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Idiopathic-type scoliosis is not exclusive to bipedalism

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Abstract

Human familial/idiopathic-type scoliosis (IS) is a complex genetic disorder for which the cause is unknown. The curve phenotype characteristically demonstrates pronounced morphological and developmental variability that is likely a consequence of biomechanical, environmental, and genetic differences between individuals. In addition, risk factors that affect the propensity for curves to progress to severity are unknown. Progress in understanding the fundamental biology of idiopathic-type scoliosis has been limited by the lack of a genetic/developmental animal model. Prior to consideration of teleosts, developmental idiopathic-type scoliosis has been considered to be exclusive to humans. Consequently, there is the notion that the syndrome is a result of bipedalism, and many studies try to explain the deformity from this anthrocentric viewpoint. This perspective has been reinforced by the choice of animals used for study, in that chickens and bipedal rats and mice demonstrate idiopathic-type curvature when made melatonin deficient, but quadrupedal animals do not. Overlooked is the fact that teleosts also demonstrate similar curvature when made melatonin-deficient. Our characterization of the guppy *curveback* has demonstrated that non-induced idiopathic-type curvature is not exclusive to humans, nor bipedalism. We hypothesize that unique morphological, developmental and genetic parallels between the human and guppy syndromes are due to common molecular pathways involved in the etiopathogenesis of both phenotypes. We explore established gene conservation between human and teleost genomes that are in pathways hypothesized to be involved in the IS syndrome. We present non-induced vertebral wedging as a unique shared feature in IS and *curveback* that suggests a similar interaction between a molecular phenotype on the level of the vertebral anatomy, and biomechanics. We propose that rather than bipedalism *per se*, expression of idiopathic-type scoliosis is dependent on normal spinal loading applied along the cranio-caudal axis that interacts with an unknown factor causing the primary curve. In this regard, a comparative biological approach using a simplified teleost model will promote discovery of basic processes integral to idiopathic-type scoliosis in teleosts and humans, and highlight human-specific aspects of the deformity.

Introduction

Familial/idiopathic-type scoliosis (IS) is a complex genetic disorder that accounts for 80% of all human spinal curvatures (MIM 181800, Online Mendelian Inheritance in Man). It is broadly defined as a three-dimensional curve deformity with no known etiology that manifests after birth and has a propensity to increase in magnitude with growth, until sexual maturity. Curve magnitude, morphology, rate of and propensity for progression are highly variable among

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individuals, due to biomechanical, environmental, developmental and possibly genetic variability between individuals.

An understanding of fundamental aspects of the deformity has been limited by the lack of a genetic/developmental animal model. Before consideration of teleost fishes, all observed forms of scoliosis in animals have been the result of congenital anomalies, or have been induced in laboratory animals [1]. Hence, it appears that idiopathic-type spinal curvature is exclusive to humans, and therefore is alleged to be a consequence of bipedalism [1-6]. Abandoning this anthrocentric perspective will help advance our comprehension of not only the cause(s) of curve onset, but also risk factors associated with progression. A comparative biological approach using a simplified teleost model will promote discovery of basic processes integral to idiopathic-type scoliosis and highlight human specific aspects of the deformity.

How the choice animal models for IS support the bipedal notion

That idiopathic-type scoliosis has never been observed in any animal other than humans certainly has encouraged the notion that the deformity is contingent on bipedalism. Experimentally, scoliosis has been produced using a variety of animals (i.e., rabbit, lamb, goat, mouse, rat, monkey, dog, pig, chicken). These all have the fundamental goal of producing a model that is comparable to IS in order to elucidate the etiology, and promote new therapeutic methods [7]. Methods for induction of scoliosis include dietary deficiency, immobilization, local procedures (i.e. damage to spinal, neural or surrounding tissues), or pinealectomy. Ultimately, because they are induced, it remains controversial whether conclusions drawn from such experiments relate to primary or secondary influences for curvature [7,8].

