Review

Genomics of Speech and Language Disorders

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Abstract: There are multiple factors involved in speech and language. Investigating animal models, mainly through songbirds, have allowed a better understanding of the language process. Verbal dyspraxia, dysarthria, speech sound disorder, and stuttering are some examples of speech disorders, and specific language disorder, aphasia, and dyslexia of language disorders. More complex syndromes such as Autism-spectrum disorders, Down’s or Fragile X have more variable features. Genetic factors, such as hereditary or de novo mutations may be responsible for their development. In addition, most of them are involved in neurodevelopment with a huge range of molecular mechanisms and pathways that interact with each other, and there may be co-morbidity with other communication disorders or develop 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 miRNAs, influence their 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 those neurological alterations that incorporate these mutations.

Keywords: genomics; epigenetic; speech; language; dysarthria; stuttering; dyspraxia; aphasia; FOXP2.

1. Introduction

The language process involves three structures of the central nervous system: cortex, basal ganglia, and cerebellum [1]. The primary language pathway begins at Wernicke’s area, located in the posterior temporal lobe. This pathway collects information from the visual and auditory cortex and is responsible for understanding language. The arcuate fasciculus connects Wernicke’s to Broca’s area, located in the inferiorposterior frontal lobe. This area generates a significant language and initiates the muscular activity involved in speech. There is a second language pathway through the angular and supramarginal gyrus, located in the posterior parietal lobe connecting with Broca’s and Wernicke’s areas [2]. Syntax-related networks are located in the opercular/triangular parts of the lower left frontal rotation and in the left lateral premotor cortex. The basal ganglia are involved in prosodic modulation and language acquisition and are responsible for language learning in adults [3]. Finally, the cerebellum is also involved in the processing of expressive and receptive language, and writing skills [4].
In many cases, 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, there are genetic factors involved in 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, and connectivity and determine neurodevelopmental characteristics [7]. Thus, the same gene may be related to different independent disorders, indicating 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 Down’s, Fragile X, and Autism Spectrum Disorders (ASD). The construction of a knowledge base of genetic etiology makes it possible to identify patients with genetic risk and to motivate the development of effective early intervention programmes [8].

There are multiple epigenetic factors involved in the development of language and speech [9-10]. In songbirds, there are epigenetic modifications in one of these immediate early genes, 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, there is a DNA methylation in the genome region upstream of the Arc that 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 arcopallium nucleus (RA) of those birds that interpret variable and plastic songs than in birds singing crystallized songs [10]. In addition, microRNAs (miRs) are of special interest, with the ability to regulate neurogenesis and thereby contribute to the organization of the brain structures underlying speech and vocal learning. miRs may have activation effects that support vocal learning and multiple miRs affect neurite growth and synaptogenesis [11]. For example, in birds the expression of 5 miRs in cortical auditory regions is affected by exposure to the specific song: miR-92, -124, and -129-5p decrease, and miR-25 and -192 increase [12]. miR-124 and miR-137 direct cell differentiation to a neuronal destination by suppressing non-neuronal transcriptions or regulate the maturation of neurons [13-15].

In this review, we attempt to characterize the genomic and epigenetic background associated with language disorders.

Table 1. List of genes involved in speech and language disorders included in this review.

<table>
<thead>
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<th>Gene</th>
<th>Name</th>
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2. Genomics of speech disorders

2.1 Verbal dyspraxia
Verbal dyspraxia (VD) is a neurological speech disorder that typically occurs in pediatric age, as opposed to verbal apraxia, which is an acquired disorder in adults [16]. The accuracy and consistency of the movements underlying speech are affected in the absence of neuromuscular deficits. 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 [17]. Although in most cases its etiology is unknown, a genetic association has proven to be related to this disorder [5]. Predicted epigenetic factors involved in the development of VD are 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 [18].

2.1.1 FOXP2

The FOXP2 gene (locus 7q31), part of the forkhead box family, was first described in the KE family, which presented speech articulation disorders, cognitive deficit and language delay [19]. Subsequently, it was reported in a small group of patients with verbal dyspraxia and multiple SLD. FOXP2 acts as a repressor transcription factor that can form heterodimers with FOXP1 [20], and its role in the development of speech and language is diverse and not entirely defined [19,6]. An RNA sequencing study identified 27 genes with differential regulation under human FOXP2 control. Also, RT-qPCR and western blot showed the differential regulation of 13 additional target genes in response to human overexpression of FOXP2 [21]. The functional deficiency of FOXP2 affects both expressive and receptive language with a central characteristic of the abnormal articulation [7]. Also, its function at central nervous system has been proven by neuroimaging studies and animal models, participating in cell signaling and communication, metabolism and catabolism, cell migration and differentiation, and expression regulation [21].

Neuroimaging studies in humans have shown that mutations in FOXP2 present alterations in grey matter in various regions of the cerebral motor cortex associated with speech, such as superior temporal gyrus and lower frontal circumscription. Also, it changes the cortical activity observed through functional studies with repetition paradigms with and without words, probably by alterations in the cortical-striatal or cortical-cerebellar pathway. FOXP2 is also 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, the expression of this gene refers only to Purkinje cells [1].

Regarding animal models, FoxP2 appears in medium spiny neurons of the dorsal striatum of mice. These neurons are involved in 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 plasticity in corticostriatal synapses decreases and extracellular dopamine levels increases in the striatum. They also exhibit associated cerebellar alterations [1].

As epigenetic mechanisms, miR-9 and -I40-5p are expressed in the X area of the zebra finch and positively regulate by singing in young and adults, associated with reduced levels of FoxP2 [22]. MiR-9 is expressed in postmitotic cortical neuron axons and induces or limits axon growth. It also acts through the regulation of FoxP1 to target the motor neuron specification or promotes neural
differentiation by suppressing proteins involved in neural stem cell proliferation. There is a Foxp2 /miR-9 feedback loop, in which miR-9 indirectly affects gene expression downstream of FoxP2 [11]. Moreover, 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 [23].

