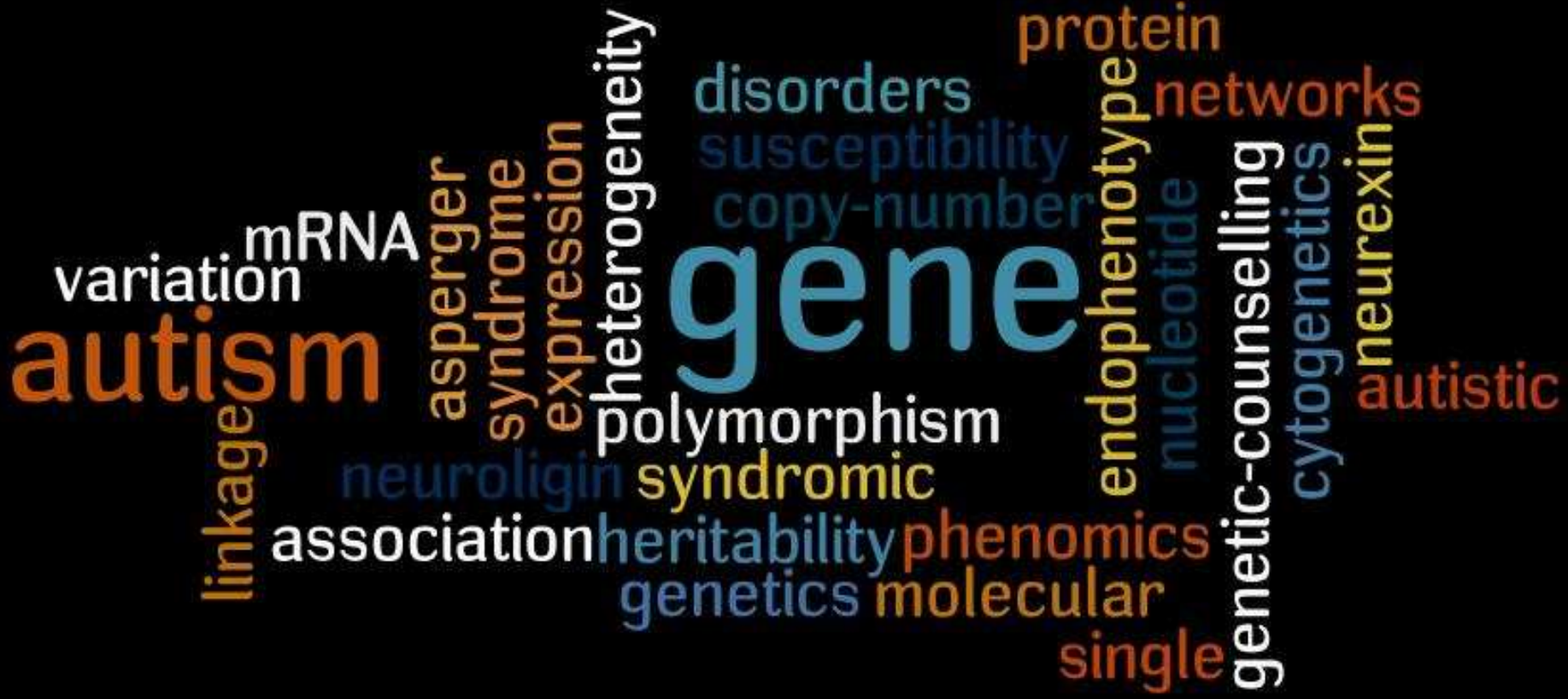
Genetics of Asperger Syndrome



Bhismadev Chakrabarti, PhD

Autism Research Centre
University of Cambridge

School of Psychology
University of Reading

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 ($p \sim 10^{-7}$)

