Review Article

Specific Language Impairment Genes, Variants and Possible Gene-based Interventions

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Abstract

Specific Language Impairment (SLI) is a communication neurodevelopmental disorder that manifests at the age of 3-5 years when a child lags his chronological speech development age by one year in the absence of medical, environmental, and psychological risk factors. SLI has been known to be highly heritable. Many studies have demonstrated different genes and loci to be implicated in SLI through linkage studies, the commonest of which were, FOX2, ATP2C2, CMIP, CNTNAP2, DCDC2, KIAA0319, DYX1C1, SRPX2, NXFL1, ERC1, SETBP1, SEMA6D, AUTS2, and GRIN2A and B. In this review, we aim to present a comprehensive summary of the genes reported to be responsible or correlated to SLI and the common non-synonymous variants for each gene, and their potential pathophysiological impact on normal speech development.

Keywords: Specific language impairment (SLI), Genetic variants, Language genes

Introduction

Specific language impairment (SLI) is an unexpected failure to develop language skills despite adequate non-verbal intelligence. It represents a heterogeneous disorder with a complex multifactorial genetic basis. It is categorized as a neurodevelopmental disorder that is highly heritable and affects 3-7% of preschool children. A person with SLI shows unexplained deficits in receptive and/or expressive language skills, with no evidence of deficits in nonverbal IQ, neurologic impairment, or environmental or emotional problems that could explain the language delays. These deficits can target one of the five global language domains; phonology (analysis of the sounds of language), syntax (word order), morphology (e.g., word formation and grammar), semantics (word meaning), and pragmatics (the practical use of language to convey purpose and emotion). Therefore, children with this neurodevelopmental disorder have trouble with the formation and learning of the rules of language and their appropriate application more than with articulation and phonology. With the wide range of SLI phenotypes, consolidated research in this area is a crucial need. Family studies along with twin
analyses, strongly support the role of a genetic background in SLI\(^{(5)}\). However, its complex pattern of inheritance suggests that several loci and environmental factors contribute to the overall risk. Many loci have been identified to be associated with SLI which allows the direct evaluation of genetic influences on language ability. In this review, we shed light on specific gene, previously identified in SLI families and correlate the nonsynonymous variants to the language deficit in the SLI children.

SLI children show great difficulty acquiring and using grammatical markers that express structural relations, such as various tense and agreement markers, including the past tense, auxiliary verbs, the third person singular and so forth. In SLI, multiple theories suggested that this impairment might be due to specific affection of phonology genes\(^{(6)}\), memory, visual learning (reading) and/or the brain processing capacity\(^{(7)}\) or some combination of all these factors\(^{(8)}\). Intriguingly, language development occurs as a buildup of different biological functions in the body. Based on gene ontology (GO) annotation, these functions can be categorized into vocal learning (GO:0042297), innate vocalization (GO:0008582), vocalization behavior (GO:00071625), learning memory (GO:0007611), learning(GO:0007612), visual learning(GO:0008542), myelination (GO:0042552) and central nervous system (CNS) development, (GO:0007399), synaptogenesis(GO:0051965), deficits in neuron migration, nervous system development, cell adhesion, axon guidance and extension, cerebral cortex and limbic system development, cell adhesion and calcium transport and homeostasis and others\(^{(9)}\). Each GO relates to a gene product. Previous studies have shown that many candidate genes have been most implicated in speech, language and reading disorders. CMIP, CNTNAP2, ATP2C2 and NFXL1 have previously been associated with common forms of SLI\(^{(10,11)}\). Another hallmark gene, the FOXP2, and its orthologue FOXP1 which are involved in a monogenic form of speech and language disorder\(^{(12)}\), and neurodevelopmental disorders\(^{(13)}\) respectively; Added to this, SRPX2 and GRIN2A, which are involved in epileptic aphasias other than speech apraxia\(^{(14)}\) and ROBO1, KIAA0319, DYX1C1 and DCDC2, which are known in developmental dyslexia\(^{(15)}\), as well as the closely related GRIN2B\(^{(16,17)}\) and ERC1, SETBP1, SEMA6D, and AUTS2, that yield speech, language and/or reading disruptions due to rare deletions or translocations\(^{(18-20)}\).

Table 1 summarizes the candidate genes, previously studied in SLI populations and the biological functions affected.