Clinically, the risk of developing SLD associated with FOXP2 among siblings depends on the type of genetic disorder present. Thus, we can observe contiguous non-recurring genetic deletions (80% are de novo, and the rest inherited in an autosomal dominant manner), FOXP2 sequence variants (70% of which are de novo and the rest inherited in an autosomal dominant manner) or maternal uniparental disomy 7, with no increase in risk for the siblings. 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 to be performed. Other tests to consider are complete genomic sequencing (GWAS) and karyotype. In the latter case, there is a balanced translocation or pericentromeric inversion involving 7q31.1 in approximately 8% of FOXP2-plus and FOXP2-plus-related disorders alone [24].

2.1.2 FOXP1

The role of the protein FOXP1 in the brain is not clear. However, some studies 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 the regulation of the Pitx3 protein [25]. The locus of FOXP1 is at 3p14, and its mutations relate to mental retardation with verbal dyspraxia and language alterations [26]. The phenotypic expression is variable. FOXP1, unlike FOXP2, contributes more significantly to global cognitive impairments that include the most severely affected expressive language [7].

Foxp1 is one of several genes present in the mouse striatum. A deletion of Foxp1 that affects the entire brain induces autistic behavior. 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 [1].

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 [27].

2.1.3 Other genes

Peter [28] identified two chromosome regions of interest through a complete sequencing of the exome in two multigenerational families, 5p15.1-p14.1 and 17p13.1-q11.1. 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, present in cortex and also involved 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 ANKRDI2. ANKRDI2 is also placed in a dyslexia candidate region, DYX6, at 18p11.22. Another gene of interest was C4orf21 (ZGRF1) at 4q25-q28.2. ZGRF1 can encode similar functions related to motor praxis and is highly present in the cerebellum.

A set of co-expressed regulatory genes in the human embryonic brain relates to the development of verbal dyspraxia. By analyzing complete genome sequences of 19 test subjects, de novo mutations in CHD3, SETD1A and WDR5 and loss of function mutations in SETBP1, KAT6A, TNRC6B, and ZFHX4 were characterized as pathogenic [29].

Other genes reported were CNTNAP2 alone or associated with overlapping VD phenotype disorders (ATP13A4, CNTNAP1, KIAA0319, and SETX) [30]. Finally, rare mutations in ELKS / ERC1 suppressions, a member of the RIM-binding protein family, have been reported [31].

2.2 Dysarthria

Dysarthria is a motor disorder of speech that causes poor coordination of the articulation with pharyngeal, laryngeal, lingual or facial muscle involvement. This disorder is due to alterations that affect the cranial nerves, neuromuscular, cerebellar, cerebellar, base ganglion or cortical-bulbar tract diseases, while it keeps the cortical function of speech [32]. Dysarthria in classified into six groups: flaccid, ataxic, spastic, hypokinetic, hyperkinetic and mixed [33] (Table 2).

Table 2. Selection of disorders that may associate dysarthria and genes involved in the development of the disease and/or dysarthria.

<table>
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<td>HLA: HLA-A3,B7,DR2</td>
<td>(early onset); HLA-A1,B8,DR3; HLA-DR4 (late onset);</td>
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<td>HLA-DR14: HLA-DQ5 (anti-Musk)</td>
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<td></td>
<td></td>
<td>FXN</td>
<td>Frataxin</td>
<td>9q21.11</td>
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<td>CACNA1A</td>
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</tr>
<tr>
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<td>Ataxic/Spastic/Syringomyelia</td>
<td>Gene</td>
<td>Chromosome</td>
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<td>Spinocerebellar ataxia</td>
<td>ATXN7, PRKCG, TTKB2, SETX, SPTBN2, SACS, MRE11, KCNC3</td>
<td>Ataxin 7, Protein kinase C, gamma, Tau tubulin kinase 2, Senataxin, Spectrin beta nonerythrocitic 2, Sacsin, Meiotic Recombination 11-Like Protein A, Potassium channel voltage-gated shaw-related subfamily member 3</td>
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2.2.1 Flaccid dysarthria

It relates to disorders of the lower motor neuron system and/or muscle. It generates continuous expiratory speech, diplophonia, and hypernasality [33]. Myasthenia gravis, amyotrophic lateral sclerosis, or Prader-Willi syndrome are some examples of flaccid dysarthria [34].

2.2.1.1 Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disorder, caused by antibody formation at the neuromuscular junction. The CHRNA1 gene is responsible for encoding the alpha subunit of the muscle acetylcholine receptor, the main target of the Abs, although there are other antibodies involved that modify the clinical expression of the disease, such as Abs against muscle-specific tyrosine kinase (MusK) [35]. There is a low percentage of genetic cases associated with other immune disorders [36]. Twin studies have shown the concordance of MG is significantly higher in monozygotic compared to dizygotic twins. Several HLAs have been identified (mainly 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 [37,35]. In MuSK Ab-positive patients, there is an association between HLA-DR14 and DQ5 [35].

Prominent bulbar symptoms with dysarthria are more common in patients with ab-MusK. MusK is necessary for the formation of neuromuscular synapses to orchestrate post-synaptic differentiation, including the clustering of receptors for the neurotransmitter acetylcholine. Anti-MusK autoantibodies are found in those seronegative patients. Although the loss of acetylcholine receptor function produces an autoimmune alteration, there are phenotypic particularities that differentiate it from the classic picture. Thus, there is a lower prevalence of ocular manifestations, greater weakness of the neck and oropharynx, and it tends to affect women and African-Americans to a greater degree [35, 38].

