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Original research article

Positive association between the progression of idiopathic scoliosis and the common variant near the LBX1 gene in Southeast European population

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ABSTRACT

This report investigates the positive association between curve progression of Southeast European population and one of the most significant polymorphisms of idiopathic scoliosis (IS). The association between rs11190870 near the ladybird homeobox 1 (LBX1) gene, the curve severity (case-control study) and the curve pattern (case-only study) was explored among 155 IS Caucasian patients and 254 unrelated controls. The genotyping of rs11190870 was carried out by the TaqMan real-time amplification technology. The results revealed the existence of a statistically significant association between rs11190870, downstream of the LBX1 gene and IS predisposition and progression in the population sample. The case-only analysis indicated also that the genetic variant rs11190870 is not correlated to a certain idiopathic curve pattern. Based on the obtained data, rs11190870 could be regarded as a predisposing and modifying genetic factor for IS in patients of Southeast European descent. In addition, replication studies are necessary to investigate the possible relationship between the LBX1 locus and certain subtypes of IS in specific population groups. Clinical relevance should be pursued further, together with the molecular genetic identification of prognostic markers, as a contemporary approach that would make an early treatment including minimally invasive procedures.

Introduction

The idiopathic scoliosis (IS) is a multifactorial disorder with genetic and non-genetic components in the etiology. The primary spinal deformity occurs in three age groups – infantile, juvenile and adolescent idiopathic scoliosis (AIS). For complex diseases with multifactorial inheritance, the hypothesis of common diseases and common genetic variants (CDCV) motivates implementation of genome wide association studies (GWAS) (Gorman et al., 2014). The purpose of GWAS is the identification of genomic markers associated with a particular disease, followed by characterization of their functional effect (Stranger et al., 2011). First, Takahashi et al. (2011) reported a positive association between AIS predisposition and the T allele of the intergenic variant rs11190870 (T/C) located near the ladybird homeobox 1 (LBX1) gene (10q24) in a whole genome study conducted in a large Japanese population sample (1376 cases/11,297 controls). Then four replication association studies in Chinese population (Fan et al., 2012; Gao et al., 2013; Jiang et al., 2013; Liu et al., 2017), and two others in Caucasian population – a GWAS study in a population sample of European descent (Chettier et al., 2015) and a complete exome sequencing study in a Scandinavian cohort (Grauers et al., 2015), confirmed the association between AIS and the same single nucleotide polymorphism (SNP) around LBX1. The LBX1 gene encodes a transcription factor, necessary for the development of inhibitory interneurons in the dorsal horns of the spinal cord, and for the migration and further differentiation of the hypaxial muscle progenitor cells in the limb buds (Schmitteckert et al., 2011).

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The authors suggest the importance of somatosensory pathways in the etiology of the disease (Takahashi et al., 2011). The outcome measure of all the above studies was the most common form of scoliosis – AIS. At the same time, most of them explore the relationship of genetic variants with susceptibility to AIS or they search for SNPs with predisposing effect, while research on SNPs with modifying effect is not so much. Common complex diseases represent a particular challenge for studying modifier genetics (Ruzzo et al., 2012). Only the case-control study conducted from Jiang et al. (2013) reported a statistically significant association of rs11190870 (T/C) with both the predisposition and the progression of AIS in a Han Chinese population sample (949 cases/976 controls). AIS patients with TT genotype have a larger mean angle by Cobb method than those with TC or CC genotype, suggesting that the wild-type T allele could possess an effect on curve progression. This is consistent with the findings that T allele is a risk predisposing factor (Fan et al., 2012; Gao et al., 2013; Liu et al., 2017; Takahashi et al., 2011). This is a possible example of both predisposing and modifying effect of the same genotype/allelic variant in a given population sample meeting certain criteria (study design varies in terms of clinical criteria and especially the assessment of progression, the patient and the control group selection). Contrariwise, it is possible participation of different genetic variants in the progressive and non-progressive IS forms. Progressive scoliosis is usually determined by a curve magnitude above 40° before skeletal maturity, requiring spine surgery. Identification of genetic markers with prognostic value is a contemporary approach to assessing the risk of curve progression and would allow a selection of IS patients for early and less invasive treatment procedures.