**Genes related to Phonology**

**FOXP2**

The discovery of a language-related gene, FOXP2, was a breakthrough in studying SLI where it provides a framework to link genes and speech through different populations\(^{(12)}\). FOXP2 is a transcription factor gene that codes for forkhead-domain protein, mainly expressed in human basal ganglia and inferior frontal cortex\(^{(20)}\). Mutations in FOXP2 cause developmental speech and language disorders in humans (MIM_id: 602081). SLI linkage and association studies have shown that no mutations were identified in exon 14 of the FOXP2 gene (R553H), however a strong association was found to the cystic fibrosis gene, CFTR marker (OMIM_id: 602421), and another marker on 7q31, D7S3052. Both markers were found to be adjacent to FOXP2, suggesting that language development regulatory regions lie near the FOXP2 gene\(^{(21)}\). Additionally, knockouts of FOXP2 gene results showed impaired vocalization, shortened syllabus and ar-
rhythmic vocalizations’ structure\textsuperscript{(23)}. It was found that FOXP2 mutations were not directly involved or associated with neurodevelopmental disorders, such as SLI, ASD or dyslexia\textsuperscript{(24)} yet a mutation in the FOXP2 gene caused a monogenic speech and language disorder (MIM\_id:602081)\textsuperscript{(25)}. Hence, FOXP2 is suggested to be mainly involved in language production but does not directly regulate language abilities altogether.

\textbf{FOXP2 related genes-CNTNAP2}\n
FOXP2 and CNTNAP2 are involved in developmental speech and language disorders where showed that FOXP2 directly regulates expression of the CNTNAP2 gene, by binding to a regulatory sequence in intron 1\textsuperscript{(25)}, CNTNAP2 (Contactin-associated protein2) (MIM\_id: 604569), is a gene that encodes a neurexin expressed in developing human cortex. Neurexin is a neuronal transmembrane protein member involved in interactions and clustering of potassium channels in myelinated axons. The nerve impulse conduction in myelinated axons depends on the generation of specialized subcellular domains to which different sets of ion channels are localized. CNTNAP2 expression was inversely related to FOXP2; that said lower in brain layers that showed highest levels of FOXP2\textsuperscript{(25)}. CNTNAP2 polymorphisms were mainly associated with significant quantitative associations with nonsense-word repetition (SLI, MIM\_id: 612514). The region containing these polymorphisms was also associated with language delays in children with autism, as described\textsuperscript{(26)}. Other than CNTNAP2, other FOXP2 downstream transcription factors were found to be affected\textsuperscript{(27)}.

\textbf{Genes related to Memory}\n
\textbf{GRIN2A}\n
The N-methyl-D-aspartate (NMDA) receptors are heterotetramers composed of 2 NMDA receptor-1 (NR1, or GRIN1; 138249) regulatory epsilon subunits; NMDAR2A (GRIN2A; OMIM\_id: 138253) and r NMDAR2B (GRIN2B, OMIM\_id: 138252) GRIN2A. Both GRIN2A and GRIN2B are expressed in the hippocampus and cerebral cortex\textsuperscript{(28)}. An NMDA is receptor is a glutamate-activated ion channel permeable to Na\(^+\), K\(^+\), and Ca \((2+)\) found at the excitatory synapses throughout the brain\textsuperscript{(29)}. Stimulation of synaptic NMDA receptors led to anti-apoptotic activity, whereas extrasynaptic NMDA receptors stimulation, on the other hand, caused loss of mitochondrial membrane potential (glutamate-induced neuronal damage marker) and cell death\textsuperscript{(30)}. GRIN2A encoded proteins of the memory formation signaling cascade important for human memory function\textsuperscript{(31)}. Deletions of GRIN2Agene were associated to early-onset focal epilepsy, severe intellectual disability, and lack of speech or delayed speech development\textsuperscript{(32)}. GRIN2B mutations, however, were mainly associated with reading dysfunction\textsuperscript{(33)}, severe intellectual disability, hypotonia, no speech, myopia, facial dysmorphism, inguinal hernia, and dislocated hips\textsuperscript{(34)}.

\textbf{Genes related to Reading (Dyslexia genes)}\n
Reading is a language-related human capacity that also involves a number of genes. Its development is inevitably dependent on language and learning abilities. Thus, many studies have found associations between language and reading genes in several speech impairment disorders.