2.2.2 Ataxic dysarthria

Ataxic dysarthria is due 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 [34]. This group includes hereditary ataxia. So far, they have identified more than 30 genotypes. Hereditary ataxia may be progressive, such as spinocerebellar ataxia (SCA) and Friedreich’s ataxia (FRDA) or episodic ataxias (EA). SPAX also refers to those ataxias that often have a prominent component of spasticity, thus modifying the patient’s dysarthric characteristics [39].

Some hereditary ataxias are related to trinucleotide expansion diseases, which are 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 with SCA1-7 and SCA17, where the repeated codon is CAG, which is coding region codes 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 [40].

For those patients in whom the genetic screening tests for SCA1, 2, 3, 6, 7, and FRDA are negative, the screening of small intragenic pathogenic variants for PRKCG, PRKCG, PRKCG, TTBK2, SETX, SPTBN2, SACS, MRE11, KCNC3 and DARS2 might be useful. It is especially useful in patients with progressive onset disorders in childhood or adolescence and/or with a family history [39]. Several studies assessed the particularities of phenotypes of disorders that generate ataxic dysarthria [41, 42, 43]. Clinical characterization of the voice helps to discriminate between different types of ataxia and guides vocal therapy [43].

2.2.2.1 FRDA

Friedreich ataxia (FRDA gene, locus 9q21.11) is the most common progressive hereditary ataxia, with an autosomal recessive inheritance pattern. It produces a degeneration, among other structures, of areas of the white matter of the cerebellum and afferent pathways of different nuclei of the brain stem. Speech disturbances are usually less severe than in spinocerebellar ataxia and are almost exclusively due to cerebellar degeneration. There is also no relationship between the severity of dysarthria and body ataxia. 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 [44].

2.2.2.2 SCA

SCA3 is the most common of the autosomal dominant ataxias 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 multisystemic affectation [39].

SCA1 (ATXN1 6p22.3) usually has a greater effect on voice dimensions. Rough and strangled voice are predictors of the severity of the disease [42].

The regularity of diadochokinetic syllable repetitions is specifically affected in SCA3 (ATXN3 locus 14q32.12 gene) 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 diadochokinetic syllable repetitions to a greater degree than other ataxias [41].

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 severity of the disease [42].

In general, articulatory speech disorders affect more to patients with SCA6 (CACNA1A gene, locus 19p13.13). Speech parameter degradations, i.e., 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 exclusively) confined to the cerebellum. Compared to many other types of SCA, cerebellar degeneration largely involves the cerebellar cortex [41-42].

Regarding SCA7 (ATXN7 gene, locus 3p14.1), voice deterioration is unrelated to age at onset and the size 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 is the result of extra-cerebellar manifestations of the disease [43].

2.2.3 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 [33]. Examples of spastic dysarthria are hereditary spastic paraplegia [45] and other mixed expression disorders such as multiple sclerosis [46].

2.2.3.1 Multiple sclerosis
Multiple sclerosis (MS) is a demyelinating disease 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 indicate a prevalence ranging from 41%-51%. The main speech disturbances are in volume control, rough voice quality and imprecise articulation [46]. It can also associate cognitive deficit such as slowed information processing speed, impaired working memory and reduced information processing efficiency. It can also manifest as a subtle, non-phasic deficit of high-level language [47]. Assessment of dysarthria may be helpful in controlling clinical and progression of subclinical disease [48].

There is a genetic susceptibility to the development of multiple sclerosis, associated with variation in certain HLA genes on chromosome 6p21, including HLA-A, HLA-DRB1, HLA-DQB1, HLA-DQA1, HLA-DRA, on chromosome 6p21.3. Other haplotypes identified were 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 [49]. There are also genes that can modify the evolution of the disease. FNI and CD24v/v are associated with earlier age at onset of MS [50-52]. In addition to this, ITGA4, SPP1, SPP1, PSMG4, and NLRP5 relate to the severity of the disease, with SNPs having an allelic dosing effect [50, 53]. PSMG4 encodes a chaperone protein involved in the assembly of the 26S proteasome, a primary protein elimination pathway. The reduced activity of proteasome 26S has proved to cause neuronal death from deterioration of abnormal protein degradation. Proteasome 26S has also been shown to hydrolyze the basic myelin protein to produce antigenic peptides for presentation to T cells [50]. CACNA1H participates in relapsing-remitting MS at clinical onset. Polymorphisms in PD-1, NLRP5 and EIF2AK1 associate with disease progression [53-54]. MC1R is related to the delayed onset of clinical symptoms [53]. Its protein encodes the melanocyte stimulating hormone receptor and the identified variant associates with the phenotype of rutilism [50].

2.2.4 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 accelerated speech, inappropriate silences and palilalia. Patients show sluggish facies, stiffness and body tremor. Parkinson's disease (PD) and other degenerative parkinsonisms represent this disorder [33].

2.2.4.1 Parkinson's disease

A relevant gene in Parkinson's disease is SCNA, which encodes α-synuclein (aSyn) [55]. This protein plays a role in the brain in maintaining a supply of synaptic vesicles in the presynaptic terminals by grouping synaptic vesicles [56]. Transgenic mice that overexpress aSyn of human wild-type (WT) under a wide neuronal promoter (Thy1-aSyn) present initial motor and non-progressive motor deficits, followed by parkinsonism with dopamine loss. Pathological aSyn is present in the periaqueductal grey substance manifesting alterations in vocalization. These vocalization deficits are early and progressive compared to WT, with alterations over time in the duration, intensity, and
profile of the call and exacerbated [57]. Other studies point to PINK1, a gene involved in susceptibility to the development of early PD with autosomal recessive inheritance. Grant [58] showed that PINK1-KO rats have significant vocalization deficits dependent on age, intensity, bandwidth, and peak frequency. PINK1-KO rats also exhibit mitochondrial breathing defects and aSyn aggregates resistant to proteinase K in various brain regions [59-60].