Because most of the animals used for study of IS are quadrupedal, they have limitations for research into an etiology that is presumed to be influenced by gravity [7]. The relevance of bipedalism and gravity to IS pathogenesis has been supported by the fact that pinealectomy (or melatonin deficiency) can induce spinal curvature in chickens, but not in quadrupedal mammals unless they are forced to be bipedal [3,9-11]. For example, pinealectomized rats and mice made melatonin-deficient do not demonstrate spinal curvature as quadrupeds, but do if their front legs and tail are amputated in order to force them to be bipedal [9,10,12].

Importantly, although never reviewed in orthopeadic studies, pinealectomy in the teleosts guppy and salmon induces spinal curvature with a physiological response similar to that in pinealectomized chickens [13-15]. Hence, the conviction that idiopathic-type scoliosis is exclusive to bipedalism and dependent on gravity has been biased by the selection of animals used for study.

Background on the *curveback* guppy

The *curveback* guppy is the first model for human IS to demonstrate spinal curvature in otherwise healthy fish that is not induced nor caused by congenital malformation of the vertebrae [16]. Our characterization of the guppy *curveback* syndrome has revealed unique morphological, developmental, and genetic parallels to human idiopathic-type scoliosis (IS).

The guppy is a small live-bearing teleost fish, and offspring are born approximately 3 weeks after conception. As with humans, the onset of curvature begins at variable ages after birth (guppy skeleton is completely ossified before birth) and can either stabilize at a moderate magnitude, resolve to normal or nearly normal, or progress to severity [16-18]. The curve phenotype is a primary sagittal lordosis of variable magnitude with most individuals exhibiting a posterior kyphosis, coronal deviation and axial rotation (figure 1). Beyond complex inheritance, the human and *curveback* idiopathic-type curvature syndromes share: a female bias for severe curve magnitude, despite an equal incidence rate among males and females;

similar variability for curve magnitude and morphology; variable age of curve onset and rate/propensity for progression; curve stabilization at sexual maturity; the incidence of resolving curves; and vertebral shape distortion at the apex of severe curves [16].

Hypothesis

Study of the teleost *curveback* provides an important insight: that idiopathic-type scoliosis is not a human exclusive deformity. Here we explore the hypothesis that common molecular pathways are involved in the etiopathogenesis of the guppy and human phenotypes. This idea is based on the fact that *curveback* demonstrates so many phenotypic parallels to IS, and that humans and teleosts share many genes involved in basic biological processes. It is possible that the same genes in human and guppy idiopathic-type scoliosis are mutated, or it is also possible that different sets of genes are mutated in guppy and human systems, but that they affect common molecular pathways. Either way, comparison of the two systems has the potential to illuminate important biological pathways involved in the maintenance of spinal stability throughout growth.

An important corollary of our hypothesis is that rather than a consequence of gravity and bipedalism *per-se*, the deformity is likely contingent on the interaction of force/loading applied along the cranio-caudal axis with the vertebral anatomy, in the presence of a genetic predisposition. An important question that emerges from our hypothesis is whether genes for idiopathic-type curvature are present in terrestrial animals, but their expression is constrained by quadrupedal biomechanics, or if indeed the primary etiology is exclusive to humans and teleosts.

Is the genetic predisposition exclusive to humans?

It is possible that the genetic predisposition and components related to curve progression for idiopathic-type curvature in guppies and humans are in the same genes or in genes controlling common genetic pathway(s). The observed phenotypic variation and lack of concordant loci identified among human linkage studies has suggested that there may be multiple predisposing genes for IS [19-22]. With complex syndromes such as IS, different polymorphisms in the same gene or in different genes within the same molecular pathway could cause observed phenotypic variability [23-26].

Fish share most developmental pathways, physiological mechanisms and organ systems with humans [reviewed in 27-29]. Comparisons between human and fish genomes have identified DNA sequences and entire gene networks that have significant functional activity in humans, many of which are in systems implicated for human IS, suggesting some gene conservation for genetic factors thought to be involved in the deformity (e.g. osteoblast and chondrocyte differentiation [30], bone formation [31,32], muscle formation [33], gene regulation [34], pineal gland (Lhx9) [35], neural development [36], somitogenesis [37], cell proliferation [38-40], pituitary(pitx) function [41], osteoclast function [42]). These include regulation of hormones that might be involved in idiopathic-type curvature (based on suggestions from human studies): e.g. calmodulin and steroidogenesis [43], nutritional regulation of growth hormone and insulin-like growth factor-I [44], IGF-binding proteins (IGFBPs) [45], growth hormone-releasing hormones and receptors [46], a neuromodulatory role for nitric oxide [47], thyroid hormones (TH) in bone remodeling [48], thyroid and muscle growth [49], the midbrain locomotor region (MLR) and descending (reticulospinal) pathways that activate spinal networks for rhythmic movements such as swimming in fishes, and walking and running in humans [50,51].

