Genetic insights into classification

Dorothy Bishop

University of Oxford

Different ways to make a diagnostic classification

- In terms of presenting difficulties
- In terms of underlying causes
- In terms of response to intervention

Which is best may depend on purposes of classification

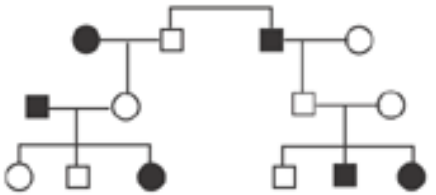
Genetic research: focus on underlying causes

- Case of FOXP2 led to expectation that we might find clearcut genetic mutations to explain all severe language impairments

- Not so! Language impairments behave like “complex multifactorial disorders”

Complex multifactorial disorders

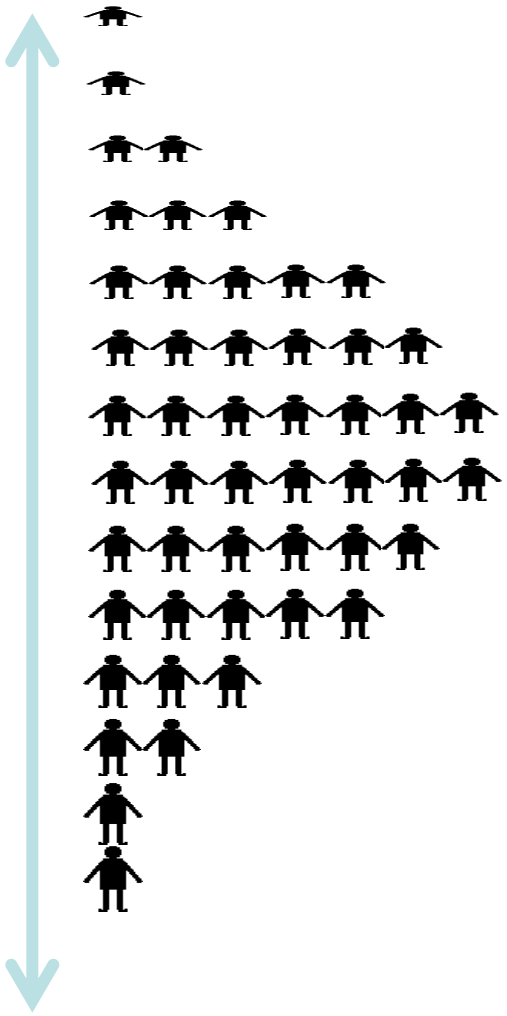
- Aggregate but do not segregate in families
  - i.e. run in families but you can't trace effect of gene through the generations according to simple Mendelian rules



Inheritance pattern (complex)

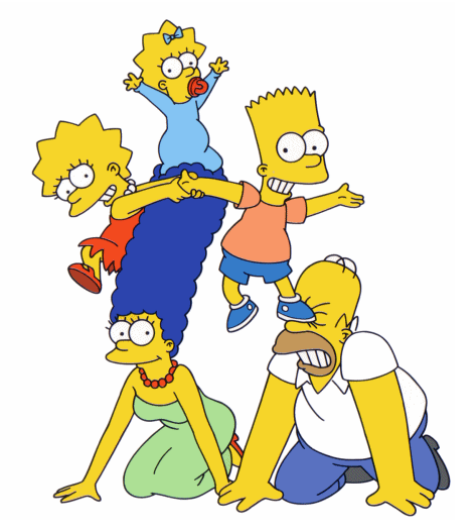
Idea of underlying continuum

Several genes, each with a small effect, combine with environmental risks to influence phenotype across the whole range



Methods for identifying genetic influence on complex multifactorial traits/disorders