Speech disturbances may be early markers of PD detection. An initial study of cognitive disorders in the Chinese population did not reveal any significant differences in neuropsychological tests in language fluency between carriers of a known PD mutation (LRRK2 S1647T) and noncarriers [61]. However, a later report with more specific criteria for the study of language in patients with asymptomatic mutations (PARK2 and LRRK2) who performed executive, semantic, verb production, and syntactic tasks, presented alterations in a syntactic test with a minimal amount of working memory. These results also suggest that these mutations may play some role in language processing [62].

2.2.5 Hyperkinetic dysarthria

Hyperkinetic dysarthria relates to alterations in the basal ganglia pathway (caudate/putamen nucleus). It generates tense speech, with swaying voice volume, suddenly forced breathing and multiple voice interruptions [33].

2.2.5.1 Laryngeal dystonia

Laryngeal dystonia (LD) 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 [63]. Dopaminergic, GABAergic, glutamatergic and cholinergic neurotransmission is involved in the pathogenesis of dystonia [64].

LD manifests itself in 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 stained voice [65].

Although there are differences between the genotype and phenotype of LD, functional connectivity alterations in the sensory-motor and lower parietal cortices are associated 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 have been the white matter in the inner capsule and cerebellum, as well as the thalamus, the corticobulbar tract and the basal ganglia [66]. Other imaging studies have also described alterations at the level of the left dorsal primary sensorimotor cortex, this characteristic is more pronounced in the abductor forms. The frontoparietal cortex is also affected, at the angular gyrus [67].
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 of LD versus relatives in the supplementary motor area (SMA) and superior temporal gyrus (STG), as well as in the superior longitudinal fasciculus that links the engine to the posterior temporal cortex. 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 history of dystonia [65].

Abnormalities in these regions associate with underlying alterations in grey matter volume, cortical thickness and white matter downstream pathways, genetic relationship with the abnormal functional connectivity of the premotor/primary sensory-motor and lower parietal cortex, the latter showing a significant relationship with age at onset [68].

Up to 12% of patients with laryngeal dystonia report a family history. 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 [69]. More than 20 different types of dystonia, called DYT, can be distinguished genetically. Some of these are considered primary dystonias or may associate with other neurological signs [67]. Some causative genes are highly expressed during early brain development [64]. 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 [70]. 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 [71].

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 associated 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 [72].

Polymorphisms may also be involved in the higher or lower risk of developing LD. Polymorphisms in the DYT1 gene have been identified as associated with adult-onset, primarily focal dystonias, including LD. Polymorphisms in the DYT1 gene have been shown to increase or decrease the risk of developing dystonia. In cases of non-familiar dystonia in the Icelandic population, a significant association was observed between dystonia and the presence of some markers comprising the DYT1 gene [73]. However, further results did not replicate the association [74]. A review reported by Sharma [70] suggested that data from different ethnic groups and different clinical populations with dystonia have given conflicting results regarding whether specific genetic polymorphisms increase or decrease the risk of developing dystonia. However, they
considered the results as a whole support the role of genetic variability in the DYT1 genome region as a risk factor in the development of focal, segmental and delayed dystonia. Also, a study conducted by the same author on a large cohort of focal and segmental dystonia, including SD and cervical dystonia patients, revealed a significant association between the presence SNP, the deletion allele in Mtdel’s SNP (rs3842225), and protection from the development of focal or segmental dystonia. However, there was just one trend toward an association between the presence of the Mtdel SNP allele and the protection of the developing isolated LD [75].

A functional magnetic resonance image (fMRI) paper 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, and it is involved directly and indirectly 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 carrier motor sequence execution compared to other LD patients. A similar level of abnormalities in the primary sensory-motor cortex appeared to be a shared characteristic of brain changes in all patients with LD compared to healthy controls. There were also greater cerebellar alterations in sporadic and familial cases without known genetic causes compared to the mutation-carrying GNAL. However, results only provide initial clues about the possible links between a particular pattern of brain activity and the genetic state in LD [69].

TUBB4 is mostly expressed and plays a role in brain development during the fetal period. The main region of expression is the amygdala, hypothalamus, thalamus and prefrontal cortex. TUBB4 mutations are involved in abnormal microtubule function, generating whispered voice DYT4 dystonia and other phenotypes of laryngeal dystonia [76].

Peng [77] described a patient with myoclonus action affecting the hands and arms carrying 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 associated with laryngeal dystonia.

2.2.5.2 Tourette syndrome

The internal mitochondrial membrane protein 2L (IMMP2L) gene in 7q22-q31 is an interesting candidate for Tourette syndrome (TS). IMMP2L encodes subunit 2 of the internal membrane peptidase, a mitochondrial protease involved in the excision of the space separation signals of the 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 [78]. Interestingly, a familial balanced reciprocal translocation t (7; 15) (q35; q26.1) has also been identified in one patient, interrupting the CNTNAP2 gene in phenotypically normal individuals [79].

The PNKD gene, widely expressed in the brain playing a role in the regulation of myofibrillogenesis, is also known for its association with TS and its involvement in speech
disorders. One report identified a G89R nonsense mutation in a child affected by intermittent ataxia, diarrhea, exercise intolerance, and speech articulation problems [80].

2.2.5.3 Huntington's disease

Huntington's disease (HD) 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 sequence of CAG 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 [81]. There are epigenetic factors identified, such as an increased methylation at site H3K9 and H3K27 with a consequent transcription activation [82].

Concerning voice disorders, Foxp1 has been involved in transcriptional HD deregulation, interacting with interaction with mHtt. The combined analysis of microarrays and ChIP-seq in a striatal cell line that overexpresses this transcription factor identified a set of target genes, including some associated with inflammatory and immunological disorders in other systems. 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 [83].

