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 translocations

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, ATP2, ATP10C, AVPR1b, BDNF, AMP-AR, CNR1, GSK3b, GAB2, DBH, DCX, DCC, IL1R1, DAX2, DEXI, DINA, DHD2, DRD3, EN2, FD, FAB1, FOG2, GABRA5, GABRA5, GABRG3, GAD1, GDNF, GRIK, GRIK, GPR35, HSPA, HOXD11, HOXD13, HEXH5, HNRAS, HTR2A, HTR7, INPP51, IPRO2C, IRAK1, JAK2, LAMR1, LRRN1, MAO-A, MAOA, MBP1, MET, MPG, PCDH, NGAM, NESP55, NEUROD1, NPY, NF2, NRG1, NRG2, NOTCH1, NR2D1, OMP3D, RAI, RALG, P3K2, PDE6, PEX2, PKC3DG, RAB14, RAY1, REN, SCN2A, SCN4A, SCLAM, SLC10A, SLC4A7, SLC24A7, SLC4A8, SLC3A2, TGF1, TGF2, TN, TLR, TRA1, TRB1, 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