Genomics of speech and language disorders

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Abstract
Multiple factors involve speech and language. Investigating animal models, mainly through songbirds, has allowed a better understanding of the verbal communication process. Speech disorders, such as childhood apraxia of speech, dysarthria or stuttering, along with language disorders, like aphasia, dyslexia or developmental language disorder are the main examples. More complex syndromes such as Autism-spectrum disorders, Down’s syndrome or Fragile X syndrome have more variable features. Genetic factors, such as hereditary or de novo mutations may influence the development of all of these conditions. Besides, most of speech and language disorders are implicated in neurodevelopment with molecular mechanisms and pathways that interact with each other, and there may be co-morbidity with other communication disorders or phenotypes unrelated to communication. Genes with heterogeneous functions in speech and language such as FOXP1, FOXP2, KIAA0319, ROBO1, APOE or CNTNAP2 are some examples. Epigenetic factors, especially microRNAs, influence the expressiveness. The genomics of these disorders allows us to understand language acquisition, carry out early detection strategies, genetic counseling and optimize future treatments, not only in communication disorders but also the neurological alterations that incorporate these mutations.

Keywords: Genomics, epigenetic, speech, language, dysarthria, stuttering, aphasia, FOXP2

INTRODUCTION
The language process requires three structures of the central nervous system: cortex, basal ganglia, and cerebellum [1]. The primary language pathway begins at Wernicke’s area, in the posterior temporal lobe. This pathway collects information from the visual and auditory cortex and it is responsible for understanding
language. The arcuate fasciculus connects Wernicke’s to Broca’s area, in the inferior-posterior frontal lobe. This area generates language and starts the muscular activity involved in speech. The second language pathway drives through the angular and supramarginal gyrus, region located in the posterior parietal lobe, and connects with Broca’s and Wernicke’s areas. Syntax-related networks are located in the opercular/triangular parts of the left inferior frontal gyrus and lateral premotor cortex. The basal ganglia are involved in prosodic modulation and language acquisition, and are responsible for language learning in adults. Finally, the cerebellum is also required in the processing of expressive and receptive language, and writing skills.

Sometimes, the causes of speech and language disorders (SLD) are acquired (due to stroke or trauma). The characteristics will depend on the damaged nerve structures and the degree of involvement. However, genetic factors involve various pathologies that may associate SLD [5,6] [Table 1]. Genetic factors associated with language contribute to various molecular, cellular and regulatory processes that shape neuronal architecture through neuronal migration, axon guidance, brain network development including connectivity and determine neurodevelopmental characteristics [5]. The same gene may be linked to different disorders, showing the great complexity of the speech and language process [6]. Also, language disabilities in children may appear along with other developmental diagnoses, such as intellectual impairments, hearing loss, and syndromes such as autism spectrum disorders (ASD), Down’s and Fragile X syndromes. The construction of a knowledge base for genetic etiology makes it possible to identify patients with genetic risk and motivate early intervention programmes [6]. In addition, it is mandatory to identify those epigenetic factors that characterize language and speech [9,10].

Because genomic knowledge of these disorders is limited, the aim of this review is to allow a rational classification of the main causes of both early and late-onset speech and language disorders and characterize their genomic and epigenetic background. Based on the definitions of each case, the genes involved in each language and speech phenotype will be described. We will observe the complex network of genetic pathways involving different disorders, and note how these disorders have important limitations due to lack of replication or information. Finally, we will attempt to demonstrate briefly the importance of these disorders as part of other more complex pathologies and how the knowledge of these genes may be useful as markers of early diagnosis and prognosis.

GENOMICS OF SPEECH DISORDERS

Dysarthria

Dysarthria is a motor speech disorder that causes poor coordination of the articulation with pharyngeal, laryngeal, lingual or facial muscle involvement. This condition is due to alterations that affect the cranial nerves, neuromuscular, cerebellar, basal ganglia or cortical-bulbar tract diseases, while it preserves the cortical function of speech [11]. Dysarthria is divided into six groups: flaccid, ataxia, spastic, hypokinetic, hyperkinetic and mixed [12] [Table 2]. Little is known about the role of dysarthria in different neurological pathologies, so we will focus on some of the genes that have been identified so far, their phenotypic characteristics and their potential applications.

Flaccid dysarthria

Flaccid dysarthria relates to disorders of the lower motor neuron system and/or muscle. It generates continuous expiratory speech, diplophonia, and hypernasality [12]. Myasthenia gravis, amyotrophic lateral sclerosis, or Prader-Willi syndrome are examples of flaccid dysarthria [13].

Myasthenia gravis: Myasthenia gravis (MG) is an autoimmune disorder, caused by antibody formation at the neuromuscular junction. CHRNA1 gene encodes the alpha subunit of the acetylcholine receptor,
<table>
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<tr>
<th>Gene</th>
<th>Name</th>
<th>Locus</th>
<th>Disorder</th>
<th>Methods</th>
<th>Comments</th>
<th>Other phenotypes</th>
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<td>CG</td>
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[154] [88] [130] [88] [129] [166] [166] [100] [165] [109] [190] [126]
the main target of the antibodies (Abs). Other Abs may also modify the clinical expression of the disease, such as Abs against muscle-specific tyrosine kinase (MuSK)\textsuperscript{14}. A low percentage of genetic cases relate to other immune disorders\textsuperscript{15}. Twin studies have shown that the concordance of MG is significantly higher in monozygotic compared to dizygotic twins. Several HLAs have been identified (HLA-A1,B8,DR3 haplotype for myasthenia gravis of early-onset and HLA-A3,B7,DR2 and HLA-DR4 for late-onset), as well as other non-HLA genes, as functional polymorphisms in the promoter of IL-10, haplotypes with TPN22, CTLA-4, TNIP1 and FOXP3\textsuperscript{14,16}. MuSK Ab-positive patients may associate with HLA-DR14 and DQ5\textsuperscript{14}.

Prominent bulbar symptoms with dysarthria are common in patients with ab-MusK. MusK is necessary for neuromuscular synapses to organize post-synaptic differentiation, including the clustering of receptors for the acetylcholine neurotransmitter. Anti-MusK autoantibodies are found in those seronegative patients. Although losing acetylcholine receptor function produces an autoimmune alteration, phenotypic particularities differentiate it from the classic MG. Thus, patients have a lower prevalence of ocular manifestations and greater weakness of neck and oropharynx. It tends to affect women and African-Americans to a greater degree\textsuperscript{14,17}.

Other relevant conditions with flaccid dysarthria: Because amyotrophic lateral sclerosis (ALS) affects both upper and lower motor neurons, the resulting dysarthria is mixed, (flaccid/spastic type). The initial symptoms include an alteration in the pattern and rhythm of speech, until it evolves into an unintelligible voice. As ALS progresses and dysarthria becomes severe, deep weakness resulting in reduced movement of the speech musculature and a severe reduction in phonation become increasingly common. However, an
<table>
<thead>
<tr>
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early speech therapy intervention improves the patient’s ability to communicate. Concerning Prader Willi syndrome, anatomical alterations in the mouth and larynx, and the underlying brain dysfunction, contribute to alterations in speech and language. Oral motor function, tone level and resonance are altered, with a characteristic flaccid pattern. A summary of the main genes involved in both conditions are included in Table 2.

Ataxic dysarthria
Ataxic dysarthria relates to disorders that alter the cerebellar pathway. It is characterized by interruptions in the articulation of speech, irregularity in the intensity of the tone and marked vocal tension. This group includes hereditary ataxia. So far, reports have identified over 30 genotypes. Hereditary ataxia may be progressive, such as spinocerebellar ataxia (SCA) and Friedreich’s ataxia (FRDA), or sporadic, such as episodic ataxia (EA). SPAX also refers to those ataxias that often have a prominent component of spasticity, thus changing the patient’s dysarthric characteristics.