Physical evidence for shared biomechanical and/or physiological factors

Distortion of vertebrae at the apex of curvature is considered an important component of the human phenotype that has not been observed in other animals unless it is induced. It is broadly suggestive of an unknown physiological dysfunction involving asymmetrical loading (the details of which are a subject of speculation) the spine during growth that directly affects the vertebral body growth plates, so that longitudinal growth of a vertebral body is modified [reviewed in 52]. Because the non-induced phenotype is (without consideration of teleosts) exclusively human, it has generated many hypotheses that are difficult to test [reviewed in 53]. Symptomatic distortion of apical vertebrae may provide valuable perspective regarding the interaction between a molecular phenotype on the level of the vertebrae and biomechanics. Therefore, study of vertebral distortion has involved simulation of the phenotype by bracing in rat and cow tails or tethering in goats or rabbits [54-58]. Importantly, the question of to what extent curvature is due to altered biomechanics and growth and how much is due to a more primary etiology cannot be answered only using physical simulations in induced models.

In both humans and guppies primary loading on the spine is along the cranial-caudal axis. In simplified terms, normal loading on human vertebrae is from the weight of the head and gravity coupled with the loading associated with bipedalism (i.e. standing and walking); in guppies, from swimming through the dense medium of water coupled with the force associated with the tail-beat motion. In guppies, non-induced distortion of apical vertebrae is similar to that observed in human IS, in which vertebral bodies are compressed on the concave side of a curve [16,59-61]. An important question in both the *curveback* and human phenotypes is whether the vertebral bodies are compromised so that they are less capable of handling normal cranio-caudal loading (*i.e.*, failure of mechanotransdution), or if the vertebral bodies are normal, but there is excessive/pathological force on the vertebrae sufficient to cause distortion (*i.e.*, dysfunctional growth). There are hypotheses to support the idea that the predisposing defect may involve vertebral bodies [62-65], and also there are hypotheses to support that there may be excessive force on the vertebrae from growth related dysfunctions [66-68].

Consequences of hypothesis

One of the main insights of the *curveback* model is that idiopathic-type scoliosis is not exclusive to bipedalism. We hope that such a consideration will provoke new ideas regarding which components of the syndrome are primary or initiating, and which are secondary (complicating, or risk factors associated with the propensity for curve progression), and how these factors might interact. Human and guppy biomechanical similarities might elucidate essential components of idiopathic-type curvature, and differences between the two animals may offer the opportunity to specify which aspects of IS are indeed exclusive to humans.

Comparative studies of guppy and human physiology and curve phenotypes might direct hypotheses regarding how biomechanics can interact with intrinsic aspects of curve etiology (i.e. genetic and molecular aspects) and/or progression (i.e. growth related aspects). Hypotheses regarding the relative contribution of factors such as tallness/length [69-73], dorsal shear force [1], pelvic association [74-76], or posture [77-81] can be critically evaluated by comparison to the anatomy of *curveback*.

With complex human syndromes that involve interactions among genetic, physiological, and environmental forces, a successful experimental approach is to first identify genes and molecular pathways in a model animal with a similar phenotype [82-85], and we have presented one for IS, the guppy *curveback*. Once genes involved in the etiology of *curveback* are identified, we can determine whether mutations in these genes are correlated to the human IS phenotype. An important question that then can be answered is whether the genetic predisposition to idiopathic-type curvature is common to all vertebrates but not expressed in

quadrupeds because of biomechanical constraints, or if unique mutations in the human lineage have lead to this prevalent syndrome.