The main objective of present study is to examine the association between one of the most significant SNPs from previous population-based studies of IS and curve progression in an independent Southeast European population sample. In order to fulfill this aim, the following associations between rs11190870 (T/C) near LBX1 and (i) curve severity (case-control study) and (ii) curve pattern (case-only study) were explored among the patients.

Materials and methods

Study population

Altogether 155 IS Southeast European patients and 254 unrelated controls were selected by the orthopedic physicians with appropriate general and specialized diagnostic methods. All participants were recruited only after the subjects or their parents signed an informed consent approved by the University Research Ethics Commission. The clinical diagnostics included detailed anamnesis, physical examinations and radiographic studies. The mean Cobb angle on standing radiographs was 47.9 ± 23.1 (IBM SPSS 19.0, NY, USA). Secondary deformities were ruled out. Radiological examination was not performed in the control group for the aims of the current study. Physical examination and previous available spinal roentgenographies excluded mild scoliosis among the control subjects. The mean age of IS onset was 11.3 ± 2.7 years (IBM SPSS 19.0, NY, USA). All the controls were selected among adult volunteers, with completed skeletal growth, to reduce the possibility of developing IS at a later stage. The general information of the IS patients and the controls, including clinical parameters as curve pattern, mean Cobb's angle, Risser sign, treatment, and demographic data as mean age of IS onset, mean age of controls, gender, is listed in Table 1. Total 127 female and 28 male patients with primary scoliosis and 50 male and 204 female controls were included in the study.

Table 1
Demographic and clinical data of cases and controls.

Group	Parameters	N/mean ± SD
Progressive cases	Females	85
	Males	21
	Age of onset	11.2 ± 2.9
	Cobb's angle	60.0 ± 17.1
Progressive cases	Th curve pattern	62
	Th-L curve pattern	34
	L curve pattern	10
	Risser sign	0–5
	Surgical treatment	106
Non-progressive cases	Females	42
	Males	7
	Age of onset	11.6 ± 2.0
	Cobb's angle	21.6 ± 6.2
Non-progressive cases	Th curve pattern	27
	Th-L curve pattern	3
	L curve pattern	19
	Risser sign	0–5
	Brace treatment	14
Controls	Females	204
	Males	50
	Age	33.3 ± 11.9

N, number of patients/controls; SD, standard deviation; Th, thoracic curve pattern; Th-L, thoracolumbar curve pattern; L, lumbar curve pattern.

Genomic DNA analysis

Taqman genotyping

Total genomic DNA was automatically extracted from peripheral venous blood specimens by a chemagic DNA Blood 10k Kit (PerkinElmer, Baesweiler, Germany) using a chemagic Magnetic Separation Module I (PerkinElmer, Baesweiler, Germany) according to the manufacturer's instructions. The genotyping of rs11190870 (T/C) was carried out by a TaqMan SNP genotyping assay available under a catalogue C_1349874_20 (Thermo Fisher Scientific, USA) using an ABI Prism 7900 H T sequence detection system (Thermo Fisher Scientific, USA) according to the manufacturer's recommendations. The analysis was repeated for some samples that were not successfully genotyped at the first real-time amplification.

Statistical analysis

The results were analyzed by the Pearson's Chi-squared Test (with calculation of Phi and Crammer's V) for the general sample and the larger case-control subgroups (N > 300) or the Fisher's Exact Test for the smaller case-control or case-only subgroups (N < 300) with a value of p less than 0.05 as statistically significant. Odds ratios (OR) with 95% confidence interval (CI) were calculated (IBM SPSS 19.0, NY, USA).

Theory

Case-control study subgroup

For the aims of the current case-control study all cases were divided into two groups according to the last Cobb angle measurement: progressive IS group (Cobb angle > 40°, mean Cobb angle = 60.0 ± 17.1) and non-progressive or slowly progressive IS group (Cobb angle < 40° at the time of skeletal maturity, mean Cobb angle = 21.6 ± 6.2). The possible association between curve severity and rs11190870 (T/C) was examined through comparison between the genotype and allele frequencies in each of these subgroups of progressive (n = 106) and non-progressive IS (n = 49) and the control group (case-control study).

