IL-13 and FOXO3 genes polymorphisms regulate IgE levels in asthmatic patients

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Abstract. Immunoglobulin E (IgE) serves a crucial role in the pathogenesis of several allergic disorders, and elevated levels of total serum IgE have been associated with asthma. IgE is responsible for the release of several asthma-associated inflammatory mediators from mast cells, such as histamine and prostaglandins. The aim of the present study was to assess the association of interleukin (IL)-13 single nucleotide polymorphism (SNP) rs20541 and forkhead box O3a (FOXO3a) SNP rs13217795 with IgE levels in asthmatic patients and a healthy control group. Genetic polymorphism analysis of SNPs was performed using PCR/restriction fragment length polymorphism. Total serum IgE levels were measured using an ELISA kit. Genotypes were grouped into three models: Co-dominant, dominant and recessive. Major and minor alleles for IL-13 SNP rs20541 and FOXO3a SNP rs13217795 were C and T, whereas for IL-13, they were G and A, respectively. There was a significant association between the IL-13 rs20541 SNP and the total IgE serum levels, in which pure minor alleles were associated with a significant reduction (~5x lower) in IgE serum levels compared with the major alleles in asthmatic subjects and to a lesser extent in the control subjects. Additionally, the FOXO3a rs13217795 SNP was associated with a significant increase in total IgE levels (~5x higher) in the asthmatic patients compared with the control subjects. In conclusion, the present study confirmed that there was a significant association between the IL-13 SNP rs20541 and asthma, and an association between the FOXO3a SNP rs13217795 with asthma pathogenicity in Jordanian subjects.

Introduction

Asthma is an inflammatory disease in which the airway is constricted, and it is caused by immunological abnormalities that develop both in adults and children. Asthma is usually associated with obstruction of the airway, wheezing, accumulation of IgE antibodies in response to inhaled allergens and bronchial hyper-responsiveness (1). These immune and inflammatory responses are orchestrated and regulated by cytokines and transcription factors, which serve a crucial role in the pathophysiology of asthma. The immunoglobulin isotype switch from antibodies to IgE is modulated by the expression of the ligand for CD40 and the secretion of interleukin (IL)-4 and IL-13 (2).

The human IL-13 gene together with other cytokines and growth factors, including IL-4 and IL-5, as well as granulocyte-macrophage colony-stimulating factor is located on chromosome 5 (5q23-31) (3) Several studies have revealed an association between the total serum IgE levels and the bronchial hyper-responsiveness with markers on chromosome 5q23-31 in patients with asthma (4,5). Additionally, several studies have reported a correlation between numerous cytokines, including IL-13, which regulates the activity of T-helper 2 immune cells and asthmatic atopic phenotypes (6,7). In healthy individuals, $CD4^+$ T-cells produce IL-13, which induces IgG_4 and IgE synthesis in cultured B cells (8). mRNA and protein levels of IL-13 are upregulated in the sputum of asthmatic patients (9).

IL-13 is produced primarily by T-cells in addition to basophils and mast cells (10). IL-13 expression and secretion are mediated by different T-cell subtypes, including activated T-helper immune cells, $CD4^+$ and $CD8^+$, memory and naïve T-cells, whereas IL-4 cytokines are produced exclusively by the activated $CD4^+$ peripheral blood T-cells (11). IL-13 operates through IL-13R, a heterodimer of the IL-4Rα and IL-13Rα1 chain (11). IL-13 knockout mice fail to generate goblet cells, which are responsible for mucus overproduction in asthma, and also produce lower levels of total serum IgE compared with wild-type mice (12).

Variants in the gene for IL-13 have been shown to be strongly associated with asthma (13), total IgE levels (14) and bronchial hyperresponsiveness (15). Two single nucleotide polymorphisms (SNPs) have been characterized in IL-13, including a promoter SNP (-1,111, rs1800925) and a coding SNP in exon 4 (Arg130Gln, rs20541). Functional studies have shown a regulatory role for the rs1800925 SNP in $CD4^+$ Th2 T cell (16) in which the substitution of arginine with glutamine reduces the affinity of the IL-13 cytokine for its α-2 receptor (17). IL-13 expression is elevated in patients who have

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been diagnosed with asthma (17). The IL-13 polymorphisms have also been shown to be associated with asthma or its intermediate phenotypes (18), as well as the serum levels of IgE antibody (19).

