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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, FOXP2, ATP2C2, CMIP, CNTNAP2, DCDC2, KIAA0319, DYX1C1, SRPX2, NFXL1, 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[(1)]. 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)[(2,3)]. 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 [(4)]. With the wide range of SLI phenotypes, consolidated research in this area is a crucial need. Family studies along with twin

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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 the light on specific gene, previously identified in SLI families and correlate the non-synonymous 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]. Intruingly, 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:0098582), vocalization behavior (GO:0071625), 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[21]. 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 [22]. Additionally, knockouts of FOXP2 gene results showed impaired vocalization, shortened syllabus and ar-

rhythmic vocalizations' structure[23]. It was found that FOXP2 mutations were not directly involved or associated with neurodevelopmental disorders, such as SLI, ASD or dyslexia[24] yet a mutation in the FOXP2 gene caused a monogenic speech and language disorder (MIM_id:602081)[25]. Hence, FOXP2 is suggested to be mainly involved in language production but does not directly regulate language abilities altogether.

FOXP2 related genes-CNTNAP2

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[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[25]. CNTNAP2 polymorphisms were mainly associated with significant quantitative associations with nonsense-word repetition (SLI4, MIM_id: 612514). The region containing these polymorphisms was also associated with language delays in children with autism, as described [26]. Other than CNTNAP2, other FOXP2 downstream transcription factors were found to be affected [27].

Genes related to Memory

GRIN2A

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 NMD AR2B (GRIN2B, OMIM_id: 138252) GRIN2A. Both GRIN2A and GRIN2B are expressed in the hippocampus and cerebral cortex[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[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 [30]. GRIN2A encoded proteins of the memory formation signaling cascade important for human memory function [31]. Deletions of GRIN2Agene were associated to early-onset focal epilepsy, severe intellectual disability, and lack of speech or delayed speech development[32]. GRIN2B mutations, however, were mainly associated with reading dysfunction [33], severe intellectual disability, hypotonia, no speech, myopia, facial dysmorphism, inguinal hernia, and dislocated hips[34].

Genes related to Reading (Dyslexia genes)

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.

DYX1C1

DYNEIN, AXONEMAL, ASSEMBLY FACTOR 4 (OMIM_id 608706) gene, encodes for a cytoplasmic axonemal dynein assembly

factor involved in the cytoskeletal structe integrity of neurons43. Translocations in the DYX1C1 gene was mainly related to dyslexia 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[35]

Table 1: A list of the biological functions of reported SLI genes and their GOs.

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:0008542	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 NFLX1
Regulation of transcription by RNA polymerase II	GO:0006357	
Axon guidance	GO:0007411	SEMA6D, ROBO1
Cerebral cortex development	GO:0021987	CNTNAP2
Thalamus development	GO:0021794	CNTNAP2
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

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 45. A translocation in the ROBO1 gene, t (3;8) (p12;q11) that disrupted intron 1 of the 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, hypothalamusmedial 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, Ca2+-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 expressed in the brain especially in 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 SLI1 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 might 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 tha is responsible for growth cone collapse. It is mainly involved in synaptogenesis. It belongs to semaphorins, a goup 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 in turn 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[20]. 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)[56,57]. However, since SLI is diagnosed in an otherwise normal child, non-synonymous are more prevalent than other variants, especially structural ones (Table 2).

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 [58]. 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 [59, 60].

Table 2: Non-Synonymous variants genes candidates identified in SLI studies [20]

Chromosome	*Location*	*SNP*	*Ref*	*Alt*	*Gene*
1	32680449	Novel	C	G	DCDC2
1	35940497	Novel	T	G	KIAA0319
3	71026982	Novel	A	T	FOXP1
3	78766524	rs80030397	A	G	ROBO1
7	111503514	Novel	G	T	DOCK4
7	111503515	Novel	T	G	DOCK4
7	111541828	Novel	T	C	DOCK4
7	148080918	rs368057493b	C	T	CNTNAP2
7	111580166	Novel	T	C	DOCK4
7	111629218	Novel	G	A	DOCK4
7	69364311	rs142957106	C	T	AUTS2
12	1137072	Novel	G	A	ERC1
12	13715865	Novel	C	G	GRIN2B
15	48063365	Novel	C	G	SEMA6D
16	84438827	rs78887288	G	A	ATP2C2
16	9916226	Novel	C	G	GRIN2A
X	99922289	rs121918363	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[61]. 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 [62]. 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 [63]. One

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.

