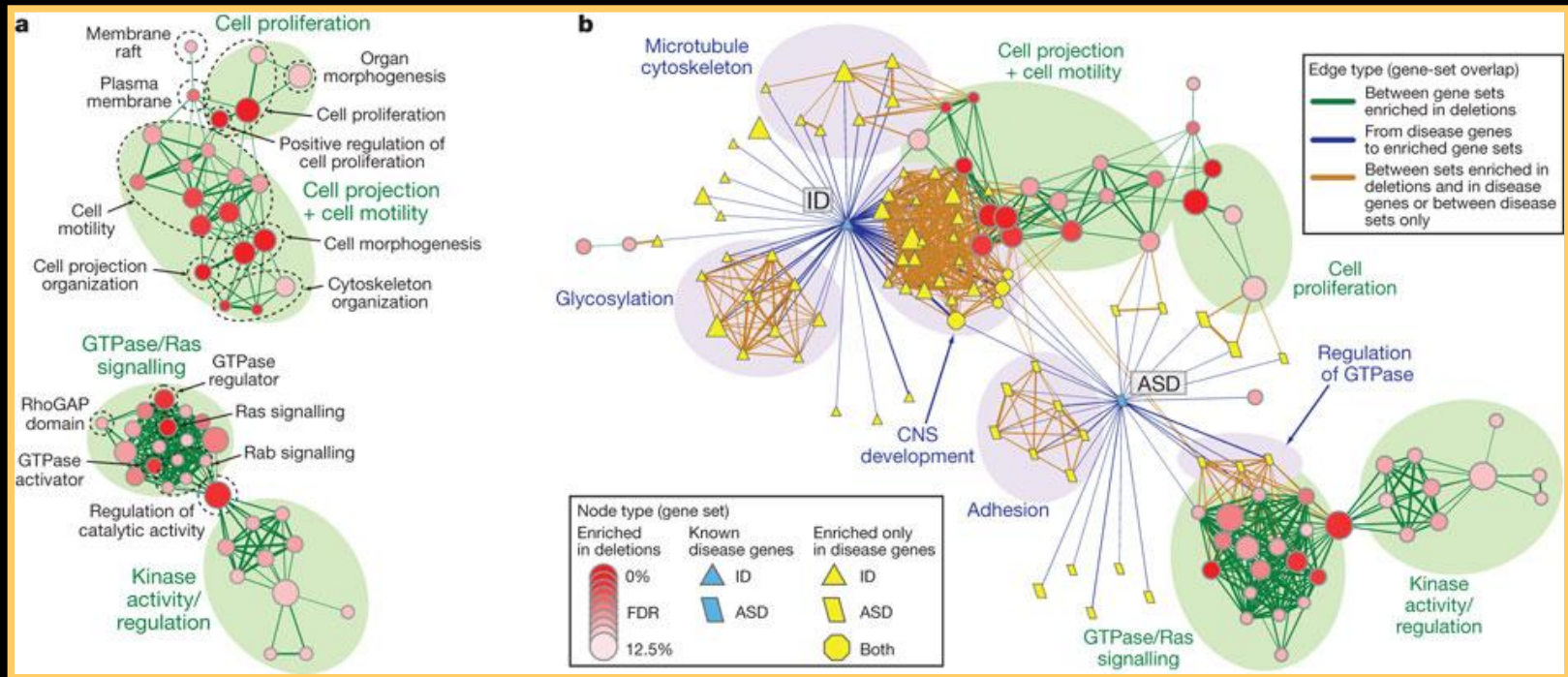
Copy Number Variations (CNVs)



