What is the best way to determine the cause of adolescent idiopathic scoliosis?

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Adolescent idiopathic scoliosis (AIS) is defined as a lateral deviation of the spine associated with rotation that is found in healthy individuals and has no known cause. These subjects do not exhibit neuromuscular conditions or other disorders until the onset of sexual maturation at approximately 10 years of age (1). Diagnosis is challenging; radiography reveals curves of more than 10 degrees by Cobb method (2) without vertebral abnormalities. Additionally, the angular deviation required for diagnosis is controversial, which further complicates diagnosis. In 1995, Winter questioned the accepted diagnostic value used to characterize the disease and proposed that a curve of 5 degrees should be considered pathological or a variation from a normal spine (3). Furthermore, it is important to observe how rotation impacts the condition, as this feature may be more characteristic of the disease than the curvature itself.

Since 1875, studies have been performed on twins to ascertain the influences of genetic and environmental factors on the manifestation of certain diseases (4). Fisher and George studied pairs of monozygotic and dizygotic twins with idiopathic scoliosis and compared their deformities. These studies revealed that environmental factors were able to modify the features and severity of the disease, especially among dizygotic twins (5). In a systematic review, Kesling and Reinker reported an agreement rate of 73% in 37 pairs of monozygotic twins and 36% in 31 pairs of dizygotic twins, thus revealing a stronger similarity between monozygotic twins (6).

Del Curto *et al*. presented a pair of monozygotic twins with AIS and curves that differed in type, direction and severity, suggesting that these differences could be attributed to environmental influences or epigenetic factors (7). Epigenetic factors regulate gene expression by mechanisms that are not directly related to the primary sequence of DNA. Three examples of mechanisms of epigenetic factors include: DNA methylation, histone modification and the action of non-coding RNAs (7).

Since 2000, linkage studies in families with multiple affected members have revealed several regions of chromosomes that may be related to the etiology of AIS. Linkage studies have been successfully used to determine the regions of DNA responsible for other diseases that are caused by one or a few genes. Linkage studies also allow facile differentiation between affected and unaffected individuals, preferably within the same family, by identifying certain molecular markers in specific regions within the human genome.

Using this technique, Wise *et al*. in 2000, described the first regions of DNA related to AIS on chromosomes 6p, 10q and 18q by studying an extended family with seven members affected by this disease (8).

In subsequent years, other family studies have suggested that AIS is related to chromosomes 6, 9, 16 and 17 (9) and to the chromosomal regions 17p11 (10), 19p13.3 (11), 8q12 (12), 9q31-q34.2, 17q25.3-qtel (1), and 12p (13) 18q12.1-12.2 (14). In 2010, Wajchenberg *et al*. found no association while studying a family with nine affected members from central Brazil and cast doubt on the use of linkage analysis to study AIS. This report criticized the Cobb method, which is used to measure the curvature of the spine. First described in 1948, the Cobb method is dependent on the examiner, and small variations may interfere with the classification of an individual as affected or normal. Thus, patients with a difference of only two degrees (nine or 11 degrees of curvature) are classified in different ways (15).

In 2011, Takahashi *et al*. performed an important multi-center study (16). In this study, 1,050 Japanese women with

AIS and 1,474 control women without AIS were evaluated using of curves greater than or equal to 15 degrees as the criterion for affected patients, which was the same as in Wise *et al*. (8) and Wajchenberg *et al*. (15). Using a genome-wide association study (GWAS), this report successfully correlated the chromosome region 10q24.31 with the disease by locating the single nucleotide polymorphism (SNP) 11190870 (odds ratio =1:56). This region is within the region 10q described by Wise *et al*. in 2000 and contains the *LBX1* gene. This gene is expressed in the dorsal region of the spinal cord and skeletal muscle, and also operates in somatosensory neurons. LBX1 may be related to the etiology of the disease due to somatosensitive dysfunction. In addition to LBX1, this DNA region contains regulators of gene expression, which could influence the manifestation of the disease depending on the polymorphism (TT, TC and CC) that is present. The authors analyzed the expression of LBX1 and detected high levels of expression in the skeletal muscle and spinal cords of adult and fetal humans.

However, as observed in a recent systematic review and meta-analysis by Chen *et al*. (17), the control group presented in the study by Takahashi *et al*., though numerous, was not subjected to the appropriate evaluation for diagnosis of idiopathic scoliosis. The authors presumed that within this group, the rate of affected patients matched that of the Japanese population.

Other authors in Asian eastern populations have also reproduced the data reported by Takahashi *et al*., but GWAS of 491 families conducted in the US detected the unrelated SNP rs11190870 among the 100 SNPs most linked to the disease (18).

In 2013, Kou *et al*. extended the Takahashi *et al*. study. Not only did this extension confirm the relationship of 10q24.31 region with AIS, but it also identified a new correlated DNA region, region 6q24.1, and related a Han Chinese population to another population of European ancestry (19). The authors also reported a relationship between the disease and the *GPR 126* gene (rs6570507 SNP—odds ratio =1.27) within the same region studied. According to the authors, neither the expression of this gene in the skeletal tissue of humans nor its relationship to scoliosis has been explored. Thus, they attempted to study its expression in various tissues, such as bone, cartilage and intervertebral disks, and they found high expression in cartilage.

AIS is a disease that is influenced by genetic factors and the environment and has a complex inheritance pattern. However, despite many studies and technological advances, it is still not possible to fully describe the genes responsible for the disease. The family studies may assist in our understanding of the disease, but great difficulty lies in labelling the affected individuals due to the high degree of phenotypic variability. This variability is largely due to doubt in the deformity measurements by the Cobb method. Still, Wise *et al*. [2000] claimed that their analyses were made in affected members of the family because the individuals who were considered normal could be carriers of the genetic alterations. However, the frequently low penetrance associated with AIS confounds their analysis.

In general, the low success rate of GWAS in identifying the genetic variants with significant effects and in accounting for the relevant contributors to the heritability of the trait of interest suggests that some common diseases may be caused by rare variants (as well as monogenic disorders of Mendelian inheritance) that cannot be identified by this approach. According to this model, the rare variants, so named because of their low population frequency, would be numerous in each affected individual and would be jointly responsible for the manifestation of the phenotype. In this way, the effect of each of the variants associated to the studied trait would be expected to be modest, and each individual contribution would not be large enough to be identified by binding studies. Additionally, according to this hypothesis, common variants cannot be ruled out as possible regulators of expression of genes pertinent to the disease, which may contribute, for example, to the clinical heterogeneity observed in AIS (20,21).

We believe that the polymorphisms identified in the studies of patients known to be affected, as performed by Aulisa *et al*. (22) (*IL-6* and *MMP-3* gene), Qiu *et al*. (23) (*DPP9* gene) Chen *et al*. (24) (*Matrilin-1* gene), Wajchenberg *et al*. (25) (*ACE* gene), Jiang *et al*. (26) (*LBX1* gene) aid in detecting regions that may influence AIS. Mostly likely, AIS is caused by genes that are responsible for the synthesis of proteins that are important for the composition of human spinal tissues. When evaluating only those patients who are affected with severe deformities (with surgical indication or, at least, bracing) the risk of underestimating the numbers of affected individuals with small curvatures related to the variable expression of the disease can be avoided. Based on these studies, the evaluation of tissue-specific gene expression using biopsies during surgical procedures may further our understanding of the disease.

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