Familial persistent developmental stuttering: genetic perspectives

Breila Vilela de Oliveira1*, Carlos Eduardo Frigério Domingues2*, Fabiola Staróbole Juste3, Claudia Regina Furquim de Andrade3, Danilo Moretti-Ferreira4

ABSTRACT

Stuttering is a disorder of oral communication that has a multidimensional character. The biological predisposition in the development of stuttering is still not well understood, but genetic contributions to this predisposition are enhanced by both references to the familial aggregation of stuttering and to familial stammering, which have appeared in the literature for over 70 years. Thus, we conducted a review as to the likely genetic factors involved in the manifestation of familial persistent developmental stuttering. The identification of genes related to stuttering, as well as alterations in their structures (e.g., mutations), contribute significantly to its understanding. The exact transmission pattern of genetic inheritance for stuttering is still not clearly defined and might probably be different among different families and populations. Genomic analysis have shown, concomitantly, the relevance of the genetic components involved and their complexity, thus suggesting that this is a polygenic disease in which several genes of different effects may be involved with the increased susceptibility of occurrence of stuttering. The clinician should be alert to the fact that a child with positive familial history for stuttering may have a strong tendency to develop the disorder chronically. It is important that the clinician is aware, in order to provide precise information about the disorder to the families. Objective evaluations and controlled treatments play an important role in the knowledge of the disorder’s development.

Keywords: Speech, language, and hearing sciences; Speech; Stuttering/etiology; Genetics; Genes; Inheritance patterns

INTRODUCTION

Speech involves linguistic (formal, segmental aspects) and paralinguistic (prosodic aspects, suprasegmental) components, processed by different neural ways, which, integrated and in sync, are basic for the constitution of one’s fluent speech that must have a continuous flow, maintaining sequence, speed, rhythm, and duration considered normal so that phonological, lexical, morphologic and/or syntactic units are adequately produced. Involuntary breaks or ruptures in any linguistic units characterize the disfluencies which can be considered common (hesitations; interjections; revisions; unfinished words; and repetition of words, segments or phrases) or stuttering (repetition of sounds or syllables; prolongations; blockades; pauses and intrusion). Stuttering is a complex disorder of the verbal communication, that cannot be considered as a single nosologic entity, as it has a multidimensional characteristic, and is often experienced by the individual as a loss of control of their own speech.(1)

During infancy, due to the complex process of language acquisition and development, it is common for children to present disfluencies (hesitations, repetition of sounds, syllables or words), tending to stabilize the speech flow after acquiring greater linguistic-phonologic and morphosyntactic-semantic-pragmatic domain. In 80% of the children these disfluencies are normal and tend to disappear in six months. However, in children who present predisponent factors for stuttering, these disfluencies will
be able to evolve into a chronic state known as developmental stuttering, which affects 5% of the children, mainly in the age group between 18 months and 7 years, taking place until 12 years of age in some cases, average prevalence of 1% in the population. Amongst the risk factors for the developmental stuttering described in the literature, age gender; duration of the disfluencies, type of ruptures, pre, peri and post natal morbidity, associated communication deficits; psychosocial stresses; positive family history for stuttering; and reaction from the child, the family and the society with respect to the problem (1).

Stuttering can also occur in additional two distinct circumstances, from injuries, in an ample range of cerebral areas, which is called acquired or neurogenic stuttering (2) and another one, involving psychological aspects.

Developmental stuttering is subdivided in: persistent developmental – present during a period equal or greater than 36 months after its manifestation; late recovery – recovered between 18 and 36 months after its onset; and early recovery – recovery before 18 months after the instauration of the disorder (3). In cases where there is recurrence in the family where two or more individuals are affected by stuttering, this is called familial developmental (4), purpose of this work. In cases where there is only one stutterer in the family, it is called isolated developmental. Thus, the classification of stuttering (1-4) can be schematically represented (Figure 1).

The biological predisposition in the development of stuttering is not yet well understood, but genetic contributions for this predisposition are strengthened by references in regard to the familial aggregation of the stuttering, that have appeared in literature for more than 70 years (5-8). Thus, due to the excellent and recent scientific findings in the biological scope, we look to establish a revision in regard to the probable genetic factors involved with the manifestation of the persistent developmental familial stuttering and in such a way to contribute with a better understanding.

LITERATURE REVIEW

The main arguments that base the involvement of genetic factors on stuttering are: studies of twins, with bigger agreement between monozygotic twins (62.5% to 90%) in relation to dizygotic twins (6.6% to 9%) (8-13); familial aggregation, where the disfluencies are more inclined to develop in consanguineous individuals, in detriment to the cases where such relation does not occur (9,14-16) and the phenotypical similarity developed among stutterers, such as repetitions, prolongations of sounds and syllables of words without being connected to differences of language and culture (15,17-19).

