Candidate gene variant effects on language disorders in Robinson Crusoe Island

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Background: Robinson Crusoe Island is a geographically and socially isolated settlement located over 600 km west of the Port of Valparíso, Chile. An unusually high incidence (30%) of the Chilean equivalent of developmental language disorder (in Spanish, trastorno especifico de lenguaje (TEL)), has been reported in Islander children, with 90% of these affected children found to be direct descendants of a pair of original founder-brothers, therefore strongly suggesting a shared genetic basis. Aim: This study reports a comprehensive examination of 34 genes that have been previously directly implicated in language-related mechanisms. It utilises whole-genome sequencing to investigate potential underlying variants in seven TEL affected and 10 unaffected islanders. The aim was to identify the underlying genetic cause of the TEL phenotype under two inheritance model paradigms; Mendelian monogenic and complex susceptibility. Subjects and methods: A targeted candidate gene approach was used to look for rare, shared variants that may underlie the diagnosis of TEL in a Mendelian genetic model. This study tested whether an overall burden of rare variants is enriched in individuals affected by TEL or with Islanders related to the founder-brother lineage. It further examined if any variants segregate with affection status or with founder-brother-related status and, therefore, may increase risk of developing a language disorder as part of a complex model. Finally, gene-based tests were performed to evaluate relationships between combined variation across candidate genes and TEL affection status. Results: No single pathogenic rare variant segregated with either affection or founder-related status within the 34 candidate genes.

Additionally, no evidence was found of an overall increased variant burden in TEL individuals compared to those with TLD. Gene-based analysis found no clear association between the combined effects of variants across the 34 genes and affection status or founder-brother-relatedness. Conclusion: The high prevalence of language disorders found on Robinson Crusoe Island is not caused by either a shared high-impact variant, or an increased burden of variants within candidate genes previously implicated in language disorders. We have comprehensively tested for ?low hanging fruit? in genes implicated in language disorders. Therefore, the underlying cause of TEL on Robinson Crusoe lies outside of these known language disorder genes, or within a complex susceptibility model.