Gene x Environment Interactions in Speech Sound Disorder

Lauren M. McGrath[1], Bruce F. Pennington[1], Erik G. Willcutt[2], Lawrence D. Shriberg[3] & Shelley D. Smith[4]

[1]Psychology Department, University of Denver, [2]Psychology Department, University of Colorado at Boulder, [3]Waisman Center, University of Wisconsin at Madison, [4]University of Nebraska Medical Center

INTRODUCTION

Gene x Environment Interactions

- Gene x environment (g x e) interactions have been relatively neglected in speech, language, and reading disorders.
- Two models make competing predictions about the direction of predicted g x e interactions.
  - Diathesis-stress model (Rende & Plomin, 1992)
    - Effects of genotype are larger in risk environments.
    - Found in psychopathologies (e.g., Caspi, 2002; 2003).
  - Bioecological model (Bronfenbrenner & Ceci,1994)
    - Effects of genotype are smaller in risk environments.
    - Found in academic traits (e.g., Turkheimer et al., 2003; Kremen et al., 2005; Rowe et al., 1999).

Speech Sound Disorder (SSD)

- SSD is a developmental disorder characterized by speech production errors that significantly impact intelligibility (Shriberg, 2003).
- SSD is associated with increased risk of reading disability (RD) (Bishop & Adams, 1990).
- Molecular genetic studies of SSD have shown linkage to previously identified RD loci (Miscimarra et al., in press; Smith et al., 2005; Stein et al., 2004; Stein et al., in press).

Goals

- Test for g x e interactions in SSD using a sib-pair linkage design.
  - Use molecular genetic measures of "g" - 3 previously identified SSD/RD loci in this sample: 1p36, 6p22, and 15q21 (Smith et al., 2005).
  - Use psychosocial measures of "e" related to speech, language, or literacy development.

METHODS

Participants

- 60 children with SSD (5-7 years) and their biological siblings (5-9 years) = 79 sib-pairs.
- Children with SSD had a history of speech therapy and/or scored below the 30th percentile on the Sounds-in-Words subtest of the *Goldman Fristoe Test of Articulation*.

Procedure

- Composite phenotypes were created based on the results of a confirmatory factor analysis: Articulation, Oral-Motor skills, Semantics, Syntax, Phonological Awareness, Phonological Memory, Letter-Naming, and Rapid Naming.
- Environmental measures were screened for those that had an impact on the phenotypes. Those that passed the screen were: parent education, shared reading, and home literacy environment.
- Environmental measures that showed g-e correlations were excluded from the analyses.
- DNA obtained from buccal brushes.
- Markers from RD candidate regions on chromosomes 1p36, 6p22, and 15q21 were typed and ibd estimates calculated using Merlin.

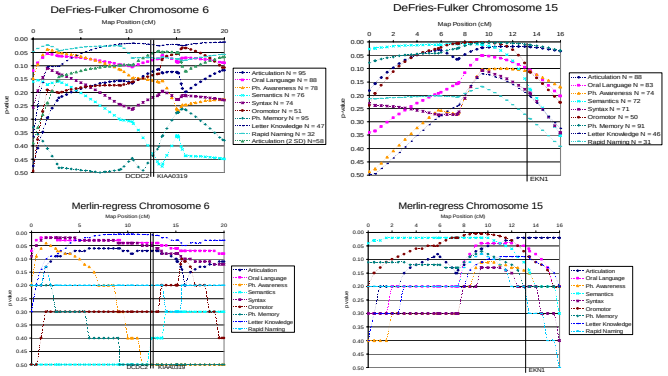
Analyses

- Regression-based approaches appropriate for selected samples:
  - DeFries-Fulker multipoint linkage
  - Merlin-Regress multipoint linkage

RESULTS

Localizing the Linkage Peaks

- Analyses first focused on localizing the linkage peaks described by Smith et al. (2005) using this new set of composite phenotypes.
  - Results showed fairly good convergence between the DeFries-Fulker and Merlin-Regress methods.
  - Evidence for linkage at 6p22 and 15q21, but not 1p36.

