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Identifying Structural Variants in a Linkage-Identified Region for Subjects with Persistent Stuttering

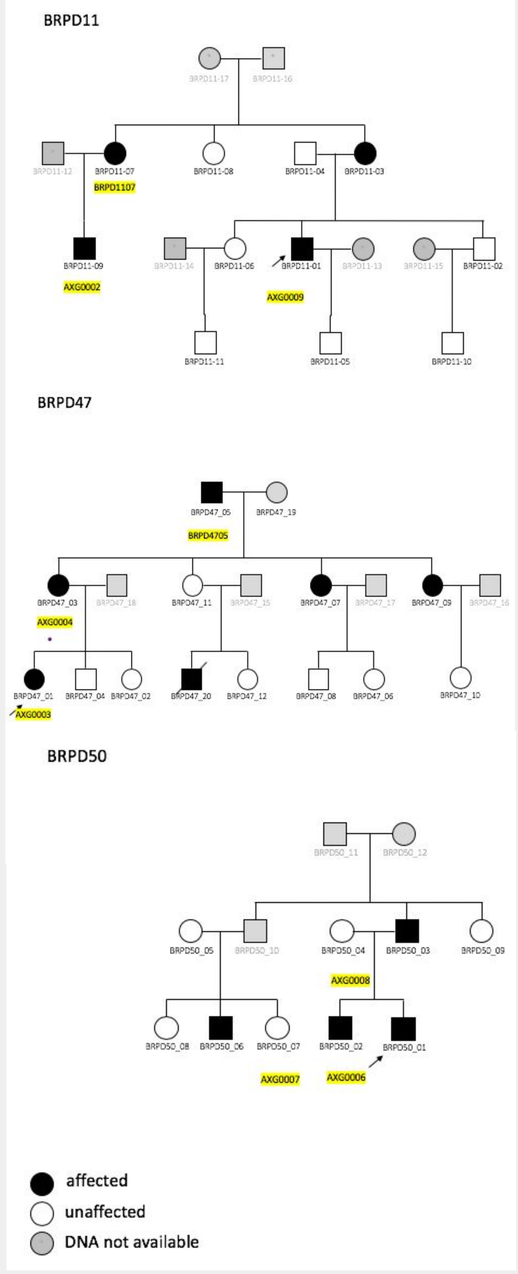
Mira Mookerjee[1], Zhi Liu[1], Carlos Eduardo Frigerio-Domingues[2], Dennis Drayna[2], Nancy Hansen[1], Jim Mullikin[1]

[1]Cancer Genetics and Comparative Genomics Branch, National Human Genome Research Institute, NIH; [2]Genetics of Communication Disorders, National Institute on Deafness and Other Communication Disorders, NIH

Comparative Genomics Analysis Unit

Introduction

Persistent developmental stuttering is a neurodevelopmental disorder affecting approximately 1% of the population. While monozygotic twin studies have produced high heritability estimates often greater than 0.80,[1] a population-based genome-wide association study (GWAS) of stuttering concluded that variants in no single gene serve as a major cause of stuttering in the overall population.[2] Subsequent linkage studies have produced definitive evidence for linkage in consanguineous families from Pakistan[3] and a large polygamous family from Cameroon.[4] A recent linkage study suggests that the 10q region of the genome may play a role in the disorder for Brazilian families.[5] To investigate this, we used 10X Genomics technology to analyze the whole genomes of 8 affected individuals from the 3 families shown below in order to identify causative variants associated with the disorder in these samples. We analyzed short phased variants, large chromosomal variants, and medium-sized deletions using data collected with 10X Genomics technology.



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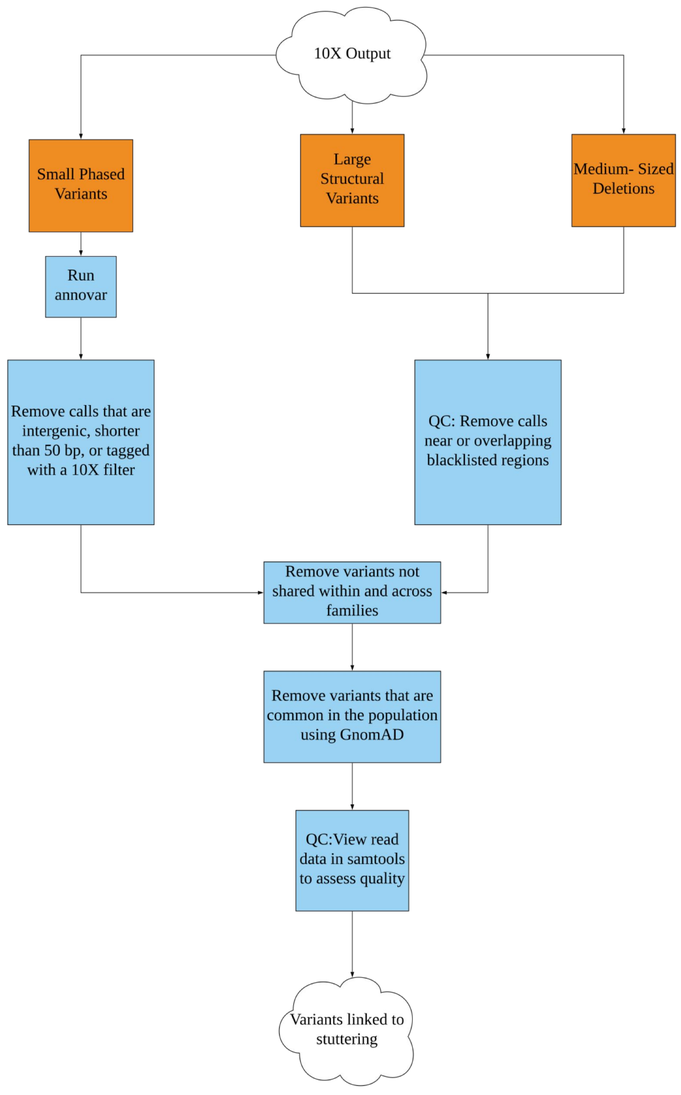
National Institutes of Health

