Genetics of Stuttering

- Family History
- Twin Studies
- Aggregation Studies
- DNA Studies

- Genes
- Environment
  - Shared
  - Non-shared (unique)
Not that simple!

- Genes affect other genes
- Environment affects genes
- Genes affect environment (e.g., production of hormones creating environment in which other genes are expressed)

Examples (from Sapolsky)

- Chuck & Arthur
- Stress & pregnancy
Recent Studies

Twins
- Andrews et al. (1991) Australian twin studies
- Felsenfeld et al. (2000) Australian twin studies
- Dworzynski et al. (2007) British twin studies
All show higher concordance rates in MZ twins
All based on questionnaires, some with telephone follow-ups

Segregation analysis
- Viswanath et al. (2004)
  - Major gene component (autosomal dominant)
    - Necessary for stuttering
    - Two covariates:
      • Sex
      • Affection status of parents
  - Polygenic – Multifactorial component
DNA Studies

DNA Linkage Analysis

- Uses DNA from blood samples
- Analyzes forms of certain known segments (markers)
  - Microsatellites
  - Single nucleotide polymorphisms (SNPs)
- Identifies which forms of which segments people who stutter have in common
- Gene for disorder may lie in region of marker
Shugart et al. (2004)

- North American & British families
- Several signals across Chr. 18
  - Big effect from one family
- Weak signals from Chr. 1, 2, 10, 13
  - (NPL between 1-1.5)

Riaz et al. (2005)

- Pakistani families, inbred
- Strongest signal on Chr. 12
- Weak signals on Chr. 1, 5, 7
Wittke-Thompson et al. (2007)

- Hutterites, inbred
- Strongest signal on Chr. 13
- Weaker signals on 1,3,5,9,15

The Illinois International Genetics of Stuttering Project

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- University of Chicago School of Medicine
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- Helsingborg Hospital, Helsingborg, Sweden
  - Cecilia Lundstrom, Marie Garsten
- Tel Aviv University, Tel Aviv, Israel
  - Ruth Ezrati
Stuttering Linkage Analysis

- Persistent and recovered stuttering
- 10K SNP (single nucleotide polymorphisms)

LOD scores

- LOD (likelihood of 2 loci inherited together, linked); >3 evidence of linkage
- HLOD – takes heterogeneity into account
- NPL – non-parametric LOD, affecteds only
X axis: centiMorgans, location on chromosome
Y axis: LOD score

All Families
Largest signal on Chr.9
Modest signal on Chr.2 & Chr.7
Conditioning on Persistent

Given:
- stuttering status persistent,

Then:
- Increase in signal on Chr. 15
- Modest increase on 13
Conditioning on Sex

Given:
- Female, ever stuttered

Then:
- Significant increase in signal on Chr. 21
Hutterites
Jacqui Wittke-Thompson

Conditioning on Sex - Male

Given:
- Male, ever stuttering

Then:
- Increase on Chr.7
- Increase on Chr.20
Hutterites Jacqui Wittke-Thompson

Large pedigree – 24 males affected
Conditioning on Locus

- Weighting families based on signal at specific locus on specific chromosome
- Analyze remaining chromosomes using family specific weights

Conditioning on 9

- Positive on Chr.9, increase on Chr.2
Conditioning on 15

- Positive on Chr.15, increase on Chr.13
- Negative on Chr.15, increase on Chr.20, same area as for analysis conditional on males
Conditioning on 7

- Positive on Chr.7, increase on Chr.12
- Negative on Chr.7, increase on Chr.2

\[ \chi^2 = 7.97, \ p = 0.0048 \]
Summary of Primary Analyses: Modest Findings

- **Ever-stuttered**
  - Chr. 9
  - Chr. 2
  - Chr. 7
- **Persistent only**
  - Chr. 15
  - Chr. 13

Summary of Conditional Analyses: Stronger Findings

- **Condition on male**
  - Chr. 7 LOD increase
  - Chr. 20 LOD increase
- **Condition on female**
  - Chr. 21 LOD increase
Summary of Conditional Analyses: Stronger Findings

- Condition on Chr. 9 (positive for 9)
  - Chr. 2 LOD increase

- Condition on Chr. 7
  - Positive – Chr. 12 LOD increase
  - Negative – Chr. 2 LOD increase

- Condition on Chr. 15
  - Positive – Chr. 13 LOD increase
  - Negative – Chr. 20 LOD increase

- Chr. 2 signal in same area as positive findings for autism and SLI
- Chr. 20 signal in males same area as that when conditioning on Chr. 15 (negative)
### Comparison of Studies

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<th>Study/Chromosome</th>
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<th>Riaz</th>
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### What Next??
Prioritizing Candidate Genes based on Sex Conditional Analyses

- **Females – Chr. 21**
  - BM-020
  - C21orf66
t-complex 10 (mouse)-like
  - TCP10L
  - h-ormonally upregulated Neu-associated kinase
  - HUNK
  - Splicing factor, arginine/serine-rich 15
  - SFRS15
  - T-cell lymphoma invasion and metastasis 1
  - TIAM1
  - Superoxide dismutase 1, soluble amyotrophic lateral sclerosis
  - SOD1
  - Keratin associated protein 19-6
  - KRTAP19-6
  - Claudin 17
  - CLDN17
  - Glutamate receptor subunit GluR5
  - GRIK1
  - BTB and CNC homology 1, transcription
  - BACH1
  - Ubiquitin specific protease 16
  - USP16
  - Zinc finger protein 294
  - ZNF294
- **Males – Chr. 7**

![Graph showing Chr. 21 - Ever Stutter Female]
Prioritizing candidates

- CLEC5F5: C-type (calcium dependent, carbohydrate-recognition domain) lectin
- MGAM: maltase-glucoamylase (alpha-glucosidase)
- PRSS2: Protease serine 2 isoform B
- TRPV5: Epithelial calcium channel
- KEL: Kell blood group
- PIP: prolactin-induced protein
- GSTK1: Glutathione S-transferase kappa 1
- CASP2: Similar to caspase 2
- CLCN1: chloride channel 1, skeletal muscle
- EPHB6: EphB6
- TAS2R41: taste receptor, type 2
- KIAA0738: PRO2751
- OR2F1: olfactory receptor, family 2, subfamily F
- CTAGE4: CTAGE-4 protein
- ARHGEF5: Rho guanine nucleotide exchange factor (GEF) 5
- CNTNAP2: contactin associated protein-like 2
- CUL1: culin 1

Prioritizing networks of candidate genes

Network Predictions

- Do these genes cluster in common networks?
- Can we elucidate any interactions within potential candidate genes?
  - Chr. 9 and Chr. 2
  - Chr. 7 and Chr. 12
  - Chr. 15 and Chr. 13
How Information about Genes May Help Us

- Determine more about the underlying nature of the deficit and possible subtypes
- Design treatment strategies to directly address deficits
- Discover/develop pharmaceuticals of use
- Design treatment strategies to compensate for deficits
- Counsel individuals and families

Bottom Line on What to Tell Clients/Families

- New information on genetic basis
- May be several different, overlapping, sets of genes in different families
- Could be related to:
  - Persistence-recovery
  - Response to treatment