Genetics of Autism

Ethics of Genetics in Research
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The Autism Phenotype

- Abnormal
  - reciprocal social interaction
  - communication
  - repetitive and restricted behaviors and interests
- Onset first three years of life

Prevalence

- Estimates range between
  - 1 in 1,000
  - 1 in 200
- Boys/girls = 4/1

Other Associated Features

- Mental retardation
- Sensory impairments
- Motor impairments
- Epilepsy (epileptiform EEGs)
- Macrocephaly
- Co-morbid psychiatric diagnoses
  - ADHD
  - Anxiety
  - Depression
  - OCD

Related Neurogenetic Disorders

- Fragile X (FRAX)
- Tuberous Sclerosis (TSC)
- Rett
- Neurofibromatosis
- Hypomelanosis
- Moebius Syndrome
- Prader Willi Syndrome
- Angelman's Syndrome
- Joubert Syndrome
- Williams Syndrome
- Cowden's Syndrome
- Phenylketonuria
- Smith-Lemli-Opitz Syndrome
- Chromosomal deletions, duplications and translocatioins

Pervasive Developmental Disorders (DSM – IV)

- Autistic disorder
- Asperger's syndrome
- Pervasive developmental disorder not otherwise specified (PDDNOS)
- Rett Syndrome
- Childhood disintegrative disorder (CDD)

Unresolved Issues

- The significance of a “spectrum”
- Delay vs deviance
- Effect of “core” difficulties on learning and development
- Co- incident conditions

Early Development

- Are there early clinical signs (before compensation)?
- < 12 mos.
- 12 – 24 mos.
- About 30% “regress” during second year

Neuroscience Hypotheses (Cognitive)

- Lack of theory of mind
- Lack of central coherence
- Deficits in executive function

Neuroscience Hypotheses (Cell and Molecular)

Candidate Genes

APOE, AR, ARX, ATF2, ATP10C, AVPR1a, BDNF, cAMP-GEFII, CHN1, COPG2, CPA1, CPA5, DBH, DCX, DDC, DLX1, DLX2, DLX6, DRD1, DRD2, DRD5, DRD5, EN2, ERa, FMR1, FOXP2, GABRA5, GABRB3, GABRG3, GAD1, GLRA2, GRIK2, GRM8, GRPR, HOPA, HOX31, HOXA1, HOXB1, HRAS, HTR2A, HTR7, INPP1, IPIK3CG, KIAA0716, LAMB1, LRRN3, MAOA, MAOB, MECP2, MEST, MHC genes, NCAM, NESP55, NEUROD1, NF1, NF2, NLGN3, NLGN4, NOTCH4, NR-CAM, OMGP62, PAI1, PCLO, PCSK2, PDYN, PENK, PICK3CG, RAB3A, RAY1, RELN, SCN1A, SCN2A, SCN3A, SCT, SERT, SLC5A12, SLC6A4, SLC6A4, SSTR5, TBR1, TDO2, TH, TRa, TSC1, TSC2, UBE2H, UBE3A, WNT2.

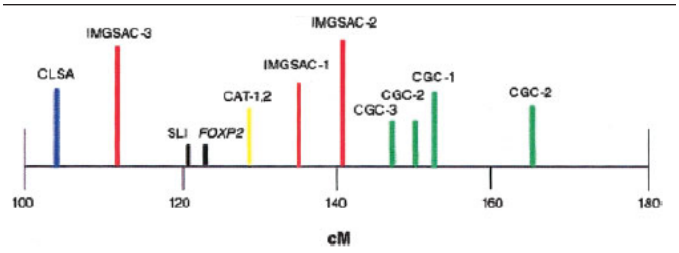
Autism is Heritable

- Gross chromosome disruptions (5%)
- Autism in other heritable disorders (5%)
- Of the remaining “idiopathic” cases (90%)
  - Siblings or dizygotic twins = 3-5%
  - Monozygotic twins > 60%

Gene Hunting

- Positional cloning – linkage analysis
  - Even the strongest signals are weak
  - Reproducibility poor
  - Hotspots on 17 of the 22 autosomes and on the X chromosome
    - 7q and 2q most frequently reported

Linkage variation



Wassink et al (2004)