\textbf{DYX1C1}\n
DYNEIN, AXONEMAL, ASSEMBLY FACTOR 4 (OMIM\_id 608706) gene, encodes for a cytoplasmic axonemal dynein assembly
factor involved in the cytoskeletal structure integrity of neurons\textsuperscript{43}. Translocations in the \textit{DYX1C1} gene was mainly related to dyslexia \textsuperscript{44} with a breakpoint occurring within a TPR domain-coding region of the gene disrupting the protein function. Two SNPs were identified, a -3A allele of a -3G-A SNP (OMIM\_id: 608706.0001) and 1249G-T transversion (OMIM\_id: 608706.0002), introducing a premature stop codon and truncating the predicted protein by 4 amino acids\textsuperscript{35}.

| Biological Function                                      | GO annotation | Genes                      |
|---------------------------------------------------------|---------------|----------------------------|
| Vocal learning, innate verbalization and vocal behavior  | GO:0042297    | FOXp2, CNTNAP2             |
|                                                         | GO:0098582    | FOXp2                      |
|                                                         | GO:0071625    | CNTNAP2                    |
| Learning memory                                         | GO:0007611    | GRIN2A                     |
| Learning                                                | GO:0007612    |                            |
| Visual learning                                         | GO:008542     | GRIN2B, KIAA039, DYX1C1, RBFOX2 |
| Synaptogenesis                                           | GO:0051965    | SPRX2                      |
| CNS development                                          | GO:0007399    | KIAA0319, SEMA6D, DCDC2, ROBO1 |
| Axon extension                                           | GO:0048675    | AUTS2                      |
| Neuron migration                                         | GO:0001764    | KIAA0319, AUTS2, DCDC2     |
| Actin cytoskeleton reorganization                        | GO:0031532    | AUTS2                      |
| Regulation of transcription, DNA-templated              | GO:0006355    | ERC1                       |
| Regulation of transcription by RNA polymerase II         | GO:0006357    | NFLX1                      |
| Axon guidance                                           | GO:007411     | SEMA6D, ROBO1              |
| Cerebral cortex development                              | GO:0021987    | CNTNAP2                    |
| Thalamus development                                     | GO:0021794    |                            |
| Limbic system development                                | GO:0021761    |                            |
| Brain development                                        | GO:0007420    |                            |
| Cell adhesion                                           | GO:0007155    | CNTNAP2, ROBO1             |
| In utero embryonic development                           | GO:0001701    | CMIP                       |
| Calcium ion transport/cellular calcium ion homeostasis/calcium ion transmembrane transport | GO:0070588    | ATP2C2                     |

\textit{ROBO1} Roundabout Guidance Receptor 1 (MIM\_id: 602430), is a gene that encodes for a growth cone receptor for a midline repellent that acts as the gatekeeper controlling midline crossing \textsuperscript{45}. A translocation in the \textit{ROBO1} gene, t (3;8) (p12;q11) that disrupted intron 1 of the \textit{ROBO1} gene, was reported in a patient with dyslexia Linkage to chromosome 3 in addition to
segregation with a specific SNP haplotype\(^{36,37}\).

**DCDC2**

Doublecortin Domain-Containing Protein 2 (OMIM\_id: 605755), another gene related to reading ability. It encodes for a ciliary protein highly expressed in the entorhinal cortex, inferior temporal cortex, hypothalamus medial temporal cortex, amygdala, and hippocampus\(^{38}\). DCDC2 enhances microtubule polymerization through binding to tubulin. RNA interference of DCDC2 resulted in altered neuronal migration, in rat embryos. Certain alleles (BV677278 alleles) were found to modify DCDC2 expression to various degrees, thus may link to changes in neural migration in the central nervous system. Several studies have identified a correlation between the DCDC2 gene and susceptibility to dyslexia with an adverse effect on the modulation of neurodevelopment\(^{39}\).

**KIAA0319**

The KIAA0319 gene encodes a plasma membrane protein with a glycosylated, extracellular domain, expressed the developing neocortex, ganglionic eminence, CP, and VZ. This protein plays a role in adhesion, attachment, neuronal migration in the developing brain with a significant role in intra- and extracellular signaling\(^{40}\). In individuals with dyslexia, the first 4 exons of KIAA0319 and a 77-kb region on chromosome 6p22.2 spanning the TTRAP gene (OMIM\_id: 605764) showed association with dyslexia in addition to a 1-1-2 haplotype comprised rs4504469, rs2038137, and rs2143340, was also reported\(^{41,42}\).

**Genes related to Brain Processing**

In addition to the above mentioned genes, other important genes have been implicated in brain processes including calcium homeostasis (ATP2C2), embryonic development (CMIP), regulation of transcription by RNA polymerase II (NFLX1, ERc1), synaptogenesis (SPRX2), SETBP1 and SEMA6D\(^{1,43,44}\).

