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SPEECH AND LANGUAGE DISORDERS AT DEVELOPMENTAL AGE

Zbornik radova
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Plenarni deo/Plenary session

MEDICAL GENETICS AND ITS IMPLEMENTATION IN SPEECH, LANGUAGE AND HEARING DISORDERS

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It is critical that speech language pathologists and audiologists understand principles of medical genetics, genetic testing and genetic counseling. Vocal communication mediated by speech and language is a uniquely human trait, and has served an important role in the development of our hearing. Scientists are beginning to uncover the neurogenetic pathways that underlie our unparalleled capacity for spoken language.

The purpose of this article is to review recent findings suggesting a genetic susceptibility for speech, language and hearing disorders.

Deficits in speech and language functions can be: aphasia, stuttering, articulation disorders, verbal dyspraxia, and dyslexia. A number of these disorders have been shown to cluster in families, suggesting that genetic factors are involved, but their molecular etiology is not well known. Linkage studies and molecular genetic analyses in a large family containing multiple individuals affected with verbal dyspraxia led to the discovery of mutations in the FOXP2 gene. In studies of stuttering, linkage and candidate gene approaches in consanguineous families identified mutations in the lysosomal enzyme-targeting pathway genes GNPTAB, GNPTG, and NAGPA, revealing a role for inherited defects in cell metabolism in this disorder. Sixty percentages of congenital deafness has a primary genetic etiology. Complete medical genetics evaluation in a young child with a significant hearing loss has a high diagnostic yield. A specific etiology can be identified in close to 90% of the cases. Two known causes of early childhood hearing loss – congenital CMV and connexin 26 mutations - each account for about 40% of the identified children.

Knowledge of genetic factors may improve diagnosis and early identification of children at risk of speech, language and hearing disorders. This early identification will allow for timely environmental intervention. Early intervention is crucial

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because of the potential of communication disorders to lead to social and educational isolation.

Key words: *medical genetics, speech disorders, language impairments, hearing disorders*

Introduction

Medical genetics is the specialty of medicine that involves the diagnosis and management of hereditary disorders. It is critical that speech language pathologists and audiologists understand principles of medical genetics, genetic testing and genetic counseling. Around two decades, evidence has been collected to support the hypothesis that specific, language and hearing disorders may aggregate in families and, therefore, may contain a genetic component (Lahey & Edwards, 1995; Bishop, North, & Donlan, 1995).

Newborn screening for hearing loss is very important process. The major impetus behind infant screening has been the improved outcome of speech and language potential in children identified early. There is however, another great advantage in identifying hearing loss early. A significant proportion of early childhood hearing loss has a genetic etiology. The family of every child identified with a significant hearing loss should be offered clinical genetics consultation. A genetics evaluation can provide several important pieces of information to the family and the child's health care providers.

Familial aggregation is compatible with a role for genetic risk factors but could be confounded by environmental influences shared between individuals of the same family. This issue can be resolved to a large extent by investigating samples of twin pairs, in which at least one member is affected with a speech and language disorder (Tomblin & Buckwalter 1998). Such studies have consistently demonstrated elevated concordance for speech and language difficulties in monozygotic (MZ) twins, who have a virtually identical genetic structure, versus dizygotic (DZ) twins, who are as genetically similar as ordinary siblings, sharing roughly half of their segregating alleles. Children with specific language impairment are four times as likely to have a family history of the disorder as are children who do not have such an impairment, and the concordance rate for the disorder is

almost twice as great for monozygotic twins as for dizygotic twins (Stromswold, 1998).

Support for genetic involvement in the etiology of speech problems has also arisen from studies of phenotypic outcomes in adopted children. In a study of 156 adopted and nonadopted children, (Felsenfeld & Plomin, 1997) demonstrated that a positive history of speech difficulties in biological parents leads to a significant increase in a child's risk of developing similar problems, even if living with adoptive parents who have no impairment. In contrast, they found no risk increase for adopted children as a consequence of living with an affected parent. Note that these data suggest the importance of genetic factors or early prenatal influences (or a combination of the two) on speech development, but the adoption design is unable to distinguish between these possibilities.

