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Summary of the first inaugural joint meeting of the International Consortium for scoliosis genetics and the International Consortium for vertebral anomalies and scoliosis, March 16–18, 2017, Dallas, Texas

Philip F. Giampietro¹, Olivier Pourquie², Cathy Raggio³, Shiro Ikegawa⁴, Peter D. Turnpenny⁵, Ryan Gray⁶, Sally L. Dunwoodie⁷, Christina A. Gurnett⁸, Benjamin Alman⁹, Kenneth Cheung¹⁰, Kenro Kusumi¹¹, Nancy Hadley-Miller¹², and Carol A. Wise^{13,14}

¹Drexel University College of Medicine, Philadelphia, Pennsylvania

²Harvard Medical School, Boston, Massachusetts

³Hospital for Special Surgery, New York, New York

⁴RIKEN Center for Integrative Medical Sciences, Tokyo, Japan

⁵Royal Devon and Exeter Hospital, Exeter, United Kingdom

⁶University of Texas, Austin, Texas

⁷Victor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia

⁸Washington University in St Louis, St. Louis, Missouri

⁹Duke University, Durham, North Carolina

¹⁰The University of Hong Kong, Hong Kong, China

¹¹Arizona State University, Tempe, Arizona

¹²University of Colorado, Anschutz Medical Campus, Aurora, Colorado

¹³Texas Scottish Rite Hospital for Children, Dallas, Texas

¹⁴University of Texas Southwestern Medical Center, Dallas, Texas

Abstract

Scoliosis represents the most common musculoskeletal disorder in children and affects approximately 3% of the world population. Scoliosis is separated into two major phenotypic classifications: congenital and idiopathic. Idiopathic scoliosis is defined as a curvature of the spine of 10° or greater visualized on plane radiograph and does not have associated vertebral malformations (VM). “Congenital” scoliosis (CS) due to malformations in vertebrae is frequently associated with other birth defects. Recently, significant advances have been made in understanding the genetic basis of both conditions. There is evidence that both conditions are etiologically related. A 2-day conference entitled “Genomic Approaches to Understanding and

Treating Scoliosis” was held at Scottish Rite Hospital for Children in Dallas, Texas, to synergize research in this field. This first combined, multidisciplinary conference featured international scoliosis researchers in basic and clinical sciences. A major outcome of the conference advancing scoliosis research was the proposal and subsequent vote in favor of merging the International Consortium for Vertebral Anomalies and Scoliosis (ICVAS) and International Consortium for Scoliosis Genetics (ICSG) into a single entity called International Consortium for Spinal Genetics, Development, and Disease (ICSGDD). The ICSGDD is proposed to meet annually as a forum to synergize multidisciplinary spine deformity research.

Keywords

congenital scoliosis; GWAS; idiopathic scoliosis; natural history; phenotypic classification; spine deformity

1 | INTRODUCTION

Current advances in high-throughput sequence analysis, genome editing, and developmental biology have enabled recent breakthrough discoveries, positioning the research community to begin to define the etiologies for scoliosis, both congenital and idiopathic. Scoliosis represents the most common musculoskeletal disorder of children, afflicting 3% of the worldwide population. Most cases of scoliosis are “idiopathic,” or of unknown cause as the name implies. Idiopathic scoliosis (IS) does not involve vertebral malformations and usually occurs during the adolescent growth spurt. It is associated with disfigurement, pain, and cardiopulmonary compromise (Giampietro, 2012). “Congenital” scoliosis (CS) due to malformations in vertebrae is frequently associated with other birth defects (Eckalbar, Fisher, Rawls, & Kusumi, 2012). Both forms of scoliosis are understudied and poorly understood. Current management of scoliosis in a growing child generally includes: 1) Observation of curves $<25^\circ$; 2) Full-time bracing for curves progressing $>25^\circ$; and 3) Spinal fusion and instrumentation for curves $>40\text{--}45^\circ$. Less than 10% of affected patients with curve magnitudes of 10° or greater will have require active treatment with a full-time thoraco-lumbar-sacral orthosis (TLSO) or surgical correction with instrumentation (Lonstein, 2006). It is becoming increasingly evident that both congenital and idiopathic scoliosis are clinically and genetically heterogeneous and are inherited as complex traits (Kou et al., 2013; Takahashi et al., 2011; Wu et al., 2015). Studies are providing intriguing evidence that both conditions are genetically and mechanistically related to one another (Hayes et al., 2014; Purkiss, Driscoll, Cole, & Alman, 2002). Both CS and IS are considered to represent developmental defects of spine formation.