Thus, it is believed that there are regions of the genome that carry important information to the human development (genes), which once modified (mutated), can promote small and subtle changes in the structure and function of the brain (20-23), in individuals with familial persistent developmental stuttering, which has led research groups to carry through ample genetic studies in the last few decades.

The familial persistent developmental stuttering is considered a disease with standard of complex or multifactorial inheritance (24). Such characteristic is a result of complex interactions of several predisponent factors such as genotype in one or more loci and diverse environmental components capable of activating, speeding up or intensifying the manifestation of the illness. Studies of genetic mapping, associated with varied and complex statistical analyses, such as studies of association and analysis link, have been extensively used in the processes of localization and identification of loci and alleles specifically involved that supply a definitive proof of the genetic contribution to stuttering (25).

The search for genes that influence complex characteristics has been much more challenging than the genetic studies of Mendelian traces (26). Some factors contribute to this problem, including etiological and genetic heterogeneity and the neces-
Stuttering and genetics

The accuracy model of transmission of the genetic inheritance in stuttering has not been well defined yet and, moreover, there is the possibility of it being different among the different populations\(^\text{27}\). There are indications that a main gene exists, responsible for the increase of the risk of occurrence of stuttering, when combined with other genes\(^\text{28}\). Several genetic studies were carried through with the objective to identify possible regions and/or genes related with the disease (Table 1).

Recent discoveries have pointed to several regions of the genome that once modified can possibly be related to stuttering as for example, genes from receiver family (DRD2; DRD3) and dopamine transporters (SLC6A3)\(^\text{29,30}\) as well as others until recently related to other illnesses, as the Mucopolysaccharidosis Type II and III - GNPTAB (N-acetylglucosamine-1-phosphate transferase, alpha and beta subunits)\(^\text{31}\). GNPTG

<table>
<thead>
<tr>
<th>Chromosomal region</th>
<th>Method</th>
<th>Sample group of disfluencies</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3q</td>
<td>Genomic selection (linkage analysis) and study of dopamine D3 receptor gene (DRD3)</td>
<td>Pakistanis n=1 family</td>
<td>Raza, Riazuddin, Drayna(^\text{30})</td>
</tr>
<tr>
<td>5</td>
<td>Study of the gene candidate dopamine transporter DAT (SLC6A3) gene</td>
<td>Chinese Population Han n=112 individuals</td>
<td>Lan et al.(^\text{29})</td>
</tr>
<tr>
<td>7q</td>
<td>Analysis of gene CNTNAP2</td>
<td>Brazilian patient</td>
<td>Petrin et al.(^\text{35})</td>
</tr>
<tr>
<td>11</td>
<td>Study of the gene candidate dopamine D3 receptor gene (DRD3)</td>
<td>Chinese Population Han n=112 individuals</td>
<td>Lan et al.(^\text{29})</td>
</tr>
<tr>
<td>12q</td>
<td>Analysis of genes GNPTAB/GNPTG/NAGPA</td>
<td>Pakistanis n=46 individuals</td>
<td>Kang et al.(^\text{32})</td>
</tr>
</tbody>
</table>
(N-acetylglucosamine-1-phosphate transferase, gammasu-
bunit), and to gene NAGPA (N-acetylglucosamine-1-phos-
phodiester alpha-N-acetylglucosaminidase) that acts in the
same metabolic way\(^\text{(32)}\). In the chromosomal regions 7q31
and 7q35 genes FOXP2 (Forkhead Box P2) and CNTNAP2
(2 Contactin-associated protein-like) are located which have
been, permanently, pointed as genes directly related to speech
and language disorders\(^\text{(33,34)}\).

Evidences of interruptions that affect correct functionalities
of the genes, such as alterations presented in the variation of
the number of copies in certain regions of the genome (CNVs),
in the chromosomal rearrangements and mutations, can imply
in a variety of genetic and, consequently, neuropathological
conditions\(^\text{(35)}\). Thus, it is believed that these alterations must in-
tervene with the whole dynamics of the neuronal development
and that disturbances in this direction result in a significant
increase of the possibilities of some form of neurologic dys-
function with probable implications in relation to the nervous
centers of speech and language\(^\text{(36)}\), which once modified, must
promote the occurrence of disfluencies that can culminate into
the development of the stuttering.

