Genetic etiology for children with Apraxia of Speech in a Brazilian cohort

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abrapraxia

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Childhood Apraxia of Speech (CAS) is a neurological childhood speech sound disorder in which the precision and consistency of movements underlying speech are impaired in absence of neuromuscular deficits (ASHA, 2007).
The first gene implicated in speech and language disorders was **FOXP2** (Lai et al. 2001). Subsequent investigation has identified associations that implicate other genes and chromosomal regions (Easing et al, 2019; Hildebrand et al., 2020; Kaspi et al., 2022) implicating around **38 genes to date.** In this work we aimed to identify genetic etiology in **93 unrelated probands** ascertained with CAS.

References
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Subjects and Methods:

Phase I	Phase II	Phase III	Phase IV	Phase V	Phase VI	Phase VII
Recruited subjects	Selecion	Protocols	Confirm diagnosis	Genetic anamnesis	Exome	Data analysisech in a Brazilian cohort
ABRAPRAXIA's children database (around 500 subscribers with primary speech development impairment referred to by their parents).	Random Selection 150 children with severe Apraxia.	The SLPs of the recruited subjects completed a protocol based on checklists for identifying discriminative signs for CAS (ASHA, 2007; Shriberg, et.al, 2010; Iuzzini-Seigel & Murray, 2017), recorded videos in different tasks speech assessment.	SLP with expertise in CAS confirm the diagnosis. The criteria recommended in the consensus described in the Technical Report (ASHA, 2007) were adopted. For minimally verbal subjects or those who did not respond to formal tests and protocols, the "sCAS" hypothesis was considered.	Genetic anamnesis - Whole exome sequencing was conducted to 93 probands (29 had already done the test in private labs).	Exome sequencing - Copy number variants (CNVs) were detected using NextGene's CNV tool.	Data analysis.

The study was approved by Human Research Ethics Committee from Instituto de Biociências, Universidade de São Paulo, CEP/USP and financially supported by ABRAPRAXIA, FAPESP (CEPID-14/50931-3) and, CNPq.

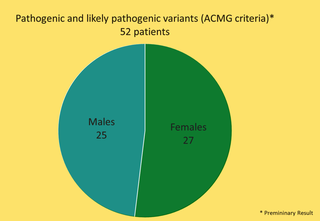
USP, University of São Paulo, as the major institution of higher learning and research in Brazil, is responsible for educating a large part of Brazilian Masters and Ph.D's.

ABRAPRAXIA is a Brazilian association founded by parents that has as mission to promote actions that enables children with CAS to reach their best potential.

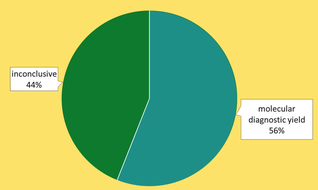
Preliminary Result

The genetic architecture of CAS is complex and heterogeneous!

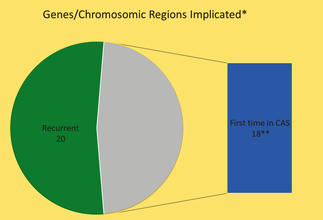
I. 52 patients (27 females, 25 males): Pathogenic and likely pathogenic variants (ACMG criteria) were confirmed.



II. molecular diagnostic yield of 56% (52 patients).

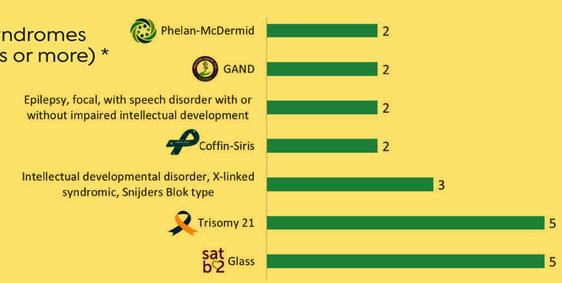


III. 38 different genes/chromosomic regions implicated, **18 for the first time**, in CAS, including SNVs (single nucleotide variants) CNVs (copy number variations) abnormal methylation and numerical chromosomal abnormality.



IV. Most of identified syndromes follow autosomal dominant pattern of inheritance (35 syndromes), syndromes with autosomal recessive (1 syndrome) and X-linked pattern of inheritance (3 syndromes) were identified.

V. Recurrent syndromes (2 probands or more) *



Note: Previous studies have identified 26% of genetic markers correlated to CAS.

* Premininary Results

Conclusion:

The preliminary results: **56%** 44%

I. Indicates the majority of severe CAS (around 56%) has genetic factors, which reinforces the importance of genetic tests in severe CAS patients.

II. Our data confirmed the heterogeneity of genetic factors implicated in CAS as well the high yield of exome analysis in this condition.

III. We established for the first time the association between CAS and 18 syndromes, as Coffin-Siris syndrome (n=2).

IV. Genetic counseling support showed to be highly relevant for the families, which was effective for psychological (anxiety, guilt) and knowledge variables (i. e. understanding of causes and implications of genetic syndromes).

Next steps:

We intend to carry out a complete genome sequencing with analysis of expression pathways, in patients whose exome result was inconclusive.