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

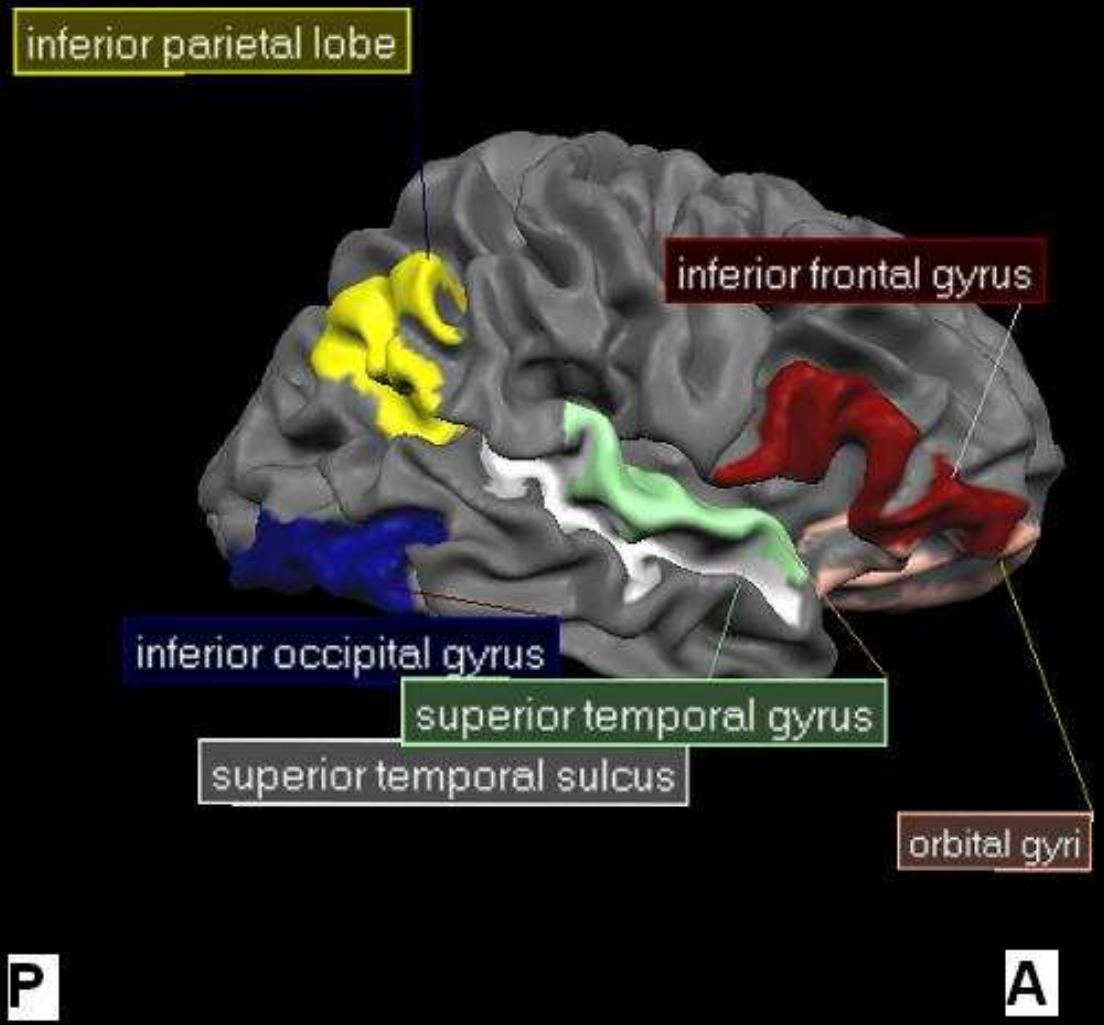
Gogtay, et al(2004), Courchesne, et al (2008)

