Genetic study of the association of specific language impairment to markers near *FOXP2* gene

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Received 03 October 2018
Accepted 13 December 2018

Middle East Journal of Medical Genetics
2018,7:118–123

Background
One important language gene is *FOXP2*, a mutation of which affects language and speech in relatively rare and severe forms. However, certain genetic markers adjacent to *FOXP2* gene are highly suspected to be involved in common forms of specific language impairment (SLI). Identification of these genetic loci related to SLI may yield new insights into its causes, along with improved diagnosis, and treatment.

Aim of the work
To study the association of SLI to two genetic markers residing near *FOXP2* gene, namely, the repeat unit GATA of D7S3052 marker and GATT tetranucleotide repeats in intron 6 of *CFTR* gene.

Patients and methods
The current study included 50 children with SLI and 50 normal controls, aged 3–8 years. All participants were subjected to genetic molecular association study as well as detailed protocol of assessment including full history and examination, and evaluation of language skills and mental ability (intelligence quotient).

Results
There was no difference between the SLI and normal groups regarding molecular results of GATT repeats of *CFTR* gene, and there was a nonsignificant difference regarding results of GATA repeats of D7S3052 marker ($P > 0.05$).

Conclusion
The association of SLI with D7S3052 marker near *FOXP2* gene in current study is statistically nonsignificant. However, a statistical significance of this association could be expected with a larger number of cases, more diversity of SLI types and degrees, and more comprehensive procedures.

Keywords:
D7S3052 marker, *FOXP2* gene, GATA repeats, molecular study, specific language impairment

Middle East J Med Genet 7:118–123
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2090-8571

Introduction

Specific language impairment (SLI) is a language disorder, in which there is a significant delay in the understanding and/or use of spoken language. It arises when children present language maturation, lagging behind their chronological age in the absence of intellectual, sensory, or psychological deficits (Armon-Lotem, 2012).

There are suggested environmental (nongenetic) etiologies for SLI, yielded mainly by prenatal, natal, and postnatal events in the children with SLI. The outcome of these events could be minor neurobiological defects in brain language areas of the children with SLI, a finding observed by several investigators (Guerreiro *et al.*, 2002; Ullman, 2004; Hage *et al.*, 2006). However, there are strong genetic factors that could result also in these neurobiological defects, and influence the development of SLI. Indeed, SLI has been shown to have moderate-to-high levels of heritability (Rice, 2012). The median incidence of positive family history of SLI is 39%. The concordance rate of SLI in twin studies is nearly 100% for monozygotic twins, and 50–70% for dizygotic twins (Stromswold, 1998).

Genes that have been linked to SLI include *FOXP2* gene (forkhead box P2) (Kaminen *et al.*, 2003), and regions located on chromosome 16 (Newbury *et al.*, 2009), chromosome 19 (SLI Consortium SLIC, 2002), chromosome 7 (7q35-q36.1) (Vernes *et al.*, 2008), chromosome 13q21 (Bartlett *et al.*, 2002), and chromosome 2q36 (Wiszniewski *et al.*, 2013). *FOXP2* was the first gene characterized, in which a mutation affects human speech and language abilities in relatively rare and severe forms. It is located on chromosome 7q31, and expressed in the developing brain (Shu *et al.*, 2001).

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The importance of *FOXP2* gene comes from the fact that it encodes a transcription protein which regulates other genes pertinent to neural pathways related to language development (Bishop, 2009). Molecular genetic studies of speech and language disorders include the report by Fisher *et al.* (1998) of linkage of a severe autosomal-dominant language and speech disorder (verbal dyspraxia) to the region of 7q31 (*FOXP2* gene) in one large pedigree (KE family). The affected members of this pedigree were found to have a mutation in the DNA-binding domain of exon 14 in this gene. Additionally, Lai *et al.* (2000) reported an unrelated individual (CS child) with a similar phenotype who was found to have a chromosomal translocation in this region also. On the contrary, the study of O'Brien *et al.* (2003) revealed no mutations in exon 14 of *FOXP2* gene in samples taken from children with SLI and their family members. However, this study showed significant association to a marker within the *CFTR* gene and another marker on 7q31, D7S3052, both adjacent to *FOXP2*, suggesting that genetic factors for regulation of common forms of SLI reside near *FOXP2*.

