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Original Article

Genetic and functional analysis of the GATA5 gene promoter in indirect inguinal hernia

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Abstract: Indirect inguinal hernia (IIH), majority of inguinal hernia, is a common surgical disease in children. A positive family history indicates that genetic factors play an important role in the IIH development. To date, genetic causes and underlying mechanisms for IIH remain largely unknown. GATA5 is a member of GATA transcription factor family, which controls the development of diverse tissues. GATA5 gene is widely expressed, including connective tissues. Mutations in GATA5 gene have been associated with human diseases. As GATA5 is a dosage-dependent regulator during the development, we speculated that changed GATA5 levels, resulting from DNA sequence variants (DSVs) within the gene regulatory regions, may contribute to the IIH development. In this study, the GATA5 gene promoter was genetically and functionally analyzed in IIH patients and ethnic-matched controls. Six DSVs, including three SNPs within the GATA5 gene promoter were identified. A heterozygous DSV, g.61051363G>C, was found in an IIH patient, but in none of controls, which significantly reduced the GATA5 gene promoter activity in cultured cells. Two heterozygous DSVs, g.61051227C>T and g.61051379-80GG>AA, were only found in controls, which did not significantly affect the GATA5 gene promoter activity. Three SNPs were found in both IIH patients and controls with similar frequencies. Therefore, the DSV within the GATA5 gene promoter may contribute to the IIH development by changing the GATA5 level.

Keywords: Indirect inguinal hernia, genetics, GATA5, promoter, DNA sequence variants

Introduction

Inguinal hernia is a common surgical disorder, including direct inguinal hernia and indirect inguinal hernia (IIH). In children, most cases are IIH. IIH is caused by delayed closure of processus of vaginalis, leading to a protrusion abdominal-cavity contents through the inguinal canal [1]. A positive family history is a significant risk factor for development and recurrence of primary inguinal hernia, indicating the genetic bases for inguinal hernia [2]. Inguinal hernia has been reported in more than 150 human syndromes, including Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Marfan syndrome and mucopolysaccharidosis [1, 3-6]. To date, several candidate genes, including angiotensin-converting enzyme, transcription factor, collagen type I alpha 1, GATA factor 6, SIRT1 and T-box transcription factors 1/2/3, have been investigated in patients with inguinal hernia [7-13]. A whole-exome sequencing study in multiple families with inguinal hernia has identified mutations in TTN gene, which encodes a protein in skeletal and cardiac muscles [14]. A recent genome-wide association study has found four novel susceptibility loci in the regions of EFEMP1, WT1, EBF2 and ADAMTS6 for inguinal hernia [15]. However, genetic causes and underlying molecular mechanisms for isolated inguinal hernia remain unclear.

GATA factor 5 (GATA5) is a member of GATA transcription factor family, which are zinc finger DNA binding proteins. GATA factors control the development of diverse tissues by regulating the cell differentiation, proliferation and survival [16-19]. The human GATA5 gene is expressed in the connective tissue, kidney, lung, prostate, testis and uterus, as well as soft tissue and muscle

tissue tumors, by an analysis of expressed sequence tag counts (NCBI, UniGene EST Profile Viewer). A recent study indicates that GATA5 is also enriched in human cardiac fibroblast cells [20]. In mice, GATA5 gene is expressed in various mesoderm- and endoderm-derived tissues, mainly including the developing heart, lung, urogenital ridge and vascular smooth muscle cells [21]. In the human and mouse embryonic stem cells, GATA5 has been demonstrated to influence the cell differentiation [22-24].

Mutations in GATA5 gene have been associated with diverse types of congenital heart disease, such as bicuspid aortic valve, septal defects and tetralogy of Fallot, as well as atrial fibrillation [25-28]. Although mice with targeted disruption of the GATA5 gene appear grossly normal, female mice exhibit defects in genitourinary tract development [29]. In addition, GATA5 deficiency causes airway constrictor hyperresponsiveness in mice [30]. Animal studies have demonstrated that GATA5 is a dosage-sensitive regulator in the development [31]. Thus, we speculated that changed GATA5 levels, resulting from DNA sequence variants (DSVs) within the GATA5 gene regulatory regions, may lead to the IIH developmental diseases. In the present study, we genetically and functionally analyzed the GATA5 gene promoter in IIH patients and healthy controls.