It is generally thought that the genetic mechanisms underlying susceptibility to speech and language disorders are polygenic in nature, involving complex interactions between several common genetic variants and environmental factors. Despite this complexity, researchers have recently begun to identify genetic factors that may play a role in the etiology of speech and language disorders (Kang et al., 2010). It is hoped that the identification of contributory genetic risk factors will allow the elucidation of biological pathways and neurological mechanisms that contribute to speech and language acquisition processes and play a critical role in the etiology of speech and language disorders.

Identifying the etiology of a hearing loss may affect clinical management, improve prognostic accuracy, and refine genetic counseling and assessment of the likelihood of recurrence for relatives of deaf and hard-of-hearing individuals. Linguistic and cultural identities associated with being deaf or hard of hearing can complicate access to and the effectiveness of clinical care. These concerns can be minimized when genetic and other health-care services are provided in a linguistically and culturally sensitive manner.

The **purpose** of this article is to review recent findings suggesting a genetic susceptibility for speech, language and hearing disorders.

Genetic factors in speech and language impairments

Language acquisition is not so straightforward and language ability is delayed or permanently impaired. Specific language impairment (SLI) is diagnosed in children who experience an unexpected difficulty in the acquisition of language skills, despite otherwise normal development and adequate intelligence. A diagnosis of SLI relies on the absence of other neurologic conditions (*eg*, cerebral palsy, autism). It has been recognized that SLI has a strong genetic component (Tomblin, Records, & Zhang, 1996). SLI is usually diagnosed through exclusionary criteria rather than on the basis of any specific clinical test. SLI affects between 5% and 8% of English-speaking (primarily UK and US) preschool children, and is a lifelong disability with an increased risk of behavioral disorders, social problems and literacy deficits (Whitehouse et al., 2009). The disorder shows significant overlap with associated developmental conditions, such as attention deficit hyperactivity disorder (ADHD), dyslexia, speech sound disorder (SSD), and autism (Pennington & Bishop, 2009).

Over the last 15 years, researchers have begun to identify genetic factors that may have roles in the etiology of language disorders. It is hoped that the study of these genes will facilitate a better understanding of the cause of language impairments, leading to the development of improved diagnostic and treatment strategies for affected individuals. In turn, knowledge regarding the cause of such impairments may further our understanding of the biological pathways that underpin normal language acquisition (Plomin, Haworth & Davis, 2009). Researchers of speech-sound disorder have applied targeted linkage studies, while investigators of SLI and stuttering have performed genome-wide linkage studies and subsequent targeted association studies. In the following text the focus is on specific genes that have been identified to have a role in speech and language impairment.

FOXP2

This is the first gene which was implicated in a speech and language disorder and was identified by the investigation of a large family affected by a distinctive form of speech impairment known as verbal dyspraxia. Verbal

dyspraxia is characterized by difficulties in the control of orofacial muscles leading to a deficit in the production of fluent speech. In addition to their speech problems, affected members of this family also had expressive and receptive language deficits and, in some cases, written language problems and nonverbal cognitive impairment (Watkins, Dronkers, Vargha-Khadem, 2002). FOXP2 gene is located on chromosome 7q (OMIM 605317). In 2001, a study by Lai and colleagues implicated mutation of FOXP2 in a monogenic form of speech and language disorder found in a three-generation pedigree (the KE family) and in an unrelated individual with a chromosome translocation (Lai et al., 2001). In both cases, the disorder was characterized by verbal (or articulatory) dyspraxia, that is, difficulties controlling the movement and sequencing of orofacial muscles, causing deficits in the production of fluent speech. In-depth studies of the KE family showed that, in these individuals, speech production problems are accompanied by a complex array of linguistic deficits that include varying degrees of expressive and written language problems and, in some members, nonverbal cognitive impairments (Watkins, Dronkers & Vargha-Khadem, 2002).