The genetic predisposition can affect the fluency in re-
gard to the capacity of the individual in relation to the motor
control of their own speech. An inefficient response to the
muscular effort and its independent response can imply in
muscular contractions in different times or the passages with
control of their own speech. An inefficient response to the
muscular effort and its independent response can imply in
disfluencies that can culminate into

**DISCUSSION**

It becomes evident that the genes that predispose stuttering,
until then listed, are being better studied and that alterations
in one or more genes can contribute significantly for the
manifestation of stuttering. Moreover, an accurate model of
transmission is not yet clearly defined and can probably be
different among different families and populations\(^\text{(27)}\).

Since this is a complex illness of multidimensional cha-
racter and inheritance, stuttering must be investigated taking
into consideration all the risk factors, for the attainment of a
precise and definite diagnosis and of the patients who have
it. The results obtained from genomic analyses, by means of
linkage and association studies, in the identification of possi-
bile candidate genes, as well as of alterations and interactions
in cellular pathways that can be connected to the phenotype,
demonstrate, concomitantly, the relevance of the involved
biological components and its complexity, what suggests in
fact, to be about a polygenic illness in which diverse genes,
of varied effects, can be involved with the increase of the
susceptibility of occurrence of stuttering\(^\text{(25)}\).

**FINAL CONSIDERATIONS**

The overlapping of several genetic factors possibly invol-
ved with the characterized manifestation of stuttering and those
already characterized to the speech and language disorders
such as Tourette syndrome, autism, the specific language
disorder and dyslexia, allow inferring that there probably is a
sharing of the involved basic molecular mechanisms, which
once supplemented from the performance of other biological
factors (secondary genes) and environmental can imply in
stuttering.

Identifying the genetic variation responsible for stuttering
is a great challenge faced by several research groups which,
once better understood is determinant for the understanding of
its primary etiology, of epidemiologic aspects and the possible
involved not-genetic factors and that has important implica-
tions in the patient’s diagnosis and the prognostic.

Thus, the speech therapist will have to be alert to the fact
that a child with positive familial history for stuttering will
have a strong tendency to develop the disorder in a chro-
nic way, in addition to possibly presenting other relatives
affected in the family. It is important that the physician is
apt to provide the families with necessary guidance about
the disorder. The objective evaluations and the controlled
treatments have a very important role in controlling the
evolution of the disorder.

**Quadro 1. continuação**

<table>
<thead>
<tr>
<th>Chromosomal region</th>
<th>Method</th>
<th>Sample group of disfluencies</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPL = 1.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(recovered and persistent stutters)</td>
<td>n=100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LOD = 1.95 - 23cM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16q</td>
<td>Genomic selection (linkage analysis)</td>
<td>1 Pakistani family of consanguineous marriages</td>
<td>Raza et al.(^\text{(38)})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=26 individuals (14 affected)</td>
<td></td>
</tr>
</tbody>
</table>

Note: *n = number of individuals in the study not available
RESUMO

A gagueira é uma desordem da comunicação oral que tem uma característica multidimensional. A predisposição biológica no desenvolvimento da gagueira ainda não é bem compreendida, mas contribuições genéticas para esta predisposição são reforçadas tanto por referências à agregação familiar da gagueira, quanto à gagueira familiar, que têm aparecido na literatura há mais de 70 anos. Assim, procuramos estabelecer uma revisão quanto aos prováveis fatores genéticos envolvidos com a manifestação da gagueira desenvolvimental persistente familiar. A identificação de genes relacionados à gagueira, bem como de alterações em suas estruturas (por exemplo, mutações), contribuem significativamente para sua compreensão. O modelo exato de transmissão da herança genética para a gagueira ainda não está claramente definida e, provavelmente pode ser diferente entre diferentes famílias e populações. As análises genômicas demonstram, concomitantemente, a relevância dos componentes genéticos envolvidos e sua complexidade, sugerindo assim tratar-se de uma doença poligênicas, na qual diversos genes de efeitos variados podem estar envolvidos com o aumento da susceptibilidade de ocorrência da gagueira. O clínico deverá estar alerta ao fato de que uma criança com histórico familiar positivo para gagueira poderá ter uma forte tendência a desenvolver o distúrbio de forma crônica. É importante que o clínico esteja atento, de modo a fornecer às famílias orientações precisas sobre o distúrbio. As avaliações objetivas e os tratamentos controlados têm um papel muito importante para o domínio da evolução do distúrbio.

Descritores: Fonoaudiologia; Fala; Gagueira/etiologia; Genética; Genes; Padrões de herança

REFERENCES