Case-only study subgroup

For the aims of the case-only study the cases were divided into three groups according to the type of the major curve: lumbar or L

($n = 29$), thoracolumbar or Th-L ($n = 37$) and thoracic or Th ($n = 89$) curve pattern. The possible association between curve pattern and rs11190870 (T/C) was examined through comparison between these three groups (case-only study).

The disease penetrance associated with a specific genotype is the risk of developing disease in individuals carrying that genotype (Clarke et al., 2011). In the individual subgroups, the associations between the genotypes and alleles of the biallelic locus near the LBX1 gene and the selected phenotypes were studied using standard models for disease penetrance: (i) genotypic (codominant, dominant and recessive) and (ii) allelic models.

Results

Case-control study

The genotypes were in Hardy-Weinberg equilibrium (χ^2-test). In the total sample, the frequencies of TT genotype and T allele of rs11190870 (T/C) were higher in IS patients compared to clinically healthy controls (TT vs. TC vs. CC, $p = 0.0006$ and T vs. C, $p < 0.0001$, χ^2-test). The higher risk of curve progression was calculated according to the relative risk, or RR value, indicating the increased risk above average or baseline risk of development of progressive scoliosis in TT carriers compared to other genotype carriers. On the basis of these results, rs11190870 (T/C) could be regarded as a predisposing genetic factor for IS in Southeast European patients (TT vs. TC + CC, RR = 1.37, 95% CI: 1.15–1.63).

In the subgroup of progressive IS (Cobb angle over 40°), the frequencies of homozygous TT genotype and T allele were also higher compared with the controls ($p < 0.05$, χ^2-test). The presence of homozygous TT genotype was associated with a 35% higher risk of curve progression above 40° according to the relative risk value (TT vs. TC + CC, RR = 1.35, 95% CI: 1.11–1.63). Therefore, rs11190870 (T/C) could be regarded as a modifying genetic factor of IS in the Southeast European caucasian patients. In the smaller subgroup of non-progressive IS (Cobb angle under 40°), a statistically significant association was also detected ($p < 0.05$, χ^2-test). These results support the predisposing role of rs11190870 (T/C) as a genetic factor for IS in Southeast European patients. This is a possible example of both predisposing and modifying effect of the same genotype/allelic variant. When we stratified the patients by gender, we observed a statistically significant association in females with progressive IS ($p < 0.05$, χ^2-test) but a larger sample of non-progressive female cases is needed to detect a possible association. The association between rs11190870 and female progressive IS is shown in Table 2.

It is evident that the risk TT genotype is associated with IS susceptibility and severity under a recessive inheritance model with the RR greatest value. It is presented graphically at Fig. 1.

Case-only study

When we compared the subgroups of patients with idiopathic thoracic, thoracolumbar and lumbar curve patterns, we found no statistically significant association between the polymorphism rs11190870 (T/C) and a particular primary curve type ($p > 0.05$, Fisher's Exact Test) but the Th-L curve pattern was more common in the progressive cases and the L curve pattern in the non-progressive cases ($p < 0.05$, Fisher's Exact Test) and there were no significant differences in the Th curve pattern distribution. The ORs in the three case-only subgroups are presented in Table 3.

Discussion

The genotype and allele frequencies of rs11190870 (T/C) near the *LBX1* gene, associated with IS from two previously reported GWAS and five replication studies in Asian and Caucasian populations, were analyzed in the general group and certain patient subgroups and compared with that of the control group (case-control study) or other patient subgroups (case-only study). We have selected only the most significantly associated polymorphic variant – rs11190870 and have not tested the other two SNPs

Table 2
Experimental results from the case-control study.