Materials and methods

Patients and controls

All IIH patients (n=146, male 122, female 24, age range from 10 months to 12 years, median age 2.67 years) were recruited from Division of Pediatric Surgery, Jining Medical University Affiliated Hospital, Jining Medical University, Jining, Shandong, China. All the IIH patients were confirmed by surgical procedures. Among these IIH patients, 83 had right-sided IIH, 49 had left-sided IIH and 14 had both-sided IIH. None of the IIH patients has familial history of inguinal hernia. Ethnic-matched healthy controls (n=161, male 119, female 42, age range from one month to 14 years, median age 5.42 years) were from the same hospital. This study was approved by the Human Ethic Committee of Jining Medical University Affiliated Hospital. Informed consents were obtained from patients and guardians.

DNA sequencing

Peripheral leukocytes were isolated from vein blood. Genomic DNAs were extracted using DNeasy Blood & Tissue kit (Qiagen, Valencia, CA, USA). GATA5 gene promoter of 836 bp (from -785 bp to +51 bp to the transcription start site) was generated with PCR with the following primers: GATA5-forward, 5'-AGTGCGAGCGGGACACGGTT-3', and GATA5-reverse, 5'-GAGCACTCACCAGCGGGCAG-3'. PCR primers were designed based on genomic sequence of the human GATA5 gene (NCBI: NC_000020.10). The PCR products were bi-directionally sequenced with 3500 Genetic Analyzer (Applied Biosystems, Foster city, CA, USA). DNA sequences were aligned and compared with the wild type sequence of the GATA5 gene promoter.

Promoter activity analysis with reporter gene assay

The DNA fragments of wild type and variant GATA5 gene promoters (836 bp, from -785 to +51 bp) were generated by PCR with the same set of PCR primers, with a KpnI site adding to the forward primer and a HindIII site to the reverse primer. Expression constructs were generated by subcloning PCR products into KpnI and Hind III sites of a reporter vector (pGL3-basic) expressing luciferase gene. Designated expression constructs were transiently transfected into HEK-293 cells (transformed human embryonic kidney cells, ATCC, CRL-1573) using Lipofectamine 2000 (Life Technologies, Carlsbad, CA, USA). Forty-eight hours posttransfection, the cells were collected and the luciferases activities were measured using dual-luciferase reporter assay system on a Glomax 20/20 luminometer (Promega, Madison, WI, USA). Expression construct expressing renilla luciferase gene (pRL-TK) was used as an internal control. Empty vector pGL3-basic was used as a negative control. The transcriptional activities of the GATA5 gene promoter were represented as ratios of luciferase activities over renilla luciferase activities. All the experiments were repeated three times independently, in triplicate.

Statistical analysis

Quantitative data were represented as mean ± SEM and compared by a standard Student's t-test. Frequencies of the DSVs within the

Table 1. The DSVs within the GATA5 gene promoter in IIH patients and controls[a]

DSVs	Genotype	Location	Controls (n=161)	IIH (n=146)	*P* value
g.61051379-80GG>AA	GG/AA	-353 bp	1	0	-
g.61051373G>A (rs80197101)	GG	-347 bp	140	127	0.600
	GA		21	18	
	AA		0	1	
g.61051363G>C	GC	-337 bp	0	1	-
g.61051327A>C (rs145936691)	AC	-301 bp	3	5	0.841
g.61051279C>T (rs77067995)	CC	-253 bp	140	127	0.600
	CT		21	18	
	TT		0	1	
g.61051227C>T	CT	-201 bp	2	0	-

[a], The DSVs are located upstream to the transcription start site (61051026, NC_000020.10).

