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Effect of *CNTNAP2* polymorphism on receptive language in children with autism spectrum disorder without language developmental delay

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Abstract

Aim: The receptive language ability of individuals with autism spectrum disorder (ASD) seems to lag behind expressive language ability. Several autism-related genes may influence this developmental delay. Polymorphism of one such gene, namely, the contactin-associated protein-like 2 gene (*CNTNAP2*), affects receptive language in individuals with language delay. However, the association between *CNTNAP2* polymorphism and receptive language in individuals with no language delay remains unclear.

Methods: We included 59 children with ASD and 57 children with typical development in this study and investigated this association using coarse-grained exact matching.

Results: We present the first evidence of an association between *CNTNAP2* rs2710102 (A-allele carrier) and reduced receptive language ability in children with ASD whose language development was not delayed. Similarly, among children with typical development, A-allele carriers had lower receptive language ability, but the difference was non-significant.

Conclusions: It is possible that the effect of rs2710102 on receptive language ability is larger in the presence of autism-related genes. Consequently, we speculate that the effect of rs2710102 on receptive language ability would be exerted in combination with other genes. These findings provide new insights into the genetic interactions between mutations associated with common language disorders and ASD and identify molecular mechanisms and risk alleles that contribute to receptive vocabulary. These findings also provide practical guidance in terms of providing candidate genetic markers that may provide opportunities for targeted early intervention to stratify risk and improve prognosis for poor receptive language development in children with ASD.

KEYWORDS

autism spectrum disorder, *CNTNAP2*, gene polymorphism, language delay, receptive language

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1 | INTRODUCTION

The receptive language ability of individuals with autism spectrum disorder (ASD) seems to lag behind expressive language abilities even in the absence of language delay.¹ Evidence suggests that some autism-related genes could contribute to this gap. For example, language impairment is reportedly influenced by dyslexia genes.² Among the autism-related genes, a single-nucleotide variation (SNV) in intron 13 of contactin-associated protein-like 2 (*CNTNAP2*) affects receptive language ability in individuals with language delay.^{3,4} In particular, rs2710102, an SNV in *CNTNAP2*, is associated with lower receptive language ability in individuals with ASD who had language delay³ as well as in individuals with specific language impairment.⁵ Moreover, we recently investigated children without apparent delay and reported that the A-allele of this SNV was significantly more frequent in children with ASD than in children with typical development (TD), and the A-allele was associated with more autistic traits among children with TD.⁶

It was speculated that the A-allele of rs2710102, which is frequent in ASD, may be associated with lower receptive language ability, which explains the lag between expressive and receptive language abilities in this population. However, it remains unclear whether this association is present in individuals without language delay, regardless of whether they had ASD or TD. Herein, we investigated the association between rs2710102 and receptive language ability in children with no language delay. The hypothesis of this study was twofold: (1) The association between rs2710102 and receptive language is ASD-independent. In particular, the A-allele of this SNV is significantly associated with lower receptive language ability after considering the effect of having ASD. (2) The association is present in both children with and without ASD.

2 | METHODS

We recruited 59 children with ASD (41 boys and 18 girls, age 40–98 months, mean IQ 99.2) and 57 children with TD (34 boys and 23 girls, age 53–90 months, mean IQ 107.1; see Table S1 for details). Genomic DNA was extracted from their buccal mucosa cells and genotyped. Intelligence was assessed with the Kaufman Assessment Battery for Children (K-ABC),⁷ and receptive vocabulary was evaluated using the Picture Vocabulary Test-Revised (PVT-R)⁸ version of the Peabody Picture Vocabulary Test (PPVT-R) adapted for the Japanese population. This questionnaire required children to point out one of four pictures that corresponded to the word spoken by the psychologist. Experienced child psychiatrists (Authors T.H. or M.K.) and speech therapists (Author Y.Y. and S.T.) confirmed that these participants had no apparent language delay based on clinical interviews of the participants and their parents.

Among the 116 participants included in this study, 92 carried the A-allele in rs2710102 (A-allele carriers; 28 and 64 had the AA and AG genotypes, respectively) and 24 did not (non-A-allele carriers, i.e., GG genotype; see Table S2 for details). First, in order to investigate

the ASD-independent effect of rs2710102 on receptive language ability, we matched the two groups in terms of developmental condition (ASD vs. TD) and age using coarsened exact matching (CEM) algorithm to control for the effect of these factors, and then applied CEM-weighted linear regression. In this analysis, we merged the two developmental conditions (i.e., ASD or TD) to increase the statistical power for detecting the effect of rs2710102 on receptive language ability. Second, in order to investigate the possibly different effects of rs2710102 on receptive language ability in ASD and TD, respectively, we matched the age between A-allele carriers and non-A-allele carriers within each developmental condition and then applied CEM-weighted linear regression. All statistical analyses were performed using Stata software (ver. 16.1; Stata Corp.).

