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Identification of two novel GATA6 mutations in an adult with acute myocardial infarction, diabetes, and atrial fibrillation: a case report

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With the aging of the world's population, the incidence of coronary atherosclerotic disease (CAD) is gradually increasing, which places a heavy burden on social development.[1] Acute myocardial infarction (AMI) is the most serious stage in the development of CAD and can lead to cardiac arrest. Globally, the number of deaths due to ischemic heart disease has increased by 16.6% from 2005 to 2015, reaching 8.9 million deaths.[2] Diabetes mellitus (DM) is a high-risk factor for promoting CAD progression, conferring an approximate two-fold increase in the risk of AMI, and is one of the chronic diseases that seriously endangers human health.[3] Atrial fibrillation (AF) is a serious type of arrhythmia that can cause significant clinical manifestations. The number of AF patients in the EU and the United States is approximately 7 million, and by 2050, that number is likely to increase by at least 2.5 times.[4] These diseases can be caused by genetic factors and acquired environmental factors. Gene dysfunction due to genetic variations can alter the function of a protein by affecting transcription and translation, thereby causing phenotypic changes. Therefore, mutations in susceptibility genes play a crucial role in the development and progression of human diseases.

GATA binding protein 6 (GATA6) is a member of the GATA family, and its gene is located on chromosome 18q11.1~18q11.2, encoding a total of 595 amino acids.[5] *GATA6* regulates the growth and differentiation of cells in the human body and plays a vital role in the survival of cells and the maintenance of body functions. Mutations in the *GATA6* gene can cause pancreatic hypoplasia, resulting in neonatal diabetes, childhood onset diabetes, or adult-onset diabetes.[6] However, *GATA6* is also involved in the cardiac conduction system (CCS) due to expression in the ductal cardiomyocytes, neural crest (NC) cells, and cardiac fibroblasts in the early development of the heart, and its genetic mutations can cause AF.[7] In this case report, we describe two novel *GATA6* gene mutations in an adult patient with AMI, DM, and AF.

The patient was a 63-year-old male who was sent to the hospital because of sudden pain in the anterior region and no relief after sublingual nitroglycerin. After a consultation with medical history, physical examination and related professional examination, the patient's admission diagnosis was acute inferior myocardial infarction, cardiac function level II (Killip classification), arrhythmia (sinus tachycardia, paroxysmal AF), high blood pressure (grade 3, high-risk group), type 2 diabetes (diabetic ketosis), and electrolyte imbalance (hypokalemia). The patient's history of hypertension and type 2 diabetes were 10 years and 24 years, respectively. After he spent the dangerous period in the Cardiac Care Unit (CCU), he was transferred to the general cardiology department to undergo coronary angiography to confirm the coronary lesions. The patient was diagnosed with three-vessel CAD, and the treatment plan was elective coronary artery bypass surgery (CABG). After effective symptomatic treatment with the drug, the patient recovered well and was discharged.

Four milliliters of blood were taken from the patient's elbow vein on an empty stomach in the morning. Genomic

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DNA was extracted using a DNA extraction kit (QIAGEN). The study was approved by the Humanities and Ethics Committee of the Affiliated Hospital of Jining Medical University, Shandong, China (2016-FY-076), in accordance with the principles of the Helsinki Declaration. Transcription initiation sites were selected approximately 2000 bases upstream of the *GATA6* gene (NC_000018.10) as gene promoter regions for analysis. Primers with a length of 1173 bp were designed using Primer 5 software. The specific sequences were GATA6-F: 5'-ACGCCTCTTGTCCTAAA GTCTC-3'; GATA6-R: 5'-CGAGCCCTAAACAAACAGC-3' and were sent to Shanghai Sheng-gong Biological Co., Ltd. for synthesis. The amplified target fragment was sent to Shanghai Sheng-gong Biological Co., Ltd., and the Sanger method was used for gene sequencing. In addition, sequencing results were analyzed using DNAMAN software. To further examine whether the variant site affects binding to other transcription factors, the JASPAR program (http://jaspar.genereg.net/) was used to perform an alignment analysis of the variant sites of the *GATA6* gene promoter region.