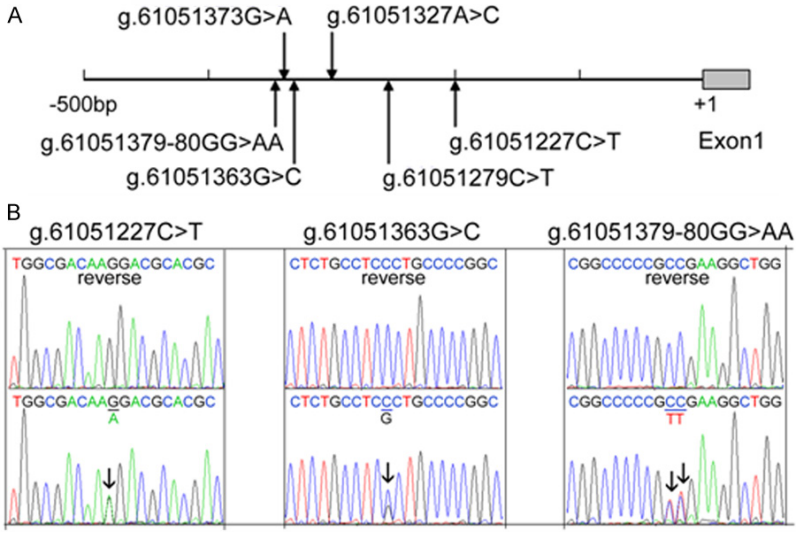

Figure 1. GATA5 gene promoter DSVs identified in IIH patients and controls. A. Schematic representation of the identified DSVs. Locations of the DSVs is defined according to the human GATA5 genomic sequences (NCBI: NC_000020.10). The transcription starts site is at 61051026 in the un-translated first exon. B. Chromatograms of the three DSVs. Sequencing orientations are indicated. Top panels show wild type and bottom panels heterozygous DSVs. The variant bases are marked with arrows.

GATA5 gene promoter were compared between IIH patients and controls using SPSS 13.0 software. Statistical significance was set as P<0.05.

Results

Total six DSVs within the human GATA5 gene promoter were identified in IIH patients and controls, including three sin-gle-nucleotide polymorphisms (SNPs). The locations of the DSVs were summarized in **Table 1** and depicted in **Figure 1A**. The chromatograms of the three heterozygous DSVs were shown in **Figure 1B**. One heterozygous DSV, g.61051363G>C, was found in a 12-year-old girl with left-sided IIH, but in none of controls. Two heterozygous DSVs, g.61051227C>T and g.61051379-80GG>AA, were only identified in th-ree controls. The three SNPs, g.61051279C>T (rs77067995), g.61051327A>C (rs145936691) and g.61051373G>A (rs80197101), were found in both IIH patients and controls with similar frequencies (P>0.05).

The GATA5 gene promoter was analyzed with TFSEARCH program (http://www.cbrc.jp/research/db/TFSEARCH.html). The results suggested that the DSV g.61051363G>C abolishd a binding sites for specificity protein 1 factor, whi-ch is a zinc finger tran-scrition factor involved in many cellular processes. The DSV g.61051227C>T created a possible binding site for E2F factor, which is involved in the cell cycle regulation. The DSV g.6105-1379-80GG>AA did not affect the binding site for known factors.

To examine the transcri-ptional activiti-es of the DSVs, expression constructs containing wild type GATA5 gene promoter (pGL3-WT) and variant promoters, g.61051227C>T (pGL3-61051227-T), g.6105-1363G>C (pGL3-6105-1363C) and g.61051379-80GG>AA (pGL3-61051379-80AA), were constructed and transfected into HEK-293 cells. Dual luciferase activities were measured and relative activities of the variants were calculated. The results showed the DSV g.61051363G>C significantly

