Do genes have anything to do with AS?

Yes

- 1% of the population have ASC
- High heritability of autism and autistic traits
Plan of the talk

- One autism, many autisms
- The genetic story so far
- Candidate processes to candidate genes
- Humans and mice
- The bigger picture
Reducing heterogeneity

Syndromic, Nonsyndromic

Multiplex, Simplex

Asperger Syndrome, Classic Autism

Disconnect between phenotypic and genetic studies in ASC
Carpet bombs & Guided missiles
Carpet bombs: Genomewide studies

- Exploratory, data-driven approach
- Categorical phenotype (usually clinical diagnosis)
- Generally focuses on common variants
- Sample size ~2000+
- Identify the most significant effects (p~10^{-7})
The score so far

See Abrahams and Geschwind (2008)
The pitfalls

● Replication difficulties
● Mechanistic explanations always post-hoc
● Effect Size ≠ Causality
● Heterogeneity within the Autism Spectrum
Guided missiles: Candidate genes

- Hypothesis driven approach
- Usually looking at one/few genes
- Can test rare and common variants
- Phenotype can be categorical/ dimensional
- Samples sizes in 100s
The pitfalls

- Replication difficulties
- Lack of statistical power
- Heterogeneity
Candidate gene association study of Asperger Syndrome and autistic traits in the general population
Candidate process: Neurodevelopment

Typical brain growth

Candidate genes: Neurodevelopment

- Neurotrophins and receptors
  - NGF, NGFR, NTRK1, BDNF, NTF3, NTRK3, NTRK2
- Homeobox proteins
  - HOXA1, EN2
- Synapse formation and stabilization
  - NLGN1, NLGN4X, NRCAM
Candidate process: Social behaviour

Chakrabarti and Baron-Cohen, 2008
The 'trust' hormone(s)

Oxytocin, Vasopressin, and the voles

Hammock and Young, 2006
Candidate genes: Socio-emotional behaviour

• Neurotransmitter action
  - \textit{GABRB3, GABRG3, GABRA6, ABAT}
  - \textit{MAOA, MAOB}

• Neuropeptide action
  - \textit{OXTR, OXT, CNR1, OPRM1, AVPR1A, AVPR1B}
Candidate process:
Sex steroid synthesis & metabolism

Auyeung et al, 2008
Candidate genes: Sex steroids

- Sex hormone synthesis
  - CYP11B1, CYP17A1, CYP19A1, CYP11B1, HSD11B1, HSD17B2, HSD17B3
- Sex hormone receptors
  - ESR1, ESR2, AR
Choosing SNPs and people

- 216 SNPs from 68 genes
- Minor allele frequency of >0.2 in Caucasians
- Buccal smear DNA

- 174 cases and 155 controls low on autistic traits
- Caucasian for 3 generations
Analysis

◆ Cochrane- Armitage Trend test (1 d.f.)
◆ Pearsons chi-square (2 d.f.)
◆ Permutations (1000), using UNPHASED
Significant associations (P<0.05)

**ESR2**
**ESR1**
**CYP11B1**
**CYP17A1**
**CYP19A1**
**LHCGR**
**SCP2**
**HSD11B1**

**NTRK1**
**NTRK3**
**ARNT2**
**IGF1**
**NTF3**

**OXT**
Autistic traits: A continuum

‘General population’

ASC
Beyond categorical phenotypes

- Autism Spectrum Quotient
- Empathy Quotient
More power with smaller samples

Potkin, 2007
Genes for autistic traits

- Same genes and SNPs
- 349 volunteers (206 females, 143 males)
- Caucasian for 3 generations
- Everyone took the AQ and EQ online
Analysis

◆ Kruskal-Wallis ANOVA (2 d.f.)
◆ Permutations (1000), using UNPHASED
Significant associations (P<0.05)

- ESR2
- ESR1
- CYP11B1
- HSD17B4
- HSD17B2

- NTRK1
- NTRK3
- ARNT2
- NLGN4X
- HOXA1
- EN-2
- IGF1
- NTF3

- OXTR
- AVPR1B
- CNR1
- GABRB3
- GABRA6
- CNR1
- MAOB
- VIPR
- WFS1
What next?

- Interaction of genes across functional categories
- Replication studies in larger, independent samples
- Gene expression studies
- Mouse models
Mouse phenotypes

Social Approach (video)

Repetitive Behaviour (video)
Mouse models

- Nlgn4 -/-: social deficits, ultrasonic vocalisations
- Oxtr -/-: Social memory deficits
- Gabrb3 -/-: Sociability deficits, cerebellar hypoplasia
Mouse models: Caveats

- The knock-on effects of a global knockout
- Conditional knockouts more difficult
- Inadequacy of current behavioural assays
The bigger picture

DNA

Protein

Neural measures

Behaviour

Diagnosis

Genotype

Endophenotype

Phenotype
Summary

● Heterogeneity in ASC can be dealt with in multiple ways

● Asperger Syndrome and Autistic traits are associated with genes involved in
  ▪ Neural development
  ▪ Sex steroid synthesis and action
  ▪ Social and emotional behaviour
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