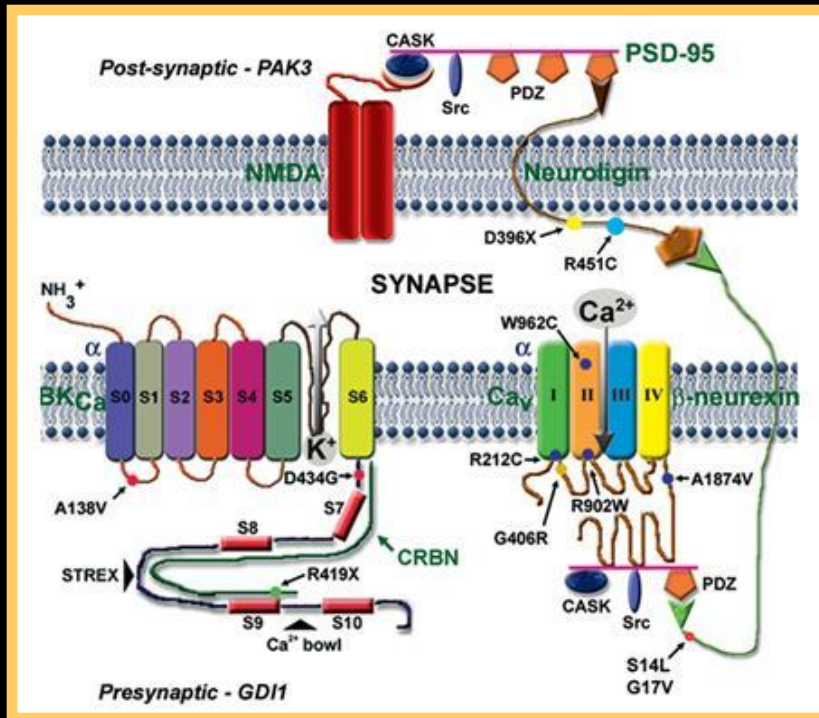
Copy Number Variations (CNVs)



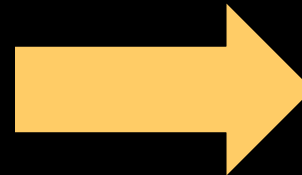
Functional Map of ASD (CNVs)



Model

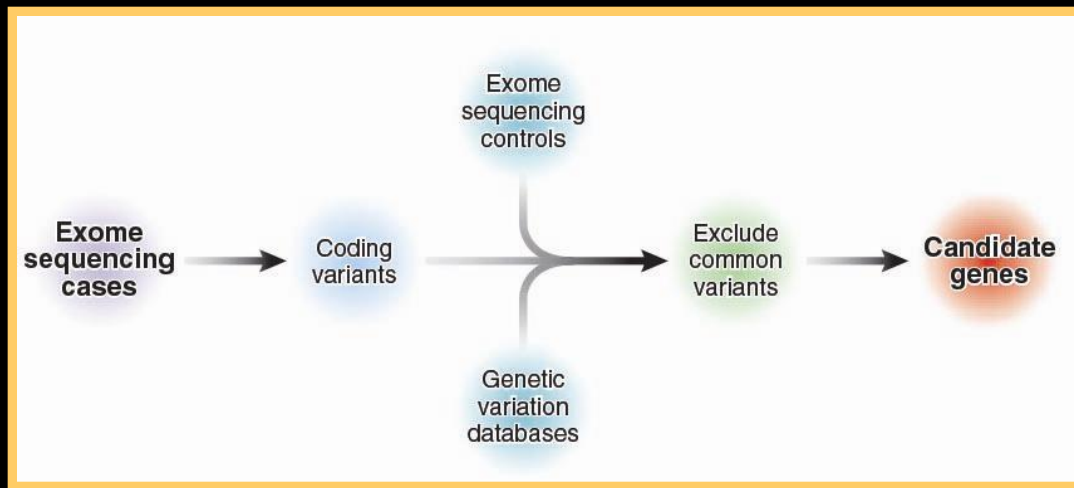


- Systems approach
- Transgenic mice



Medical Genomics - Exome

- Whole exome sequencing
- Filtering Methodology (dbSNP, HapMap*)



*HapMap total of 270 people. The Yoruba people of Ibadan, Nigeria, provided 30 sets of samples from two parents and an adult child (each such set is called a trio). In Japan, 45 unrelated individuals from the Tokyo area provided samples. In China, 45 unrelated individuals from Beijing provided samples. Thirty U.S. trios provided samples, which were collected in 1980 from U.S. residents with northern and western European ancestry by the Centre d'Etude du Polymorphisme Humain (CEPH).