Trinucleotide expansion diseases relate to some hereditary ataxias, with mutations where repetitions of trinucleotides in certain genes or introns exceed the normal stable threshold that differs by gene, by unstable microsatellites that occur throughout all genomic sequences. This is the case of SCA1-7 and SCA17, where the repeated codon is CAG, which is the coding region for glutamine (Q), resulting in a polyglutamine (polyQ) tract. FRDA, SCA8, and SCA12 are other examples, but they do not code for glutamine and categorize as non-PolyQ diseases.

For those patients in whom the genetic screening tests for SCA1, 2, 3, 6, 7, and FRDA are negative (The most frequent ataxias), the study of small pathogenic intragenic variants for PRKCG, TTBK2, SETX, SPTBN2, SACS, MRE11, KCNC3 and DARS2 might be useful, as these are more prevalent secondary groups. It is especially helpful in patients with progressive onset disorders in childhood or adolescence and/or with a family history. Several studies assessed the phenotypic particularities of disorders that generate ataxic dysarthria. Clinical characterization of the voice helps to discriminate between different types of ataxia and guides vocal therapy.

Friedreich ataxia (FRDA): Friedreich ataxia (FRDA gene, locus 9q21.11) is the most common progressive hereditary ataxia, with an autosomal recessive inheritance pattern. It produces degeneration, among other structures, of white matter cerebellar areas and afferent pathways of different brainstem nuclei. Speech
disturbances are usually less severe than in spinocerebellar ataxia and are almost exclusively due to cerebellar degeneration. No relationship between the severity of dysarthria and body ataxia exists. Some characteristic features of speech show a difficulty in maintaining a constant tone, with vocal instability during the speech or a reduction in the maximum speed of syllable repetition.

Spinocerebellar ataxia (SCA): SCA3 is the most common autosomal dominant ataxia worldwide, followed by SCA1, 2, 6 and 7. The phenotype of SCAs varies and can affect only the cerebellum or other brain structures. For example, SCA6 and SCA5 generate a pure cerebellar syndrome due to cortical ataxia, while SCA1 and SCA3 have a diffuse affection.

SCA1 (ATXN1 6p22.3) has a greater effect on voice dimensions. Rough and strangled voice are predictors of disease severity.

SCA3 (ATXN3 locus 14q32.12 gene) affects specifically the regularity of diadochokinetic syllable repetitions (DSR) if compared to the rest of hereditary ataxias. Also, the characteristics of the non-verbal oral motor deteriorate significantly in SCA3. The more widespread process of the brain and brain stem degeneration in SCA3 may compromise non-speech tasks, such as DSR to a greater degree than other ataxias.

SCA5 (SPTBN2 locus 11q13.2 gene) usually generates less dysarthric involvement than the rest of spinocerebellar ataxias. Unlike SCA1, only the strangled voice is a prognostic factor in the disease severity.

Articulatory speech disorders especially affect to patients with SCA6 (CACNA1A gene, locus 19p13.13). Speech parameter degradations (frequency and modulation) are worse at SCA6. The speech parameters in prosodic modulation are also particularly vulnerable. It is due to neurodegeneration in SCA6, which is largely (though not only) confined to the cerebellum. In contrast to many other types of SCA, cerebellar degeneration largely implicates the cerebellar cortex.

Regarding SCA7 (ATXN7 gene, locus 3p14.1), voice deterioration is unrelated to age at onset and the length of the cytosine-adenine-guanine triplet tract. Surprisingly, the results of the acoustic analysis (jitter and shimmer) correlate with Inventory of Non-Ataxia Symptoms, but not with Scale for the Evaluation and Rating of Ataxia scores, which implies that voice deterioration results from extra-cerebellar clinical manifestations. No other relevant studies that specifically assess the characteristics of dysarthria in other ataxic variants have been reported.

Spastic dysarthria
Spastic dysarthria is related to alterations in the upper motor neuron system. Unilateral involvement of the upper motor neuron is usually classified as a separate type. Patients have slow-moving speech, a tense voice and multiple breaks in pitch. Examples of spastic dysarthria are hereditary spastic paraplegias and other mixed expression disorders such as multiple sclerosis.

Multiple sclerosis (MS): Multiple sclerosis is a demyelinating condition of unknown etiology in which environmental and genetic factors are involved. It generates a spastic, ataxic or more frequently mixed (spastic-ataxic) dysarthria. Studies of dysarthria in MS show a prevalence ranging from 41% to 51%. The main speech disturbances are in volume control, rough voice quality and imprecise articulation. It may show cognitive deficits such as slowed information processing speed, impaired working memory and reduced information processing efficiency. It can also manifest as a subtle, non-phasic high-level language deficits. Assessment of dysarthria may be helpful in controlling clinical and progression of a subclinical disease.

A genetic susceptibility to the development of multiple sclerosis may exist, associated with certain HLA genes, including HLA-A, HLA-DRB1, HLA-DQB1, HLA-DQB1, HLA-DRA, on chromosome 6p21.3. Other haplotypes identified are HLA-DRB1* 1501-DQB1* 0602 (HLA-DR15). Additional MS susceptibility loci
include MS2 on chromosome 10p15, MS3 on chromosome 5p13, MS4 on chromosome 1p36 and MS5, influenced by the variation in the TNFRSF1A gene on chromosome 12p13. Several genes can modify the evolution of the disease. FN1 and CD24v/v are associated with an early-onset MS. MS3, MS4, and MS5 relate to the disease severity, with SNPs having an allelic dosing effect. PSMG4 encodes a chaperone protein implicated in the assembly of the 26S proteasome (a primary protein deletion pathway). The reduced activity of proteasome 26S has proved to cause neuronal death from abnormal protein degradation. Proteasome 26S hydrolyzes the basic myelin protein to produce antigenic peptides for presentation to T-cells. CACNA1H takes part in relapsing-remitting MS at clinical onset. Polymorphisms in PD-1, NLRP5 and EIF2AK1 associate with disease progression. MC1R relates to late-onset clinical symptoms. Its protein encodes the melanocyte stimulating hormone receptor, and the identified variant associates with the phenotype of rutilism.

Hypokinetic dysarthria
Alterations in the circuit that controls the basal ganglia (substantia nigra) cause hypokinetic dysarthria. The patients who suffer this disease speak in a monotone voice, with a reduction in tonal volume, a tendency to a speed up speech, inappropriate silences and palilalia. Patients show unexpressive facies, rigidity and body tremor. Parkinson’s disease (PD) and other degenerative parkinsonisms represent this disorder.

Parkinson’s disease: A relevant gene in Parkinson’s disease is SCNA, which encodes α-synuclein (αSyn). This protein plays a role in the brain, maintaining a supply of synaptic vesicles in the presynaptic terminals by grouping synaptic vesicles. Transgenic mice that over-express human wild-type αSyn under a broad neuronal promoter (Thy1-αSyn) present initial motor and non-progressive motor deficits, followed by parkinsonism with dopamine loss. These motor deficits include early and progressive vocalization disorders. PINK1 is a gene involved in early-onset PD. Pink1-KO rats have mitochondrial abnormalities, and proteinase K-resistant αSyn aggregates in different brain regions. Additionally, rats exhibit significant vocalization deficits dependent on age, intensity, bandwidth, and peak frequency. Speech disturbances may be early markers for PD detection. A preliminary study of cognitive disorders in the Chinese Han population revealed an absence of significant differences in neuropsychological tests in language fluency between carriers of a known PD mutation (LRRK2 S1647T) and noncarriers. However, a later report with more specific language criteria in Argentinian patients with asymptomatic mutations (PARK2 and LRRK2) who performed executive, semantic, verb construction, and syntactic tasks, showed alterations in a syntactic test with a minimal amount of working memory. These results suggest that these mutations may play a role in language processing.