Methods



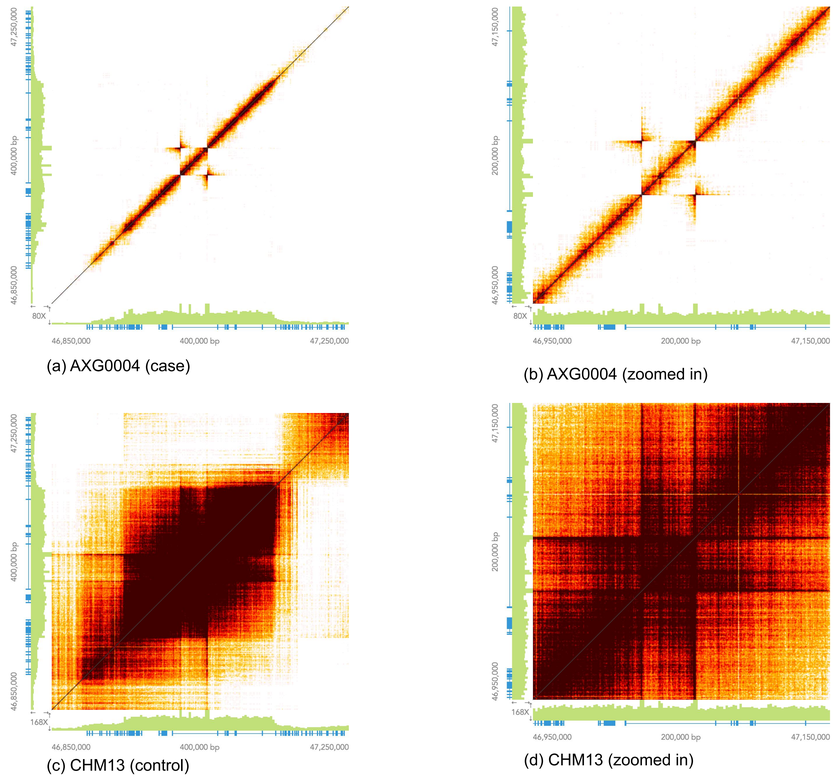
Results

Small Phased Variants

Gene	Position (hg19)	Variant Type	Families	AF
ECHS1	chr10:135182849-135182948	99 base intronic deletion	All	1.23e-4
PCDH15	chr10:55725741-55725828	87 base intronic deletion	All	3.22e-5
WDR11-AS1	chr10:122605345-122605408	63 base intronic ncRNA deletion	BRPD11, BRPD47	N/A
SYCE1	chr10:135380340-135380410	70 base intronic deletion	BRPD47, BRPD50	3.37e-5

Figure 1. The small phased variants in the table above were present in all members of at least two of the three families. Additionally, they had significantly low allele frequencies (< 0.03), indicating that these variants are rare in the population. However, investigation into these regions in eight 1000 Genomes controls using samtools tview revealed that the calls may have been false positives. Therefore, further analysis of these variants is suggested (see **Future Directions**). Variants in all eight samples are highlighted.

Large Structural Variants



(a) AXG0004 (case)

(b) AXG0004 (zoomed in)

(c) CHM13 (control)

(d) CHM13 (zoomed in)

Figure 2. These images show the barcode overlap matrices for a duplication in region 10:46950000-47150000. This was the only large structural variant that passed QC and was present in all members of at least two out of three families. Because the duplication is present in the controls, we conclude that it is likely not associated with persistent stuttering in these samples. However, the duplication was not present in gnomAD and dbVar did not give a frequency for the mutation, so further investigation into this mutation is suggested (see **Future Directions**).

Medium-Sized Deletions

Genes	Position	Families	AF
Intergenic	chr10:131595177-131595473	BRPD50, BRPD47	N/A
Intergenic	chr10:43274200-43274532	BRPD11, BRPD50	0.4838

Figure 3. The medium-sized deletions in the table above were present in all members of at least two out of three families. However, both deletions are found in intergenic regions. Mutations in intergenic regions are less likely to have as pronounced of a phenotypic effect as persistent stuttering, although it is via the regulation of expression of nearby genes[6] (see **Future Directions**). We conclude for now that none of the medium-sized deletion calls are associated with persistent stuttering in these samples.

Conclusion

- We identified four genes containing small variants that may have a role in stuttering in these eight samples. Two of these variants are found in all eight samples. However, there is evidence to suggest that these calls may have been false positives.
- One large structural variant is present in all eight samples, but the variant is also present in our two controls.
- Two medium-sized deletions were found in all members of at least two families, but they both occur in intergenic regions of the genome, and one has a high allele frequency of 0.4838. No medium-sized deletions were found in all eight samples.

Future Directions

- Determine whether the small phased variants identified in Figure 1 are false positives
- Investigate the allele frequency of the large duplication in the population
- Explore the potential effects of intergenic mutations in the 10q region on persistent stuttering

References

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