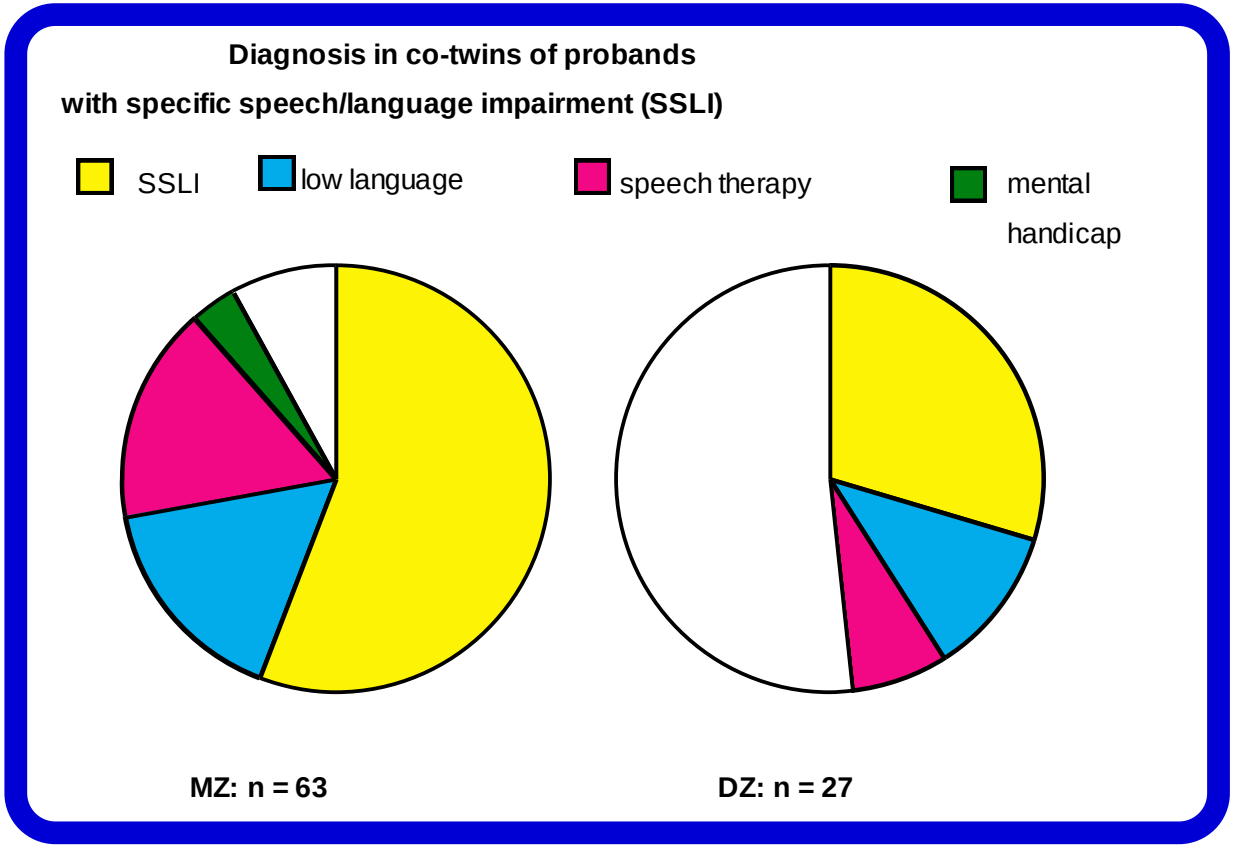
1. Studies of how behavioural similarities between people can be predicted by genetic relationships



2. Molecular genetics: identifying genetic variants associated with phenotypes

Mapping between genes and behaviours very imprecise

Example 1: Behavioural study of twins



MZ twins have same DNA sequence, yet can see different levels of severity, and different comorbidities

Mapping between genes and behaviours very imprecise

Example 2: Molecular study of genes

CNTNAP2 gene – downstream target of FOXP2

Common variants of the gene associated with:
- Autism
- Specific Language Impairment
- Dyslexia
- ADHD
- Schizophrenia
- Age at language acquisition in general population

Disruptions of gene associated with:
- Tourette syndrome (translocation)
- Epilepsy (assoc. with mutations in Amish)

Why so much variation?

- An analogy: tuberous sclerosis – the same mutation can lead to major brain malformation or minor problems with skin
- Genes associated with language impairment likely to affect very early neural development
- Precise impact may depend on which neuronal areas affected, which may depend on:

1. Other genes (effects may be interactive)
2. Environmental factors
3. Random effects

Classification for education

- Not sure genetics will help:
  - e.g. Grouping children by CNTNAP2 status would not yield a homogenous group
- May be more sensible to aim for classification based on *response to intervention*
- Regardless of cause, want to identify those who will benefit from placement