The aim of the current work was to study association of SLI in an affected sample of Egyptian children to two genetic markers residing near *FOXP2* gene, namely, repeat unit GATA of D7S3052 marker, and GATT tetranucleotide repeat in intron 6 of *CFTR* gene related to *FOXP2* gene. Identification of these genetic loci related to SLI, may yield new insights into its causes, along with improved diagnosis, classification, treatment, and linkage to human genome.

Patients and methods

The current study was conducted on two groups of children: 50 patients with SLI (42 males and eight females) and 50 normal controls (33 males and 17 females). Their ages ranged from 3 to 8 years. They were attending the Phoniatric Unit and the Otorhinolaryngology (ENT) Clinic, Ain Shams University, and the outpatient clinic of Clinical Genetics Department, National Research Centre, in Egypt. The study extended from the year 2012 to 2015.

Written informed consent was obtained from the parents after explanation to them the aim of the study. All the patients' data were confidential. Approval was taken to conduct this research from the ethical committee of Ain Shams University, and the ethical committee of the National Research Centre in Egypt.

According to the Language Assessment Protocol of the Phoniatric Unit of Ain Shams University Hospitals, all participants were subjected to the following: full personal, family, medical, perinatal, and developmental history; full clinical examination; thorough language evaluation using modified Preschool Language Scale-4th Arabic edition (El-Sady *et al.*, 2011); and articulation test (Kotby *et al.*, 1985), as well as the evaluation of mental ability [intelligence quotient (IQ)] using Stanford-Binet Intelligence Scale-5th edition (Thorndike *et al.*, 1986).

The participants were subjected to molecular genetic study at the Medical Molecular Genetics Department, National Research Centre, for association of two genetic markers (namely, the tetranucleotide repeat unit GATA of D7S3052 marker near *FOXP2* gene, and the tetranucleotide repeat unit GATT in intron 6 of *CFTR* gene related to *FOXP2* gene) with SLI. Blood samples were taken from all patients to carry out the genotyping molecular method used in our study. The DNA was extracted using standard procedures (Miller *et al.*, 1988). As described by O'Brien *et al.* (2003), the samples were then examined for the microsatellite GATA and GATT repeats (markers) in chromosome 7 by amplification of the region by PCR. The PCR product was run on denaturing 10% polyacrylamide gel electrophoresis, and bands were visualized via ethidium bromide staining. All samples were then genotyped for each of the two genetic markers in the current study.

For the statistical analysis, quantitative data were analyzed using SPSS, version 16 (IBM® SPSS®, Chicago, Illinois, USA), with mean values for continuous variables compared using Student's *t* test, and differences between proportions were assessed using χ^2 test. Correlation between variables was done using Pearson's correlation.

Results

The current study included 100 patients (with normal hearing, and vision) who were subdivided into two groups: SLI group consisting of 50 patients (obtaining IQ ≥90% and total standard language score <77.5), and normal control group consisting of 50 patients (obtaining IQ ≥90% and total standard language score ≥77.5).

There are 42 males and eight females within the SLI group, and 33 males and 17 females within the normal group, with a statistically significant difference between the two groups ($P < 0.05$), showing more male predominance in the SLI group (having a male-to-female sex ratio of 5.25: 1).

The mean ages were 4 years and 4 months and 4 years and 6 months for patients of SLI group

and patients of normal group, respectively, with a statistically nonsignificant difference between the two groups ($P > 0.05$). The mean IQ scores were 93.52 and 95.38 for patients of SLI group and patients of normal group, respectively, with a statistically significant difference between the two groups ($P < 0.05$). In the SLI group, the mean total, expressive, and receptive standard language scores were 56.88, 55.52, and 63.76, respectively. In the normal group; the mean total, expressive, and receptive standard language scores were 85.34, 85.72, and 87.32, respectively. The differences between the two groups regarding all standard language scores were statistically highly significant ($P < 0.001$) (Table 1).