The International Consortium for Vertebral Anomalies and Scoliosis (ICVAS) and The International Consortium for Scoliosis Genetics (ICSG) were formed in 2006 and 2012, respectively, for the purpose of fostering multidisciplinary research to support collaborative genetic studies of these conditions, and stimulate translational research essential to the goals of developing prevention and treatment strategies.

The ICVAS was established in 2006 by scientists and clinicians interested in understanding the causes of vertebral anomalies and scoliosis. The primary objective of ICVAS is to

provide members with the tools (DNA and clinical data) necessary to facilitate research into the causes of scoliosis. The first meeting was held at Stowers Institute for Medical Research in Kansas City and consisted of approximately 20 attendees from the United States, Puerto Rico, Canada, and Europe. ICVAS members have met in person and through regularly scheduled teleconferences. These meetings have stimulated productive collaboration amongst members and have led to a series of publications authored by ICVAS members. A subgroup met in Amsterdam in 2007 in order to develop a classification scheme for congenital vertebral malformations that have been presented internationally and recently published (Offiah et al., 2010). Additional collaborations among ICVAS members have led to the identification of mutations in *MESP2* associated with spondylothoracic dysostosis (STD) and notch signaling gene-environment interactions associated with the development of congenital scoliosis (Cornier et al., 2004; Sparrow et al., 2012).

The ICSG was organized in 2012 with funding from Fondation Yves Cotrel, with the purpose of fostering collaborative studies, particularly in the area of idiopathic scoliosis etiology. Membership includes clinical geneticists, molecular biologists, developmental biologists, and clinicians. The first ICSG meeting was held in 2012 at Texas Scottish Rite Hospital for Children in Dallas, TX, USA with about 30 attendees from three continents. ICSG has met four times since then, at the London Royal College of Surgeons, UK, in 2013, at Fondation Yves Cotrel, Paris, France, in 2014, in conjunction with the Scoliosis Research Society meeting in Minneapolis, MN, USA in 2015 and in conjunction with the SpineWeek meeting, Singapore, 2016. Each meeting has been a workshop-style format with themed discussions. The first ICSG-led study was a meta-analysis of IS association near the *LBX1* gene, published in 2014 (Londono et al., 2014).

The “Genomic Approaches to Understanding and Treating Scoliosis” was proposed in recognition of the overlap in goals and memberships between ICVAS and ICSG. A three-day NIH-sponsored conference was held March 16–18, 2017 at Texas Scottish Rite Hospital for Children in Dallas, TX, bringing together national and international researchers in the fields of both congenital and idiopathic scoliosis. A primary purpose was to review progress in scoliosis research and to determine where gaps exist, in order to help develop consensus research strategies to address specific deficits in knowledge. Sponsorship was also provided by the Scoliosis Research Society, Fondation Yves Cotrel, and industry. We summarize keynote research presentations and subsequent discussions at the conference below.

2 | KEYNOTE PRESENTATIONS

1. Olivier Pourquié: Somites develop from the presomitic mesoderm through a clock and wavefront mechanism involving coordinated expression through an oscillation of Notch, Wnt, and Fgf signaling pathways (Hubaud & Pourquie, 2014). Notch signaling is thought to play a role in the control of clock oscillation. The clock sets the rhythm for this process and the wave front defines cellular properties which allow cellular competency for response to the clock. A “dynamic quorum” of cells in the presomitic mesoderm provides a sensory effect for triggering oscillations.

