GENETIC ETIOLOGY FOR CHILDHOOD

Apraxia of Speech in a Brazilian Cohort

NOVEL CANDIDATE GENES

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Childhood Apraxia of Speech (CAS) is a neurological disorder that affects the precision and consistency of movements involved in producing speech (ASHA 2007). The genetic architecture of CAS is still poorly understood and previous research have identified associations between CAS and 35 genes to date (Easing et al, 2019; Hildebrand et al., 2020; Kaspi et al., 2022; Morgan et al., 2024). In this work we aimed to identify genetic etiology in 93 unrelated probands (35 females, 58 males) ascertained with CAS, contributing to a better understanding of genetic architecture of CAS.

SUBJECTS AND METHODS

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

RECRUITMENT

- The probands were recruited by ABRAPRAXIA

CAS CONFIRMATION

- 182 children with primary speech development impairment were evaluated by a group of speech language pathologists (SLPs). The final confirmation was done by E. Giusti.

GENETICS

- 93 children (2-18y) were evaluated by USP's geneticists2.
- Whole exome sequencing was conducted for probands, except for those diagnosed by karyotype. Copy number variants (CNVs) were detected using NextGene's CNV tool. Additionally, it was performed molecular co-expression analysis of all genes associated with CAS, based on the literature and the genes identified in this study, using Brainspan (RNAseq).

CONCLUSION

I. Most CAS cases in our cohort are complex.

II. The cohort's sequencing yield was 55.9%, which is higher compared to the sequencing yield for autism, epilepsy, or intellectual disability.

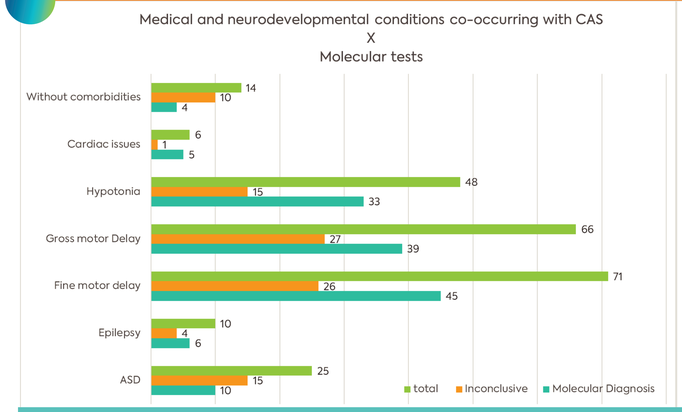
III. CAS probands with motor delay, hypotonia, or those who were female had an increased yield in molecular testing.

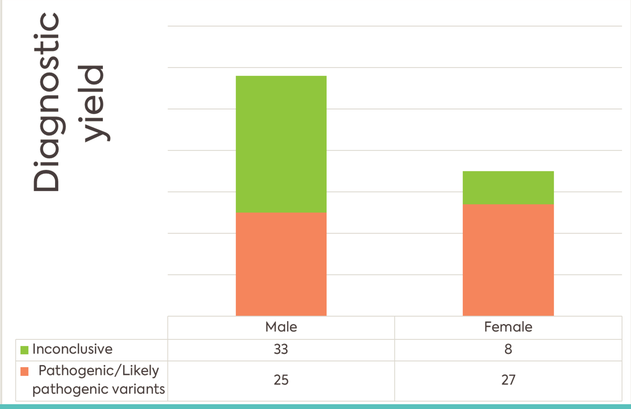
IV. For the first time, a relationship was established between CAS and 17 genes, as well as 3 chromosomal regions, increasing the number of CAS-associated genes by 34%.

V. Additionally, likely pathogenic (LP) variants were identified in four potential new candidate genes for neurodevelopmental disorders (NDDs) and CAS.

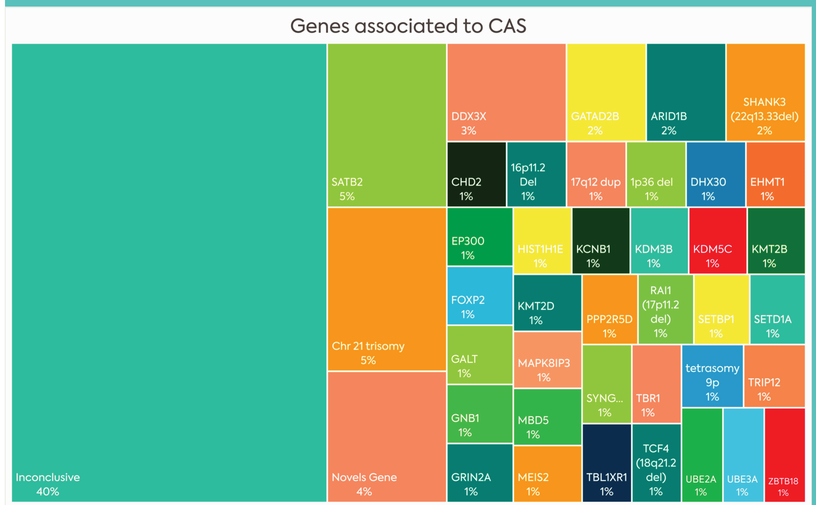
RESULTS

Most cases are complex, with fine and gross motor delay being the most common co-occurring conditions. The detection yield, considering pathogenic (P) and likely pathogenic (LP) variants, based on ACMG criteria, was 55,9%. A positive association was observed between positive molecular diagnosis and motor comorbidities (fine and gross motor delay and hypotonia) (OR=5,46,95% CI [0.46,3.12], p value =0,011). Additionally, a positive association was found between diagnostic yield and sex (OR=0.234, 95% CI [-2.54, -0.45], p value =0,006).





For the first time, an association is being proposed between CAS and 17 OMIM genes (MBD5, TBR1, KMT2B, MAPK8IP3, SYNGAP1, ARID1B, KDM3B, EP300, HIST1H1E, CHD2, UBE2A, DHX30, TBL1XR1, EHMT1, PPP2R5D, RAI1 [17p11.2], and TCF4 [18q21.2del]), as well as three specific chromosomal regions (1p36del, 9p tetrasomy, and 17q12dup). Also, it was identified likely pathogenic (LP) variants in four genes, until now not associated to any OMIM disease, but connected to neurodevelopmental disorders (NDDs) in the literature, suggesting their potential role as novel candidates for NDDs and CAS. These 20 novel CAS candidates expanded the number of CAS-associated genes by 34%.



Co-expression analysis revealed that these genes exhibit correlated expression patterns during brain development. Two modules, M9 and M12 showed significant enrichment for our list of CAS-associated genes (n = 62). Gene ontology analysis of modules M9 and M12 indicated that both modules were enriched for DNA, histone and ATP binding and transcription regulator activity terms in molecular function.

NEXT STEPS

New genetic research will be conducted, increasing the number of children by up to 300, aiming to enhance the understanding of CAS genetics.

Another research will be conducted involving two treatment methods in groups of children with genetic syndromes/ levels of CAS.

PROJETO DISCOVERY
PESQUISA GENÉTICA

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