After the detection of the target gene, we found two variant sites (g.22168944G>A and g.22169265G>A) in the *GATA6* gene promoter region of the patient. In addition, these two variant sites were identified as two single nucleotide polymorphisms (SNPs) (rs144923558 and rs146748749) after a search in the dbSNP database. The gene locus of the two SNPs is shown in Figure 1A. At the same time, the DNA sequencing chromatograms of the two SNPs are shown in Figure 1B. To confirm the presence of linkage disequilibrium between the two SNPs (rs144923558 and rs146748749) in the patient's *GATA6* gene promoter region, we used the online browser of the vertebrate genome Ensembl (http://www.ensembl.org/index.html) for linkage disequilibrium analysis. The results (in the Han population of Beijing, China) showed that the two SNPs were in complete linkage disequilibrium (D' = 1.000, r^2 = 1.000). As summarized in Table 1, the two SNPs identified in the patient may abolish and create the putative binding sites for transcription factors. The SNP [g.22168944G>A (rs144923558)] may abolish the binding sites for MGA and NEUROD2, and create the binding sites for DLX6, ISL2, BSX and GSX1. The SNP [g.22169265G>A (rs146748749)] may abolish the binding site for MZF1 and create the binding site ESRRA.

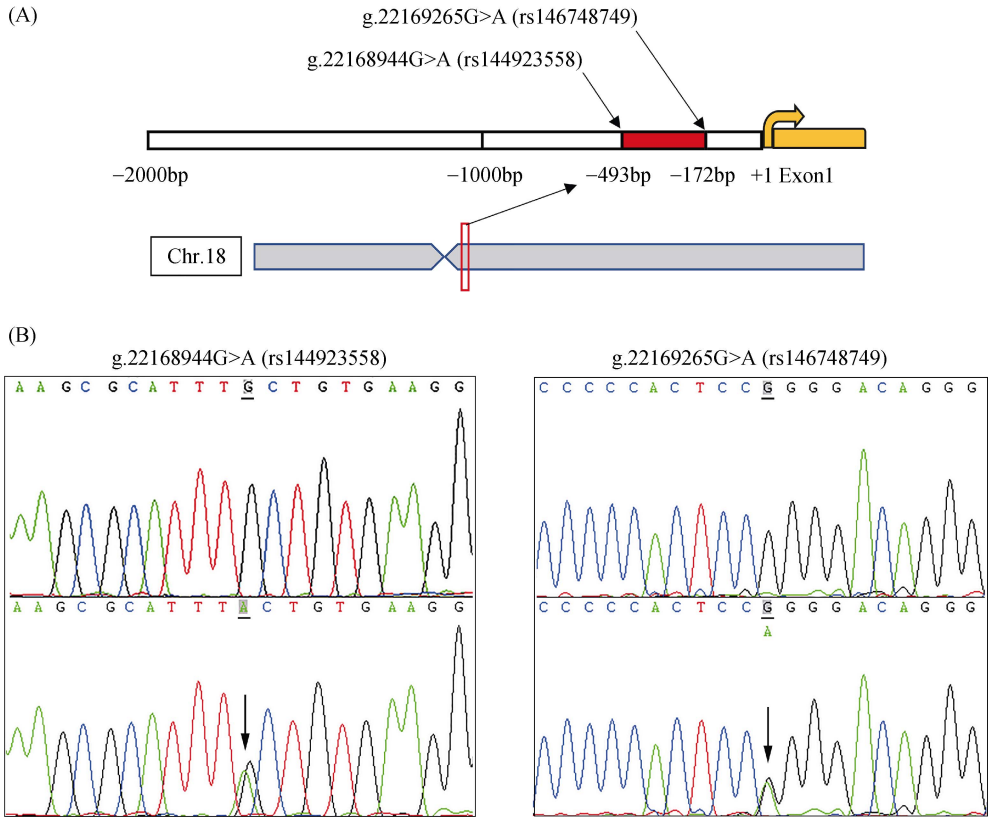

Figure 1. Gene locus and DNA sequencing chromatograms of two SNPs. (A): The two SNPs were named according to their locations in the GATA6 genomic sequences (NCBI: NC_000018.10); and (B): all sequence orientations of the two SNPs are forward. Top panels show wild-type and bottom panels heterozygous SNPs, which are marked with arrows. GATA6: GATA binding protein 6; SNPs: single nucleotide polymorphisms.