2. Cathy Raggio: Natural history studies of idiopathic scoliosis should differentiate types of scoliosis, such as early onset scoliosis versus adolescent idiopathic scoliosis. The age of presentation of scoliosis should be differentiated from the age of onset of scoliosis. Presently it remains unclear whether isolated vertebral malformations represent a different etiologic category of malformation as opposed to vertebral malformations in conjunction with other birth defects. The genetic relationship between congenital and idiopathic scoliosis needs to be further delineated. For both congenital and idiopathic scoliosis, phenotyping remains a fundamental necessity which can assist with better understanding prognosis and natural history. Some important variables include for idiopathic scoliosis, the type of curve (long, short, left curve). For congenital scoliosis variables include the types of vertebral malformation and associated birth defects.
3. Shiro Ikegawa: Genome-wide association studies (GWASs) have identified a transcription network of the genes related with the susceptibility for adolescent idiopathic scoliosis (AIS), including *LBX1* (Takahashi et al., 2011), *GPR126* (Kou et al., 2013), *BNC2* (Ogura et al., 2015), and *PAX1* (Sharma et al., 2015). *LBX1* influences dorsal spinal cord neural development through Wnt/ β -catenin signaling (Guo et al., 2016). *GPR126* increases expression of cartilage-associated genes COL2A1 and AGC1 through SOX9 to mediate enchondral ossification (Kou et al., 2013). The mechanisms through which *BNC2* and *PAX1* contribute to scoliosis are not well understood at the present time. A locus associated with severity of AIS has also been identified (Miyake et al., 2013). All these works were accomplished by the collaboration among ICSG members.
4. Sally Dunwoodie: Environmental factors in humans such as diabetes are associated with the development of vertebral malformation (VM), however there is a scarcity of systematic experimental studies which have provided mechanistic insight into the pathogenesis of VM. In mice, hypoxia has been found to inhibit FGF signaling and disrupt Notch signaling in the presomitic mesoderm, which is the vertebral progenitor tissue (Sparrow et al., 2012). The response to hypoxia is influenced by mutations in Notch signaling pathway associated genes. Hypoxia induces endoplasmic reticulum stress and the unfolded protein response (UPR) in embryos, this leads to inhibition of FGF signaling (Shi et al., 2016). This suggests that any environmental stress that induces the UPR might disrupt FGF signalling and induce VM.
5. Ryan Gray: CS and IS are likely to have a diverse set of genetic etiologies which exert their influence through alteration of bone, connective tissue, muscle and nervous system development. Conditional ablation of *Gpr126* osteochondroprogenitor cells (*Col2Cre*) in mouse generates a model of IS, without overt vertebral dysplasia, however, subtle changes in annulus fibrosis are observed. Defects in ependymal cell cilia contribute to postnatal scoliosis, without vertebral dysplasia, as well as structural brain defects in zebrafish. This may serve as a platform for understanding the etiologies of both scoliosis and structural brain defects in humans.

6. Peter Turnpenny: Thus far, six Notch signaling pathway genes have been linked to generalized or multiple vertebral segmentation disorders—the spondylocostal dysostoses. Of these, mono-allelic mutations in *TBX6*, a transcription factor necessary for Notch signaling, and a high risk *TBX6* haplotype, are associated with a range of phenotypes, from a severe lethal form of spondylothoracic dysostosis to congenital scoliosis. (Wu et al., 2015; Lefebvre et al., 2017)—allelic *TBX6* mutations are also associated with Mullerian derived structural abnormalities such as Mayer-Rokitansky-Kuster syndrome (congenital absence of vagina, absent uterus, presence of fallopian tubes, and ovaries) (Sandbacka et al., 2013). Phenotype-genotype correlation is beginning to emerge, according to the nature of DNA variants/mutations. Chromosome 16p11.2 duplications in humans encompassing *TBX6* are associated with mild neurodevelopmental delay, obesity, and large head size, and an increased risk of congenital scoliosis due to segmentation anomalies.
7. Christina Gurnett: Rare variants in genes responsible for Mendelian connective tissue disorders are also found frequently in individuals with idiopathic scoliosis, and likely represent mildly deleterious mutations in these genes. Rare variants in *FBN1* and *FBN2* are enriched in patients with idiopathic scoliosis and tend to be associated with tall stature, larger spinal curve and slightly more Ghent criterion features, although the patients lack the cardiac manifestations or other complications that are typical of patients with Marfan syndrome or congenital contractural arachnodactyly (Buchan et al., 2014). Idiopathic scoliosis is also associated with a greater percentage of rare variants in musculoskeletal collagen variants as compared to controls (Haller et al., 2016).

3 | MEETING SUMMARY

At the present time the majority of causes for CS and IS are undefined. Suggestions from Consortium members to provide a road map for advancing the field include the following:

1. Uniformity of scoliosis phenotyping through clinical exam parameters such as height, skeletal features, and x-ray parameters is necessary to correlate with genetic findings.
2. Zebrafish are an excellent model organism for genetic studies of scoliosis and can be used to develop hypothesis-driven research pertaining to environmental effects and penetrance of various mutations.
3. Whole genome sequencing will facilitate genetic analyses of both coding and noncoding regulatory elements that are associated with spine development.
4. Collection of multiple tissues during surgery including skin fibroblasts, intervertebral disc tissue in addition to plasma can be of benefit for functional studies and genetic investigations of mosaicism.
5. The combined ICVAS/ICSG meeting should continue as an important venue for clinical and basic researchers interested in multidisciplinary studies of spine development and deformity.

6. A major outcome of the meeting was a proposal to formally merge ICVAS and ICSG. Both groups have subsequently approved this measure and elected to name themselves the International Consortium for Spinal Genetics, Development, and Disease (ICSGDD).
7. ICSGDD meetings are planned to take place on an annual basis. The next meeting is scheduled to be held April 6–8th 2018 in China at The University of Hong Kong Shenzhen Hospital in Shenzhen and Sun Yat-Sen University in Guangzhou.

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