Regarding the molecular genotyping results of GATA tetranucleotide repeats (of D7S3052 marker), of the 50 SLI cases, 20 cases showed homozygous repeat units, whereas 30 cases were heterozygous (having two different repeat units). On the contrary, of the 50 normal controls, 25 were homozygous, and 25 were heterozygous (Fig. 1). Comparison between the molecular results of GATA repeats of the two groups by χ^2 test showed statistically nonsignificant difference (Table 2). However, the molecular results of GATA repeats, being variant in the two groups, were correlated with the total standard language score in the 100 patients, and revealed a nonsignificant correlation ($r = 1.010$) (Table 3).

Regarding the molecular genotyping results of the GATT tetranucleotide repeats (of *CFTR* gene), the GATT tetranucleotide repeat was homozygous in all SLI cases and all normal controls, with no difference in the allele size (Table 2 and Fig. 1). Subsequently, no statistical comparison was done, as there is no difference between the two groups regarding the molecular results of GATT repeats. Furthermore, the absence of this variation between the two groups made it not feasible to correlate the molecular results of GATT repeats with any variable, including the total standard language score.

For the SLI cases specifically, correlations between GATA repeat results and each of the total, expressive, and receptive standard language scores were done, and revealed to be all nonsignificant (Table 4).

Discussion

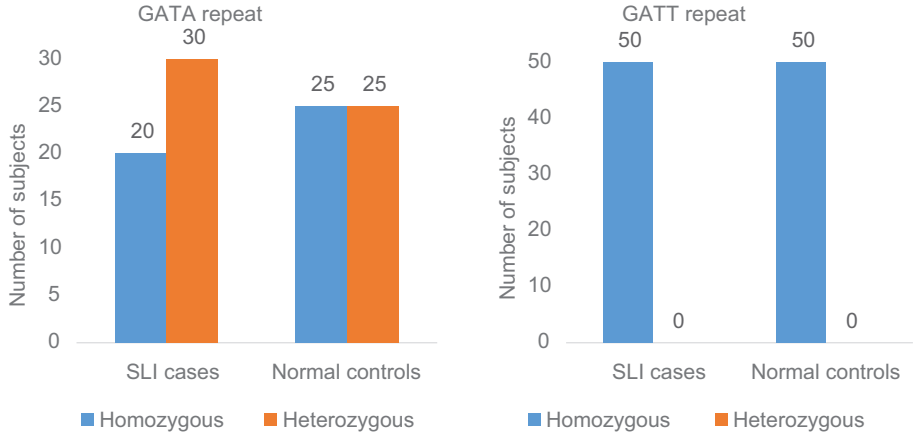
As evidenced in the strong familial aggregation noticed with many cases of SLI, it is now generally accepted that SLI is a strongly genetic disorder. This is also supported by the increase in SLI concordance rate in monozygotic twins (being nearly genetically similar) over that of dizygotic twins (Hayiou-Thomas, 2008). So, gene involvement is highly suspected in the development of SLI. The isolation of relevant genetic

Table 1 Distribution of standard language scores among the specific language impairment and normal control groups

	Standard total language score	Standard expressive language score	Standard receptive language score
SLI cases (*n*=50)	56.88±8.537	55.52±7.279	63.76±14.068
Normal controls (*n*=50)	85.34±7.496	85.72±7.337	87.32±7.844
t test	17.714	20.661	10.343
P value	0.000 (*P*>0.001)	0.000 (*P*<0.001)	0.000 (*P*<0.001)
Significance	HS	HS	HS

HS, highly significant; SLI, specific language impairment.

Figure 1



The number of patients with homozygous or heterozygous results of GATA repeat (D7S3052 marker), and GATT repeat (CFTR gene) among the SLI and normal control groups. SLI, specific language impairment.

Table 2 Distribution of molecular results (GATA and GATT repeat results) among specific language impairment and normal control groups

	GATA repeat (D7S3052 marker) [*n* (%)]		GATT repeat (CFTR gene) [*n* (%)]	
	Heterozygous (*n*=55)	Homozygous (*n*=45)	Heterozygous (*n*=0)	Homozygous (*n*=100)
SLI cases	30 (60)	20 (40)	0 (0)	50 (100)
Normal controls	25 (50)	25 (50)	0 (0)	50 (100)
χ^2	1.010		–	
P value	0.315 (*P*>0.05)		–	
Significance	NS		–	

SLI, specific language impairment.