Hyperkinetic dysarthria
Hyperkinetic dysarthria relates to alterations in the basal ganglia pathway (caudate/putamen nucleus). It generates tense speech, swaying voice volume, suddenly forced breathing and multiple voice interruptions.

Laryngeal dystonia (LD): Laryngeal dystonia is a form of focal dystonia characterized by intermittent spasms in the vocal folds that selectively affect speech production. Its etiology is multifactorial and polygenic. Metabolic, neurodegenerative, and environmental factors such as exposure to viruses or voice abuse can induce LD in genetically predisposed patients. Dopaminergic, GABAergic, glutamatergic and cholinergic neurotransmission is required in the pathogenesis of dystonia.

LD shows different clinical forms. In the most common adductor form, over-adduction of the vocal folds leads to voice interruptions in the vowels and the quality of the tense voice. The abductive form is rarer, with voice breakdowns in the consonants and whispered voice.

Although the genotype and phenotype characteristics of LD are different, functional connectivity alterations in the sensory-motor and frontoparietal cortex correlates with polygenic risk and may represent
an intermediate endophenotype and primary marker of LD. Meanwhile, the genes involved in synaptic transmission and the development of neurons may be related to the molecular pathogenesis of this disorder. Patients with LD have abnormal functional connectivity that affects speech production and auditory-motor integration as phenotypic characteristics. Structures initially described were the internal capsule and the cerebellum, as well as the thalamus, the corticobulbar tract and the basal ganglia. Other imaging studies have reported alterations at left dorsal primary sensorimotor cortex, especially in the abductor forms. It also affects the frontoparietal cortex, at the angular gyrus, and shows a significant relationship with the age at onset. Abnormalities in these regions correlate with underlying alterations in grey matter volume, cortical thickness and white matter downstream pathways as well as the genetic relationship with the functional connectivity of the premotor/primary sensory-motor and frontoparietal cortex.

LD genotypes are associated with structural changes in the extra Sylvian superior order regions and their pathways, suggesting a role for the temporal lobe in the pathogenesis of LD. Genotypic alterations are present in sporadic cases vs. familiar LD in the supplementary motor area (SMA) and superior temporal gyrus (STG), as well as in the superior longitudinal fasciculus. Computerized tomography (CT) differences in SMA may reflect different processing from the motor functions closest to those performed by the primary motor cortex. Other specific genotypic alterations in LD were located at the anterior portion of STG, where functional identification has shown greater activation in association with vocal auditory stimuli compared to non-voice sounds. Also, these abnormalities in STG may particularly affect individuals without a familiar background of dystonia.

Up to 12% of patients with LD report a familiar background. Genetic mutations suggest a weak predisposition that contributes to mechanisms that cause a non-progressive abnormality in the control of the laryngeal motor neuron for speech but not for vocal emotional expression. More than 20 different types of dystonia, called DYT, can be distinguished genetically. Some of these associate with other neurological signs. Some causative genes are highly expressed during early brain development. The most common cause of primary generalized dystonia in childhood is DYT1 dystonia, caused by a 3 bp deletion (ΔGAG) in the TOR1A gene that encodes the Torsin A protein. Symptoms usually occur before the age of 21 with sustained involuntary muscle contractions caused by the position of a foot, leg or arm, with laryngeal involvement in some cases. Genetic variation captured by the polygenic risk score and encompassing genes related to these biological processes may be directly relevant to the pathogenesis causing LD.

DYT6 dystonia typically affects the cranial muscles and arms, with voice involvement as the predominant characteristic. The causative gene is a protein associated with apoptosomes that contain the protein domain correlated with Thanatos 1 (THAP1), which encodes a DNA-binding protein. THAP1 can generate both generalized and isolated cases of dystonia. Identification of this mutation only appears in a few patients, usually middle-aged women.

Polymorphisms may also be implicated in the higher or lower risk for developing LD. In the DYT1 gene, polymorphisms have been identified as associated with adult-onset primarily focal dystonias, including LD, and may increase or decrease the risk for developing dystonia. In cases of non-familiar dystonia in the Icelandic population, a significant association was observed between dystonia and some markers comprising the DYT1 gene. However, further results did not replicate the association. Also, a study conducted by Sharma et al. on a large cohort of focal and segmental dystonia, including LD and cervical dystonia patients, revealed a significant association between SNP rs3842225 and protection from the development of focal or segmental dystonia.

A functional magnetic resonance image (fMRI) study compared a single carrier of GNAL mutations with a larger group of isolated LD cases without known mutations. GNAL encodes the G-protein stimulating
subunit α, Golf, required in the dopaminergic, adenosine and corticotropin signaling pathways. The effects of striatal dopaminergic abnormalities may be reflected in aberrant frontoparietal cortical activity, leading to further alterations in the integrative preparatory and sensory-motor stages of GNAL mutation carriers compared to other LD patients. TUBB4 is mostly expressed in brain development during the fetal period. The main regions of expression are the amygdala, hypothalamus, thalamus and prefrontal cortex. TUBB4 mutations implicate abnormal microtubule function, generating whispered voice DYT4 dystonia and other phenotypes of LD. Some reports of isolated cases exist, such as the one proposed by Peng et al. that described a patient with myoclonus, affecting the hands and arms, harboring the most common mutation in mitochondrial DNA causing myoclonic epilepsy with ragged red fibers syndrome (MERRF) [A->G substitution in the 8344 nucleotide tRNA (Lys) gene] that correlated with LD. Other genes involved in dystonia affecting laryngeal function are summarized in Table 2.

Tourette syndrome: The internal mitochondrial membrane protein 2L (IMMP2L) gene (7q22-q31) is an interesting candidate for Tourette syndrome (TS). IMMP2L encodes subunit 2 of the internal membrane peptidase, a mitochondrial protease involved in cleaving the space-sorting signals of mitochondrial membrane proteins. Defective IMMP2L can lead to altered mitochondrial function. The breakpoint in chr7 was assigned to 7q22-q31, between D7S515 and D7S552. This gene is also involved in autism and SLD. Interestingly, a familial balanced reciprocal translocation t(7;15)(q35;q26.1) has been identified in one patient, interrupting the CNTNAP2 gene in phenotypically normal individuals.

The PNKD gene, widely expressed in the brain, regulates myofibrillogenesis and has been associated with TS and speech disorders. One report identified a G89R nonsense mutation in a child affected by intermittent ataxia, diarrhea, exercise intolerance, and speech articulation problems.

Huntington’s disease (HD): Huntington’s disease is an inherited neurodegenerative disorder that causes motor, cognitive and neuropsychiatric disorders. It follows a pattern of autosomal dominant inheritance, initiating symptoms in the middle-aged, although it may also appear earlier or later. An unstable expansion of a CAG sequence within the Huntingtin gene (HTT) causes this disorder, located on chromosome 4. The protein encoded by the HTT gene plays a role in the normal development of the brain and neurons. The expanded CAG sequence leads to the production of an abnormal protein that causes brain cell dysfunction and ultimately neuronal cell death primarily in the basal ganglia, but also the thalamus and cerebral cortex.

FOXP1, one of the most studied genes involved in a range of speech and language disorders and will be described in more detail later, implicates transcriptional HD dysregulation, interacting with mHtt. The combined analysis of microarrays and ChIP-seq in a striatal cell line that over-expresses this transcription factor identified a set of target genes, including those associated with inflammatory and immunological disorders. According to in vitro results, viral transduction of Foxp1 mainly led to the suppression of genes related to the immune system in the adult striatum.

