FAMILIAL IDIOPATHIC SCOLIOSIS: EVIDENCE OF AUTOSOMAL SUSCEPTIBILITY LOCI

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Introduction: Familial idiopathic scoliosis is a common structural lateral curvature of the spine whose genetic determinants and pattern of inheritance are not clear. The goal of this research is to define the genes responsible for this disorder utilizing a large, well-defined population. Each family within the study population has at least two first-degree relatives with scoliosis diagnosed through consistent radiographic criteria. This strategy is based on the high prevalence of the disorder within the general population (2-3%), and the wide variability of disease presentation suggesting significant clinical and genetic heterogeneity.

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. Figure 1 shows a representative pedigree of a family exhibiting an autosomal dominant type inheritability pattern. A genomic-wide scan of the identified population (202 families, 1208 individuals) was completed by the Center of Inherited Disease Research utilizing a standard automated fluorescent marker set (Weber Screening Set 9). This marker set consists of approximately 387 primer pairs spaced approximately every ten centimorgans throughout the genome. Model-independent sib-pair linkage analyses for both quantitative and discrete traits implemented in SIBPAL were utilized to screen each trait for evidence of linkage to each genetic marker. Model-dependent two-point linkage analysis was performed using Mlink from the LINKAGE software package, initially assuming an underlying autosomal dominant with incomplete penetrance.

Results: Due to the complex genetic nature of this disorder, multiple statistical strategies have been utilized in order to identify potential genomic locus(i) that influence disease expression. Scoliosis was first categorized as a quantitative trait, that is, a measurable degree of sagittal spinal curvature. A second approach is to consider scoliosis as a qualitative or dichotomous (affected/unaffected) trait. The application of a ‘threshold’ of spinal curvature measurement, which indicates a significant deviation from the norm, would define the presence or absence of the disease trait. Within the studied population, when families exhibiting an autosomal dominant mode of inheritability and when scoliosis was considered a quantitative trait significant values were obtained in regions of chromosomes 1, 6, 8, 9, and 16 (p<0.01, which corresponds to a lod score of 1.45). When scoliosis was considered a qualitative trait, and the threshold criteria for a positive disease status is considered ten, and then twenty degrees, significant p values were obtained in the same chromosomal locations (p<0.01), and in 2 of the areas p values were <0.001 with a corresponding lod score of 2.36. These areas averaged forty centimorgans in size.

Discussion: Genomic screening combined with statistical linkage analysis is an effective method in the identification of genetic loci and specific genes responsible for complex disorders. The results here support the identification of a number of genetic loci that segregate with the observed phenotype in the study population. 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 analyses will yield meaningful results. By first categorizing scoliosis as a quantitative trait, an arbitrary threshold or definition of the disease state is not required, and one utilizes all of the information available from the dataset. As a qualitative trait, one restricts the definition of the phenotype, thus, potentially eliminating mild, sporadic forms of the disease within the population (‘phenocopies’), which may confound statistical analysis. The combination of these approaches utilized in a step-wise fashion has resulted in evidence of significant genetic linkage of scoliosis to several potential loci in the face of significant heterogeneity. Further work will include the fine mapping of these genetic loci in order to corroborate preliminary findings and to narrow the identified linkage intervals. The initial identification of a locus for familial idiopathic scoliosis is an essential step in the understanding of the genomic influences related to this disorder.

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