Forkhead box (FOX) transcription factors serve crucial roles in immune homeostasis; for example, loss of function variants may be linked with chronic inflammation (20). FOXO is related to the FOX family of transcription factors, and are encoded by four genes; FOXO1, FOXO3a, FOXO4 and FOXO6 (21). FOXO3 is located on chromosome 6q21 and is a protein encoding gene. Its variants have been reported to possess redundant roles in the aetiology of several pulmonary disorders, such as bronchiolitis, idiopathic fibrosis and chronic obstructive pulmonary disease (22-24). Several studies have implicated a regulatory role for FOXO3a in the reduction of an inflammatory response via suppression of dendritic cell cytokine expression and promotion of initiation of the transforming growth factor-β1 regulatory pathway in monocytic white blood cells (25). Through this pathway, pro-inflammatory cytokine expression, such as that of IL-4 and -13, is reduced by FOXO3a activity (26). Accordingly, SNP analysis demonstrated a novel correlation between the rs13217795 SNP substitution of the FOXO3a gene and an individuals susceptibility to asthma (1,27). Thus, the aim of the present study was to assess the association between the IL-13 rs20541 and FOXO3a rs13217795 SNPs with IgE levels in asthmatic and healthy subjects.

Materials and methods

Subjects. The present study involved 145 asthmatic patients, consisting of 109 females and 36 males with a median age of 37.5 years old (age range 18-84 years old) and 104 healthy individuals, consisting of 49 females and 55 males with a median age of 39.3 years old (age range 18-76 years old), who were used for IL-13 gene testing. For testing of the FOXO3a genes, 116 asthmatic patients, consisting of 90 females and 26 males with a median age of 47.5 years old (age range 18-84 years old), and 95 healthy controls, consisting of 44 females and 51 males with a median age of 37.5 years old (age range 18-73 years old) were recruited. All of subjects involved in the present study visited the chest clinic in the Jordan University Hospital (JUH). Control subjects had no respiratory symptoms and no history of asthmatic disorders. Asthmatic patients were diagnosed based on their clinical presentation, pulmonary tests and physical examination. The study protocol was approved by the Institutional Review Board of JUH (approval no. IRB# 67/2011/2012). All patients and control subjects provided signed informed consent, and all procedures performed in the studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and adhered to the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards (28). According to the records of the JUH, an average of 800 Jordanian asthmatic patients without any other chronic diseases attended this hospital between August 2016 and January 2020. It was calculated that a sample size of 145 patients would be required to represent the asthmatic patients, using the power of test 1-β=0.8, 5% margin of error, and 95% confidence level (CI).

DNA extraction. Peripheral blood specimens were collected from all patients at the JUH Chest or Ear, Nose and Throat clinic in 5 ml tubes containing ethylenediaminetetraacetic acid. Following blood sample collection, DNA extraction was performed using a Wizard Genomic DNA Purification kit, according to the manufacturer's protocol (Promega Corporation).

PCR and genotyping. IL-13 (rs20541) and FOXO3a (rs13217795) genotyping was performed using the PCR/restriction fragment length polymorphism technique. The primer sequences and restriction enzymes for FOXO3a (1) and IL-13 (29) were adapted from previous studies. Briefly, 100 ng of the extracted genomic DNA was amplified using a C1000 Touch Thermal Cycler PCR thermal cycler (Bio-Rad Laboratories, Inc.). Reagents and buffers for the PCR consisted of dNTPs, Taq polymerase and Taq polymerase buffer, all of which were added to the reaction tubes according to manufacturer's protocols (all from Genei Laboratories Private, Ltd). The PCR thermocycling conditions were: Initial denaturation at 95˚C for 5 min; followed by 25 cycles of 95˚C for 30 sec, annealing for 30 sec at 62˚C or 67˚C for FOXO3a and IL-13, respectively, and extension for 1 min at 72˚C. The final extension step was a 5-min incubation at 72˚C. The resulting PCR products were subjected to digestion using *Pag*I and *Nla*IV restriction enzymes for FOXO3a and IL-13, respectively (New England Biolabs, Inc.). The resulting FOXO3a and IL-13 fragments were separated using a 3% agarose gel and then visualized under ultraviolet light.