The FOXP2 gene encodes a winged helix/forkhead DNA-binding protein from the FOX family. This protein acts as a transcriptional repressor and has four alternative isoforms (Schroeder & Myers, 2008). The FOXP2 gene shows a widespread pattern of expression across the majority of tissues and developmental time points. Nonetheless, within each tissue its expression appears to be tightly regulated in a complex pattern of expression with a high degree of conservation across species (Ferland et al., 2003).

Although the exact contributions of FOXP2 to the development of speech and language remain unclear, the consensus from expression studies, neuro-imaging data and animal models is that this gene is of particular importance in the CNS, such that its dysfunction disturbs the development and function of the motor cortex, striatum and cerebellum. Investigations of the properties of FOXP2 and its downstream targets are beginning to identify networks of genes that could be crucial players in neural circuits that facilitate language acquisition (Newbury, Fisher & Monaco, 2010).

FOXP1

On the basis of FOXP2 data, researchers have suggested that other forkhead binding genes represent good candidates for involvement in speech and language disorders. The human FOX gene family consists of over 40 members classified into 19 subfamilies (designated FOXA to FOXS) according to specific motifs within the DNA binding domain (Hannenhalli and Kaestner, 2009). The FOXP subfamily includes four genes (FOXP1-4) with diverse functions. The proteins encoded by these genes are found to bind to each other to form active heterodimer DNA binding molecules (Li et al., 2007). In particular, it has been suggested that FOXP1 and FOXP2 may have a particularly close relationship with overlapping functions that allow them to work in a cooperative manner during tissue development (Shu et al., 2007).

FOXP1 disruptions are likely to account for the similarities in patient phenotype, namely deficits in motor development and speech delays. This hypothesis has recently gained support from a large-scale study for chromosome abnormalities in 1523 individuals with learning disability (Horn et al., 2010). This investigation identified deletions of the FOXP1 gene in three unrelated patients (two males, one female) with moderate learning disabilities, global developmental delays, and severe speech and language disorders. MRI and electroencephalography of the patients did not reveal any gross structural brain abnormalities, and a similar chromosome deletion was again observed in a control individual who was not reported to have learning difficulties.

The function of the FOXP1 protein in the brain remains unclear, but recent studies suggest that it may play a role in motor neuron diversification, through its interactions with Hox proteins (Rousso et al., 2008); in neuronal migration, by gating Reelin signaling pathways (Palmesino et al., 2010); and in neuronal differentiation, via regulation of the Pitx3 protein (Konstantoulas et al., 2010). Those data suggests that, like FOXP2, FOXP1 may also be involved in the determination of neural circuitry important for the development of speech and language.

CNTNAP2

The *CNTNAP2* gene on chromosome 7q (OMIM 604569) was the first gene to be associated with genetically complex forms of SLI. This association was achieved through a candidate gene approach that arose from downstream target screening studies of *FOXP2*. They discovered that FOXP2 directly binds a regulatory region of the *CNTNAP2* gene (Vernes et al., 2008). CASPR2, the protein encoded by *CNTNAP2*, is a member of the neurexin family, a family that is particularly interesting from a functional point of view as members are known to interact with neuroligins to adhere presynaptic neuronal membranes to postsynaptic ones. In the case of CASPR2, the protein mediates interactions between neurons and glia during nervous system development and is also involved in localization of potassium channels within differentiating axons. Furthermore, both neurexins and neuroligins have been strongly implicated in autistic disorder, a neurodevelopmental condition that shows strong overlap with SLI (Lawson-Yuen et.al., 2008).

CNTNAP2 encodes a neurexin protein that is responsible for the localization of potassium channels in developing neurons and plays an important role in the facilitation of axonal-glial interactions. Brain expression studies indicate that while this gene is evenly expressed across the rodent brain, it shows a specific pattern of expression in the song control nuclei of male songbirds and is enriched in the frontal cortex of humans. Structural MRI studies of population cohorts found that individuals who carry two copies of the genetic ‘‘risk’’ variants previously associated with autistic disorder have significantly reduced volumes of gray and white matter across several brain regions, including the prefrontal cortex, fusiform gyri, occipital cortices, and cerebellum, which have previously been shown to be important in autistic disorder. Thus current data suggest that CNTNAP2 plays a fundamental role in neuronal development and that perturbations of its function may contribute to susceptibility to a diverse range of neurodevelopmental psychiatric disorders as well as normal variations in brain function (Newbury and Monaco, 2010). It is likely that a gene such as *CNTNAP2* functions in overlapping and intersecting neurodevelopmental pathways and thus even a seemingly subtle disruption of its function may affect a variety of processes. The eventual outcome at the organ or organism