References

1. Newbury DF, Fisher SE & Monaco AP. Recent advances in the genetics of language impairment. Genome Med2010; 2, 6.
2. Leonard LB. Language Learnability and Specific Language Impairment in Children. Appl. Psycholinguist. 1989; 10, 179–202
3. Tomblin JB, Records NL, Buckwalter P et al. Prevalence of Specific Language Impairment in Kindergarten Children. J. Speech Lang. Hear. Res. 1997; 40, 1245–1260.
4. Parviainen T, Helenius P, Salmelin R. Cortical Differentiation of Speech and Nonspeech Sounds at 100 ms: Implications for Dyslexia. Cereb. Cortex 2005; 15, 1054–1063.
5. Ghandour H, Eldin SK, Sallam Y, Mahmoud S. Associated comorbidities of specific language impairment. Benha Med J 2018; 35:115-21
6. Joanisse MF. Specific Language Impairments in children phonology, semantics, and the English past tense. Current Directions in Psychological *Science*. 2004; 13:156–160.
7. Bishop DV. Grammatical errors in specific language impairment: Competence or performance limitations? Applied Psycholinguistics. 1994; 15:507–550.
8. Leonard LB. Children with specific language impairment and their contribution to the study of language development. J Child Lang. 2014;41 Suppl 1(0 1):38-47.
9. Thomas P.D. The Gene Ontology and the Meaning of Biological Function. In: Dessimoz C, Škunca N (eds) The Gene Ontology Handbook. Methods in Molecular Biology, vol 1446. Humana Press, NY, 2017.
10. Newbury, D. F. et al. CMIP and ATP2C2 modulate phonological short-term memory in language impairment. Am J Hum Genet 2009(85); 264–272.
11. Villanueva P, Nudel R, Hoischen A et al. Exome Sequencing in an Admixed Isolated Population Indicates NFXL1 Variants Confer a Risk for Specific Language Impairment. PLoS Genet 2015;11(3):e1004925
12. Fisher SE & Scharff C. FOXP2 as a molecular window into speech and language. Trends Genet 2009; 25, 166–177
13. Bacon C & Rappold GA. The distinct and overlapping phenotypic spectra of FOXP1 and FOXP2 in cognitive disorders. Hum Genet 2012;131, 1687–1698.
14. 14.Roll P, Rudolf G, Pereira S, et al. SRPX2 mutations in disorders of lan-