Measurement of total IgE levels. Total IgE levels were measured using a specific ELISA kit (cat. no. RE59061; IBL International, Corp.) and absorbance was measured at a wavelength 450 nm using an ELISA microplate reader. The detection range of the kit was 5-1,000 IU/ml.

Statistical analysis. Statistical analysis was performed using GraphPad Prism version 7.0 (GraphPad Software, Inc.). The normality of data was determined using a Pearson normal distribution curve, and the results showed that all data were normally distributed. Data are presented as the mean ± standard error of the mean. Differences were compared using a Student's t-test for dominant and recessive models and a one-way ANOVA followed by a post-hoc Tukey's test for co-dominant models. A two way ANOVA test followed by a post-hoc Tukey's test was used to measure the association between rs13217795 and rs20541 SNPs with the F-ratio and total IgE serum levels. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 211 and 249 samples were assessed to evaluate the association of the rs13217795 SNP on the FOXO3a gene and the rs20541 SNP on the IL-13 gene, respectively, with the total IgE levels in patients with asthma (Table I). Genotypes were grouped into three models: Co-dominant, dominant and recessive. Major and minor alleles for the FOXO3a gene were C and T respectively, whereas for IL-13, they were G and A, respectively.

Table I. Characteristics of the study population.

Characteristic	FOXO3 Control	IL-13 Asthma	Control	Asthma
Number of participants	95	116	104	145
Median age, years (range)	37.5 (18-73)	47.5 (18-84)	39.3 (18-76)	45.1 (18-84)
Sex, n				
Females	44	90	49	109
Males	51	26	55	36

FOXO3, forkhead box O3; IL-13, interleukin.

Table II. IgE levels in the asthmatic patients and control group based on the different alleles.

A, FOXO3a

Model	Genotype	Control group IgE levels, IU/ml (n), n=95	IgE mean comparison	P-value	Asthmatic group IgE levels, IU/ml (n), n=116	IgE mean comparison	P-value
Co-dominant	CC	18.6±5.9 (19)	CC vs. CT	0.6726[c]	29.5±1.4 (11)	CC vs. CT	0.0003[b,c]
	CT	17.4±2.9 (54)	CC vs. TT	0.2927[c]	59.3±6.3 (59)	CC vs. TT	0.0040[b,c]
	TT	19.6±4.4 (22)	CT vs. TT	0.3433[c]	132.0±3.3 (46)	CT vs. TT	0.6495[c]
Dominant	CC	18.6±5.9 (19)		0.4865[d]	29.5±1.4 (11)		<0.0001[d]
	CT+TT	18.0±4.8 (76)			91.1±4.9 (105)		
Recessive	CC+CT	17.7±4.1 (73)		0.2651[d]	54.6±5.2 (70)		0.5281[d]
	TT	19.6±4.4 (22)			132.0±3.3 (46)		

B, IL-13

Model	Genotype	Control group IgE levels, IU/ml (n), n=104	IgE mean comparison	P-value	Asthmatic group IgE levels, IU/ml (n), n=145	IgE mean comparison	P-value
Co-dominant	GG	19.1±2.7 (72)	GG vs. GA	0.9686[c]	107.5±4.2 (99)	GG vs. GA	0.2323[c]
	GA	15.6±3.9 (25)	GG vs. AA	0.0097[c]	92.2±2.3 (42)	GG vs. AA	0.0033[a,c]
	AA	11.6±3.2 (7)	GA vs. AA	0.0345[c]	19.2±3.0 (4)	GA vs. AA	0.0618[c]
Dominant	GG	19.1±2.7 (72)		0.2781[d]	107.5±4.2 (99)		0.0833[d]
	GA+AA	14.7±3.4 (32)			85.8±3.5 (46)		
Recessive	GG+GA	18.1±3.1 (97)		0.0082[d]	102.9±3.6 (141)		0.0062[b,d]
	AA	11.6±3.2 (7)			19.2±3.0 (4)		

[a]P<0.01; [b]P<0.001. [c]Student's t-test; [d]One-way ANOVA. FOXO3, forkhead box O3; IL-13, interleukin; IgE, immunoglobulin E.