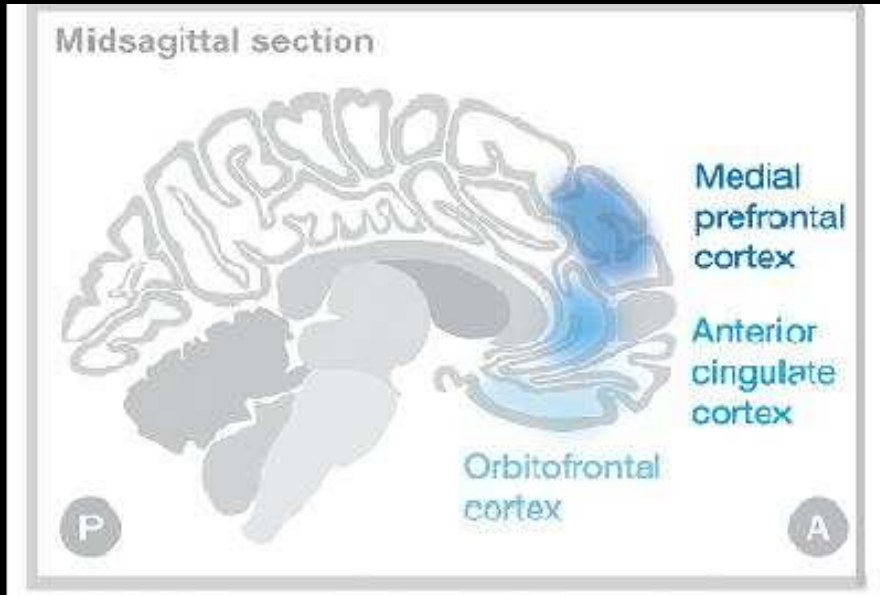
Candidate genes: Neurodevelopment

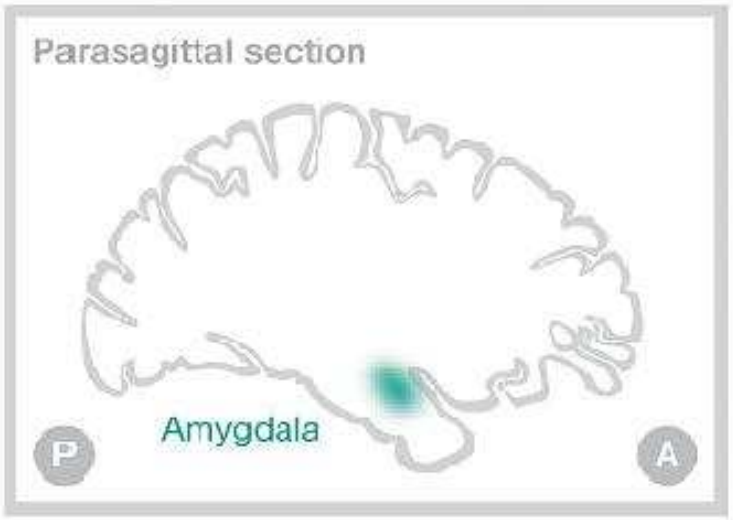
- Neurotrophins and receptors
  - *NGF, NGFR, NTRK1,BDNF, NTF3, NTRK3, NTRK2*
- Homeobox proteins
  - *HOXA1, EN2*
- Synapse formation and stabilization

- *NLGN1, NLGN4X, NRCAM*

Candidate process: Social behaviour







Chakrabarti and Baron-Cohen,

The 'trust' hormone(s)

