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Review

Teleosts as models for human vertebral stability and deformity ☆

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Abstract

Vertebral development is a dynamic and complicated process, and defects can be caused by a variety of influences. Spinal curvature with no known cause (idiopathic scoliosis) affects 2–3% of the human population. In order to understand the etiology and pathogenesis of complex human skeletal defects such as idiopathic scoliosis, multiple models must be used to study all of the factors affecting vertebral stability and deformity. Although fish and humans have many of the same types of offenses to vertebral integrity, they have been overlooked as a resource for study. The most common morphological deformity reported for fish are those that occur during the development of the spinal system, and as with humans, curvature is a common morphological consequence. Here we review spinal curvature in teleosts and suggest that they are an unexploited resource for understanding the basic elements of vertebral stability, deformity, development and genetics. Fish can be a value to vertebral research because they are tractable, have a diversity of non-induced vertebral deformities, and substantial genomic resources. Current animal models lack non-induced deformities and the experimental tractability necessary for genetic studies. The fact that fish are free of an appendicular skeleton should allow for analysis of basic spinal integrity without the biomechanical constraints observed in quadrupedal and bipedal models. To illustrate the point we review human idiopathic scoliosis and the potential contribution teleosts can make for the identification of causes, risk factors, and treatment options.

Keywords: Development; Genetic model; Guppy; Scoliosis; Spinal deformity; Teleost; Vertebral system; Scoliosis

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1. Introduction

Many factors can compromise the integrity of the vertebral system. Because it is integrated into the body both structurally and functionally, defects of the spinal system have the potential to produce complex phenotypes for which the primary causes are convoluted by secondary phenotypes. Models used so far

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Table 1
Types of progressive/structural spinal deformities in humans* and reported occurrence in teleosts

Deformity types	Observed in fish?	Circumstances
Idiopathic	Yes	Curvature in aquarium guppy.
Congenital	Yes	Many types: seen in cultured and wild fish.
Neuromuscular	Yes	Laboratory zebrafish
In association with neurofibromatosis	No	Neurofibroma of the Damselfish is a model for NF1 in humans, although there are no reports of spinal curvature.
Traumatic	Yes	In cultured and wild fish.
Due to infection	Yes	*Mycobacterium* (*M. marinum*, *M. chelonei*, *M.fortuitum*)
Due to tumors	Yes	In cultured and wild fish.
Miscellaneous conditions:		
Deformities in adults	Yes	Curvature in older aquarium fish.
Spondylolistheses	?	

*According to the Terminology Committee of the Scoliosis Research Society (1976).

are insufficient to study all of the factors affecting spinal stability and deformity, and thus many of the factors that maintain basic vertebral integrity are unstudied. With regard to complex disorders in humans, multiple models are critical for the investigation and manipulation of etiological factors. The value of teleosts as tools for biomedical research has rapidly become recognized, partly because genomic tools have shown strong human/teleost homology. In this review we discuss the potential of teleost fish as a tool to fill-in some of the gaps in human vertebral research. Defects of the vertebral system in fish and humans have many of the same causes including genetic, physiological (*e.g.* calcium regulation), developmental (*e.g.* fused vertebrae) and infectious (viruses, parasites) (Table 1). In fact, the most common type of deformity seen in fish is vertebral, and most of these occur during development (Brown and Nunez, 1998). Fish systems could be of enormous benefit to vertebral research because they are tractable, exhibit a diverse range of deformities, are free from an appendicular skeleton, and substantial genomic resources have been developed for several species. Here we review spinal curvature in model teleosts and suggest that they are an unexploited resource for understanding the basic elements of vertebral stability, deformity, development and genetics. We illustrate this point by our research into the mutant guppy *curveback* (Fig. 1) as a model for human familial/idiopathic curvature.

2. Spinal curvature in humans

The human spine is normally straight in the coronal plane. At birth there is a slight kyphosis (dorsally directed sagittal curve) from the crown of the head to the buttocks. As a consequence of bipedalism four natural curves develop in the sagittal plane. Control of the head induces cervical lordosis (ventrally directed sagittal curve), and standing causes a lumbar lordosis. Therefore in the normal spine there are cervical and lumbar lordoses and thoracic and sacral kyphoses (Dickson, 2004). There is natural variation among individuals for the magnitude of sagittal curves. Exaggerations of normal curvature are considered abnormalities when they become dysfunctional.

In addition to exaggerations of innate curvature, aberrant spinal curvature can be caused by a variety of influences. Consequently, deformities are classified according to their presumed etiology (Terminology Committee of the Scoliosis Research Society, a glossary of scoliosis terms, 1976). Each etiological category is defined by characteristics that are imposed by the pathophysiology of an underlying condition. Structural curves are those that have the ability to progress during growth (Dickson, 2004). Congenital anomalies (curvature caused by vertebral malformation), idiopathic curvature (curvature with no apparent cause), neuromuscular disorders, neurofibromatosis, connective tissue disorders, and skeletal dysplasia are structural curves specific to the pediatric age group. Although not recognized as an etiological category, (the Scoliosis Research Society) genetics have been identified as the underlying etiology in an increasing number of structural curves. Such is the case for Marfan syndrome, a disorder affecting the connective tissue (Kumar and Guille, 2001; Coucke et al., 2006), and Friedreich's ataxia, a disorder affecting neurological control (Labelle, 2001; Pandolfo, 2006). For curvature such as idiopathic scoliosis and Scheuermann's kyphosis, a genetic basis is widely accepted but there is still no established etiology (Ogilvie et al., 2006; Damborg et al., 2006).

3. Idiopathic scoliosis

Human familial/idiopathic scoliosis represents the largest subgroup of human spinal curvatures. Eighty percent of all

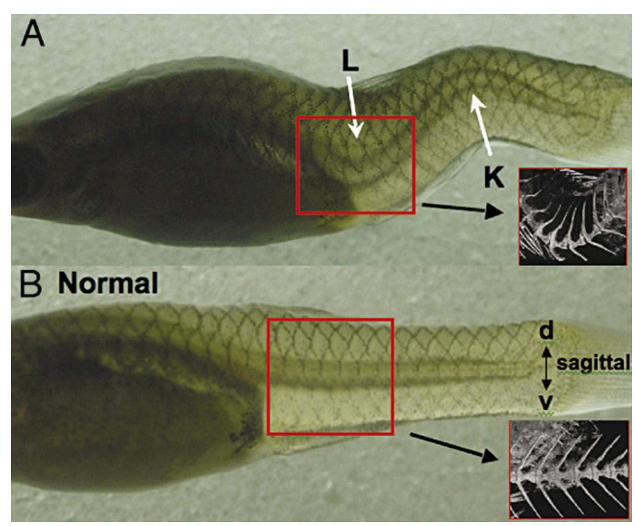

Fig. 1. A: The *curveback* phenotype is a primary anterior lordosis (L) and a secondary posterior kyphosis (K) occurring on the sagittal plane. CT scan shows no vertebral breaks or fusion associated with curvature (some individuals demonstrate coronal deviation—not shown). B: Normal fish with sagittal plane and dorsal/ventral axes shown. Digital photos of anaesthetized adult females taken on a standard light table under 3X magnification, CT scans consist of 350 0.4 mm slices. Images taken at the University of Texas High-Resolution X-ray CT Facility, (datasets of scans available for view at http://www.digimorph.org/index.phtml).