Exome Technology

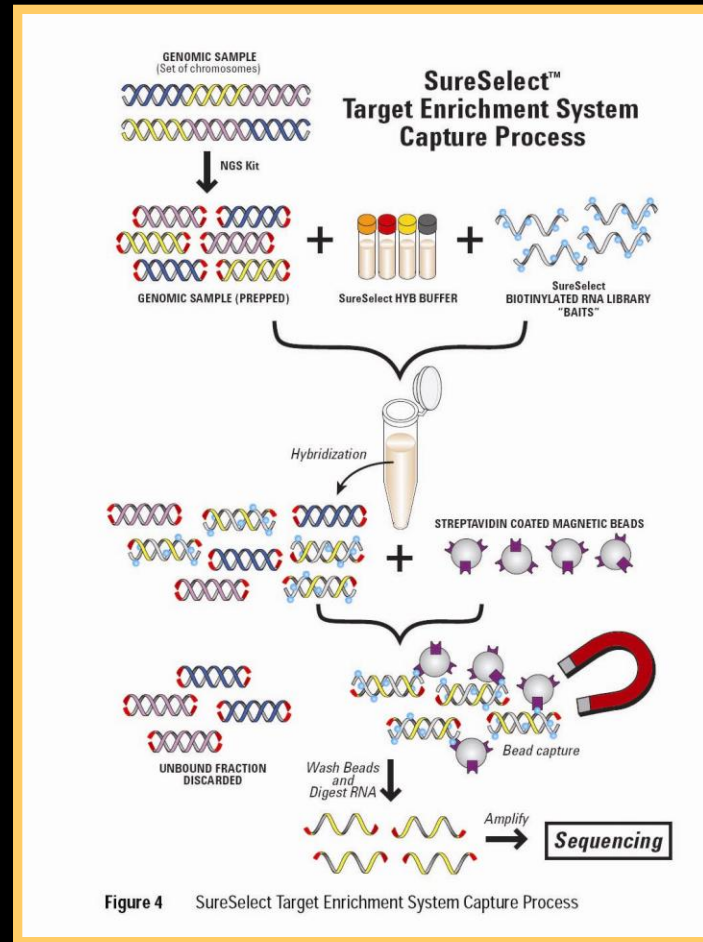
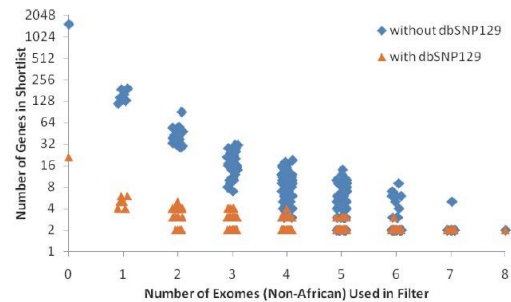
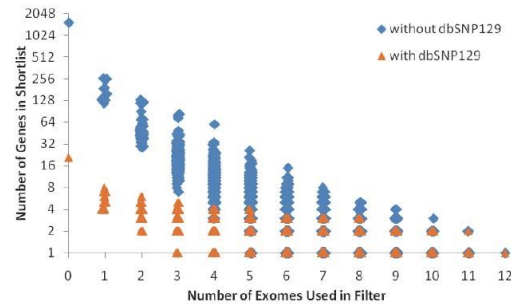


Figure 4 SureSelect Target Enrichment System Capture Process

Medical Genomics - Exome



Supplementary Figure 2. Number of candidate genes vs. number of unaffected exomes in filter. The results of adding more unaffected exomes as a filter for novel variants is shown for the recessive model, i.e. requiring at least two novel variants for a gene to qualify as a candidate. For this analysis, either all twelve previously sequenced exomes (Ng et al., 2009) were used (top), or only the eight non-Yoruba exomes from the same study (bottom), and results from all possible combinations of the specified number of exomes are represented. Results of the same filtering with (orange) and without dbSNP129 (blue) are also shown. The single gene identified when using all twelve exomes was DHODH (top); when only non-Yoruba exomes were used, the list also included ESPNL.

Ng, S.B. et al. Targeted capture and massively parallel sequencing of 12 human exomes. *Nature* (2009).

Weill Cornell Autism Research Project (WCARP)

WCMC

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