Multidisciplinary investigation of backward-speech trait suggests a link between RIC3, RIPK1, ZBED5 and working memory

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Introduction

Working memory (WM) is a limited capacity system involved in the transient storage and processing of information, which is important for learning, reasoning and comprehension. Although the model and components of WM are still debated, there is a consensus that WM is essential for the development of many language-related traits including speech production and processing and language learning. It has been suggested that the rare trait of backward-speaking is linked to WM. Two strategies of word reversal were reported: (1) reversal according to the phonetic structure of the words (speech sounds) or (2) reversal according to their spelling (letters).

Methods

We employed behavioral tests to describe the trait and neuroimaging (EEG and fMRI) to study the neural processing behind backward-speech. Moreover, we investigated coding sequence changes through exome sequencing and copy number variations using SNP array data in this family. We have tested whether the mutation in RIC3 gene is functional using patch clamp. Furthermore, we explored where SNPs in RIC3 are associated with any phenotype related to WM in ALSPAC and SLIC cohorts.

Case

In this report, we describe individuals from a Serbian family who present with the ability to speak backwards voluntarily. The father (59 years of age) and one of the daughters (26 years of age; hereinafter referred as the “proband”) self-report that they developed this ability at a young age (Fig. 1). In the father and proband, backward-speaking is guided by the phonetic structure, and reversal of sentences is characterized by preserved order of the words, while the phonemes (speech-sounds) of the individual words are reversed. Both the father and the proband deny explicitly learning or practicing speaking backward.

Left:
In lexical decision tasks the subject had to decide whether a word is a real word or a pseudo-word. Both the father and the proband were highly accurate in distinguishing between forward-, backward- or pseudo-words, with performance that consistently exceeded control individuals, in both visual and auditory lexical decision task.

Right:
Performance of the proband on various behavioral tests.

Exome sequencing of the family

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr</th>
<th>Start chr posn (hg19)</th>
<th>End chr posn (hg19)</th>
<th>RIC3 in SLI: ALSPAC and SLIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERC2</td>
<td>chr3</td>
<td>28491062</td>
<td>10874596</td>
<td>rs1055233, strong associations with receptive language score in SLIC, while rs4340037 is associated with reading in ALSPAC.</td>
</tr>
<tr>
<td>TMF1</td>
<td>chr11</td>
<td>69097012</td>
<td>83677185</td>
<td>rs4758042, located downstream or in the 3UTR of RIC3 gene, associated with phenotype related to WM in ALSPAC and SLIC cohorts.</td>
</tr>
</tbody>
</table>

Left:
Exome sequencing of six family members uncovered three rare exonic mutations in the RIC3, RIPK1 and ZBED5 genes that co-segregated with the trait in this family.

Right:
Sanger sequencing validation.

SNPs in located downstream or in the 3'UTR of RIC3 gene showed strongest associations with receptive language score in SLIC, while rs4340037 is associated with reading in ALSPAC.

Conclusion

Our findings in a family with a peculiar phenotype point towards a specific relevant neural mechanism and new candidate genes and molecular pathways for working memory and speech-related memory tasks. The functional and association study on RIC3 gene provide further evidence on the involvement of this gene in WM-related tasks.

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You can read more about our research at www.well.ox.ac.uk/newbury

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