Genetic Contributions to Specific Language Impairment (SLI)

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Specific Language Impairment (SLI)

• Impairment in acquisition and use of language
  – Severe
    • Impairs every day functioning
  – Persistent
    • Not language delay
  – Unexpected
    • Adequate opportunity of acquisition
    • Adequate intelligence
    • No hearing loss
    • No neurological/psychiatric disorders
    • Twinning, bilingualism
Specific Language Impairment (SLI)

- SLI affects 2-7% of preschool children
- Highly heritable
- Overlaps with other neurodevelopmental disorders
Genetic Disorders

• Classic genetic syndromes usually involve gross changes to the DNA sequence
• They may involve:
  – An alteration to the composition of the sequence
  – The deletion or duplication of genetic material
• These syndromes are usually very severe and very rare
• Most genetic conditions are not caused by a single deleterious mutation
Mutations and Variations

• Mutation
  – Change to the DNA sequence that has **big, direct effect** upon protein function
  – **Rare** in populations

• Variation
  – Change to the DNA sequence that has **little effect** upon protein function
  – **Common** in populations
  – ~15 million DNA variants catalogued
Complex Genetic Disorders

- Caused by interactions between **genetic variants** and **environmental** factors
- The more of genetic ‘**risk**’ **variants** an individual carries the more likely they are to develop the disorder
Complex Genetic Disorders

• Caused by interactions between **genetic variants** and **environmental** factors

• The more of genetic ‘risk’ **variants** an individual carries the more likely they are to develop the disorder
  – The exact **combination** of risk variants causing disease varies from person to person
  – Each single variation in isolation, only has a very small effect
  – The risk can often be **modified by the environment**
  – Complex disorders cannot be ‘corrected’

• 4-10 variants?
GWAS

- Genome wide association studies (GWAS)
- >1 million SNPs
- GWAS do not explain a large proportion heritability/variance
- Risk loci increase risk by 1.1-1.2 fold
Missing Heritability

• Power
  – Many risk variants each with a small effect size

• Alternative genetic risk models
  – Rare variants
  – Copy number variants (CNVs)
  – Interactions (gene-gene, gene-environment)
  – Parent of origin effects
  – Epigenetics
Really Complex Genetic Disorders

- Your risk is a balance between:
  - Rare mutations or CNVs with high risks
  - Common variations or CNVs with low risks
  - Environmental and background modifier effects
  - Model needs to allow for interactive risk variables
Genetic Architecture of SLI & Dyslexia

• SLI and dyslexia are (really) complex disorders
• **Linkage and association** techniques have been used to identify candidate genes
  – *CMIP, ATP2C2, CNTNAP2*
  – *KIAA0319, DCDC2, Dyx1c1, ROBO1, MRPL19/C2orf3*
• Some variations contribute across disorders
• **Common variants** that play a role in a classical complex disorder model
Genetic Architecture of SLI & Dyslexia

• Predisposition to disorder or contribution across the range?
  – KIAA0319 & CMIP contribute across the range
  – ATP2C2 & DCDC2 specific disorder risks

• Evidence for overlapping risk effects?
  – Dyslexia and SLI candidate genes separate
    • KIAA0319 & CMIP associated with language and reading
  – CNTNAP2 associated with SLI & ASD

• Are there high effect rare variants?
  – Copy Number Variants (CNVs)
Copy Number Variants

- Submicroscopic **deletions or duplications**
  - 6-10 common copy number changes per individual
  - Rare and *de novo* CNVs
  - Presence can be inferred from SNP data
- Autism, ADHD, ILD
  - Increased burden of **rare, large, genic CNVs**
- Autism singletons
  - Higher rate of **de novo CNVs**
- Dyslexia
  - No difference in large CNV burden in dyslexia
CNVs in SLI

- 127 SLI cases, 269 adult UK population controls
  - Increased burden
  - Larger events
  - Higher gene hit rate

- No large (>500Kb events)

- Rare and de novo events
  - No difference between cases and controls
CNVs in SLI

- Similar trends seen for common events in family members
  - Unaffected sibs/parents
  - Affected sibs/parents

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![Bar chart showing comparison of CNV numbers and gene hits across different groups](chart.png)

- Controls
- Cases
- Family members
- Affected family members
- Unaffected family members

- Manuscript in preparation
CNVs in SLI

• Similar trends seen for common events in family members
  – Unaffected sibs/parents
  – Affected sibs/parents
• CNVs may play a role in SLI aetiology
  – Likely to be driven by common events that are generally increased in affected families
  – Hit position in affected family members

  – Manuscript in preparation
Homozygous microdeletion of exon 5 in ZNF277 in a girl with specific language impairment

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- Homozygous deletion
- 21Kb across exon 5 ZNF277
- Novel microdeletion
- Leads to a frameshift (stop codon exon 7)
- AUTS1 locus, chromosome 7
ZNF277 Cosegregation

- Deletion **inherited** by proband
  - One copy from each parent
  - Father – speech impairment
  - Mother - dyslexia
- Not inherited by siblings
  - Sister – SLI
  - Brother – language delay
ZNF277 Screen

- **SLI families**
  - 322 families, 1234 individuals
  - 545 parents, 318 probands, 371 siblings

- **Population Controls**
  - 130 sequence controls
  - 224 ECACC controls

- **ASD families**
  - 252 families, 1021 individuals

![Bar chart showing frequency of SLI, Controls, and ASD in Families, Probands, Parents, and Sibs]
Characterization of a Family with Rare Deletions in CNTNAP5 and DOCK4 Suggests Novel Risk Loci for Autism and Dyslexia


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**DOCK4 Microdeletion**

- Microdeletion in *DOCK4*
  - Lead to an *IMMP2L-DOCK4* fusion transcript
  - Described in an ASD family & a dyslexia family
  - Incomplete cosegregation
  - Do not affect the expression levels of *ZNF277*

- *DOCK4* and *ZNF277* microdeletions confer **independent** risks
- Rare variants with moderate risk
ZNF277 Microdeletions

- Microdeletion in ZNF277
  - Deleterious upon gene function
  - More frequent in SLI families than controls
  - Specifically affect the expression levels of ZNF277
    - ZNF277 function may contribute to SLI
    - ZNF277 microdeletion may represent a risk variant for SLI
  - No more frequent in ASD families than controls
  - Do not affect the expression levels of flanking genes
    - Does not contribute to risk of ASD
    - Flanking genes may contribute to ASD risk
Complex Contributions

• **ZNF277 microdeletions**
• More common in children with SLI
• But incomplete cosegregation
• Variations in risk factor distribution and effects
• Even within same family
Really, Really Complex Disorders

- Even in a **single family**, the risk variables may be a complex mix of factors.

- Your risk is a balance between:
  - **Rare mutations or CNVs** with high risks
  - **Common variations or CNVs** with low risks
  - **Environmental** and background **modifier** effects
  - Model needs to allow for **interactive risk variables**
Summary

• Genes and proteins interact in networks to regulate cell mechanisms
• They are part of a complex and dynamic system
• New genetic technologies mean that it is easier to identify genetic changes at a higher resolution
  – SNPs, CNVs, mutations
• But we need to learn how to interpret identified changes
  • Importance of sample sizes
  • Importance of understanding modifier effects
  • Integration of comprehensive data across fields
  • Integration of factors into statistical modelling
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