2.2.5.4 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 [84]. It may associate with other parts of the body and, as with essential tremor, may also improve with alcohol intake [84-85]. Genes associating systemic clinical symptoms with dysarthria include DRD3 (3q13.31), FUS (16p11), TENM4 (11q14), 2p25-p22 and 6p23 [86].

2.3 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 involuntary pauses or blockages in which the person stuttering cannot make sounds. Multiple mechanisms explain the genesis of stuttering, with a strong genetic correlation. 9% of patients with a family history have an association with the GNPTAB, GNPTG, and NAGPA genes. 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 [87].

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-acetylg glucosamine-1-phosphotransferase. It was the first gene implicated in stuttering, identifying non-sense mutations in several families regarding inbreeding [88].
Through a systemic sequence of candidate genes, it was identified **GNTPG** and **NAGPA** genes at 16p13 in isolated stuttering cases. Also, the variants in these two genes observed in the cases were almost exclusively non-sense amino acid substitutions. **GNPTG** catalyzes the initial step in the synthesis of the mannose 6-phosphate (M6P) determinant required for efficient intracellular targeting of newly synthesized lysosomal hydrolases to the lysosome. It encodes a protein subunit that combines with the product of the **GNPTAB** gene to form the functional phosphotransferase enzyme. **NAGPA** is responsible for catalyzing 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 for lysosome [87].

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)) of that gene. The stuttering cases had many predicted variants of loss of function in **AP4E1**, including deletions, frame changes, nonsense, and splice site variants, while only nonsensical substitutions were observed in the controls. All the mutations in cases and controls were present in a single copy [87].

Other authors also observed association in other chromosome regions [89-91]. In addition to the involvement of **FOX2-CNTNAP2** pathways, alterations in intracellular lysosomal functions play an important role in their development [7].

### 2.4 Speech sound disorder

This is a speech disorder in which there are difficulties in the formation of phonemes that interfere with verbal communication. It can cause articulation disorders, phonemic or mixed [92]. Speech sound disorder (SSD) can also alter the literacy process by concurring with other language disorders, such as dyslexia and specific language impairment, to determine patients’ literacy skills, and share genetic determinants [93].

**DCDC2** and **KIAA0319** are strongly associated with phonological awareness, influencing language and cognitive traits [80, 94]. Other associations involved dopaminergic genes related to **ANKKK1** and **DRD2**, and nicotinic genes related to **CHRNA3** and **BDNF** with case and articulation control status. These results support previous reports involving dopaminergic and nicotinic neural signaling in human communication and cognitive development [94]. In **SSD**, the analysis of phonological memory binding and decoding traits identified regions on chromosomes 3, 1, 6, 15, while the genome of the entire family subtype on 8q, 6p, and 7q [7].

Nopola-Hemmi [95] analyzed a large Finnish family and found a link with **DYX5** (3p12-q13). Other reports involve **DYX8** (1p36-34), whose role is unknown. **CYP19A1** (15q21.2), involved in the synthesis of lipids and hormones has been associated with **SSD** and dyslexia [96]. Some reports associate **DYX1C1** with phenotypes of **SSD**. Although subsequent studies have not replicated the
association of ROBO1 with dyslexia, it has been found a link to SSD. Other candidate genes include ELP4, PAX6, and FOXP2 [7].

3. Genomics of language disorders

3.1 Specific language impairment

Specific language impairment (SLI) is a disorder diagnosed in childhood in which the child has a delay or disturbance in language development for no apparent reason. 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 SLI, receptive language is also affected [97]. Predicted miRs involved in SLI are miR-1207-5p, miR-188-3p, miR-1225-3p, and miR-299-3p [18].

3.1.1 CNTNAP2

CNTNAP2 is a downstream gene regulated by the transcription factor FOXP2 [5]. It encodes a protein, neurexin, which plays its role in shaping potassium channels in developing neurons (nodes of Ranvier) and plays an important role in facilitating axonal-glial interactions and cell growth [98]. It locates on chromosome 7q, and it presents a wide range of alterations in other neurological disorders. It was the first chromosome to be associated with genetically complex forms of SLI and involved in early language acquisition [25]. However, its association with SLI needs replication as the specific causal variants and underlying mechanisms by which it may contribute to language alteration have not been elucidated yet. Deletions of CNTNAP2 in children with verbal dyspraxia unrelated to SLI have been reported, which implies the great phenotypic heterogeneity of this gene [99].

Cntnap2 can affect the development of neurons by increasing the number of active synaptic sites and facilitating network activity. In mice, Cntnap2 knockdown had the most pronounced effects on network activity in the hippocampus [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 focal epilepsy syndrome [100]. Cntnap2 expression in 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 LMAN, with a uniform Cntnap2 distribution throughout striatopallidum. Interestingly, in young females, Cntnap2 is enriched in AR to the same degree as for males and decreases to the level of the surrounding arcopallium 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 [101].

3.1.2 CMIP AND ATP2C2

Additional genes are likely to contribute to vocal learning [11]. Using a positional cloning approach, which involved a GWAS study followed by targeted high-density association research,
two genes involved in language capacity: the c-maf-inducing protein (CMIP) and the calcium-importing ATPase, type 2C, limb 2 (ATP2C2) [102]. Analysis of GWAS in these families revealed a strong and consistent link signal at locus 16q24 with the nonword 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 [97]. Linkage analysis and subsequent directed association analyses have suggested that CMIP and ATP2C2 relate to language disorders (especially nonword repetition) and phenotypic measures well characterized in these disorders. Although both molecules express in the brain, their functions are still poorly understood. There is a known significant association between short-term memory and these genes. Considering that there is a relationship between wordless repetition test performance and short-term memory, 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 link to these genes has appeared in subsequent studies, their association with SLI has not repeated yet. ATP2C2 has also proved to be linked to attention deficit hyperactivity disorder [25].