Hammock and Young, 2006

Oxytocin, Vasopressin, and the voles

Candidate genes: Socio-emotional behaviour

- Neurotransmitter action

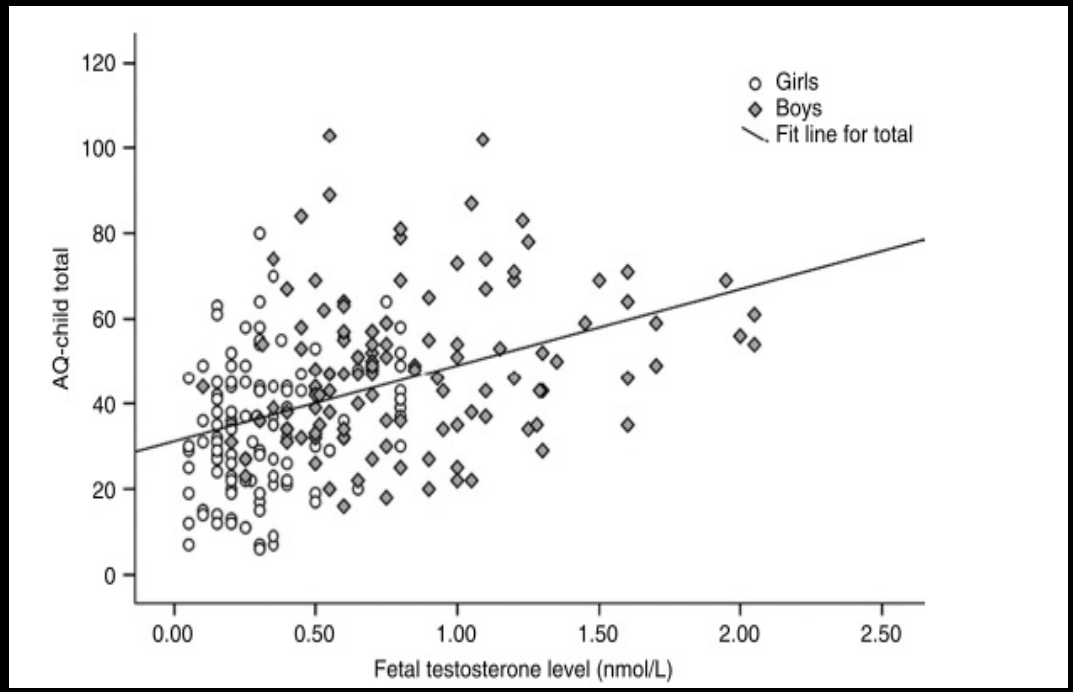
- GABRB3, GABRG3, GABRA6, ABAT

- MAOA, MAOB

- Neuropeptide action

- 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