Table II illustrates the association between genotypes of both the FOXO3 and IL-13 assessed SNPs and total IgE levels of healthy and asthmatic subjects. Amongst the 116 tested asthmatic patients, the most frequent genotype for the FOXO3 gene was the heterozygous (n=59) followed by the minor homozygous (n=46) and then the major homozygous (n=11) genotype. The results showed that the presence of at least one minor allele (T) was significantly associated with higher IgE serum levels. Interestingly, patients with the minor homozygous genotype (TT) had the highest IgE serum levels (132 IU/ml) amongst the tested asthmatic subjects. A significant association with total IgE serum level was observed with respect to the comparison between major homozygous and heterozygous genotypes in addition to major homozygous and minor homozygous genotypes in asthmatic subjects (P=0.0003 and 0.0040, respectively). However, no significant association was found in the case of asthmatic heterozygous genotypes compared with the minor homozygous genotypes. Notably, the significance of the association was model-dependent with the dominant model showing significance (P=0.0001) in contrast to no significance

in the recessive model (P=0.5281) in asthmatic patients. In the control group, IgE serum levels were less variable and showed no significant association with the relative genotype models of the FOXO3a gene. In general, asthmatic subjects showed higher IgE serum levels with FOXO3a genotypes compared with the same genotypes in the control subjects.

Conversely, analysis of the IL-13 SNP showed an inverse association with IgE serum levels (Table II). Serum levels of IgE were observed to be notably decreased with the presence of at least one minor allele. In particular, patients with a minor homozygous genotype showed the largest decrease in IgE serum levels in both asthmatic and control subjects (19.2 and 11.6 IU/ml, respectively). Conversely, the association of the IL-13 SNP and IgE levels in asthmatic and control subjects was insignificant when compared with the major homozygous (GG) and heterozygous (GA) genotypes (P=0.2323 and 0.9686, respectively). However, a significant association was observed amongst the major (GG) and minor homozygous (AA) genotypes when comparing asthmatic and control subjects (P=0.0033 and 0.0097, respectively). The heterozygous vs. minor homozygous comparison resulted in a significant association for control subjects (P=0.0345); however, the same genotypic comparison was not statistically significant for asthmatic patients (P=0.0618), even though IgE serum levels were notably decreased in subjects with the AA minor homozygous genotype (19.2 IU/ml) compared with the IgE levels of the heterozygous (92.2 IU/ml) or major homozygous genotypes (107.5 IU/ml). Moreover, the data showed an insignificant association for the dominant genotypic model of IL-13 SNP in both the asthmatic and control groups (P=0.0833 and 0.2781, respectively). Alternatively, such an association was significant for the recessive model in the asthmatic and control subjects (P=0.0062 and 0.0082, respectively).

Table III summarizes the results of the statistical analysis between the tested SNPs and the clinical respiratory parameters [forced expiratory volume (FEV1) and forced vital capacity (FVC)]. The F-ratio is the ratio between the FEV1 and FVC of both the control and asthmatic subjects. Furthermore, in Table III, the results of the association of the SNPs with both serum IgE levels and F-ratio using a two-way ANOVA are shown. With regards to the associations between the SNPs and the F-ratio, there was a significant association between the FOXO3a rs13217795 major (CC) and minor homozygous (TT) genotypes in asthmatic patients (P=0.0221). In the 2-way ANOVA of SNPs with both serum IgE levels and F-ratio, significant associations were found between FOXO3a and IL-13 SNPs with both IgE levels and F-ratio in control subjects only.

Discussion

The IgE antibody is crucial for the pathogenicity of allergic disorders, and elevated serum levels of IgE antibodies have been correlated with asthma (30). IgE is responsible for the release of numerous inflammatory mediators, such as histamine and prostaglandins, from mast cells, in asthmatic patients. These inflammatory mediators promote further constriction of airways by causing excessive mucus secretion (31). The results of the present study are in agreement with previous results; significantly elevated levels of IgE antibodies were observed amongst the asthmatic patients compared with the healthy individuals (3,32,33). The results of the present study showed a significant association between the rs20541 SNP of IL-13 and total IgE serum levels, in which pure minor alleles were significantly associated with reduced IgE serum levels (~5x lower) compared with major alleles in asthmatic subjects. Alternatively, such changes were less notable in the control subjects compared with the asthmatic group. Additionally, the results confirmed a significant association between the rs13217795 SNP of the FOXO3a gene and a significant increase in IgE levels in the serum of asthmatic patients in the Jordanian population; an association which was not observed in the healthy individuals.