3.1.3 Other genes

FOXP1, previously described and KIAA0319 genes, appear to be involved in SLI [103]. A haploinsufficiency in SETBP1 (locus 18q12) is a factor also involved in VD, responsible for interacting with an oncogene involved in DNA replication [104-105].

Other genes identified were ABCC13, FLNC, RBFOX2, and ROBO2, and they relate to quantitative measures of language skills. GWAS studies of test subjects with language problems have also highlighted possible risk variants in NDST4, ZNF385D, COL4A, and NOP9. Other studies involve rare genetic events that may have greater penetrance. Also, the coding variants within NFXL1 confer a higher risk of SLI within a complex genetic model [106]. A study conducted by Centanni [98] detected 15q11.2 (CNTNAP2 region) as a region of susceptibility for SLI in four of the eight selected patients, although these also showed copies in the number of additional variants in many other previously linked regions. Finally, it has been described a balanced t(10;15) translocation in a male patient with developmental language disorder [107].

3.2 Aphasia

Aphasia is an alteration in the understanding and/or production of acquired language caused by brain damage. 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 AD, cognitive impairment extends beyond language and typically involves episodic memory, while in PPA there is a gradual deterioration of 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 there is clear anomic aphasia, and comprehension is affected. During the moderate and severe stages of AD, there is a loss of fluency, increased use of the wrong words, incorrect pronunciation, and poor comprehension. Finally, advanced stages include echolalia (repetition of words or phrases pronounced by another person) and verbal stereotypes (repetition of words or phrases without meaning). Primary progressive aphasia, on the other hand, is classified as fluent or non-fluent. In the fluent variant, prosody is normal, well articulated and grammatically correct, but progressively circumlocutative and devoid of words of content. The alteration of language associates 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. In a study of patients with a pathologically proven AD, PPA patients had a higher proportion of neurofibrillary tangles in language-related neocortical areas relative to the entorhinal cortex compared to patients with an amnesic presentation [108].

3.2.1 APOE

APOE and other genetic and environmental factors affect the anatomical distribution of AD pathology, which in turn influences neuropsychological presentation. In a study conducted by Mez [109] with 1368 participants divided into different subgroups, they reported that a language subgroup with AD had different demographic characteristics, genetic profile, and course of disease in addition to cognitive phenotype. The language subgroup was less likely to carry at least one APOEε allele relative to the memory subgroup. While this difference was present at all ages, it was more striking at a younger age. Compared to the memory subgroup, the language subgroup increased over time 35% faster on the Functional Assessment Questionnaire and 44% faster on the sum of CDR boxes. Also, there are studies in which a non-memory phenotype appears in approximately 25% of patients with early onset Alzheimer's disease [110].

APOE4 is over-represented in PPA, so it is likely to act as a genetic risk factor in the development of the disease [111]. A study by Daniele [112] showed that women with the APOE genotype ε2/ε4 showed an increased risk of PPA compared to women with homozygosis ε2/ε2 or ε4/ε4, suspecting that the allele ε3 might play a protective role in PPA and frontotemporal dementia (FTD). Interestingly, Seripa [113] showed an association in the chromosomal region 19q13-q13.2, which included in addition to APOE, the TOMM40, and APOC1 genes.

3.2.2 PSEN1 AND GLI3

In Alzheimer's disease, cases of visual or apraxic and language phenotypes are more frequent, with reports of atypical presentation with speech alteration, in mutations of Presenilin 1 (PSEN1), a protein that is part of the γ-secretase complex involved in the production of beta-amyloid. A study by an association of magnetic resonance image (MRI) and GWAS, MRI showed brain atrophy in semantic and language areas with GLI3 identification, which is one of three early developmentals expressed GLI zinc finger transcription factors that are normally involved in the pattern of brain
structures as an important mediator downstream of the Sonic Hedgehog pathway. That 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 for some forms of an autosomal dominant AD, including mutations with an aphasic phenotype [114].

3.2.3 Other genes

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. There is a significant and specific association between rs1456031 TT and rs17137124 TT genotypes and verbal fluency scores, with left frontal hypoperfusion [111,115].

GRN is a gene that encodes progranulin and leads to a haploinsufficiency syndrome. In these families, some 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 language bark of the left hemisphere. Although limited by an over-representation of PPA with speech disease, which often predicts the pathology of Alzheimer’s disease, 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 associated with PPA [116].

Prion protein gene (PRNP) modulates PPA disease, leading to specific regional hypoperfusion according to different molecular pathways [111,117]. Methionine/valine polymorphism of codon 129 may be overrepresented in this disease compared to controls, bvFTD, and motor neuron disease, with the possibility that codon 129 polymorphisms may influence the selective susceptibility of the language network to neurodegeneration, even when the disease is not related to prion disorders. However, subsequent studies have failed to replicate the results [117].

3.3 Dyslexia

Dyslexia (DL) is a reading disorder in patients with normal intelligence. Problems can include difficulty in spelling words, reading quickly, writing words, “pronouncing” words mentally, pronouncing words when reading aloud, and understanding what the individual is reading [118]. As described, reading skills can be explained by genetic factors. In a study conducted by [119] comparing COMT Val / Met polymorphism found in SNP rs4680, and reading and reading-related skills were found associations between variation in the COMT gene and performance in behavioral measures. In pairs of each genotype, they revealed significantly better performance for Met / Met relative to Val / Val and Val / Met relative to Val / Val in several reading skills. Apart from genetic factors, there are neuroanatomical and epigenetic implications, such as miR-548c-3p, that explain its development [119-120].