**ATP2C2**

(ATPase, Ca\(^{2+}\)-transporting, type 2c, member 2, (OMIM\_id:613082) is an ATPase that transports Ca (\(^{2+}\)) and Mn (\(^{2+}\)) into the Golgi lumen for protein sorting, processing, and glycosylation. It is also involved in Ca (\(^{2+}\)) signaling, independent of its ATPase activity\(^{10}\).

**CMIP:** C-MAF-Inducing Protein (OMIM\_id: 610112) is one of the largest proteins expressed in the brain especially in subthalamic nucleus and amygdala. A significant association was found between non-word repetition, which is a measure of phonologic short-term memory, and SNPs in the CMIP gene (rs6564903) and rs11860694 in the ATP2C2 gene. Both genes are located in the SL1\_1 region on chromosome 16q. When combined with other susceptibility factors, variants in CMIP and ATP2C2 can modulate phonologic short-term memory\(^{11}\).

**NFXL1**

Nuclear transcription factor, X-box binding like 1, a novel protein, identified by exon sequencing\(^{11}\), that encodes for a protein that is predicted to be a transcription factor based on domain similarities with NFX1, a repressor of HLA class II genes, implicated in specific language impairment. It shows variable spatial expression; in the brain, a high expression level was found the cerebellar hemisphere and the cerebellum, two regions implicated in some language-related pathologies. NFXL1 did not show nuclear localization, suggest
ing that, if it regulates transcription, certain conditions may be required for it to translocate to the nucleus\(^{(45)}\).

**ERC1**

Elks/Rab6-Interacting/Cast Family, Member 1, a fusion of RET with ELKS would cause the kinase domain of RET to be expressed inappropriately in thyroid cancer tissue ELKS is a critical component of DNA damage-induced pathways especially NF-kappa-B activation. A recent study has shown a correlation between this gene and childhood apraxia\(^{(46)}\).

**SETBP1**

SET-Binding Protein 1 (OMIM id: 611060). The SETBP1 gene encodes for the SET binding protein 1, which is widely distributed throughout somatic cells. The SETBP1 protein binds mainly to the promoter regions of genes. It is highly expressed during the brain development especially before birth. SETBP1 protein is thought to control genes that are involved in these developmental processes. SETBP1 is related to Schinzel-Giedion syndrome through gain-of-function mutations in contrast to the SETBP1 disorder which is a loss-of-function consequence for mutations in SETBP1. The SETBP1 disorder or Mental Retardation, Autosomal Dominant is a condition that involves speech and expressive language problems, distinctive facial features, and intellectual disability. Speech development is limited to a few words or no speech. With affected individuals using gestures or mimicking the expressions of others for communicating \(^{(47)}\). Intellectual disability in individuals with SETBP1 disorder ranges from mild to moderate. They may also have behavioral problems, such as autistic behaviors, attention-deficit/hyperactivity disorder (ADHD) that affect communication and social interaction. Affected individuals may have delayed development of motor skills, weak muscle tone (hypotonia); or recurrent seizures (epilepsy). Multiple variants with variable phenotypes were reported\(^{(48)}\).

**SEMA6D**

Semaphorin 6D is a protein in in brain and spinal cord that is responsible for growth cone collapse. It is mainly involved in synaptogenesis. It belongs to semaphorins, a group of receptors predominantly modulated in dyspraxia and SLI\(^{(49)}\).

**Non-synonymous Variants in SLI**

Language acquisition is a complex process that is unlikely related to a single gene. It is an orchestrating interaction between language genes expression, epigenetic and environmental factors\(^{(50,51)}\). Language genes can show genetic variation that influence the neurophysiology of the brain and subsequently affect how people respond differently to the environmental language input. Added to this, language phenotypes are associated with some genes influencing a range of cognitive abilities\(^{(52)}\). Understanding the function and the type of gene variation would influence decisions of medical intervention in terms of modulating epigenetics and neurotransmitter regulation in addition to effective teaching methods that aid in effective language acquisition. Some genetic variants in FOXP2 are known to cause language disorders\(^{(53)}\). Single nucleotide polymorphism (SNP) of FOXP2, rs6980093, in addition to intragenic deletions were observed to be related to both language and reading traits with increased risk to developing CAS\(^{(54,55)}\). Variation in these genes influences the reading ability. For instance, two haplotypes and six SNPs of DCDC2, namely rs807724, rs2274305, rs4599626, rs9467075, rs6456593 and rs6922023, were found to be associated with developmental dyslexia among Chinese Uyghur
children. CNTNAP2 is linked to language in ASD-affected individuals, at SNP rs17236239. Many genes have been identified to correlate with SLI either alone or in association with other neuropsychiatric disorders like dyslexia, attention deficit hyperactivity disorder (ADHD) or autistic spectrum disorder (ASD). However, since SLI is diagnosed in an otherwise normal child, non-synonymous are more prevalent than other variants, especially structural ones (Table 2).