A combination of hereditary and environmental factors, such as exposure to allergens and air pollution, are the primary factors underlying development of asthma (34). In response to an allergen, helper T-cells perpetuate the disease by secreting several cytokines, including IL-4, -5 and -13. IL-13 serves an important role in airway inflammation and remodelling in asthmatic patients (11). This finding is further supported by immunohistochemical findings in human lung specimens, showing that functional IL-13R is expressed in bronchial tissues in asthmatic patients (35). Concordantly, Heinzmann *et al* (35) demonstrated that a variant of IL-13RA1 on the X chromosome was significantly associated with IgE levels in British subjects. The pathogenesis of asthma is mediated by $CD4^+$ Th2, producing a type 2 cytokine profile that includes the induction of IgE production and recruitment of mast cells (36). Several studies have shown that IL-13 is the primary regulator of IgE antibody expression and secretion (6,19). Interestingly, IL-13 SNP rs20541 results in a substitution of arginine to glutamine, which induces conformational changes at the site of interaction with the IL-13 receptor. Functional analysis has shown that rs20541 enhances IL-13 activity and its downstream signalling pathway, including IgE production and secretion (37). Interestingly, IL-13 SNP rs20541 adversely affects asthmatic patients and causes a significant decrease in IgE levels in their serum. A possible explanation for these findings is the compounding effects of multiple factors, such as epigenetic, environmental and genetic factors, which are all involved in the predisposition and pathogenicity to asthma. Importantly, the results indicate that Arg130Gln (rs20541) polymorphism is not associated with lung function in both control and asthmatic patients. This suggests that the predominant genetic effect of the Arg130Gln (rs20541) polymorphism is on the allergic response, but not asthma per se.

SNPs in IL-13 were revealed to be associated with allergic phenotypes in different ethnic populations and may affect total serum IgE levels (38). Additionally, Maier *et al* (39) revealed that allelic variation in the IL-13 gene was significantly correlated with IgE levels. In the present study, the presence of such an association was also confirmed in the Jordanian population. These findings are also consistent with data obtained from a study in the Chinese population, which revealed that IL-13 rs20541 and rs1800925 were risk factors for asthma, and were significantly associated with total serum IgE levels (40). Moreover, Smolkova *et al* (41) reported that the minor allele (A) of Arg 130Gln was significantly associated with a decrease in total serum IgE levels in Slovak children.

Table III. Association between the lung function of the asthmatic patients with FOXO3a and IL-13 SNPs and IgE levels.

A, FOXO3a

	Asthma, n=116				Control, n=95			
SNP	F-ratio, mean ± SEM	IgE levels, IU/ml (n)	Association between SNP and F-ratio[b], P-value	Association between SNP, F-ratio and IgE level[c], P-value	F-ratio (n)	IgE levels, IU/ml (n)	Association between SNP and F-ratio[b], P-value	Association between SNP, F-ratio and IgE level[c], P-value
CC	77.0±2.7	29.5±1.4 (11)	CC vs. CT, 0.1040		100.7±1.88	18.6±5.9 (19)	CC vs. CT, 0.2136	
CT	78.0±1.4	59.3±6.3 (59)	CC vs. TT, 0.0221	0.6609	101.9±0.84	17.4±2.9 (54)	CC vs. TT, 0.9468	<0.0001[a]
TT	76.6±1.7	132.0±3.3 (46)	CT vs. TT, 0.5459		101.7±1.45	19.6±4.4 (22)	CT vs. TT, 0.869	