Group	Genotype/allele, N	*p*	OR [95% CI]
General			
General sample	TT (101/121) vs. CC (7/33)	0.0009	3.93 [1.67–9.27]
(n_1 = 155, n_2 = 254)	TT + TC (148/221) vs. CC (7/33)	0.0051	3.16 [1.36–7.33]
	TT (101/121) vs. TC + CC (54/133)	0.0006	2.06 [1.36–3.10]
	T (249/342) vs. C (61/166)	<0.0001	1.98 [1.42–2.77]
Progressive IS	TT (68/121) vs. CC (5/33)	0.0060	3.71 [1.38–9.95]
(n_1 = 106, n_2 = 254)	TT + TC (101/221) vs. CC (5/33)	0.0199	0.33 [0.13–0.87]
	TT (68/121) vs. TC + CC (38/133)	0.0042	1.97 [1.23–3.14]
	T (169/342) vs. C (43/166)	0.0008	1.91 [1.30–2.80]
Non-progressive IS	TT (33/121) vs. CC (2/33)	0.0307	4.5 [1.03–19.73]
(n_1 = 49, n_2 = 254)	TT + TC (47/221) vs. CC (2/33)	0.0741	3.51 [0.81–15.1]
	TT (33/121) vs. TC + CC (16/133)	0.0115	2.27 [1.19–4.32]
	T (80/342) vs. C (18/166)	0.0048	2.16 [1.25–3.72]
Females			
General sample	TT (82/97) vs. CC (6/27)	0.0031	3.80 [1.50–9.66]
(n_1 = 127, n_2 = 204)	TT + TC (121/177) vs. CC (6/27)	0.0119	3.08 [1.23–7.68]
	TT (82/97) vs. TC + CC (45/107)	0.0025	2.01 [1.27–3.17]
	T (203/274) vs. C (51/134)	0.0004	1.95 [1.34–2.82]
Progressive IS	TT (57/97) vs. CC (3/27)	0.0039	5.29 [1.53–18.2]
(n_1 = 85, n_2 = 204)	TT + TC (82/177) vs. CC (3/27)	0.0137	4.17 [1.23–14.1]
	TT (57/97) vs. TC + CC (28/107)	0.0025	2.25 [1.32–3.81]
	T (139/274) vs. C (31/134)	0.0004	2.19 [1.41–3.41]
Non-progressive IS	TT (25/97) vs. CC (2/27)	0.0859	3.48 [0.77–15.6]
(n_1 = 42, n_2 = 204)	TT + TC (40/177) vs. CC (2/27)	0.1862	3.05 [0.7–13.36]
	TT (25/97) vs. TC + CC (17/107)	0.1573	1.62 [0.83–3.18]
	T (65/274) vs. C (19/134)	0.0652	1.67 [0.96–2.90]

N, number of genotypes/alleles; p, probability value; OR, odds ratio; CI, confidence interval; n_1, number of cases; n_2, number of controls; IS, idiopathic scoliosis.

