Genetic Risk Factors of Language Impairment on Robinson Crusoe Island

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BACKGROUND

Disorders of language and communication disrupt social, emotional and educational development increasing the risk of behavioural disorders, unemployment and mental health issues.

Language impairment is a common childhood issue, with 5-7% of five year old children presenting with unexplained language difficulties. Despite the high prevalence of speech and language disorders in the community, we have little understanding of the biological processes that underlie speech development.

Previous studies have shown that language disorders are highly heritable, however only a small number of causative variants have been identified, suggestive of complex inheritance. We expect genetic factors to contribute to the risk of language and communication disorders but there are likely to be many contributory genetic variants, each with only a small risk.

LANGUAGE IMPAIRMENT ON ROBINSON CRUSOE ISLAND

We have been investigating an isolated population from the Robinson Crusoe Island, who are affected by a particularly high rate of language and communication disorders. The Robinson Crusoe Island lies 677km west of mainland Chile. The island was founded in 1876 by 64 individuals from whom the majority of the current population of 633, are descended.

• 35% of the children aged 3-9 have a specific language impairment (i.e. they are developing normally in all other areas except language),
• 27.5% of children have language deficits associated with other pathologies (e.g. learning disability or hearing loss),
• 37.5% of children have normal language skills.
• The incidence of language disorders on the island is 10-fold higher than in the general population.

• Over 80% of the individuals affected by language impairment are descendants of a single pair of founder brothers (below) (Villanueva et al 2008).

STUDY FINDINGS TO DATE:

• Linkage analyses performed on 42 individual islanders identified five chromosome regions that are more similar in individuals affected by language disorders than we would expect chance alone, on chromosomes 6q, 7, 12, 13 and 17 (Villanueva et al 2011).
• Whole exome sequencing performed on 5 affected islanders revealed a dominant p.N150K mutation in exon 4 of NFXL1 in 39% of affected islanders (Villanueva et al 2016).
• The p.N150K mutation is present with a minor allele frequency of 4.2% in Columbian controls and 7.4% in Chilean controls.
• The mutation was also found in 10% of islanders with typical language development (p = 2.04 x10^-4).
• The NFXL1 mutation likely represents a risk variant with a complex model of inheritance.

CURRENT INVESTIGATIONS

We hypothesise that the language disorders seen on Robinson Crusoe Island are caused by rare genetic mutations, or combinations of genetic variants that together confer a high risk of language impairment, and that the NFXL1 mutation only accounts for about 30% of risk. This project aims to fully investigate the cause of speech and language disorder on Robinson Crusoe Island by:

• Investigating complex risk factors or modifiers of high effect size across language disorders.
• Examine possible monogenic effects in the Robinson Crusoe population.

This will use recently generated whole genome sequencing of 24 case and control family members, and high density genome-wide SNP genotyping data from 154 family members. Ancestral genetic clustering of the pedigree was performed using SNP data from 154 islanders allowing selection of the most informative cases and controls for sequencing analysis.

REFERENCES

Villanueva, Nudel et al 2016. Exome sequencing in an admixed isolated population indicates NFXL1 variants confer a risk for specific language impairment. PLOS Genetics. 11(5).