level may in turn be modulated by the ability of downstream genes and proteins to compensate for these variations. We can therefore view *CNTNAP2* as a neuronal buffer; subtle disruptions of this gene alone may be insufficient to cause disorder but may place a critical load on neurological systems, which manifest in different ways depending on the nature of additional load factors. Once a critical threshold of load is exceeded, it is likely that neurological imbalance will ensue.

ATP2C2 and CMIP

The calcium-transporting ATPase 2C2 (*ATP2C2*) and c-MAF inducing protein (*CMIP*) genes, both on chromosome 16q, were identified as SLI candidates by a positional cloning approach, which involved a genome-wide linkage study followed by a targeted high-density association investigation. Genome-wide linkage analyses in these families revealed a strong and consistent linkage signal on chromosome 16q with a measure of non-word repetition (The SLI Consortium, 2002). Although this does not preclude the presence of a genuine association, as it may be caused by differences in linkage disequilibrium patterns, it does highlight the need for careful interpretation of this result as well as for further replication in additional cohorts. Both *ATP2C2* and *CMIP* show expression in the brain and, although little is known about their role in this tissue, hypothetical links can be made between their putative functions and language and memory-related processes. The CMIP protein forms part of the cellular scaffold linking the plasma membrane to the cytoskeleton, and cytoskeletal remodeling represents a critical step in neuronal migration and synaptic formation processes. In addition, CMIP has been shown to interact with filamin A and nuclear factor κB, both of which have important neurological functions. ATP2C2 is responsible for the removal of calcium and manganese from the cytosol into the Golgi body. Calcium is an important ion in the regulation of many neuronal processes, including working memory, synaptic plasticity and neuronal motility, and manganese dysregulation has been linked to neurological disorders. Interestingly, in a recent meta-analysis of genetic data for ADHD, which shows significant co-morbidity with SLI, chromosome 16q was highlighted as the most consistently linked region for this disorder. Concurrent genome-wide association studies described

significant association with a variant in *ATP2C2*, reinforcing the fact that, as discussed above, the correlation between genetic susceptibility and surface phenotype is far from straightforward (Newbury, Fisher & Monaco, 2010).

As with *CNTNAP2*, the specific causal variants and the underlying mechanisms by which *ATP2C2* and *CMIP* might contribute to language impairment have yet to be elucidated. The characterization of these factors will not only provide definitive evidence for the involvement of these genes but may also lead to the identification of further neurological pathways that contribute to language acquisition. Given the proposed reliance of non-word repetition performance on short-term memory ability, one can postulate that the investigation of *ATP2C2* and *CMIP* may 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 converging routes of investigation will enable the characterization of overlapping and interacting neurological systems that serve the acquisition of language (Newbury, Fisher & Monaco, 2010).

Genetic factors in hearing disorders

A significant difference in the cause of hearing impairment is whether its origin is genetic or nongenetic. Genetic hearing losses are due to single or multiple lesions throughout the genome that may be expressed at birth or sometime later in life. Nongenetic "acquired" hearing loss, on the other hand, is a consequence of environmental factors that result in hearing impairment, with no regard to inheritance. Such factors might include infections such as meningitis and otitis media, traumatic injuries such as perforation of the eardrum, skull fractures and acoustic trauma, and use of toxic drugs such as aminoglycoside antibiotics or cisplatin. However, even when speaking of environmental causes, genetic factors may be involved as modifying genes that may have an impact on onset, severity, and progressiveness of nongenetic hearing loss (Shalit, and Avraham, 2008).

