

Genetic studies of stuttering in a founder population

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Abstract

Genome-wide linkage and association analyses were conducted to identify genetic determinants of stuttering in a founder population in which 48 individuals affected with stuttering are connected in a single 232-person genealogy. A novel approach was devised to account for all necessary relationships to enable multipoint linkage analysis. Regions with nominal evidence for linkage were found on chromosomes 3 ($P=0.013$, 208.8 centiMorgans (cM)), 13 ($P=0.012$, 52.6 cM), and 15 ($P=0.02$, 100 cM). Regions with nominal evidence for association with stuttering that overlapped with a linkage signal are located on chromosomes 3 ($P=0.0047$, 195 cM), 9 ($P=0.0067$, 46.5 cM), and 13 ($P=0.0055$, 52.6 cM). We also conducted the first meta-analysis for stuttering using results from linkage studies in the Hutterites and The Illinois International Genetics of Stuttering Project and identified regions with nominal evidence for linkage on chromosomes 2 ($P=0.013$, 180–195 cM) and 5 ($P=0.0051$, 105–120 cM; $P=0.015$, 120–135 cM). None of the linkage signals detected in the Hutterite sample alone, or in the meta-analysis, meet genome-wide criteria for significance, although some of the stronger signals overlap linkage mapping signals previously reported for other speech and language disorders.

Educational objectives: After reading this article, the reader will be able to: (1) summarize information about the background of common disorders and methodology of genetic studies; (2) evaluate the role of genetics in stuttering; (3) discuss the value of using founder populations in genetic studies; (4) articulate

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the importance of combining several studies in a meta-analysis; (5) discuss the overlap of genetic signals identified in stuttering with other speech and language disorders.

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1. Introduction

Developmental stuttering is a common disorder of speech disfluency that affects 5% of children with an average population prevalence of 1% (Craig, Hancock, Tran, Craig, & Peters, 2002; Felsenfeld, 2002). The overt symptomatology of the disorder is characterized by excessive repetitions of sounds, syllables, and monosyllabic words, as well as sound prolongations and complete blockages of the vocal tract. Any of these characteristics may be accompanied by physical tension or movements, especially in the head and neck areas (Conture & Kelly, 1991; Wingate, 1964). Young children are often first diagnosed between ages 2 and 5, when they begin forming sentences and connecting thoughts verbally, with a higher occurrence in males than females at a ratio of 2:1. Nearly 80% of these affected children recover naturally from stuttering within one to four years of onset (Andrews & Harris, 1964; Mansson, 2000; Yairi & Ambrose, 1999). More females recover than males, resulting in a more skewed male-to-female ratio of 4:1 in older children and adults (Bloodstein, 1995; Buchel and Sommer, 2004; Felsenfeld, 2002; Yairi & Ambrose, 1999).

Twin and family studies have indicated a strong genetic component to stuttering. Three twin studies showed considerably higher concordance levels of stuttering in monozygotic twins (20–90%) compared with dizygotic twins (3–19%) (Andrews, Morris-Yates, Howie, & Martin, 1991; Bloodstein, 1995; Felsenfeld et al., 2000; Howie, 1981). When the monozygotic and dizygotic twin correlations are used to model the additive genetic and environmental components, both Andrews et al. (1991) and Felsenfeld et al. (2000) concluded that approximately 70% of the phenotypic variance is due to additive genetic effects and approximately 30% to non-shared effects. Several studies have shown a higher incidence of stuttering in first degree relatives (20–74%) than in the general population (1.3–42%) (Kidd, Heimbuch, & Records, 1981; Yairi, Ambrose, & Cox, 1996). Both the concordance of stuttering among monozygotic twin pairs and the familial aggregation of stuttering are consistent with a genetic component to stuttering.

Several genetic models have been suggested for the inheritance of stuttering within families. Kidd, Kidd, and Records (1978) performed a segregation analysis (a statistical procedure that provides maximum likelihood values to allow testing of models of genetic transmission) in 511 families to identify the mode of inheritance that would account for the observed skewed sex ratio. They concluded that the model most consistent with the observed data was a sex-modified transmission model in which males and females have different genetic thresholds, with females requiring more susceptibility alleles than males to express a stuttering phenotype. This model was also proposed several years later in a study of a large Utah pedigree in which 38 individuals of a 269-member family stuttered (MacFarlane, Hanson, Walton, & Mellon, 1991). The sex-modified transmission of stuttering was consistent with both a multifactorial-polygenic model (many genes with small effect, as well as environmental components) and a single-locus genetic model (one gene with large effect, with numerous genes with small effects and environmental components) (Kidd, 1977). In 1993, Ambrose, Yairi, and Cox conducted a segregation analysis in 69 families in which at least one child stuttered and found that a single major genetic locus was the best

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