Essential tremor: Essential laryngeal tremor has phenotypic characteristics of hyperkinetic dysarthria. It occurs in greater proportion in women from the seventh decade of life onwards, and there may be a family component. It may associate with other parts of the body and, as with essential tremor, improves with alcohol intake. Genes correlating systemic clinical symptoms with dysarthria include DRD3 (3q13.31), FUS (16p11), TENM4 (11q14), and two loci: 2p25-p22 and 6p23.
Stuttering

Stuttering is a speech disorder in which the flow of speech is interrupted by involuntary repetitions and prolongations of sounds, syllables, words or phrases, as well as pauses or blockages in which the patient is not able to make sounds. Numerous mechanisms explain the genesis of stuttering, with a strong genetic correlation. In this review we will only cite those genes that are present in non-syndromic stuttering. Around 9% of patients with a familiar background associates with the GNPTAB, GNPTG, and NAGPA genes. The importance of these genes is based on replication in subsequent studies, confirming a key role in stuttering. These genes may also be affected in mucolipidosis. Unlike mucolipidosis, the characteristics of the mutations found in stuttering lie in their typically heterozygous character, with nonsense mutations, a modest reduction of enzyme function and different mutation sites.

GNPTAB catalyzes the addition of mannose 6-phosphate label to hydrolytic enzymes, allowing lysosomal configuration. The gene is located at locus 12q23.3 and encodes the enzyme N-acetylglucosamine-1-phosphotransferase. It was the first gene implicated in stuttering, with non-sense mutations in several families regarding inbreeding.

Through a systemic sequence of candidate genes, the GNPTG and NAGPA genes at 16p13 were identified in isolated stuttering cases. Variants of two genes were almost exclusively non-sense amino acid substitutions. GNPTG catalyzes the initial step in the synthesis of the mannose 6-phosphate (M6P) required for efficient intracellular targeting of newly synthesized lysosomal hydrolases. It encodes a protein subunit that combines with the product of the GNPTAB gene to form the functional phosphotransferase enzyme. NAGPA catalyzes the second step in hydrolytic enzyme labeling for lysosomal orientation. It encodes the N-acetyl glucosamine-1-phosphodiester alpha-N-acetylglucosaminidase enzyme. These two enzymes comprise a simple two-step biochemical pathway, which serves to bind a remainder of mannose 6-phosphate that acts as a signal to a diverse group of hydrolytic enzymes in lysosomes.

Another interesting gene is AP4E1, which encodes the adaptive protein complex 4, subunit epsilon 1. A study in one Cameroonian family identified two cis mutations in the same haplotype [p.Val517Ile (c.G1549A) and p.Glu801Lys (c.G2401A)]. The stuttering cases had many predicted loss of function variants in AP4E1, including deletions, frame changes, nonsense, and splice site variants, while only nonsense substitutions were observed in the controls. All the mutations in cases and controls were present in a single copy.

Other authors described association in additional chromosomal regions. Using high density genotyping, SLC6A3 and DRD2 were identified as other candidate genes in the Chinese Han population. FOXP2 and CNTNAP2 variants do not seem to be involved in the genetics of familial persistent ST, although the reports of some authors question this categorical assertion.

Childhood apraxia of speech

Childhood apraxia of speech (CAS) is a neurological speech disorder that affects the accuracy and consistency of the movements underlying speech. It may occur as a result of a known neurological impairment, in association with complex neurobehavioral disorders of known or unknown origin, or as an idiopathic neurogenic speech disorder. Although in most cases its etiology is unknown, a genetic association has proven to be related to this disorder. Authors define a synonymous for adults, verbal apraxia, albeit with particularities that differentiate it from CAS.

FOXp2

The FOXp2 gene (locus 7q31), part of the forkhead box family, was first described in the KE family (medical name designated for a British family), which showed speech articulation disorders, cognitive deficit and language delay. It is the first and one of the most studied genes involved in speech and language
disorders with a wide phenotypic expression\textsuperscript{[79,81]}. FOXP2 acts as a repressor transcription factor that can form heterodimers with FOXP1\textsuperscript{[80]}. Its role in the development of speech and language is not entirely defined\textsuperscript{[6,79]}. A study identified 27 genes with differential regulation under human FOXP2 control. \textit{RT-qPCR} and western blot studies showed the differential regulation of 13 additional target genes in response to human over-expression of FOXP2\textsuperscript{[82]}. The functional deficiency of FOXP2 affects both expressive and receptive language with a central characteristic of the abnormal articulation\textsuperscript{[7]}. Its function at central nervous system has been proven by neuroimaging studies and animal models, participating in cell signaling and communication, metabolism, migration, differentiation, and expression regulation\textsuperscript{[82,83]}. Neuroimaging studies in humans have shown that mutations in FOXP2 show alterations in grey matter in various regions of the cerebral motor cortex associated with speech, such as the superior temporal and inferior frontal gyrus. FOXP2 is highly expressed in the dorsal striatum during human development. The mutation of this gene seriously alters this anatomical structure, altering the production and learning of speech. In the cerebellum, FOXP2 expression is mainly affected in Purkinje cells\textsuperscript{[1]}. In addition, patients with intragenic FOXP2 deletions demonstrate a reduction in volume and activation in caudate nucleus, globus palidus, thalamus and hippocampus by repeating nonsense words\textsuperscript{[84]}. Regarding animal models, Foxp2 appears in medium spiny neurons of the mouse dorsal striatum. These neurons are required for the regulation of the glutamatergic signal in the cortex and the dopaminergic inputs in the midbrain, in addition to controlling motor behaviors. In Foxp2 heterozygous mice, synaptic corticostriatal plasticity decreases and extracellular dopamine levels increases in the striatum. They also exhibit cerebellar alterations\textsuperscript{[1]}. Clinically, the risk of developing SLD associated with FOXP2 among siblings depends on the genetic disorder. Thus, contiguous non-recuring genetic deletions (80% de novo mutations, 20% autosomal dominant inheritance), FOXP2 sequence variants (70% de novo mutations, 30% autosomal dominant inheritance) or maternal uniparental disomy 7, with no increased risk for siblings are the acquisition patterns of FOXP2 mutations. Because large, non-recurring deletions that include FOXP2 and flanking DNA cause approximately 52% of the SLD related to FOXP2, chromosomal microarray analysis is the first genetic test recommended. Other tests to consider are whole exome sequencing (WES), whole genome sequencing (WGS) and karyotype\textsuperscript{[85]}. Some genetic alterations detected in this case are missense mutations and intragenic deletions\textsuperscript{[84]}. In the karyotype screening, a balanced translocation or pericentromeric inversion involves 7q31.1 in almost 8% of FOXP2-plus and FOXP2-plus-related disorders alone\textsuperscript{[85]}. Patients usually present mild cognitive impairment\textsuperscript{[81]}.

\textit{FOXP1}

Another relevant gene that participates in brain development with CAS background is FOXP1. The role of FOXP1 (locus 3p14) in the brain is not clear. However, some reports suggest that it may play a role in the diversification of motor neurons, through their interactions with Hox proteins, in neuronal migration, by activating Reelin signaling pathways, and in neuronal differentiation, through regulating Pitx3 protein\textsuperscript{[81]}. FOXP1 mutations relate to mental retardation with apraxia of speech and language alterations\textsuperscript{[86,87]}. The phenotypic expression is variable. FOXP1, unlike FOXP2, contributes more significantly to global cognitive impairments that include the most severely affected expressive language\textsuperscript{[5]}.