Regarding animal models, silencing of Dcdc2, Kilia0319 and Dyx1c1 genes produces deficits in neuronal migration, dyslexia, and alterations in working memory, auditory processing and visual
attention. Homozygous Dalc2 KO mice exhibit auditory processing, and memory deficits as well as electrophysiological changes in cortical neurons with normal brain development. Dyx1c1 knockdown in zebrafish resulted in alterations in the primary cilia, such as body curvature disorders, hydrocephalus, renal cysts, and organ inversion left-right asymmetry. Animal models have revealed unexpected roles for DYX1C1 in primary cilia, which are typical phenotypes of ciliary defects with similar results in KO mice [121].

3.3.1 DYX1C1

In animal models, DYX1C1 (15q21) mutations generate a delay in neuronal migration associated with dyslexia after a translocation t (2; 15) (q11; q21). Taipale [122] reportedly identified an erroneous sense mutation in some families of DL: rs57809907, 1249G> T, which results in Glu417X and truncates the protein by four amino acids by sequence analysis of the DYX1C1 coding regions. However, these results have not been subsequently reproduced. Later reports found an association with the common G allele. Interestingly, a study of DR in Chinese children also found a strong association with the G allele. Studies of a transcription factor binding in the promoter region have shown that allele A shows decreased binding to a repressive transcription factor. Lim [123] hypothesized that allele A is protective compared to allele G which regulates downward and those cases in which allele A appears to associate with DL may be secondary to linkage imbalance with a second nearby causal variant. Two other SNPs, rs12899331 and rs16787, in the promoter region were also found to be involved in the union of the transcription factor, but they did not associate with DL in subsequent studies. Its protein can also adhere to the estrogenic receptor, suggesting an involvement of hormonal pathways in dyslexia [124].

3.3.2 ROBO1

According to animal models, this gene is involved in axonal development across the midline of the CNS and spinal cord [96,125]. Partial haploinsufficiency can cause dyslexia in humans [126].

3.3.3 DCDC2

Initial analysis of association defined the DYX2 locus on chromosome 6p22, and several subsequent studies have reported associations with the doublecortin-2 gene (DCDC2) within the region. In addition to influencing DL, the SNPs in DCDC2 have been associated with overactive and attentive forms of ADHD, indicating that this gene may affect both disorders. There is evidence that DCDC2 contributes to the risk of autism in families with dyslexia and autism [82]. The gene structure is analogous to the DCX gene linked to X, which is known to be involved in the microtubule structure and influences neural migration. In rats, the fall of DCDC2 causes delays in neural migration in the embryonic brain. Also, DCDC2 affects neuronal fibers, increasing excitability and compromising peak time. The DCX gene mutation causes lissencephaly in men and cortical abnormalities in women [82]. Sequence analysis of DCDC2 coding regions in families with DL has not identified causal mutations; however, the association of DL was reported with a deletion in intron 2, called BV67727278, which appeared to contain sites of transcription factor binding [127]. In vitro studies showed that sequences in the region act as enhancers of DCDC2 expression. Also, these differences in gene expression may have a measurable phenotypic effect on brain structure,
where BV677278 variants are associated with differences in grey matter volume in unselected individuals [82].

3.3.4 KIAA0319

Although the function of this gene is unclear, decreased expression in the rat’s embryonic brain leads to delayed neural migration. KIAA0319 participates in the clathrin endocytosis pathway, a protein that forms the lining of cell membrane where lipoprotein receptors are located, and is an epigenetic regulator [7, 128]. SNPs at 5’UTR, the first untranslated exon and the first intron, suggest regulatory functions. It has been proven that the expression of the allele containing the SNP haplotype associated with dyslexia in this region of KIAA0319 decreases in cell lines of individuals with this pathology. Another SNP, rs9461045, has proven to have a regulatory function. Reporter trials showed that the risk allele, which was believed to create a binding site for the OCT-1 repressor, resulted in a decrease in vitro expression of KIAA0319 and a drop in restored expression of OCT-1. Regions of acetylated histones in and around the gene were mapped on a neuroblastoma cell line to identify promoting regions and show the likely influence of epigenetic mechanisms on the expression of KIAA0319 on the etiology of dyslexia. It has been found an acetylated region of 2.7 kb covering the 5’UTR, first exon and first intron of KIAA0319, corresponding to the location of 5 SNPs that associate with DL phenotypes in other studies. SNPs within or very close to the acetylated region have been associated with language-disturbing phenotypes, and linkage to the DCDC2 / KIAA0319 region has been reported for SSD [96]. A polymorphism of KIAA0319 / TTRAP / THEM2 influences the laterality of activation in the upper temporal gyrus, so these genes seem to influence the activity of the two hemispheres asymmetrically in areas related to language function [129].

3.3.5 Other genes

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 an allele of MRPL19 and C2ORF3 decreased in individuals carrying risk haplotypes in the adjacent region, as determined by heterozygous SNPs within the coding regions of the two genes. It suggested that a mutation unknown in the SNP association region affects the gene expression of both genes [82].

TTRAP (6p22.3) involved in DNA binding and repair, and magnesium ion binding [96], and ROBO2, with locus 3p12.3, are other factors. This latter is involved in the guidance of axon and tumor molecular signaling and necrosis factor [96, 130]. Finally, as additional candidates, CMIP, MC5R, DYM, NEDD4L and DGK1 genes [7].

4. Other complex genetic disorders with speech and language disorders

4.1 Autism-spectrum disorders

The great clinical heterogeneity of autism spectrum disorder (ASD) implies variability in the phenotypic characteristics of language and speech. ASD has comorbid phenogenotypes, such as
ADHD [131]. Thus, there may be alterations in the comprehension, dyspraxia or motor alterations [132]. The inversion of the pronoun, echolalia and a delay in understanding the reduced or even inverted production are the most frequent language alterations [133]. Along with the genetic factors involved, there are epigenetic factors described in the development of ASD. Concerning the controls, it has been observed hypermethylation at oxytocin receptor gene (OXTR) in peripheral blood, and the temporal cortex of patients [134].