### Table 2: Non-Synonymous variants genes candidates identified in SLI studies

| Chromosome | Location | SNP | Ref | Alt | Gene |
|------------|----------|-----|-----|-----|------|
| 1          | 326,804,49 | Novel | C   | G   | DCDC2 |
| 1          | 359,404,97 | Novel | T   | G   | KIAA0319 |
| 3          | 710,269,82 | Novel | A   | T   | FOXP1 |
| 3          | 787,665,24 | rs800,303,97 | A   | G   | ROBO1 |
| 7          | 111,503,51 | Novel | G   | T   | DOCK4 |
| 7          | 111,503,51 | Novel | T   | G   | DOCK4 |
| 7          | 111,541,82 | Novel | T   | C   | DOCK4 |
| 7          | 148,080,91 | rs368,057,493b | C   | T   | CNTNAP2 |
| 7          | 111,580,16 | Novel | T   | C   | DOCK4 |
| 7          | 111,629,21 | Novel | G   | A   | DOCK4 |
| 7          | 69,364,31 | rs142,957,106 | C   | T   | AUTS2 |
| 12         | 113,707,2 | Novel | G   | A   | ERC1 |
| 12         | 137,158,65 | Novel | C   | G   | GRIN2B |
| 15         | 480,633,65 | Novel | C   | G   | SEMA6D |
| 16         | 844,388,27 | rs788,872,88 | G   | A   | ATP2C2 |
| 16         | 991,622,6 | Novel | C   | G   | GRIN2A |
| X          | 999,222,89 | rs121,918,363 | A   | G   | SRPX2 |

Since mostly, SLI children have no underlying psychological or emotional disturbances, behavioral therapy or psychological therapy will not be the best options for them. Additionally, the one-to-one speech therapy sessions along with cognitive ones, would still need to be supported by more potent interventions that can successfully target either the molecular pathways affected, or the genes mutated. New directions are evolving in the Genome editing. This includes not only the insertion, deletion, or replacement of nucleotides, but also the modulation of gene expression and epigenetic editing. Emerging technologies like CRISPR/Cas systems and others have extended genome manipulation boundaries and promoted genome editing techniques to the level of promising strategies for counteracting genetic diseases. Although spatial and temporal editing of gene expression through non-viral and viral approaches of mammalian brain in vivo is achievable, error-prone mechanisms remain dominant after CRISPR/Cas9 execution. One

### SLI Gene-treatment options

Knowing the causal pathways may provide more specific information to guide gene-treatment decisions, in ways similar to current personalized medicine approaches. Identifying genes related to SLI and possible genetic variants is crucial in identifying various and novel personalized intervention modalities. Also, controlling epigenetic factors like nutrition is crucial for maintaining an intact program of treatment.

(20) Eldesouki RE (2021) An update on the role of CRISPR/Cas9 in personalized medicine. J Genet Genomics 48(4):243-250.
documented reason was the difficulty of post-mitotic neurons to utilize the HDR mechanism efficiently for gene of interest replacement integration. Therefore, new alternatives to ensure therapeutic potential in non-dividing are required. An example for such modalities is the homology-independent targeted integration HITI\(^{(64)}\). On the other hand, a new wave of non-viral delivery systems is approaching. Coupling with stable ribonucleoproteins complexes of Cas9 (RNP complexes) will allow remarkably novel ways to treat neurological disorders without the need for such invasive procedures. Cas9 RNP delivery may be used to target neuroinflammatory processes and neurodegenerative diseases\(^{(65)}\).

**Conclusion**

Multiple genes involved in speech and language have been reported with interacting molecular pathways being identified. Monogenic and polygenic affection was also reported; inherited or syndromic. Identifying genes may be useful for an early diagnosis, predicting the disease progression or designing personalized management options taking into consideration the epigenetic factors.

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