



## Is Idiopathic Scoliosis Idiopathic?

Jessica Morton, Shaleen Vira, Samantha R Horn, Gregory W Poorman and Peter G Passias\*

Department of Orthopaedic Surgery, Hospital for Joint Diseases at NYU Langone Medical Center, New York, USA

### Editorial

Adolescent Idiopathic Scoliosis (AIS) is the most common form of Idiopathic Scoliosis (IS) with a prevalence of 3% - 5.2% among children [1]. Disease progression and sequelae depend on the location, severity, and rate of progression of the curve. Curves tend to progress most rapidly during growth phases [1,2]. Treatments and are focused on early bracing to stem curve progression and surgical curve correction. Despite a concordance rate of 73% in monozygous twins, familial clustering, and Genome Wide Association Studies (GWAS) the etiologies of AIS development and progression have remained largely unknown [1-4]. Historically, the lack of etiopathogenesis has been attributed to genetic heterogeneity and lack of adequate animal models.

Recent research, with improved genome wide and familial linkage studies combined with newly validated animal models has provided convincing support of the role of the Wnt/ beta-catenin pathway and disrupted motile cilia as the underlying etiopathology of AIS [3,5-7]. This article will discuss current hypotheses regarding the WNT/ B-catenin pathway as an origin of AIS as suggested by human genetic studies and the role of cilia and cerebrospinal fluid flow as the biological basis of disease validated in the zebrafish model [6,8,9].

The Wnt/ B-catenin signaling system was recently implicated by four stage genome wide association study that found novel SNPs and confirmed association with previously identified genes LBX1 and PAX3 [5]. Both the newly defined variants and previously defined genes are part of the WNT/B-catenin pathway. A newly identified variant, an intron of TNF, is a regulatory element of the beta-catenin transcription complex. Confirmed genes LBX1 and PAX3 are both downstream mediators of the WNT/B-catenin pathway [3]. Furthermore, local tissue sample of the bilateral paraspinal muscles of patients with AIS demonstrated significantly decreased gene expression levels of Beta-Catenin, TNF, PAX3, and LBX1 on the convex side of the curve as compared to the concave side [5]. This differential expression at the tissue level is novel in IS research. The WNT/B-catenin pathway, responsible for patterning, is hypothesized to cause this asymmetry of expression and scoliosis. The mechanism by which the Wnt/B-catenin pathway influences scoliosis and asymmetry is best described in the zebrafish model.

Recently, Zebrafish have been described as a faithful model of human IS with highly conserved WNT/B-catenin pathways and naturally occurring scoliosis [8,9]. Zebrafish with mutation of PTK, an atypical receptor tyrosine kinase implicated in Wnt signal transduction, develop three-dimensional curvature of the spine at the late larval to early adolescent period that is associated with onset of accelerated growth. Female mutants demonstrate clear bias toward more severe curves, and curve progression does not visibly progress after physical maturity. This disease pattern in zebrafish exhibits clear correlates to human IS [9].

Using the Zebrafish model researchers demonstrated Wnt/B-catenin signaling is critical in development of polarized cell movements and body axis formation, especially the anterior-posterior patterning of the CNS through the action of cilia. In specialized cells, long motile cilia direct extracellular fluid flow through polarized beating. Cerebrospinal fluid flow is directed by such cilia through polarized beating of long motile cilia of the ependymal cells. Cerebrospinal fluid flow has been shown to be critical to CNS homeostasis and left right symmetry within early embryonic organization. Zebrafish with disruption in Wnt/B-catenin signaling by mutant ptk have been shown by scanning electron microscope and tagged fluorescent beads to have sparse cilia lacking posterior polarization with aberrant CSF flow. The same zebrafish subsequently developed scoliosis [8]. In contrast wild type zebrafish demonstrated a clear anterior to posterior polarization with a dense network of cilia.

To investigate, if disruption of motile cilia of ependymal cells and aberrant CSF flow is the sole biological basis for the development of scoliosis in mutant zebrafish, researchers used transgenes to reintroduce wild type ptk function exclusively in motile ciliated cells. The restoration of cilia

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#### \*Correspondence:

Peter G Passias, New York Spine Institute, New York University Medical Center - Hospital for Joint Diseases, 301 East 17<sup>th</sup> St., New York 10003, USA, Tel: 516-357-8777; Fax: 516-357-0087;

E-mail: Peter.Passias@nyumc.org

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function in ependymal cells by transgene expression, completely resolved the scoliosis and aberrant CSF flow in all zebrafish [6,8]. This data provides a strong case that disrupted motile cilia and aberrant CSF flow is the underlying mechanism leading to idiopathic scoliosis.

Additional support was lent by temperature-shift experiments with alternate mutations, again affecting cilia motility. Due to the important role of motile cilia in development, all proved lethal in initial knockout. However, using heat stable variants and temperature shift experiments a critical period of development was identified. Within that period of development, a lack of adequate motile cilia led to scoliosis [6,9]. This time period, as in humans, is during periods of accelerated adolescent growth. Remarkably, restoring the function of motile cilia, at any time point, blocked further curve progression. The therapeutic implications of stopping curve progression without surgery or bracing cannot be understated.

The impressive implications that in zebrafish disruption of motile cilia and CSF flow is the biological basis of AIS, unifies not only the research in the Wnt/Beta-catenin pathway but other genomic linkage studies as well. In brief, familial genome linkage studies also implicated POC5 as a potential genetic cause of IS. Although there is little data on the function of POC5 in humans, the protein localizes to the distal region of centrioles which interact and assist with motile cilia function. Researchers propose that disruption of motile cilia and impaired CSF flow leads to IS in these patients as well. Again, the zebrafish model demonstrated that disruption of this gene at defined critical stage resulted in a phenotype analogous to IS [3,6,10].

In light of new research on candidate human genes and faithful models implicating the biological basis for idiopathic scoliosis development, perhaps not all idiopathic scoliosis is idiopathic. Instead, perhaps it is a group of heterogeneous mutations with a final common pathway leading to disruption of motile cilia and aberrant CNS flow. The Wnt/B-catenin pathway and its mediators may prove an exciting new target for research and transgenic targeting.

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