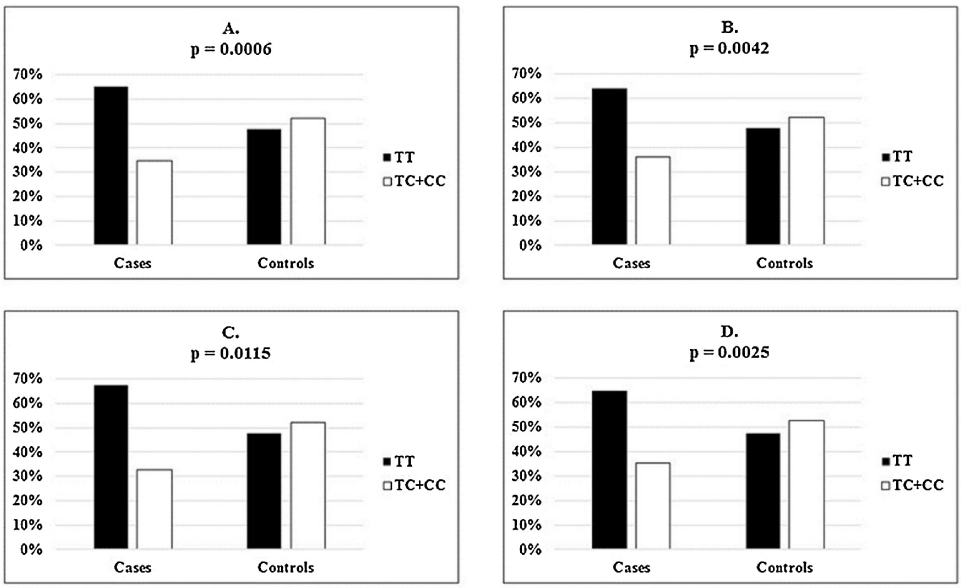

Fig. 1. Recessive genetic model of (A) TT/(TC + CC) in general sample, (B) progressive IS, (C) non-pogressive IS, and (D) female IS.

reported by Takahashi et al. The previously found genetic association between rs11190870 (T/C) and IS in two Caucasian population-based studies (Chettier et al., 2015; Grauers et al., 2015) was confirmed in an Southeast European population sample. The RR value indicating a 1.37 times higher risk of developing primary scoliosis in homozygous TT genotype carriers means that individual impact of the genetic marker is modest (Nsengimana and Bishop, 2012). As many other multifactorial diseases, genetic predisposition to IS probably involves multiple genetic variants with modest to moderate individual impact and a likely additive effect on the etiopathogenesis of the disease. It should be noted that only patients with AIS, a subset of late onset IS, were included in the aforementioned studies. The results from the current case-control analysis suggest that rs11190870 (T/C) might be associated with late and early onset IS both. In any case, genetic research on the rare infantile (early onset) and juvenile (early and late onset) IS is insufficient to draw conclusions at this stage.

There are many conditions in which the phenotype is affected not only by causative genotypes but also by sequence variations of so-called modifier genes (Turnpenny and Ellard, 2011). Association studies in different populations demonstrated that some genetic factors could also have an influence on curve progression (Chen et al., 2009; Jiang et al., 2012; Moon et al., 2013; Peng et al., 2012; Ryzhkov et al., 2013; Yeung et al., 2006; Zhang et al., 2009; Zhao et al., 2009a). So far, only one study investigated the relationship between rs11190870 (T/C) and curve progression (Jiang et al., 2013). A case-only analysis in a Han Chinese population found that AIS patients with the TT genotype had a significantly higher mean Cobb angle than those with the TC and CC genotype ($p = 0.005$, χ^2-test). The mean Cobb angle is not necessarily an accurate indicator of the correlation between genotype and progression, as it may vary significantly due to delayed treatment, i.e. it is influenced to a large extent by external factors. Therefore, for the aims of present analysis, we divided the cases into two subgroups according to the curve severity. In the progressive subgroup (Cobb angle over 40°), rs11190870 (T/C) was also associated with IS ($p = 0.004$, χ^2-test). These results are similar to those from the previous study in an Asian population group. Replication studies in different population and ethnic groups are needed to evaluate whether rs11190870 is a modifying genetic factor of IS.

The idiopathic thoracic curve pattern is usually considered as a risk factor for spinal deformity progression (Katz et al., 2008; Wong, 2015). We found no significant differences in the The curve pattern distribution between progressive and non-progressive cases. This well could be explained by the overall high frequency of this curve type (Suh et al., 2011). At the same time, there are some

Table 3
Experimental results from the case-only study.

Curve pattern of IS	Genotype/allele, N	*p*	OR [95% CI]
Th/Th-L + L	TT (60/40) vs. CC (5/4)	1	1.20 [0.30–4.74]
(n_1 = 89, n_2 = 66)	TT + TC (84/62) vs. CC (5/4)	1	1.08 [0.28–4.20]
	TT (60/40) vs. TC + CC (29/26)	0.4	1.34 [0.69–2.61]
	T (144/102) vs. C (34/30)	0.48	1.25 [0.72–2.16]
Th-L/Th + L	TT (20/82) vs. CC (2/6)	1	0.73 [0.14–3.90]
(n_1 = 37, n_2 = 118)	TT + TC (35/112) vs. CC (2/6)	1	0.94 [0.18–4.86]
	TT (20/82) vs. TC + CC (17/36)	0.11	0.52 [0.24–1.10]
	T (55/194) vs. C (19/42)	0.18	0.63 [0.34–1.16]
L/Th-L + Th	TT (21/79) vs. CC (2/7)	1	0.93 [0.18–4.81]
(n_1 = 29, n_2 = 126)	TT + TC (27/119) vs. CC (2/7)	1	0.79 [0.16–4.04]
	TT (21/79) vs. TC + CC (8/47)	0.39	1.56 [0.64–3.81]
	T (48/198) vs. C (10/54)	0.59	1.31 [0.62–2.76]

