FAMILIAL IDIOPATHIC SCOLIOSIS: EVIDENCE OF AN X-LINKED SUSCEPTIBILITY LOCUS

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Introduction
Familial idiopathic scoliosis is believed to be a complex genetic disorder in that its expression may depend upon multiple factors. Previous studies from various populations have suggested a Mendelian pattern of inheritance of an autosomal dominant or X-linked type. The current study investigates the existence of loci on the X chromosome for idiopathic scoliosis within a large population of families diagnosed through consistent radiographic criteria.

Materials and Methods
Families with two or more affected individuals identified through evidence of a ten-degree sagittal curvature (Cobb angle) on standing anterioposterior radiographs were recruited with IRB approval. Initially, twenty-four polymorphic X-chromosome markers in 14 families were typed and analyzed through model-independent and dependent linkage analysis. Analyses in the second phase of the study included genotyping data from a genomic screen of 202 families (1208 individuals). Arbitrary models were assumed for X-linked (XLD) and autosomal dominant (AD) modes of inheritance. The likelihood of each family to represent either an XLD or an AD mode of inheritability pattern was calculated using VITESSE. Families were then ranked in a distribution from an upper end (XLD subset) into a lower end (AD subset). Figure 1 shows a representative pedigree of a family within the XLD subset.

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Results
When analyzing the families that ranked in the top 70% of the initial pilot group of families, two-point linkage analysis revealed positive LOD scores at 6 of 8 adjacent markers with peaks at recombination fractions between 0.2 and 0.3. When analyzing the 202 families using model-independent linkage analysis, no significant p-value was obtained for any marker when analyzing the entire population of families. However, two-point linkage analysis of the families ranked in the top 25% of the distribution resulted in positive lod scores for 5 of 8 adjacent markers at a recombination fraction of 0.3. The highest lod score was 1.12 (theta=0.3) for marker CXS1725. Analysis of the top 15% of families resulted in 6 out of 8 adjacent markers positive at a recombination fraction of 0.3. A lod score of 1.85 at a recombination fraction at 0.2 was obtained from markers CXS1725. Genotyping of three additional flanking markers in this area also resulted in positive lod scores.

Discussion
Genetic linkage analysis is an effective method in the identification of genetic loci and specific genes responsible for complex disorders. The results presented support that within a subset of families affected by familial idiopathic scoliosis a genetic determinant on the X-chromosome predisposes individuals to this disorder. Secondly, the overall work supports the hypothesis that the manifestation of this complex orthopedic disorder is influenced by genetic heterogeneity. Given the variability of familial idiopathic scoliosis, a large carefully identified population has been selected for study in order to enhance the possibility that statistical analysis will yield meaningful results. However, with the identification of subsets of families within the large population, it is possible that further mapping of this area within the identified families representing an X-linked inheritability pattern will not aid in the comprehensive study of this locus. Recruitment of additional families may be necessary to further identify the predisposing genetic loci on the X-chromosome. This initial identification of a susceptibility locus for idiopathic scoliosis is an essential step in the understanding of the genomic influences related to this disorder.

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