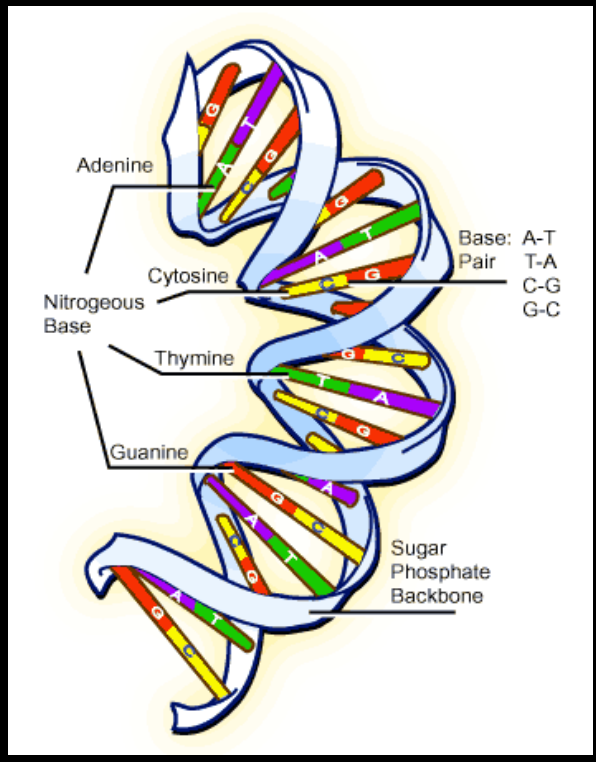
- Sex hormone receptors

  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

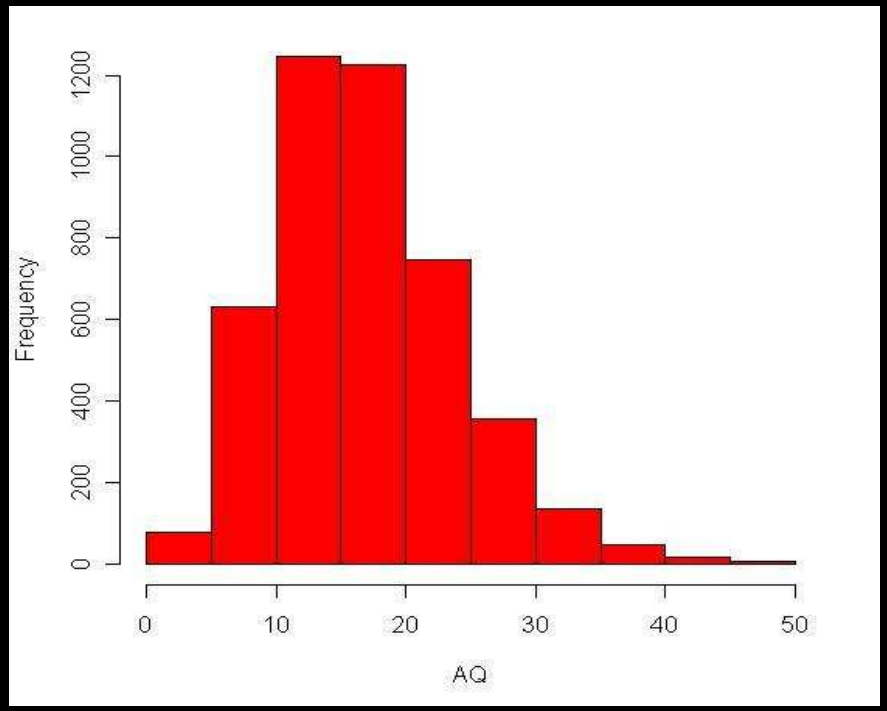
Autistic traits: A continuum

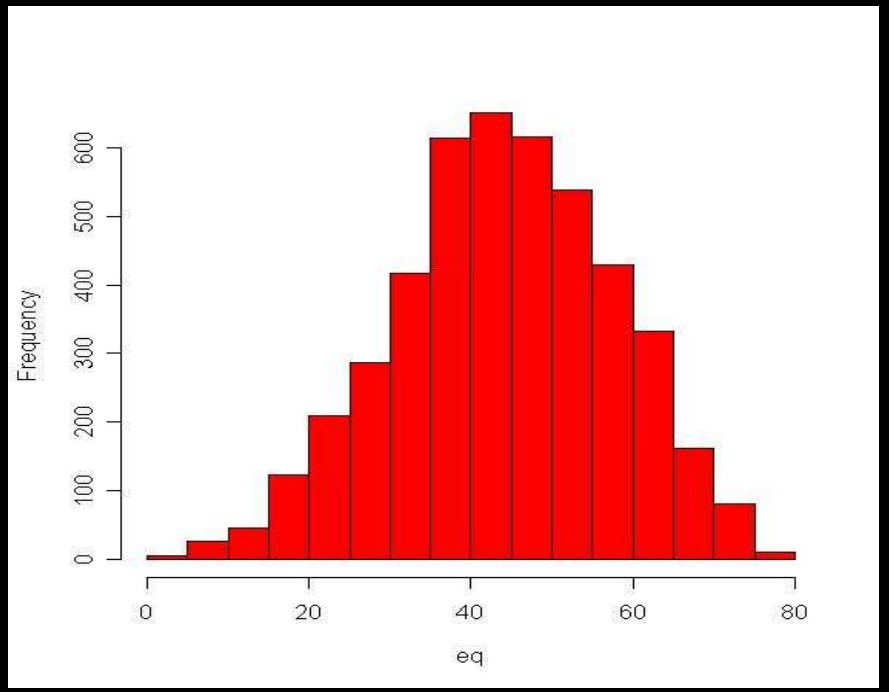
‘General population’