Genetic hearing loss occurs 1 in 2000 to 1 in 650 live births [Morton & Nance, 2006]. About 70% of the cases are nonsyndromic. Studies show that 75% of nonsyndromic hearing loss (NSHL) are inherited as autosomal recessive [Tekin et al., 2001]. 10-20% of cases are inherited as autosomal

dominant and 1-5% are X-linked recessive. Approximately, 1% of human genes, i.e 200 to 250 genes are responsible for hereditary hearing loss [Finsterer & Fellinger, 2005]. So far, more than one hundred loci and 55 genes have identified which are involved in nonsyndromic hearing loss.

Nonsyndromic genetic hearing loss

A high frequency of genetic hearing loss occurs without any abnormality in other organs classified as non-syndromic hearing loss. Different patterns of inheritance have been observed in NSHL. Variety of protein coding genes such as gap junctions (connexin encoding genes), motor proteins (myosins) cytoskeletal (e.g. actin), ion channels, structural proteins (Tectorin alpha, Otoancorin, Stereocilin, etc), transcription factors (POU3F4, POU4F3 and Eyes absent 4 or EYA4), and additionally microRNA genes are involved in hearing loss (Mahdieh et al., 2010). *GJB2* mutations are seen in 50% of autosomal recessive hearing loss in the Caucasians (Tekin et al., 2001). Some genes e.g. *GJB2* gene is expressed in a variety of organs of the body while others such as *OTOA*ncorin is only expressed in the inner ear.

Autosomal recessive non-syndromic HL (ARNSHL) was first described in 1846. It is the severest form of congenital HL in which there is a defect in cochlea in nearly all cases. Loci of ARNSHL are designated as the DFNB; DF stands for Deafness and B indicates the autosomal recessive pattern of inheritance. Up to date, 46 genes and nearly 100 loci have been identified for hearing loss. Regarding different studies, connexin 26 gene mutations differ depending on geographical place and ethnicity (Mahdieh & Rabbani, 2009). The most common genes causing ARNSHL are: GJB2 and GJB6 genes and connexins, MYO15A gene in DFNB3 locus, *SLC26A4* gene in DFNB4 locus, *TMC1* gene in DFNB7/11 locus, *TMPRSS3* gene in DFNB8/10 locus, *OTOF* gene in DFNB9 locus, *CDH23* gene in DFNB12 locus, *TMHS* or LHFPL5 genes in DFNB67 locus (Shalit, and Avraham, 2008).

Late onset, mild and progressive forms of hearing loss are the usual phenotypes associated with autosomal dominant form of deafness. About 25 genes and more than 60 loci have been reported for autosomal dominant non-syndromic hearing loss (ADNSHL). There is no frequent gene mutated in

ADNSHL but mutations in some genes including *WFS1*, *KCNQ4*, *COCH* and *GJB2* have been suggested to be common (Higert et al., 2009).

There are fewer X-linked forms of hearing loss (DFNX) than ARNSHL and ADNSHL. X-linked form of deafness has been reported as prelingual or progressive in different families. Five loci and three genes (POU3F4, *SMPX* and *PRPS1*) have been reported for X-linked hearing loss. To date, only one locus has been linked to chromosome Y (DFNY1) that was found in a very large Chinese family (seven generations). They reported that the ages of onset for the patrilineal relatives were from 7 to 27 years. *PCDH11Y*, encoding a protocadherin, was suggested to be the causality (Wang et al., 2004).

Due to the important function of mitochondria in producing chemical energy through oxidative phosphorylation, mitochondrial DNA mutations can cause systemic neuromuscular disorders such as hearing loss. mtDNA mutations may be inherited or acquired. The inherited mitochondrial mutations can cause many clinical features including myopathy, neuropathy, diabetes mellitus and sensorineural hearing loss (Finsterer & Fellinger, 2005). Acquired mitochondrial mutations may be associated with aging and age related hearing loss or presbycusis (Fischel-Ghodsian, 1999).