\textit{Foxp1} is one of several genes expressed in the mouse striatum. Deletions encompassing FOXP1 have been found in autistic patients with severe phenotype. Haploinsufficiency of FOXP1 may be directly implicated in the disorder by deregulation of FOXP2. Relevant Foxp1 haploinsufficiency produces altered vocal communication, deregulation of the Foxp2 target genes in the striatum and changes in excitability of the medium spiny neurons\textsuperscript{[6]}. Guerra et al. J Transl Genet Genom 2019;3:9. I https://doi.org/10.20517/jtgg.2018.03
Other genes potentially associated with childhood apraxia of speech

There are multiple reports of diverse genes that in isolated form have been associated with CAS. We highlight, by the variety of genes described and their technique, some of them. Peter et al. identified two chromosome regions of interest (5p15.1-p14.1 and 17p13.1-q11.1) through copy number of variants (CNV) and complete exome sequencing in two multigenerational families. The primary gene of interest was CDH18, expressed primarily in the cerebellum. They described other genes with possible additive effects, such as MYO10, which has high levels of gene expression in the basal ganglia and thalamus; NIPBL, which is present in basal ganglia, the cerebellum and the corpus callosum; GLP2R, expressed in cortex and also implicated in other language disorders, such as autism; NCOR1, present in basal ganglia and cerebellar cortex; FLCN, present in dentate rotation and the cerebellar cortex and other genes with more dispersed expression, especially in the cerebellum, such as SMCR8, NEK8 and ANKRD12. ANKRD12 is located in a dyslexia candidate region, DYSX, at 18p11.22. Another gene of interest is C4orf21 (ZGRF1) at 4q25-q28.2. ZGFR1 encodes a protein with similar functions related to motor praxis, highly expressed in the cerebellum. A set of co-expressed regulatory genes in the human embryonic brain also relates to CAS. By analyzing whole genome sequences of nineteen subjects, de novo mutations in CHD3, SETD1A and WDR5 and loss of function mutations in SETBP1, KAT6A, TNRC6B, and ZFHX4 were characterized as pathogenic. Other genes described were CNTNAP2 alone or associated with overlapping CAS phenotype disorders (ATP13A4, CNTNAP1, KIAA0319, and SETX) Rare mutations in ELKS/ERC1 suppressions, a member of the RIM-binding protein family, have been reported. Surprisingly, in this case the ANKRD12 gene, among others, were considered variants of uncertain significance. Through array comparative genomic hybridization other candidate genes were identified in a multigenerational London pedigree, at locus 2p16, 5q22, 6p21, 13q21, 15q4, 16p13, 16q23.2, and 19. Newbury et al. described dual copy number variants involving 16p11 (a region of genes involved in speech disorders already described such as SETD1A and FUS) and 6q22 in a CAS case-report with developmental disorder.

Other speech sound disorders

This section includes other speech disorders in which the patient has difficulties in the formation of phonemes that interfere with verbal communication. It can cause articulation, phonemic or mixed alterations. These conditions can also alter the literacy process by concurring with other language disorders, such as dyslexia and developmental language disorder, to determine patients’ literacy skills, and share genetic determinants.

In other speech sound disorders (SSD), several chromosomal alterations have been identified (chromosomes 1, 3, 6, 7, 8 and 15). DCDC2 and KIAA0319 strongly correlate with phonological awareness, influencing language and cognitive traits. Nopola-Hemmi et al. analyzed a large Finnish family and found a link with DYSX (3p12-q13). Others reported involvement of DYSX (1p36-34), whose role is unknown. CYP19A1 (15q21.2), implicated in the synthesis of lipids and hormones, has been associated with SSD and dyslexia. Some reports correlate DYSX1C1 with SSD phenotypes. A ROBO1 linkage has been found to other SSD. Additional candidate genes include ELP4, PAX6 and FOXP2.

GENOMICS OF LANGUAGE DISORDERS

Aphasia

Aphasia is an alteration in the understanding and/or production of language because of damage to specific brain regions. Stroke is the most common cause of aphasia with alterations normally limited to the injured area, although neurodegenerative diseases such as Alzheimer’s disease (AD) or primary progressive aphasia (PPA) may also associate with more diffuse lesions. In these conditions, the genes involved in the development of aphasia have been studied in a more in-depth perspective. In AD, cognitive impairment extends beyond language and typically involves episodic memory, while in PPA affects gradually language skills with acceptable retention of nonverbal skills and activities of daily living. The type of aphasia seen
in AD depends on the phase of the disorder. In the early stages, anomalous aphasia, occasional semantic substitutions, occur due to difficulty in finding the right words (paraphasia), but speech is preserved. Later on, these individuals exhibit transcortical sensory aphasia, in which the patient has a clear anomic aphasia, and comprehension is affected. During moderate and severe stages of AD, lost fluency, increased use of wrong words, incorrect pronunciation, and poor comprehension is found. Finally, advanced stages include echolalia and verbal stereotypes. Primary progressive aphasia, on the other hand, classifies as fluent or non-fluent. In the fluent variant, prosody is normal, well-articulated and grammatically correct, but progressively circumlocutory and lacking in content words. The alteration of language correlates with a degradation of semantic memory and, therefore, the fluent variant is often mentioned as semantic dementia. In the non-fluent variant, speech is strained and hesitant, with phonemic paraphernalia.

**Apolipoprotein E**

Because of its relevance in Alzheimer’s disease and cerebrovascular metabolism, Apolipoprotein E (APOE) needs to be highlighted for its role in aphasia. A non-memory AD phenotype appears in approximately 25% of patients with early-onset disease. Compared to the memory phenotype, language AD phenotype has different demographic characteristics, genetic profile, and course of disease. This subgroup has smaller odds to carry at least one APOE4 allele relative to the memory subgroup, especially at an early-onset.

APOE4 is over-represented in PPA, so it is likely to act as a genetic risk factor in the development of the disease. A study by Daniele et al. showed that women with the APOE genotype ε2/ε4 showed an increased risk for PPA compared to women with homozygosis ε2/ε2 or ε4/ε4, suspecting that the ε3 allele might play a protective role in PPA and frontotemporal dementia (FTD). Interestingly, Seripa et al. showed an association in the chromosomal region 19q13-q13.2, which included in addition to APOE, the TOMM40, and APOC1 genes.

**Presenilin-1 and GLI family zinc finger 3**

Presenilin-1 (PSEN1) plays an important role in AD. Cases of visual or apraxic and language phenotypes are more frequent, with reports of atypical presentation with speech alteration, in carriers with PSEN1 mutations. It encodes a protein that takes part in the γ-secretase complex involved in the production of beta-amyloid. However, considering language performance certainly GLI family zinc finger 3 (GLI3) is more remarkable. A study that associated magnetic resonance image (MRI) and GWAS showed brain atrophy in semantic and language areas in GLI3 variants. This gene is one of the three GLI zinc finger transcription factors that are normally implicated in patterning brain structures as an important mediator downstream of the Sonic Hedgehog pathway. It may act as an activator or repressor in the presence or absence of Sonic Hedgehog. GLI3 is negatively regulated in the presence of PSEN1, which ultimately leads to decreased neuronal differentiation. Mutations in the PSEN1 gene are responsible of several autosomal dominant AD, including mutations with an aphasic phenotype.

**Other genes potentially associated with aphasia**

In a study of patients with clinically diagnosed FTD spectrum syndromes, genetic variations within FOXP2 do not pose a genetic risk per se but modulate the presentation of FTD. A significant and specific association between rs1456031 TT and rs17137124 TT genotypes and verbal fluency scores occurs, with left frontal hypoperfusion.