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

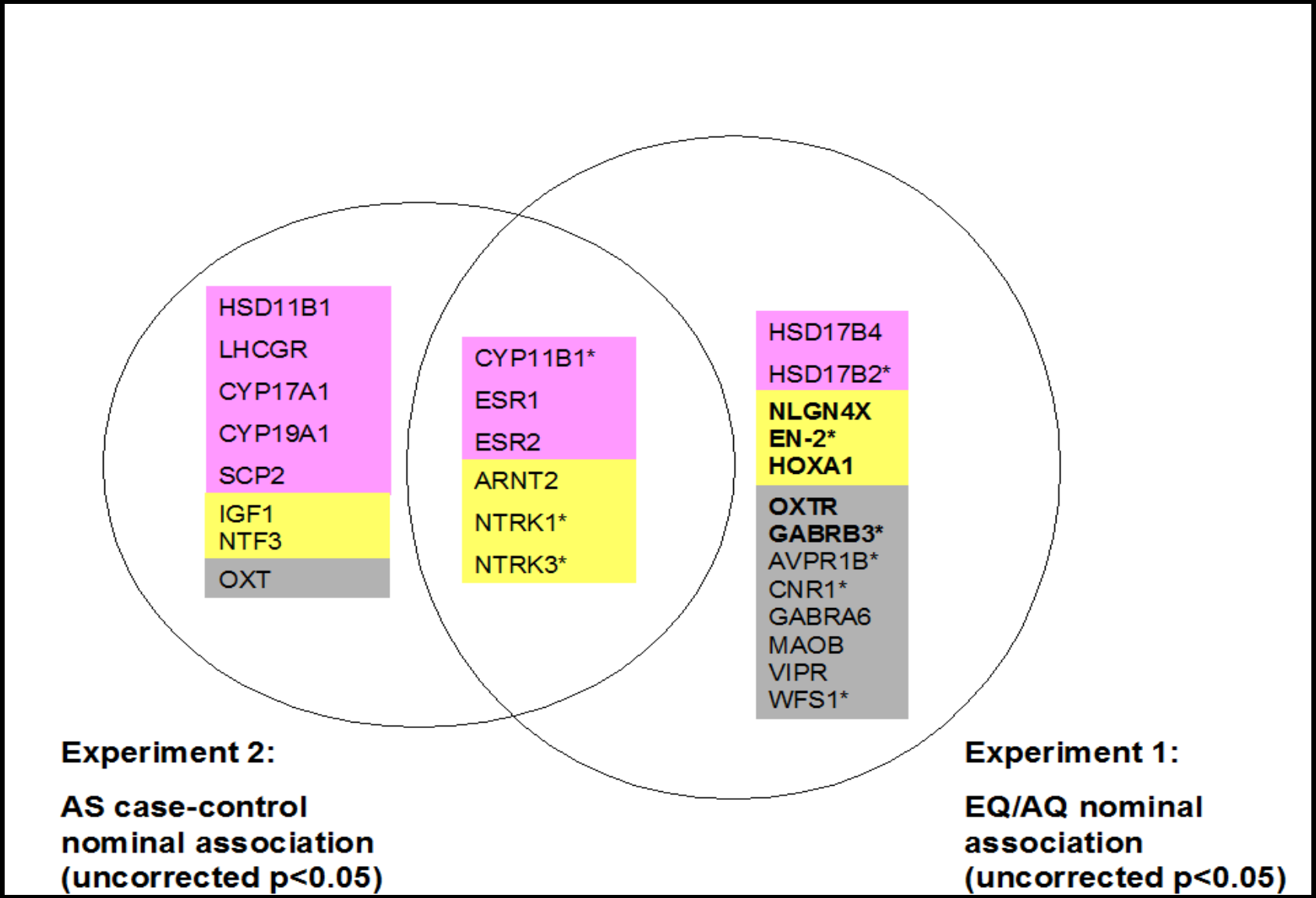
Significant associations (P<0.05)

ESR2
ESR1
CYP11B1
HSD17B4
HSD17B2

NTRK1
NTRK3
ARNT2
NLGN4X
HOXA1
EN-2
IGF1
NTF3

OXTR
AVPR1B
CNR1
GABRB3
GABRA6
CNR1
MAOB
VIPR
WFS1

Shared genes



Chakrabarti et al, 2009

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)