IS, idiopathic scoliosis, N, number; p, probability value; OR, odds ratio; CI, confidence interval; n_1, n_2, number of cases; Th, thoracic; Th-L, thoracolumbar; L, lumbar.

studies indicating that the thoracolumbar curve pattern is associated with a higher risk of progression than single and double thoracic curve patterns (Berdishevsky et al., 2016). The Th-L curve pattern was more common in the progressive cases (Table 1). The primary lumbar curve has been associated with a lower risk of progression and smaller preoperative angles (Yong et al., 2012). The L curve pattern was more frequent in the non-progressive cases (Table 1).

It is evident that some genetic variants could be associated with certain curve types of IS (Bae et al., 2012; Liu et al., 2010; Zhao et al., 2009a,b). To date, there is no study of the association between rs11190870 (T/C) and curve pattern. The present subgroup analysis showed that rs11190870 (T/C) could not be associated with a particular curve pattern of IS in Southeast European patients (Table 3). The major limitation of current case-only analysis is the relatively small sample size which could affect the statistical power of results. Extended studies will be needed to examine possible relationship between genes and curve pattern in the context of curve progression.

The common variant rs11190870 (T/C) is located near the LBX1 gene region [10q24.31]. The LBX1 gene is a key regulator of muscle precursor cell migration (Schäfer and Braun, 1999) and is important for specification of neurons in the dorsal spinal cord (Gross et al., 2002; Müller et al., 2002). In mutant mice (LBX1 −/−), the neural circuits in the posterior horns are abnormal, suggesting that LBX1 is a crucial factor for the development of somatosensory pathways in the spinal cord (Müller et al., 2002). Studies on dorsal rhizotomized animals show a higher incidence of scoliosis and support the view that IS may develop as a result of asymmetrical weakness of the paraspinal muscles due to the loss of proprioceptive innervation (Barrios et al., 1987; Pincott and Taffs, 1982; Pincott et al., 1984; Suk et al., 1989). Clinical studies reveal that children with disturbances of the somatosensory pathways are more susceptible to AIS compared with age-matched controls (Kouwenhoven and Castelein, 2008). Conversely, in AIS patients, frequency of somatosensory functional or organic disorders is higher than that in general population (Cheng et al., 1998,1999; Guo et al., 2006). The authors of the first GWAS assume that abnormal LBX1 gene expression plays a role in AIS development by somatosensory dysfunction (Takahashi et al., 2011).

It is possible that common polymorphisms denote genomic regions containing intrinsic predisposing and modifying factors. On the basis of experimental animal models and observations on IS patients with somatosensory dysfunction, a genetic correlation has been suggested to exist between the LBX1 gene and IS etiopathogenesis. The current association between rs11190870 near LBX1 and the severe form, requiring surgical treatment, gives reason to suspect a relationship not only with IS susceptibility but also with the risk of further curve progression.

Conclusions

The present case-control study revealed the statistically significant association between rs11190870, downstream of the LBX1 gene and IS predisposition and progression in Southeast European population sample. The case-only analysis indicated that the genetic variant rs11190870 is not correlated to a certain idiopathic curve pattern. On the basis of these results, rs11190870 could be regarded as a predisposing and modifying genetic factor for IS in Caucasian patients. Molecular genetic identification of prognostic markers is a contemporary approach that would make an early treatment including less invasive surgical or non-surgical procedures possible. Further replication studies are necessary to investigate the possible relationship between the LBX1 locus and certain subtypes of IS in specific population groups.

Conflict of interests

The authors have no conflict of interests to disclose. All patients and parents provided informed consest.

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