Syndromic genetic hearing loss

Hearing impairment is denoted as an integral clinical phenotype in more than 400 genetic syndromes (Nance 2003). The presence of clinical features accompanying hearing impairment can vary on a wide scale, while hearing abnormalities are often mild, unstable, or a late-onset trait in these syndromes. Syndromic forms of hearing loss are estimated to be responsible for up to 30% of prelingual deafness, although in general, it endows only a small portion of the broad spectrum of hearing loss. The prominent portion of these disorders are monogenic (Friedman et al. 2003), meaning that their hereditary component is derived from one mutated gene throughout the genome. Most common syndromes which are associated with hearing loss are: Usher syndrome, Pendred syndrome, Alport syndrome, Waardenburg syndrome, Branchio-oto-renal syndrome, and Stickler syndrome.

Genetic evaluation

The main problem in the diagnosis of disorders such as deafness is its heterogeneity. Genetic study of hearing loss has considerable benefits for patients which are as follows: identifying the medical and non medical decisions e. g cochlear implant; carrier testing and prenatal diagnosis; prediction for the progressive state of the disease; eliminating unnecessary tests and investigations; providing appropriate genetic counseling before marriage, especially when they have heterogeneous conditions that carry different mutated genes. Genetic evaluation should be considered for children with newly diagnosed loss of hearing especially if no specific cause is determined. For example, there is no need for genetic evaluation of the family of a child with HL due to meningitis; although, they may need assurance of not transmitting the disease to the next generation. Based on previous studies, deaf people have positive assortive marriage. It is estimated that 90% of deaf individuals marry deaf. Depending on the pattern of inheritance they might have a deaf child. For example if both parental recessive alleles are similar, there is 100% chance of having a deaf child; and if one of the parents carry a dominant form of hearing loss and the other carry the recessive form of hearing loss the chance would be 50% for the dominant gene. Early diagnosis of hearing loss is important in gaining speech progression and social skills of the children which would lead to better life of these individuals and would later help them in cochlea implant. Hereditary or genetic understanding of the causes of HL is important. The benefits of this understanding and knowledge, not only allows physicians to help the families of at risk but also may help in treatment and control of hearing loss. Sometimes it is possible to prevent hearing loss from worsening. Hearing loss may be one of the clinical signs of a syndrome and if the genetic cause of hearing loss is determined it may help to predict and treat other clinical complications (Extivill et al., 1998).

Conclusions

The genetics evaluation of a young child is complex, and is best accomplished in the context of an interdisciplinary team. Important components of this team would include specialists in clinical genetics,

genetic counseling, otolaryngology, ophthalmology, audiology, speech pathology and vestibular physiology.

Increased understanding of the role of family risk and the genetic pathways of communication disorders is important for researchers and clinicians. For researchers and clinicians, understanding genetic factors helps to bridge gaps between different disciplines and may lead to a more comprehensive understanding of communication disorders.

The last two decades has seen an explosion in our understanding of the genetic basis of speech, language and hearing disorders. The identification of FOXP2 precipitated a whole field of research that continues to advance our understanding of the foundations of speech and language. Although *FOXP2* mutations seem to contribute to only a relatively small number of language disorder cases, it seems likely that variations in the genes it controls, such as *CNTNAP2*, may be implicated in common forms of language impairment. Studies of SLI has enabled the identification of two candidate genes on chromosome 16 (ATP2C2 and CMIP) as another candidate mechanism.

Hearing loss is the most common sensory defect affecting human beings. Genetic factors can be traced in half of the cases. Nonsyndromic hearing loss can follow any of the Mendelian inheritance patterns, but the majority are autosomal recessive nonsyndromic. Approximately 50 genes have been reported to be involved in hearing loss, and based on an estimation nearly 200 to 250 genes may cause hearing loss. Genetic understanding of the causes of hearing loss and finding the molecular mechanism of hearing process are valuable for genetic counseling, prevention and development of new therapeutic approaches. New technology and strategies such as next generation sequencing can help to discover new genes for deafness in future.

Knowledge of genetic factors may improve diagnosis and early identification of children at risk of speech, language and hearing disorders. This early identification will allow for timely environmental intervention. Early intervention is crucial because of the potential of communication disorders to lead to social and educational isolation.

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