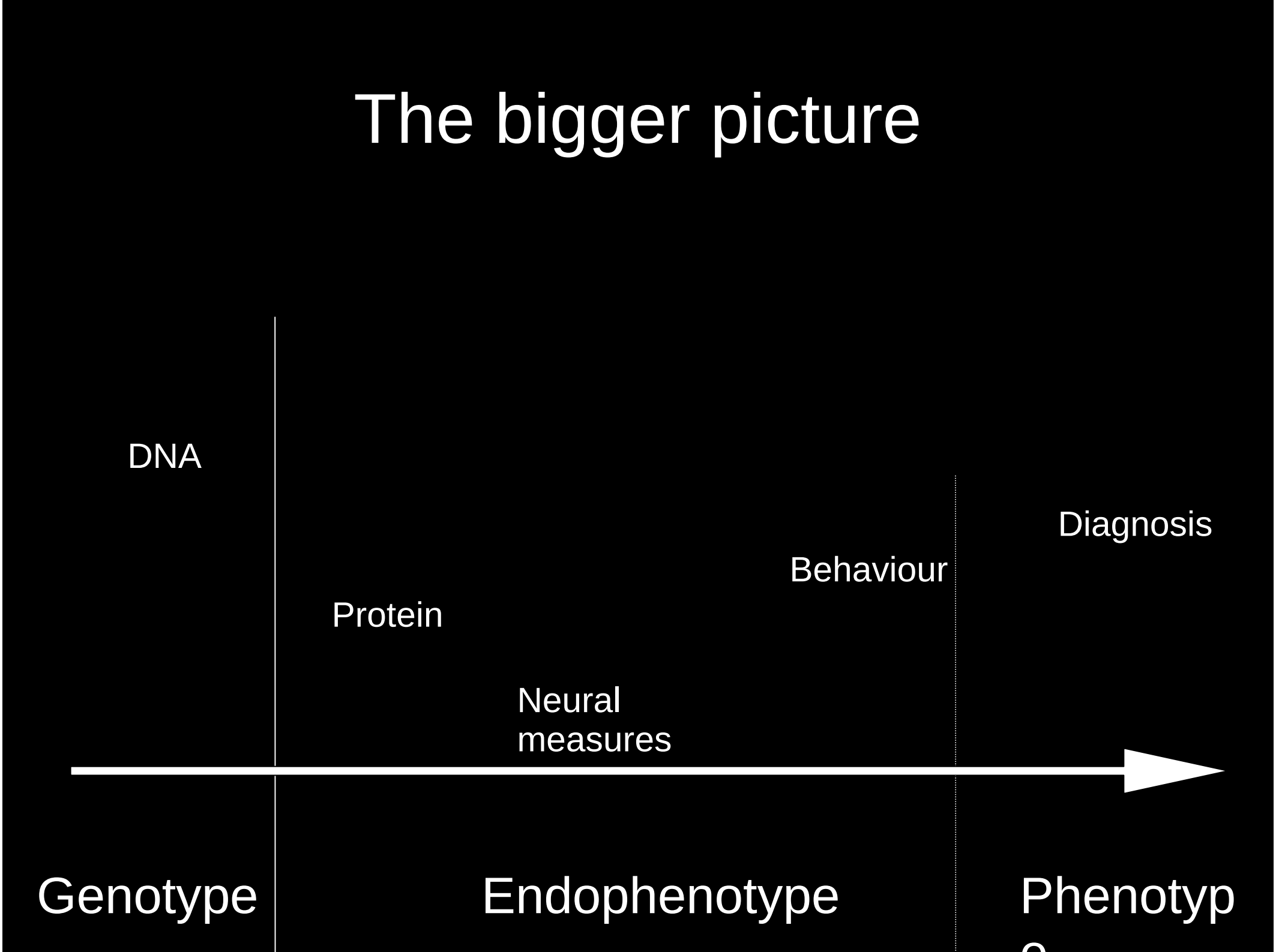
Mouse models

- 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



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

Acknowledgements

- Simon Baron-Cohen
- Frank Dudbridge
- Lindsey Kent
- Ian Craig
- Uma Mallya
- Jon Breidbord
- Carrie Allison
- Sally Wheelwright
- Stefanie Suessenbachers
- Bonnie Aueyeung
- Allen Chan
- Silvia Kelemenova