Granulin (GRN) is a gene that encodes progranulin and leads to a haploinsufficiency syndrome. In these families, affected individuals may show PPA phenotype, while others show the behavioral variant FTD phenotype (bvFTD). A family study reported that inclusions containing the transactional response DNA-
binding protein 43 (TDP-43) were distributed asymmetrically with a higher concentration in the left hemisphere language cortices\textsuperscript{[111]}. A retrospective report suggested that the mutations in the three genes most commonly associated with FTD [GRN, open-reading chromosome 9-frame 72 (C9ORF72); the microtubule-associated tau protein (MAPT)] were not correlated with PPA\textsuperscript{[112]}. However, these results must be taken with caution as the resulting sample had an over-representation of PPA with speech disease, which often predicts the pathology of AD.

Prion protein gene (PRNP) modulates PPA disease, leading to specific regional hypoperfusion according to different molecular pathways\textsuperscript{[106,111]}. Methionine/valine polymorphism of codon 129 may be over-represented in this disease compared to controls, bvFTD, and motor neuron disease, with the possibility that codon 129 polymorphisms could influence the selective susceptibility to the language network to neurodegeneration, even when the condition is unrelated to prion disorders. However, subsequent studies have failed to replicate the results\textsuperscript{[111]}.

**Developmental language disorder**

Developmental language disorder (DLD) is a disorder diagnosed in childhood with a delay or disturbance in language development. An early sign is a delay in language acquisition, and then they take time to put words together to form sentences. Spoken language can be immature. In many children with DLD, receptive language is also affected\textsuperscript{[113]}.

CNTNAP2

This gene has been highlighted previously in several speech disorders. However, its link to language deficits is also relevant. CNTNAP2 expression is regulated by the transcription factor FOXP2\textsuperscript{[5]}. It encodes a protein, neurexin, which plays its role in shaping potassium channels in developing neurons (nodes of Ranvier) and plays an important function in facilitating axonal-glial interactions and cell growth\textsuperscript{[114]}. It locates on chromosome 7q, and it shows a wide range of alterations in other neurological disorders, including neuropsychiatric conditions, such as schizophrenia, ADHD or bipolar disorder. Homozygous mutations lead to CASPR2 deficiency disorder (CDD), a rare and severe syndrome with epilepsy, language impairment and intellectual disability\textsuperscript{[115]}. CNTNAP2 was the first gene to be associated with genetically complex forms of DLD and involved in early language acquisition\textsuperscript{[116]}. However, its association with DLD needs replication, as the specific causal variants and underlying mechanisms by which it may contribute to language alteration have not been elucidated. CNTNAP2 deletions in children with apraxia of speech unrelated to DLD implies the great phenotypic heterogeneity of this gene\textsuperscript{[117]}. However, a study conducted by Toma et al.\textsuperscript{[115]} that exhaustively examined the role of CNTNAP2 in susceptibility to psychiatric disorders demonstrated that the distribution of CNVs from previous reports was no different from the controls in the genomic variant database. These gene-based association tests found no common variants in psychiatric phenotypes such as autism and schizophrenia. Cntnap2 alters neurons by increasing the number of active synaptic sites and facilitating network activity. In mice, Cntnap2 knockdown had the most pronounced effects in the hippocampus\textsuperscript{[11]}. Initially, outbred KO Cntnap2 mice had no macroscopic anatomical or neurological abnormalities, but when these mice were crossed with the C57BL/6j strain, subsequent generations exhibited neurologic abnormalities. Their abnormalities are similar to patients with cortical dysplasia and focal epilepsy syndrome\textsuperscript{[118]}. Cntnap2 expression in robust nucleus of the arcopallium (RA) is important for the proper production of learned vocalizations in songbirds. In adult zebra finches, the Cntnap2 transcription is enriched in cortical nuclei in the song production system. Adult females have moderate transcription levels in RA and the lateral magnocellular nucleus of the anterior neostriatum (LMAN), with a uniform Cntnap2 distribution throughout striatopallidum. Interestingly, in young females, Cntnap2 is enriched in RA to the same degree as for males and decreases to the level of the surrounding RA with age. The reduction in gene expression coincides with the sensorimotor period of song learning in male, a time when the songbird begins to practice singing. The percentage of cells that express the protein in female RA decreases at this time\textsuperscript{[119]}.
C-maf inducing protein and ATPase Secretory Pathway Ca\(^{2+}\) Transporting 2

These additional and closely related genes are likely to contribute to vocal learning\(^{[11]}\). Applying a positional fine-mapping approach, which required a GWAS study followed by targeted high-density association research, two genes were implicated in language capacity: the c-maf-inducing protein (CMIP) and the calcium-importing ATPase, type 2C, limb 2 (ATP2C2)\(^{[126]}\). GWAS analysis in these families revealed a strong and consistent linkage to locus 16q24 with the non-word repetition test. In other tissues, CMIP is involved in a cascade of cell signaling, such as the T-cell pathway and in the binding of phospholipids. ATP2C2 hydrolyzes ATP and is part of a pathway responsible for transporting divalent ions to the Golgi apparatus, such as calcium\(^{[113]}\). Linkage analysis and subsequent directed association analyses have suggested that CMIP and ATP2C2 relate to language disorders (especially non-word repetition) and phenotypic measures well characterized in these disorders. Although both molecules express in the brain, their functions are still poorly understood. These genes implicate a significant association with short-term memory. Considering that a relationship between wordless repetition test performance and short-term memory exists, ATP2C2 and CMIP can provide a biological link between memory-related pathways and language acquisition. The fact that neither ATP2C2 nor CMIP have been identified as downstream targets of FOXP2 suggests that the eventual combination of information from convergent research pathways will allow the characterization of overlapping and interacting neurological systems that serve for language acquisition. Although the linkage to these genes has documented in subsequent studies, their association with retardation, intelligence and features that differentiate it from language impairments in patients with mental retardation have not been replicated yet. ATP2C2 has also proved to be linked to attention deficit hyperactivity disorder (ADHD)\(^{[121,125]}\).

Other genes potentially associated with developmental language disorder

FOXPl and KIAA0319 genes appear to be involved in DLD\(^{[122]}\). A haploinsufficiency in SETBP1 (locus 18q12) is a factor implicated in CAS, but also in language impairment, responsible for interacting with an oncogene implicated in DNA replication\(^{[123,124]}\). Other genes potentially related to language skills are ABCC13\(^{[125]}\), FLNC, RBFOX2\(^{[126]}\), and ROBO2\(^{[127]}\). GWAS studies have highlighted risk variants in NDST4, ZNF385D, COL4A2\(^{[128]}\), and NOP9\(^{[129]}\). Other studies involve rare genetic events that may have greater penetrance. Also, the coding variants within NFXL1 confer a higher risk for DLD within a complex genetic mode\(^{[130]}\). A study conducted by Centanni et al.\(^{[131]}\) evaluated 15q11.2 as a region of susceptibility for SLI, finding two deletions in seven patients with CAS but none in 8 SLI. The main limitation of this study was the small number of patients (8 subjects). In a report looking for rare copy number variants in 58 subjects and their relatives, deletions were found on chromosome 16p11.2 in 3.4% of the probands. Other detected deletions were identified in 18p11.32-p11.22 and Xp22.31-p22.33 loci. Although the proportion is low, it should be noted that this locus overlaps with other neurodevelopmental disorders\(^{[131]}\). Several other minor reports exist, such as a balanced t(10;15) translocation in a male patient with developmental language disorder\(^{[132]}\). This last example, although interesting, is just a case-report, so results cannot prove causation and may not be generalizable.