Table 3 Correlation between standard total language score and GATA repeat results (homozygous or heterozygous) in the 100 patients in the study

Variables	Standard total language score
GATA repeats (*n*=100)	
Pearson's correlation	1.010
P value (2-tailed)	0.315 (*P*>0.05)
Significance	NS

effects will yield new insights into the causes of SLI, along with improved classification, diagnosis, and treatment.

It is suggested that there are many different genes that can influence language learning, and SLI results when a child inherits a particularly detrimental combination of risk factors, each of which may have only a small effect. However, it has been hypothesized that a mutation of the *FOXP2* gene may have an influence on the development of SLI to a certain degree, as it regulates other genes pertinent to neural pathways related to language development (Bishop, 2009). In the current work, a molecular genetic study was done for the association of two genetic markers near *FOXP2* gene (namely, the GATA repeat unit of D7S3052 marker, and the GATT repeat unit in intron 6 of *CFTR* gene) with SLI.

The SLI group in the current study scored lower than the normal group regarding total, receptive, and expressive standard language scores, with highly significant differences between the two groups. This is consistent with the fact that SLI is diagnosed if the child scores below normal cut-off points on standardized language tests, having a nonverbal IQ of 90 or above, and no other exclusionary criteria. Each of the children with SLI in the current study had a total standard language score less than the normal cut-off point in modified Preschool Language Scale-4th, which is 77.5. Although this was enough to diagnose Delayed Language Development (DLD) in the SLI group, there were several SLI cases that obtained receptive standard language scores that are comparable with those of the normally developing children (even though the mean receptive standard score of the whole SLI group is still lower than that of the normal group). So that, the gap between receptive and expressive language skills is generally wider in the SLI patients of the current study compared with the normally developing patients. The presence of this gap in SLI is in partial agreement with the study of Kim *et al.* (2011) who reported that the receptive language was better than expressive language in SLI group, compared with mild intellectual disability group (rather than normal children).

In the current work, there was no difference at all between the SLI and normal groups regarding molecular results of GATT repeats of marker within *CFTR* gene, and there was a nonsignificant difference regarding results of GATA repeats of D7S3052 marker. Each of the previous two genetic markers are related to *FOXP2* gene on chromosome 7q31; the first one is located within the *CFTR* gene, 3 Mb distal to *FOXP2* on 7q31, and the second one is located 5 Mb proximal to *FOXP2* on 7q31. These two markers are located very close to *FOXP2* gene on chromosome 7q31 and believed to affect speech and language attributes in a manner resembling to far extent the *FOXP2* gene itself. The previous results regarding these two genetic markers (in relation to *FOXP2* gene) do not support association with SLI. This is in agreement with the study of Newbury *et al.* (2002) who found no association between quantitative language scores of SLI probands and six markers within *FOXP2* gene. They concluded that coding-region variants in *FOXP2* do not underlie relevant linkage, and that the gene is unlikely to play a major role in SLI. Moreover, they suggested that the role of *FOXP2* in speech and language disorders does not generalize (beyond the severe rare speech and language disorder in KE family and CS child) to more common forms of SLI. However, they stated that owing to diverse range of impairments falling under SLI, it remains possible that *FOXP2* variations may be involved in specific and distinct forms of SLI not represented within their sample. Furthermore, several other studies of SLI have not found linkage or association to *FOXP2* or chromosome 7, like those of SLI Consortium SLIC (2002), Bartlett *et al.* (2002), and Meaburn *et al.* (2002).

On the contrary, the association between SLI and the two genetic markers in the current study was found to be significant in the study of O'Brien *et al.* (2003).

Table 4 Correlations between GATA repeat results and standard language scores in specific language impairment cases

Variables	Total standard language score	Expressive standard language score	Receptive standard language score
GATA repeat results in SLI cases			
Pearson's correlation	14.120	11.616	17.500
P value (2-tailed)	0.590 (*P*>0.05)	0.708 (*P*>0.05)	0.556 (*P*>0.05)
Significance	NS	NS	NS

SLI, specific language impairment.