guage cortex and cognition. Hum Mol Genet 2006; 15, 1195–1207.
15. Lesca G, Rudolf G, Bruneau N, et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. Nat Genet 2013; 45, 1061–1066.
16. 16.Carrion-Castillo A, Franke B & Fisher SE. Molecular genetics of dyslexia: an overview. Dyslexia 2013; 19, 214–240.
17. Ocklenburg S, Arning L, Hahn C, et al. Variation in the NMDA receptor 2B subunit gene GRIN2B is associated with differential language lateralization. Behav Brain Res 2011; 225, 284–289.
18. Thevenon J, Callier P, Andrieux J et al. 12p13.33 microdeletion including ELKS/ERC1, a new locus associated with childhood apraxia of speech. Eur J Hum Genet 2013; 21, 82–88.
19. Filges I, Shimojima K, Okamoto N, et al. Reduced expression by SETBP1 haploinsufficiency causes developmental and expressive language delay indicating a phenotype distinct from Schinzel-Giedion syndrome. J Med Genet 2011; 48, 117–122.
20. Chen X, Reader R, Hoischen A. et al. Next-generation DNA sequencing identifies novel gene variants and pathways involved in specific language impairment. Sci Rep 2017; 7, 46105.
21. Spiteri, E, Konopka G, Coppola G, Bomar J, et al. Identification of the transcriptional targets of FOXP2, a gene linked to speech and language, in developing human brain. Am. J. Hum. Genet. 2007; 81: 1144-1157,
22. O'Brien EK, Zhang X, Nishimura C, Tomblin JB, Murray JC. Association of specific language impairment (SLI) to the region of 7q31**.** Am. J. Hum. Genet. 2003; 72: 1536-1543.
23. Castellucci G, McGinley M & McCormick D. Knockout of *Foxp2* disrupts vocal development in mice. Sci Rep 2016; 6, 23305.
24. Harlaar N, Meaburn EL, Hayiou-Thomas ME, et al. Genome-wide association study of receptive language ability of 12-year-olds. J Speech Lang Hear Res. 2014; 57(1):96-105.
25. Ernes SC, Newbury DF, Abrahams BS, et al. A functional genetic link between distinct developmental language disorders**.** New Eng. J. Med. 2008; 359: 2337-2345.
26. Arking DE, Cutler DJ, Brune CW, et al. A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. Am. J. Hum. Genet. 2008; 82: 160-164,
27. Mendoza E and Scharff C. Protein-Protein Interaction Among the FoxP Family Members and their Regulation of Two Target Genes, VLDLR and CNTNAP2 in the Zebra Finch Song System. Front. Mol. Neurosci. 2017; 10:112.
28. Chen N, Luo T, Raymond LA. Subtype-dependence of NMDA receptor channel open probability**.** J. Neurosci. 1999;19: 6844-6854.
29. Matta JA, Ashby MC, Sanz-Clemente A, Roche KW, Isaac JTR. mGluR5 and NMDA receptors drive the experience- and activity-dependent NMDA receptor NR2B to NR2A subunit switch**.** Neuron 2011; 70: 339-351.
30. Gielen M, Retchless BS, Mony L, Johnson JW, Paoletti P. Mechanism of differential control of NMDA receptor activity by NR2 subunits**.** Nature 2009; 459: 703-707.
31. de Quervain DJ, Papassotiropoulos A. Identification of a genetic cluster influencing memory performance and hippocampal activity in humans**.** Proc. Nat. Acad. Sci. 2006; 103: 4270-4274.
32. Reutlinger C, Helbig I, Gawelczyk B, et al. Deletions in 16p13 including GRIN2A in patients with intellectual disability, various dysmorphic features, and seizure disorders of the rolandic region**.** Epilepsia 2010; 51: 1870-1873.
33. Endele S, Rosenberger G, Geider K, et al. Mutations in GRIN2A and GRIN2B encoding regulatory subunits of

NMDA receptors cause variable neurodevelopmental phenotypes. Nat Genet. 2010; 42(11):1021-6.
34. de Ligt J, Willemsen MH, van Bon B. et al. Diagnostic exome sequencing in persons with severe intellectual disability. New Eng. J. Med. 2012; 367: 1921-1929 .
35. Tarkar A, Loges NT, Slagle CE, et al. DYX1C1is required for axonemal dynein assembly and ciliary motility. Nature Genet. 2013; 45: 995-1003.
36. Kidd T, Brose K, Mitchell KJ, Fetter RD, Tessier-Lavigne M, Goodman CS, Tear G. Roundabout controls axon crossing of the CNS midline and defines a novel subfamily of evolutionarily conserved guidance receptors**.** Cell 1998; 92: 205-215.
37. Hannula-Jouppi K, Kaminen-Ahola N, Taipale M, Eklund R, Nopola-Hemmi J, Kaariainen H, Kere J. The axon guidance receptor gene ROBO1 is a candidate gene for developmental dyslexia**.** PloS Genet 2005; 1: e50, Note: Electronic Article.
38. 38.MengH, Smith SD, Hager K etal. DCDC2 is associated with reading disability and modulates neuronal development in the brain**.** Proc. Nat. Acad. Sci. 2005; 102(47):17053-8
39. Girard M, Bizet AA, Lachaux A, et al. DCDC2 mutations cause neonatal sclerosing cholangitis**.** Hum. Mutat. 2016; 37: 1025-1029.
40. Paracchini S, Thomas A, Castro S, Lai C, et al. The chromosome 6p22 haplotype associated with dyslexia reduces the expression of KIAA0319 a novel gene involved in neuronal migration. Hum. Molec. Genet. 2006;15: 1659-1666.
41. Francks C, Paracchini S, Smith SD, et al. A 77-kilobase region of chromosome 6p22.2 is associated with dyslexia in families from the United Kingdom and from the United States. Am. J. Hum. Genet. 2004;75: 1046-1058,
42. Cope N, Harold D, Hill G, et al. Strong evidence that KIAA0319 on chromosome 6p is a susceptibility gene for developmental dyslexia. Am. J. Hum. Genet. 2005;76: 581-591.
43. Carrion-Castillo A, Franke B & Fisher SE. Molecular genetics of dyslexia: an overview. Dyslexia 2013; 19, 214–240
44. Mozzi A, Forni, D, Clerici M. et al. The evolutionary history of genes involved in spoken and written language: beyond FOXP2. Sci Rep 2016; 6, 22157
45. Nudel, R. An investigation of NFXL1, a gene implicated in a study of specific language impairment. J Neurodevelop Disord 2016; 8, 13.
46. Wu Z-H, Shi Y, Tibbetts RS, Miyamoto S. Molecular linkage between the kinase ATM and NF-kappaB signaling in response to genotoxic stimuli**.** Science 2006; 311: 1141-1146,
47. Hoischen A, van Bon BW M, Gilissen C, et al. De novo mutations of SEPTBP1 cause Schinzel-Giedion syndrome. Nature Genet. 2010; 42: 483-485.
48. Coe BP, Witherspoon K, Rosenfeld JA, et al. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nature Genet. 2014; 46: 1063-1071,.
49. Qu X, Wei H, Zhai Y, et al. Identification, characterization, and functional study of the two novel human members of the semaphorin gene family**.** J. Biol. Chem. 2002; 277: 35574-35585.
50. Sriganesh R, Joseph Ponniah R. Genetics of language and its implications on language interventions. J Genet. 2018 97(5):1485-1491.
51. Huang B, Jiang C, Zhang R. Epigenetics: the language of the cell? Epigenomics. 2014; 6(1):73-88.
52. Kovas Y, Plomin R. Generalist genes: implications for the cognitive sciences, Trends in cognitive sciences 10.2006; 198–203.
53. Estruch SB, Graham SA, Chinnappa SM, Deriziotis P and Fisher SE. Functional characterization of rare FOXP2 variants in neurodevelopmental disorder. J. Neurodev Disord. 2016; 8, 44.
54. Chandrasekaran B, Yi HG, Blanco NJ,