Table 1. Predicted binding sites for transcription factors affected by the two SNPs.

SNPs	Mode of action	Transcription factors
g.22168944G>A (rs144923558)	abolish	MGA
		NEUROD2
	create	DLX6
		ISL2
		BSX
		GSX1
g.22169265G>A (rs146748749)	abolish	MZF1
	create	ESRRA

BSX: brain specific homeobox; DLX6: distal-less homeobox 6; ESRRA: estrogen related receptor alpha; GSX1: GS homeobox 1; ISL2: ISL LIM homeobox 2; MGA: MAX dimerization protein MGA; MZF1: myeloid zinc finger 1; NEUROD2: neuronal differentiation 2; SNPs: single nucleotide polymorphisms.

The occurrence and development of many human diseases are affected by the dysregulation of gene expression programs, such as cardiovascular disease, diabetes and inflammation. Gene mutations play a crucial role in the initiation of the dysregulation of gene expression programs. To date, relevant studies have shown that polymorphisms in single or multiple genes have a direct impact on the onset of AMI.[8,9] However, the *GATA6* gene not only regulates early differentiation and development of the heart, but also participates in the development, differentiation and apoptosis of vascular smooth muscle cells.[10] Therefore, mutations in the promoter region of the *GATA6* gene may affect the transcriptional activity of the gene or affect its binding to other transcription factors, leading to changes in cardiac structure and dysfunction of vascular smooth muscle, and thus may be a risk factor for the development of AMI. At the same time, epidemiological studies have shown that the incidence of CAD in patients with congenital heart disease (CHD) is significantly higher than that in healthy people.[11,12] The results of these findings suggest that dysregulation of cardiac developmental genes may contribute to the pathogenesis of CAD. Of course, this still requires basic and clinical research for verification. In addition, since the *GATA6* gene is also involved in the CCS, its sequence variation can cause abnormal gene function and arrhythmia, such as the occurrence of AF. The *GATA6* gene also plays an important role in the development of the human pancreas. DM can be triggered by genetic mutations that affect the normal function of the pancreas in adults. However, specific molecular genetic mechanisms still need to be explored and studied.

For the patient in this case, we developed an effective treatment plan centered on saving patients' lives in clinical treatment. After initial diagnosis, we performed antithrombotic and anti-myocardial ischemia procedures, improved circulation, maintained homeostasis, controlled heart rate to correct arrhythmia, lowered blood sugar to correct diabetic complications, and administered lipid-lowering and anti-infection treatment. After excluding the surgical contraindications, the patient underwent coronary angiography to determine the coronary vascular disease to develop the best treatment. Finally, we chose CABG for this patient. Fortunately, our effective combination of drug therapy and surgical treatment not only relieved the patient's life-threatening risk from AMI, but also improved the patient's quality of life in the future. Perhaps, for similar cardiovascular diseases, the main treatments in the world are still drug maintenance and symptomatic treatment, coronary intervention or surgical bypass surgery and health management education. However, with the rapid development of technology, gene sequencing detection and gene editing technology have been continuously developed and improved. For example, methods for genome-wide association studies are widely used throughout the world, and CRISPR/Case9 technology has also been used as a molecular biology tool for genome editing.[13]

In such an era of advocating precision medicine and individualized treatment, the rapid development of genetic diagnosis and gene therapy can not only greatly contribute to the improvement of medical standards in the world, but also reduce the physical trauma and economic burden caused by surgery. In this case, we report two SNPs (rs144923558 and rs146748749) present in the promoter region of the *GATA6* gene in this patient. These results provide not only case support for understanding the relationship between genes and human disease phenotypes, but also a genetic basis for future studies on the molecular mechanisms of gene dysfunction. At the same time, they can also promote the genetic diagnosis and individualized gene therapy era of related diseases in the future.

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