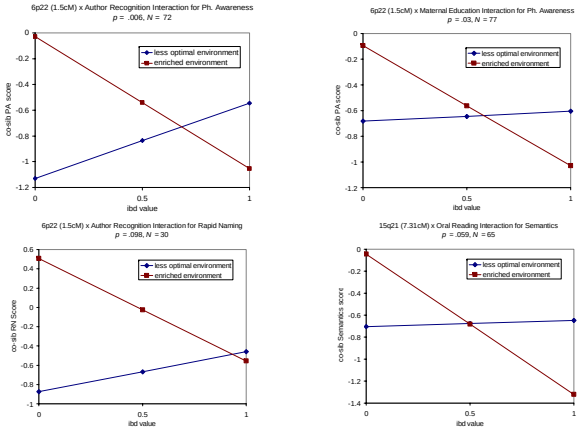


Gene x Environment Interactions

- Test for differential heritability of a locus by adding a g x e interaction term to the DeFries-Fulker linkage equation: $C = B_1P + B_2\pi + B_3e + B_4Pe + B_5\pi e + K$

  (C=co-sib, P=proband, π = ibd status, e = environmental variable)

- The figures below depict continuous interactions by dichotomizing the environment (less optimal environment = 1 SD below the mean, enriched environment = 1 SD above the mean).
- The co-sib's score is plotted as a function of his/her genetic relationship with the proband (ibd). The y-axis is scaled in terms of SD units below the control mean and the proband mean is -1.
- The slopes of the lines reflect the heritability of the locus, such that a steeper negative slope reflects a greater heritability. Each of the g x e interactions shows that the heritability of the locus is larger in enriched environments, consistent with the bioecological model.



DISCUSSION

Chromosome 6

- Phenotypes showing converging evidence of linkage: Phonological Awareness and Letter Knowledge.
- The graphs were complicated and showed 2 separate linkage peaks.
  - One of the linkage peaks was very close to the 2 proposed RD candidate genes on 6p22, *KIAA0319* and *DCDC2* (Cope et al., 2005; Francks et al., 2004; Meng et al., 2005; Schumacher et al., 2006).
  - The other linkage peak is more distal to these genes although significant linkage peaks have also been reported in this region (Grigorenko, 1997).

Chromosome 15

- Phenotypes showing converging evidence of linkage: Articulation, Semantics, and Oral-Motor skills.
- The linkage peaks were remarkably consistent and close to the proposed candidate gene in this region, *EKN1* (or *DYX1C1)* (Taipale et al., 2003).
- Notably missing among the phenotypes showing linkage were the pre-literacy variables.

Gene x Environment Interactions

- Significant and trend-level g x e interactions were detected at the 6p22 and 15q21 loci with measures of the home environment to predict language and pre-literacy skills.
  - The bioecological direction of the g x e interactions suggests:
    - The poor performance of children in less optimal environments was multi-determined.
    - The poor performance of children in enriched environments was most likely due to genetics.
- Limitations
  - Small sample size
  - The range of represented environments is skewed toward higher SES so we cannot comment on how children in truly impoverished environments would perform.

Summary

- The linkage findings were consistent in showing linkage of speech, language, and pre-literacy phenotypes to the previously identified RD risk loci on 6p22 and 15q21.
- G x e interactions at these loci with measures of the home environment were detected.
- The direction of the g x e interactions was consistent with the bioecological model.

FUTURE DIRECTIONS

- Final confirmation of these results will await identification and replication of candidate genes for SSD and RD.
- In the meantime, these linkage-based methods could be used in larger samples and different developmental disorders to inform theory about g x e models.
- Specifically, more research is needed to determine what factors are important for determining the direction of a g x e interaction:
  - Type of disorder (psychopathology vs. cognitive)?
  - Type of environmental factor (risk vs. protective)?
  - Type of genetic factor (risk vs. protective)?