McGeary J E and Maddox W T. Enhanced procedural learning of speech sound categories in a genetic variant of FOXP2. J. Neurosci. 2015; 35, 7808–7812.
55. Mozzi A, Riva V, Forni D, et al. common genetic variant in FOXP2 is associated with language-based learning (dis)abilities: evidence from two Italian independent samples. Am. J. Med. Genet. Part B 2017; 174, 578–586
56. Chen Y, Zhao H, Zhang YX and Zuo PX. DCDC2 gene polymorphisms are associated with developmental dyslexia in Chinese Uyghur children. Neural Regener. Res. 2017; 12, 259–266.
57. Vernes SC, Newbury DF, Abrahams BS, et al. A functional genetic link between distinct developmental language disorders. N. Engl. J. Med. 2008; 359, 2337–2345.
58. Rice ML. Children with Specific Language Impairment and Their Families: A Future View of Nature Plus Nurture and New Technologies for Comprehensive Language Intervention Strategies. Semin Speech Lang. 2016; 37(4):310-318.
59. Rice ML. Language growth and genetics of specific language impairment. Int J Speech Lang Pathol. 2013;15(3):223-233.
60. Bjornsson HT, Fallin MD, Feinberg AP. An integrated epigenetic and genetic approach to common human disease. Trends Genet. 2004; 20(8):350-8.
61. den Hoed J, Fisher SE. Genetic pathways involved in human speech disorders. Curr Opin Genet Dev. 2020; 65:103-111.
62. Duarte F, Déglon N. Genome Editing for CNS Disorders. Front Neurosci. 2020;14: 579062.
63. Suzuki K, Tsunekawa Y, Hernandez-Benitez R, Wu J, Zhu J, Kim E J, et al. *In vivo* genome editing *via* CRISPR/Cas9 mediated homology-independent targeted integration. Nature 2016; 540, 144–149.
64. Cota-Coronado A, Díaz-Martínez NF, Padilla-Camberos E, Díaz-Martínez NE. Editing the Central Nervous System Through CRISPR/Cas9 Systems. Front Mol Neurosci. 2019; 12: 110.
65. Campbell LA, Richie CT, Maggirwar NS, Harvey BK. Cas9 Ribonucleoprotein Complex Delivery: Methods and Applications for Neuroinflammation. J Neuroimmune Pharmacol. 2019; 14(4): 565-577.