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Basic Science

Candidate gene analysis and exome sequencing confirm *LBX1* as a susceptibility gene for idiopathic scoliosis

Anna Grauers, MD[a,b,c], Jingwen Wang, MSc[d,e], Elisabet Einarsdottir, PhD[d,e], Ane Simony, MD[f], Aina Danielsson, MD, PhD[g], Kristina Åkesson, MD, PhD[h], Acke Ohlin, MD, PhD[h], Klas Halldin, MD, PhD[g], Pawel Grabowski, MD, PhD[i], Max Tenne, MD, PhD[h], Hannele Laivuori, MD, PhD[j,k], Ingrid Dahlman, MD, PhD[l], Mikkel Andersen, MD, PhD[f], Steen Bach Christensen, MD, PhD[f], Magnus K. Karlsson, MD, PhD[h], Hong Jiao, MSc, PhD[d,e], Juha Kere, MD, PhD[d,e,m,*], Paul Gerdhem, MD[b,c,*]

[a]*Department of Orthopedics, Sundsvall and Härnösand County Hospital, SE-85186, Sundsvall, Sweden*
[b]*Department of Orthopedics, Karolinska University Hospital, K54, SE-14186, Stockholm, Sweden*
[c]*Department of Clinical Sciences, Intervention and Technology (CLINTEC) Karolinska Institutet, SE-14186, Stockholm, Sweden*
[d]*Department of Biosciences and Nutrition, Karolinska Institutet, Novum, Hälsovägen 7-9, SE-14183, Huddinge, Sweden*
[e]*Center for Innovative Medicine, Karolinska Institutet, Novum, Hälsovägen 7-9, SE-14183, Huddinge, Sweden*
[f]*Sector for Spine Surgery and Research, Middelfart Hospital, Middelfart, Denmark*
[g]*Department of Orthopedics, Sahlgren University Hospital, Gothenburg, Sweden*
[h]*Department of Orthopedics and Clinical Sciences, Lund University, Skane University Hospital, Malmö, Sweden*
[i]*Department of Orthopedics, University Hospital of Umeå, Umeå, Sweden*
[j]*Department of Medical Genetics and Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[k]*Institute for Molecular Medicine Finland, University of Helsinki, Tukholmankatu 8, Helsinki, Finland*
[l]*Department of Medicine, Lipid Laboratory, Karolinska Institutet, SE-14186, Stockholm, Sweden*
[m]*Molecular Neurology Research Program, University of Helsinki and Folkhälsan Institute of Genetics, Helsinki, Finland*

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* Corresponding authors. Department of Biosciences and Nutrition; and Center for Innovative Medicine, Karolinska Institutet, Novum, Hälsovägen 7-9, SE-14183 Huddinge, Sweden. Tel.: (46) 73 4213550.

E-mail address: Juha.kere@ki.se (J. Kere) or Paul.gerdhem@karolinska.se (P. Gerdhem)

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Abstract

BACKGROUND CONTEXT: Idiopathic scoliosis is a spinal deformity affecting approximately 3% of otherwise healthy children or adolescents. The etiology is still largely unknown but has an important genetic component. Genome-wide association studies have identified a number of common genetic variants that are significantly associated with idiopathic scoliosis in Asian and Caucasian populations, rs11190870 close to the *LBX1* gene being the most replicated finding.

PURPOSE: The aim of the present study was to investigate the genetics of idiopathic scoliosis in a Scandinavian cohort by performing a candidate gene study of four variants previously shown to be associated with idiopathic scoliosis and exome sequencing of idiopathic scoliosis patients with a severe phenotype to identify possible novel scoliosis risk variants.

STUDY DESIGN: This was a case control study.

PATIENT SAMPLE: A total of 1,739 patients with idiopathic scoliosis and 1,812 controls were included.

OUTCOME MEASURE: The outcome measure was idiopathic scoliosis.

METHODS: The variants rs10510181, rs11190870, rs12946942, and rs6570507 were genotyped in 1,739 patients with idiopathic scoliosis and 1,812 controls. Exome sequencing was performed on pooled samples from 100 surgically treated idiopathic scoliosis patients. Novel or rare missense, nonsense, or splice site variants were selected for individual genotyping in the 1,739 cases and 1,812 controls. In addition, the 5′UTR, noncoding exon and promoter regions of *LBX1*, not covered by exome sequencing, were Sanger sequenced in the 100 pooled samples.

RESULTS: Of the four candidate genes, an intergenic variant, rs11190870, downstream of the *LBX1* gene, showed a highly significant association to idiopathic scoliosis in 1,739 cases and 1,812 controls ($p=7.0\times10^{-18}$). We identified 20 novel variants by exome sequencing after filtration and an initial genotyping validation. However, we could not verify any association to idiopathic scoliosis in the large cohort of 1,739 cases and 1,812 controls. We did not find any variants in the 5′UTR, noncoding exon and promoter regions of *LBX1*.

CONCLUSIONS: Here, we confirm *LBX1* as a susceptibility gene for idiopathic scoliosis in a Scandinavian population and report that we are unable to find evidence of other genes of similar or stronger effect.

Keywords: Idiopathic scoliosis; Genetics; Ethiology; *LBX1*; Association study; Exome sequencing; Adolescent; Juvenile

Introduction

Idiopathic scoliosis is a spinal deformity affecting approximately 3% of otherwise healthy children or adolescents. In approximately 10% of the affected individuals, the deformity is progressive, requiring treatment with brace or spinal fusion surgery [1].

The etiology of idiopathic scoliosis is still largely unknown; heredity, however, is an important contributing factor [2,3]. Recent genome-wide association studies have identified common genetic variants close to, or within, the ladybird homeobox 1 (*LBX1*), cell adhesion molecule L1-like (*CHL1*), and G protein-coupled receptor 126 (*GPR126*) genes, as well as an intergenic variant on 17q, in Asian and Caucasian populations [4–7]. One exome sequencing study has identified novel, rare variants associated with idiopathic scoliosis in the *Fibrillin 1* and *2* genes in a European population [8]. However, these variants explain only a small part of the heritability of this disorder. The aim of the present study was to investigate the genetics of idiopathic scoliosis in a Scandinavian cohort by performing a candidate gene study of variants previously shown to be associated with idiopathic scoliosis and exome sequencing of idiopathic scoliosis patients with a severe phenotype.

Methods

This is a Swedish and Danish multicenter case-control study. Five Swedish and one Danish orthopedic department participated: the Karolinska University Hospital, the Skåne University Hospital, the Sahlgren University Hospital, the Sundsvall and Härnösand County Hospital, and the University Hospital of Umeå, all in Sweden, and Middelfart Hospital, Denmark.

Subjects and samples collection

Cases

Between 2004 and 2013, individuals with idiopathic scoliosis were invited to participate in the study. Details of the recruitment of patients have been published elsewhere [9–11]. Inclusion criteria were a juvenile or adolescent idiopathic scoliosis with a Cobb angle greater than or equal to 10° [12]. Only patients with a normal neurologic examination and without history or clinical sign of a