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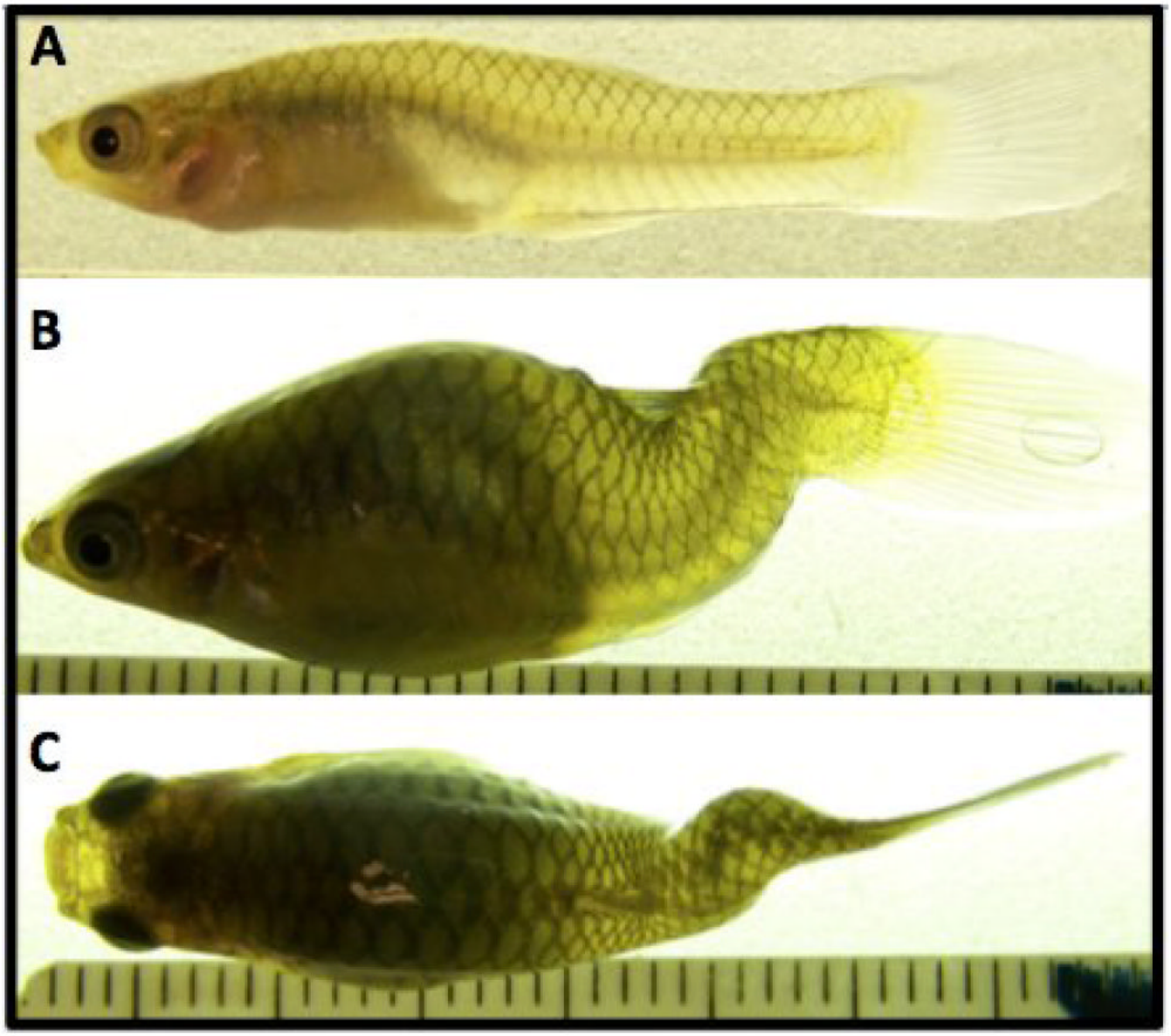

Figure 1. Example of *curveback* phenotype

A and B: Sagittal profile of a normal (**A**), and curved (**B**) adult female *curveback* guppy. **C:** Coronal profile of the same female as shown in **B**. Photos taken on euthanized fish with digital camera (Kodak Easyshare Z612) under 3X magnification on a light table (scale shown in mm).