Dyslexia

Dyslexia (DL) is a complex term characterized as a reading disorder. Subjects usually have normal intelligence and features that differentiate it from language impairments in patients with mental retardation\(^{[133]}\). Problems can include difficulty in spelling or writing words, reading quickly, pronouncing words mentally or when reading aloud, and understanding what the individual is reading\(^{[134]}\). Some authors consider dyslexia as an associated condition of developmental language disorder\(^{[135]}\) or ADHD\(^{[136,137]}\). As noted, the truth is that many patients exhibit alterations in speech and language. Silencing of some of the most important genes involved in rodents, such as DCDC2, KIAA0319 and DYX1C1, produces deficits in neuronal migration, dyslexia, and alterations in working memory, auditory processing and visual attention\(^{[138]}\). Within the human genome, genetic mapping reports have identified regions of different chromosomes, known as DYX loci\(^{[139-143]}\) and other related genes.

Dyslexia susceptibility 1 candidate gene 1

In animal models, DYX1C1 (15q21) mutations generate a neuronal migration disorders that correlates with DL. DYX1C1 knockdown in zebrafish results in alterations in the primary cilia, such as body curvature
disorders, hydrocephalus, renal cysts, and organ inversion left-right asymmetry. Other animal models have revealed unexpected roles for DYX1C1 in primary cilia which are typical phenotypes of ciliary defects with similar results in KO mice. Taipale et al. identified a missense mutation (rs57809907, 1249G>T) in some families with DL. This mutation results in Glu417X with a truncated protein. Later reports found a correlation with the common G allele. Interestingly, a report of DL in Chinese children also found a strong association with the G allele. A allele shows decreased binding to a repressive transcription factor. Lim et al. hypothesized A allele is protective compared to G allele. Two other SNPs, rs12899331 and rs16787, in the promoter region were found to be involved in the binding to the transcription factor, but they did not associate with DL in subsequent studies. Its protein can bind to the estrogenic receptor, suggesting an involvement of hormonal pathways in dyslexia.

DCDC2
The gene structure is analogous to the DCX gene linked to X, involved in the microtubule structure and neural migration. Defective DCDC2 causes delays in neural migration in the embryonic brain. The DCX gene mutation causes lissencephaly in men and cortical abnormalities in women. In vitro studies showed that sequences in the region act as enhancers of DCDC2 expression. Differences in gene expression may have a measurable phenotypic effect on brain structure. Homozygous Ddc2 KO mice exhibit auditory processing and memory deficits, as well as electrophysiological changes in cortical neurons with normal brain development.

Early findings showed that DCDC2 would be a strong candidate for developmental dyslexia. However, some further studies did not find its association. Sequence analysis of DCDC2 coding regions in families with DL has not identified causal mutations; the only correlation of further studies did not find its association. Sequence analysis of association with the haplotype (rs3765502-1087266) were significantly different between cases and controls. The gene were mapped on a neuroblastoma cell line to identify promoting regions. Reporter trials showed that the risk allele, which was believed to create a binding site for the repressor, resulted in a decreased expression of DCDC2. Two other SNPs, rs761100 and rs2274305, in the promoter region were found to be involved in the binding to the transcription factor, but they did not associate with DL in subsequent studies. Its protein can bind to the estrogenic receptor, suggesting an involvement of hormonal pathways in dyslexia.

KIAA0319
Although the role of this gene is unclear, decreased expression in the rat’s embryonic brain leads to delayed neural migration. SNPs at s’UTR, the first untranslated exon and the first intron, suggest regulatory functions. The first reports linking this gene to dyslexia were described by Francks et al., identifying it as a 77-kilobase region of chromosome 6p22.2. Further mapping studies identified KIAA0319 as the susceptibility gene for dyslexia with risk effects indexed by the T-G-C-T of the four-marker haplotypes (rs9295619-rs807701-rs807724-rs2274305) and the T-A of the two-marker haplotype (rs3765502-1087266) were significantly different between cases and controls.

KIAA0319/TTRAP/ THEM2 polymorphisms influence the laterality of activation in the superior temporal sulcus. Thus, these genes seem to influence the activity of the two hemispheres asymmetrically in areas related to language function.

Other genes potentially associated with dyslexia
According to animal models, Robo1 gene participates in axonal development across the midline of the central nervous system and spinal cord. Partial haploinsufficiency may cause dyslexia in humans.

MRPL19 and C2ORF3 are two genes in which their role as co-regulators in dyslexia has been theorized. The MRPL19 protein is a component of the mitochondrial ribosome, but the function of the C2ORF3 gene
is unknown. In one study, transcripts of one allele from MRLP19 and C2orf3 decreased in individuals carrying risk haplotypes in the adjacent region suggesting that a mutation unknown in the SNP association region might affect the expression of both genes\textsuperscript{[18]}: TTRAP (6p22.3), required in magnesium ion binding and DNA binding and repair\textsuperscript{[99]}, and ROBO2 (3p12.3) are other genes potentially involved in DL. ROBO2 is implicated in the guidance of axon and tumor molecular signaling and necrosis factor\textsuperscript{[98,159]} . Landi et al.\textsuperscript{[160]} found a COMT Val/Met polymorphism (rs4680) associated with reading skills. Other relevant genes are CMIP, MC5R, DYM, NEDD4L and DGK\textsuperscript{[161,154]}.

Other suggested associations reported by Eicher et al.\textsuperscript{[162]} were dopaminergic genes related to ANKK1 and DRD2, and nicotinic genes related to CHRNA3 and BDNF with case-control status and articulation. DRD2 has demonstrated its role in vocabulary alterations and a direct association with dyslexia\textsuperscript{[165,166]} . ASPM is another gene whose alterations involve dysfunctions in vocabulary and reading, and AVPR1A with them and phonological memory\textsuperscript{[183]} . These results support previous reports involving dopaminergic and nicotinic neural signaling in human communication and cognitive development.

Several CNV studies identified genes involved in dyslexia. Thus, the interruption of a gene involved in learning, cognition, and memory through dendritic spinal synaptic plasticity, the PCDH11X protocadherin gene (by duplication or elimination of the gene) located in Xp21.3, could be caused by unequal recombination between the X transposed region (XTR) of Yp11.2 and the X chromosome\textsuperscript{[165]} . The same authors in a subsequent report with similar methods identified rearrangements at 17q21.31, with KIAA1267, LRRC37A, ARL17A/B, NSFP1, and NSF as candidate genes. Some of these genes seem to play a role in membrane fusion and synaptic transmission\textsuperscript{[166]} . A further study searching for another large group of genes including, among others, CHRNA7, Corf22, IMMP2L and CNTNAP2 found no substantial proportion of variance in DL\textsuperscript{[167]} .

**OTHER COMPLEX GENETIC DISORDERS WITH SPEECH AND LANGUAGE IMPAIRMENTS**

As observed in dysarthria, there are multiple disorders that can be associated with speech and language impairments. Several genetic syndromes such as Worster-Drought or Flotaing-Harbor are characterized by alterations in verbal communication\textsuperscript{[85]} . In this section of the review we will focus on some of the most prevalent genetic syndromes.

**Autism-spectrum disorders**

The great clinical heterogeneity of ASD implies variability in the phenotypic characteristics of language and speech. ASD has comorbid phenogenotypes, such as ADHD\textsuperscript{[168,169]} . Therefore, there may be alterations in the comprehension, dyspraxia or motor alterations\textsuperscript{[170]} . The inversion of the pronoun, echolalia and a delay in understanding the reduced or even inverted production are the most frequent language alterations\textsuperscript{[171]} . Because of this complexity, this review will focus on the major known genes directly associated with oral communication disorders.