4.1.1 SRPX2

The sushi domain protein SRPX2 is one of the targets of FOXP2 [135]. Historically, it has been primarily studied as a complement cascade regulator in the innate immune system. It is involved in neural development and migration. In the GABA-B receptor acts as signals directed to the axon. SRPX2 encodes a secreted protein that regulates synapse formation and ultrasonic vocalization in mice, and mutations in SRPX2 in humans have been linked to SLD, such as verbal dyspraxia caused by rolandic seizures.

The SPRX2 knockout mouse shows a decrease in VGlut2 synapse density in the IV layer of the somatosensory cortex, as well as a decrease in VGlut1, VGlut2 and VGAT synapse densities in the CA2 region of the hippocampus. SRPX2 KO mice show an abnormal ultrasonic vocalization ontogenetic profile [136]. Interestingly, SRPX2 KO mice show a reduced preference for social novelty, which can establish a relationship between SRPX2 and autism-related behaviors [137].

4.1.2 MED13L

MED13L is involved in neural crest induction and is highly expressed in the cerebellum after birth [138]. Also, MED13L relates functionally to EP300 and CREBBP products, link proteins between the FOXP2 and ROBO1 pathway, already described above [139]. In a case-report described by Jimenez-Romero [140] a change was identified in MED13L (chr12: 116675396A> G, G, GRCh37) that exhibited a profound language disturbance in the expressive domain, cognitive retardation, behavioral disturbances and an autism-like phenotype.

4.1.3 Other genes

Bartlett [141] identified two loci related jointly to SLI and ASD (15q25.1 and 16p12.3). Interestingly, the two link signals showed specificity by alterations of oral language for 15q and by deterioration of written language for 16p. These results show that there is a subset of individuals with reading problems that do not have a comorbid oral language deficit.

High gene expression of FOXP1 may contribute to the pathogenesis of ASD [26]. There are reports of de novo mutations in FOXP1. In a study conducted by Chien [142] using RT-qPCR showed a significant rise in FOXP1 mRNA levels in patients with ASD compared to the control group. However, the study was limited by factors such as the small sample size, differences between the ages of the case and control groups, and the absence of brain study.
The association of other genes involved in SLD in autism has yielded conflicting results. The association of CNTNAP2 has been reported. In the Chinese Han population, susceptibility to autism showed that a common non-coding variant (rs10500171) was related to increased risk, and TA (rs7794745- rs10500171) and ATA (rs10244837- rs7794745- rs10500171) haplotypes also showed evidence of association [143]. A Spanish case-control association study did not find those common variants of FOXP2 that contributed to the susceptibility of autism, which is consistent with previous reports [144-145]. Moreover, the association of two CNTNAP2 single nucleotide polymorphisms (rs2710102 and rs7794745) gene previously reported with autism was not replicated [145].

Purkinje-cell Tsc1 mutant mice lead to behaviors relevant to ASD, including changes in vocalizations [146]. Other genes involved in autism involving communication impairments and ASD are MET, CTTNBP2, EN2, NBEA, HRAS, and PTEN. It is also possible that somatic mutations affecting a subset of neurons may cause language deficits in ASD [139].

4.2 Other disorders

Patients with Down syndrome (trisomy 21) have more altered expressive language than receptive language [147]. Typically, children tend to have altered syllable structure, group reduction, and final consonant elimination. There is also a higher prevalence of stuttering [148]. As they grow up, language has shorter and less complex statements than you would expect from nonverbal mental age. In senescence, SLD overlap with the increased risk of dementia [147].

Fragile X syndrome (FXS) is the leading inherited cause of intellectual disability, accounting for 40% of all X-linked mental retardation. The syndrome is the result of a mutation in the FMRI1 gene, which locates on the X chromosome (Xq27.3). The mutation induces an expansion of CGG triplet repetition within FMRI1. FMRI1 encodes fragile X mental retardation protein (FMRP) [149]. As epigenetic mechanisms of this syndrome, a promoter hypermethylation induces a transcription repression [82]. In songbirds, FMRP expresses in the HVC, LMAN, RA, and X-area song nuclei [11]. FMRP enriches in male RA from the beginning of the sensorimotor learning phase. There is a high co-morbidity between FXS and autism, which modifies the phenotypic characteristics of the patient. A characteristic of the language alteration in an FXS patient is the appearance of repetitive language. Other alterations involve delays in the development of vocabulary, comprehension, and syntax. Also, FXS patients also have significant weaknesses in pragmatics, and their ability to identify and provide the necessary informative details in language discourse is affected more than expected by their levels of cognitive development [150].
5. Conclusion

The speech and language process involves environmental factors that overlap with other genetic and phenotypic factors that affect multiple, correlated, neuronal and motor structures while highlighting at the same time an underlying deficiency of inheritable hereditary traits. Identification of novel candidate genes and variants may enable a better understanding of the biological basis of communications disorders. As stated above, multiple genes are involved in its development, but also a single gene may be involved in different communication disorders. The knowledge of these genes allows us to differentiate the phenotypic expression of a disorder, identify those patients at risk of developing disorders in verbal communication and promote early detection mechanisms (Figure 1). The genomic investigation also evaluates at an early stage treatments aimed at restoring...
vocal communicative function. However, it should take into account that the subjectivity of case definitions in speech and language disorders may limit the identification of multiple different loci. Regarding this, the unification of criteria, the development of endophenotypes and Mendelian transmission studies would provide more robust results [152].

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