B, IL-13

	Asthma, n=145				Control, n=104			
SNP	F-ratio, mean ± SEM	IgE levels, IU/ml (n)	Association between SNP and F-ratio[b], P-value	Association between SNP, F-ratio and IgE level[c], P-value	F-ratio (n)	IgE levels, IU/ml (n)	Association between SNP and F-ratio[b], P-value	Association between SNP, F-ratio and IgE level[c], P-value
GG	76.5±1.1	107.5±4.2 (99)	GG vs. GA, 0.1999		101.8±0.78	19.1±2.7 (72)	GG vs. GA, 0.6885	
GA	77.6±1.3	92.2±2.3 (42)	GG vs. AA, 0.8187	0.8079	100.4±1.49	15.6±3.9 (25)	GG vs. AA, 0.7705	<0.0001[a]
AA	76.5±4.7	19.2±3.0 (4)	GA vs. AA, 0.4661		102.7±1.12	11.6±3.2 (7)	GA vs. AA, 0.9804	

[a]P<0.001. [b]One-way ANOVA; [c]Two-way ANOVA. FOXO3, forkhead box O3; IL-13, interleukin; IgE, immunoglobulin E; SNP, single nucleotide polymorphism; SEM, standard error of the mean.

Halwani *et al* (42) reported that IL-13 minor A alleles for rs20541 SNP were associated with a significantly higher risk of asthma in the Saudi Arabian population. In contrast, another study on Egyptian children reported that the minor allele (A) of Arg 130Gln was significantly associated with an increase in total serum IgE levels (43). This previous study was limited by its small sample size and lack of consideration of total serum IgE levels as a quantitative feature. Another possible explanation for the conflicting findings may be indicative of the complex interactions with the genetic and epigenetic variations that come with different ethnicities. Such variations amongst different populations may influence the overall impact of the tested SNPs, and may result in different biological outcomes. Meta-analyses have demonstrated that targeting the IL-13 pathway is a promising therapeutic approach for treating asthma (44,45). Furthermore, the association of IL-13 with the pathophysiology of asthma and reduced corticosteroid sensitivity suggests the potential value of anti-IL-13 therapy in refractory asthma (46).

The association between FOXO3a SNP rs13217795 and asthma has been reported amongst Jordanian asthmatic patients previously (27). Such an association was also explored in the Indian population (1). To date and after an extensive review, the present study leads the association studies of IgE levels with the SNPs of FOXO3a in the Jordanian population. The present study highlights the possible association of the assessed FOXO3a SNPs and total serum IgE levels in asthmatic patients. The results of the present study showed that rs13217795 SNP appears to be significantly associated with the increase in total IgE serum levels in asthmatic patients. In contrast, such an association was insignificant in the control healthy group. FOXO3a regulates the production of anti-inflammatory cytokines, such as IL-10, whilst also maintaining the unfettered proliferation of T cells and neutrophils, hence serving a crucial role in inflammatory pathways (47). Alternatively, mice with a deletion of the FOXO3a gene exhibited sustained proliferation of lymphocytes and hyperactivity of Th2 immune cells along with persistent inflammation of the lungs, thus confirming the notion that FOXO3a may serve an important regulatory role in suppressing rather than activating T-cells, and in the subsequent pulmonary inflammation (47). This concept explains the results of the present study, in which the regulatory effect of FOXO3a was attenuated in asthmatic patients with both minor alleles of rs13217795 SNP, resulting in a significant increase in IgE serum levels. Interestingly, these results indicate that FOXO3a is significantly associated with the respiratory function of the asthmatic group, but not the control subjects. Such an association may highlight FOXO3a as an attractive target for treatment of asthmatic patients, by providing a means of targeting both the allergic and inflammatory components of asthma.

In conclusion, the present study confirmed the significant association of IL-13 SNP rs20541 with asthma, and the association of FOXO3a SNP rs13217795 with asthma pathogenicity. Further studies are required to investigate the diverse effects of IL-13 rs20541 SNP on IgE serum levels in asthma and its clinical outcomes. Moreover, more associative studies are required to investigate the correlation between FOXO3a and IL-13 SNPs on IL-13 cytokine expression and subsequent IgE serum levels.

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Availability of data and materials

The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

AI, TAT and MZ conceived the study. AI and MZ designed the study. AI, TAT and MZ performed the experiments. AI and MZ analysed the data. AI, TAT and MZ wrote and edited the manuscript. All authors have read and approved the final manuscript. AI, TAT and MZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of JUH (approval no. IRB# 67/2011/2012). All patients and control subjects provided signed informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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