The sushi domain protein SRPX2 is a FOXP2 target\textsuperscript{[172]} . Historically, it has been primarily studied as a complement cascade regulator in the innate immune system. SRPX2 is involved in neural development and migration. It encodes a protein that regulates synapse formation and ultrasonic vocalization in mice. SRPX2 mutations in humans have been linked to SLD, such as apraxia of speech in cases with rolandic seizures. The Sprx2 knockout mouse shows a decrease in VGlut2 synapse density in the IV layer of the somatosensory cortex, and a reduction of VGlut1, VGlut2 and VGAT synapse densities in the CA2 region of the hippocampus. Sprx2 KO mice show an abnormal ultrasonic vocalization ontogenetic profile\textsuperscript{[173]} . Interestingly, Sprx2 KO mice show a reduced preference for social novelty, which may prove a relationship between SRPX2 and autism-related behaviors\textsuperscript{[174]} .
**MED13L** is implicated in neural crest induction and is highly expressed in the cerebellum after birth\[^{175}\]. **MED13L** relates functionally to EP300 and CREBBP products, link proteins between the FOXP2 and ROBO1 pathway\[^{176}\]. In a case-report described by Jimenez-Romero et al.\[^{177}\] a SNP was identified in **MED13L** (chr12: 116675396A> G, G, GRCh37), which associates with a profound language disturbance in the expressive domain, cognitive retardation, behavioral disturbances and an autism-like phenotype.

Regarding other genes potentially associated, locus 16p11.2, previously described in domain, cognitive retardation, behavioral disturbances and an autism-like phenotype. **MED13L**

Other syndromes that associate with speech and language disorders

Patients with Down syndrome (trisomy 21) have a more altered expressive than receptive language\[^{194}\]. Children tend to have altered syllable structure, group reduction, and final consonant elimination. Prevalence of stuttering is also higher\[^{195}\]. As they grow up, language has shorter and less complex statements. In senescence, SLD overlap with the increased risk of dementia\[^{194}\].

Fragile X syndrome (FXS) is the main inherited cause of intellectual disability, accounting for 40% of all X-linked mental retardation. The syndrome results from a mutation in the FMR1 gene, which locates on the X chromosome (Xq27.3). The mutation induces an expansion of CGG triplet repetition within FMR1. FMR1 encodes fragile X mental retardation protein (FMRP)\[^{196}\]. In songbirds, FMRP expresses in the HVC, LMAN, RA, and area X\[^{11}\]. FMRP enriches in male RA from the beginning of the sensorimotor learning phase. Autism is a common comorbid condition in people with FXS, modifying the phenotypic characteristics of the subject. A characteristic communicative alteration in FXS patients is a repetitive language. Other alterations implicate delay progress of vocabulary, comprehension, and syntax. FXS patients have significant weaknesses in pragmatics. Their ability to recognize and provide the necessary informative details in language discourse affects more than expected their levels of cognitive development\[^{197}\].
**EPIGENETICS OF SPEECH AND LANGUAGE**

In songbirds, epigenetic modifications related to call are reported on early-expressed genes. These genes are associated with the activity of the cytoskeleton (Arc) that interacts with endocytosis-related proteins and facilitates the removal of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors from the cell membrane. Thus, a DNA methylation in the genome region upstream of the Arc is differentially regulated through the critical period of song development. In canaries, the gene induction of histone H3.3B and Gadd45b is higher in robust nucleus of the arcopallium (RA) of those birds that interpret variable and plastic songs than in birds singing crystallized songs\(^{[19]}\). In addition, microRNAs (miRs) are of special interest, with the ability to regulate neurogenesis and thereby contributing to the organization of the brain structures underlying speech and vocal learning. In songbirds, miRs may have activating effects that support vocal learning and multiple miRs affect neurite growth and synaptogenesis\(^{[19]}\). For instance, the expression of 5 miRs in cortical auditory regions is affected by exposure to the specific song. In this way, miR-92, -124, and -129-5p decrease, and miR-25 and -192 increase\(^{[19]}\). miR-124 and miR-137 conduct cell differentiation to a neural destination by suppressing non-neuronal transcriptions or regulate the maturation of neurons\(^{[200-202]}\).

As epigenetic mechanisms in Foxp2, miR-9, -132\(^{[203]}\) and -140-5p express in the area X of the zebra finch and positively regulate by singing in young and adults, associated with reduced levels of Foxp2\(^{[204]}\). miR-9 is express in postmitotic cortical neuron and induces or limits axon growth. It also acts through regulating Foxp1 to target the motor neuron specification or promotes neural differentiation by suppressing proteins involved in neural stem cell proliferation. miR-9, as a Foxp2 /miR-9 feedback loop, indirectly affects gene expression downstream of Foxp2\(^{[199]}\). The other miRs control neural maturation\(^{[201,204]}\). miR-3666 is another factor that regulates FOXP2 levels in neurodevelopment and may contribute to the pathogenesis of neurological disorders such as schizophrenia and autism\(^{[198]}\). Moreover, Histone variant H3.3 and miR-128 are involved in learned vocal communication\(^{[199]}\). In FOXP2 3′ untranslated region, let-7a, miR-9, and miR-129-5p regulate its expression\(^{[201,205]}\). Active neuronal enhancers were predicted by strong histone-3-lysine-4-monomethylation (H3K4Me1) and histone-3-lysine27-acetylation (H3K27Ac) within the 3C fragments at 330 and 843 kb. The 3C fragment at -37 kb encompassed a weak neural enhancer, predicted by strong H3K4Me1 and weak H3K27Ac. In some neuronal roadmap epigenomics samples parts of the same fragment were annotated as active transcriptional start sites, predicted by an absence of H3K4Me1 and strong H3K9Ac\(^{[202]}\). Furthermore, amongst the 61 peaks with human-specific loss of H3K4me3 is a 700-bp sequence upstream of FOXP2 transcription start site (TSS)\(^{[206]}\). In songbirds, unlike Foxp2, whose differential expression at the core of the song depends on behavior, the Foxp1 signaling pathway regulates the singing process, with mRNA enrichment in the surrounding tissues of area X of male birds, high-level vocal center nucleus (HVC) and RA\(^{[203]}\).

Regarding epigenetic factors involved in the different speech and language disorders, *in silico* tests identified as factors implicated in the development of CAS to miR-182, miR-34c-5p, miR-34a, miR-449a, miR-449b, miR-1271, miR-96, miR-9, miR-647, miR-604, miR-214, and miR-657\(^{[207]}\). The same author implicated in DLD to miR-1207-5p, miR-188-3p, miR-1225-3p, and miR-299-3p\(^{[207]}\). Epigenetic mechanisms may affect the expression of KIAA0319 in the etiology of dyslexia. For instance, miR-548c-3p, may define the development of DL\(^{[208]}\). Concerning ASD, it was reported a hypermethylation at oxytocin receptor gene (OXT)R in peripheral blood, and the temporal cortex of patients\(^{[208]}\). As epigenetic mechanisms of FXS, a promoter hypermethylation induces a transcription repression\(^{[64]}\). An increased methylation at site H3K9 and H3K27, which modify transcription activation, have been reported in HD\(^{[64]}\).

**CONCLUSION**

1. Multiple genes involved in speech and language have been reported. *FOXP1, FOXP2, CMIP OR GNPTAB* are genes in which associations have been replicated. However, in other genes, further studies are needed to demonstrate their linkage. The unification of criteria, the development of endophenotypes or observational studies of genetic variants, such as GWAS, are needed to provide more robust results.
2. Epigenetic factors modulate verbal communication. Songbird studies bring a better understanding of the human communication process. *In silico* predictive analysis can identify the epigenetic factors involved in disorders of speech and language.

3. Their mechanisms of action have not been fully elucidated and there are several molecular pathways involved in communication that interact with each other.

4. Speech and language disorders may be inherited or syndromic, associated or not with neurological and psychiatric disorders. In associated cases, identifying genes may be useful for an early diagnosis or predicting the disease progression.

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**Authors’ contributions**

Made substantial contributions to conception and design of the review and interpretation: Guerra J Read, adjusted and approved the final manuscript: Cacabelos R

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