No markers within *FOXP2* gene itself were significant overall in the study by O'Brien *et al.* However, both D7S3052 and *CFTR* markers near *FOXP2* gene were significantly associated with discrete language phenotype in their study. Accordingly, they suggested the presence not of a major locus but, rather, one or more regions that modify language phenotypes (regulatory regions), located outside known coding sequence of *FOXP2* gene on chromosome 7q31. Furthermore, they stated that the significant association of SLI to markers on 7q31 in their study was found using the discrete language phenotype of SLI, not only quantitative language score, supporting the theory that SLI is a distinct language disorder rather than just DLD at the lower end of the continuum.

Rather than the association with markers within or near *FOXP2*, there are point mutations across *FOXP2* gene reported in many studies like the studies of MacDermot *et al.* (2005), Turner *et al.* (2013), and Adegbola *et al.* (2015). However, most of these studies did not directly relate with SLI, and instead established an association between *FOXP2* point mutations and an autosomal-dominant disorder closely related to SLI. This disorder is caused by heterozygous mutations in the *FOXP2* gene, and characterized by severe developmental verbal dyspraxia, which results in marked disruption of speech associated with expressive and receptive language difficulties, extending to problems with receptive and expressive grammar, the clinical picture first seen in KE family and CS child.

Noting that language and speech disorders resulting from mutations of *FOXP2* gene (and possibly its vicinity) tend to be autosomal-dominant, with only affected one copy (allele) of *FOXP2* gene enough to cause the disorder, the nonsignificant difference between the two groups of the current study regarding the results of GATA repeat of D7S3052 marker in the vicinity of *FOXP2* gene could be considered. With 30 cases out of the 50 SLI cases in the study being heterozygous (having two different repeat units), there is tendency to heterozygosity regarding the results of D7S3052 marker in the children with SLI of the study. This is in comparison with the normal group of children in the study having equivalent heterozygous and homozygous results. It is possible that each heterozygous sample of the children with SLI in the study has one affected allele that can cause the disorder. However, the nonsignificant difference in the study could be attributed to the relatively small sample size, the use of relatively simple genetic procedures, the diversity of disorders falling under SLI (with some not represented in the sample), or the location of the causative genetic mutation on other loci on chromosome 7q or other genes on different chromosomes.

The nonsignificant correlation between GATA repeats of D7S3052 marker and all the standard language scores of the SLI patients in the current study means that there is no association between this marker and language skills of children with SLI in this study. This confirms the previously mentioned result in the study that showed no significance of the difference between the SLI and normal control groups regarding molecular results of GATA repeats of D7S3052 marker. The consistency of the two results comes from the fact that the only diagnostic difference between the SLI and normal control children is based on their language scores. Furthermore, the study did not reveal significant correlation between the molecular results of GATA repeats of D7S3052 marker and the total standard language score in all the 100 patients of our study. This could mean that variants of D7S3052 marker near *FOXP2* gene is not associated with variation of language skills in the general population, not only the SLI patients. This result is in agreement with the study of Mueller *et al.* (2016) which examined the association between common variants in *FOXP2* and a quantitative measure of language ability in a population-based cohort of 812 individuals (not diagnosed as SLI). They found no significant associations and concluded that although genetic variants in *FOXP2* may be significant for rare forms of language impairment, they do not contribute appreciably to individual variation in the normal range as found in the general population.

Conclusion

Identification of genes related to SLI heralds a new era of investigations and management of language disorders linking it to human genome. However, the correlation of SLI with genetic marker near *FOXP2* gene in the current study is statistically nonsignificant.

Recommendations

Larger studies on *FOXP2* gene and its vicinity are needed including all types and degrees of SLI especially verbal dyspraxia and severe degrees of DLD in SLI. Furthermore, thorough investigation of the most suspected loci of SLI in one panel (not only one gene) is required, noting the possible variability and multiplicity of gene affection across patients with SLI. This could represent a move away from isolated studies of individual genes toward an understanding of molecular networks that may go away in neurodevelopmental disorders affecting language.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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