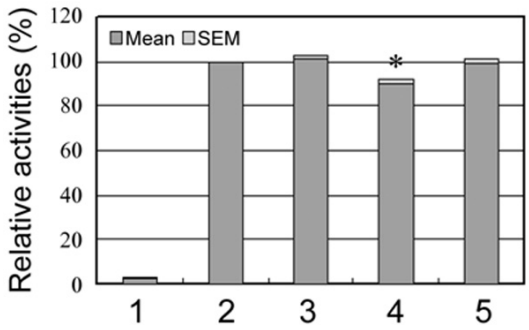

Figure 2. Relative activities of the wild type and variant GATA5 gene promoters. Reporter gene expression constructs were transfected into HEK-293 cells and dual-luciferase activities were measured. The relative transcriptional activity of wild type GATA5 gene promoter was designated as 100%. The *data* were represented as mean ± SEM from three independent transfection experiments, in triplicate. Lanes 1, pGL3-basic; 2, WT, wild type; 3, pGL3- 61051227T; 4, pGL3-61051363C; 5, pGL3-61051379-80AA. *, P<0.01, compared to pGL3-WT.

reduced transcriptional activities of the GATA5 gene promoter (P<0.01) (**Figure 2**). In contrast, the DSVs g.61051227C>T and g.61051379-80GG>AA, did not significantly changed the GATA5 gene promoter activity (P>0.05).

Discussion

Misregulation of gene expression programs have been implicated in a broad range of human diseases, including cancer, inflammation, diabetes and cardiovascular diseases [32]. In the present study, we identified a heterozygous DSV within the GATA5 gene promoter in an IIH patient. In cultured cells, the DSV significantly reduced the transcriptional activities of the GATA5 gene promoter, probably by abolishing a SP1 binding site. The DSVs identified in controls did not affect the GATA5 gene promoter activity, likely due to weak effects of the DSVs. Therefore, the GATA5 gene promoter DSV may mediate the IIH development by changing GATA5 levels as a rare risk factor.

The human GATA5 gene has been mapped to chromosome 20q13.2-q13.3 [33]. The regulation of GATA5 gene expression has been poorly understood. The GATA5 gene promoter has been partially characterized. The human GATA5 gene has been shown to be regulated by USF1 (upstream stimulatory factor 1) binding to an E box motif within the GATA5 gene promoter [34]. In human embryonic stem cells, overexpression of GADD45G gene, a key regulator of the cell cycle, upregulates GATA5 gene expression [23]. In mice, an alternative promoter of GATA5 gene has been identified, which controls reporter gene expression in gastric epithelial cells in transgenic mice [35]. In animal experiments, a proximal 868 bp fragment has been shown to be sufficient to direct transgene expression in a variety of mesodermal and endodermal cells [36]. The GATA5 gene promoter DSV identified in this study, located -337 bp upstream to the transcription start site, may reduce GATA5 levels during the embryonic development.

GATA5 has been extensively studied in the developing heart. In other tissues, little has been done and reported for the functions of GATA5. Expression of cardiac genes, such as atrial natriuretic factor (ANF), beta-myosin heavy chain and endothelin-1 gene is regulated by GATA5 alone, or GATA5 associated with other GATA factors (GATA4 and GATA6), p300 protein and leukemia inhibitory factor [33, 37-40]. GATA5 cooperates with nuclear factor of activated T-cells (NF-ATc) in the differentiation of cardiogenic cells [41]. GATA5 is also involved in regulating intestinal genes, including fatty acid binding protein 2, lactase-phlorizin hydrolase, mucin and sodium-hydrogen exchanger isoform 3 genes [42-46]. GATA5, together with hepatic nuclear factor-1 alpha (HNF1a), binds to the proximal promoter of the liver fatty acid binding protein gene (Fabpl) [47]. Therefore, GATA5 may regulate the genes in the same ways in the connective tissues, smooth muscle cells and other components in the inguinal ring. Altered GATA5 levels may interfere with the formation of inguinal ring, leading to the IIH development. The exact molecular mechanisms need to be explored.

In conclusion, we identified a heterozygous DSV within the GATA5 gene promoter in IIH patients, which significantly reduced the GATA5 gene promoter activity in vitro. The DSV may change GATA5 levels and contribute to the IIH development as a risk factor by affecting the formation of inguinal ring. Our findings may provide important information for surgeons in treating IIH patients.

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Disclosure of conflict of interest

None.

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