3 | RESULTS

In the first model on the merged participants, a linear regression with CEM weights indicated that A-allele carriers had significantly lower PVT-R scores compared with non-A-allele carriers [$t(100) = -2.46$, $P = 0.016$] after controlling for the effect of the developmental condition and age. Among children with TD, A-allele carriers had lower PVT-R scores, but the difference was nonsignificant [$t(46) = -1.13$, $P = 0.265$] after controlling for the effect of age. Among children with ASD, A-allele carriers had significantly lower PVT-R scores compared with non-A-allele carriers [$t(52) = -2.31$, $P = 0.025$] after controlling for the effect of age (Figure 1 and Appendix S1 and S2).

4 | DISCUSSION

To our knowledge, this is the first evidence proving the association of the rs2710102 genotype, an SNV in intron 13 of *CNTNAP2*, with receptive language ability in children with no language delay. As we hypothesized, after controlling for the effect of having ASD and the effect of age in the merged participants, children who carried the A-allele have significantly lower receptive language ability. In this sense, we extended the results from previous studies^{3,4,5} by showing that the effect of this SNV is independent of the presence of language delays or ASD.

As we expected, A-carrying children with ASD showed significantly lower receptive language ability than non-A-allele carriers. Similarly, among children with TD, A-allele carriers had lower receptive language ability, but the difference was nonsignificant. This nonsignificance may be explained by the lower frequency of A-allele carriers in this population, which would result in reduced statistical power. It is also possible that the effect of rs2710102 on receptive language ability is greater in the presence of autism-related genes. From this perspective, we speculate that the effect of rs2710102 on receptive language ability would be exerted in combination with the effect of other genes. ASD-related genes might increase its impact on receptive language, which would partly explain the gap in expressive and receptive languages in this population.

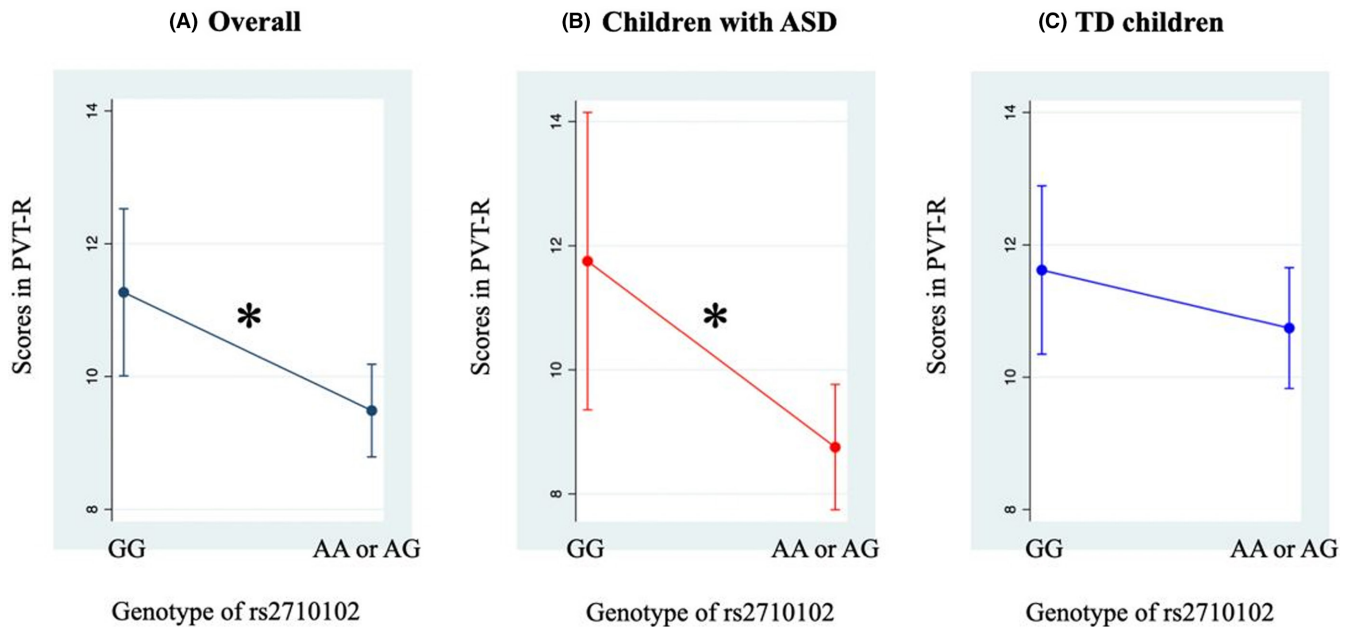


FIGURE 1 Adjusted prediction of the scores of the Picture Vocabulary Test-Revised (PVT-R) with 95% confidence intervals (CIs). To visualize the significant effects of rs2710102 genotype on the PVT-R scores, we predicted the marginal means from each of the fitted linear regression models with coarsened exact-matched weights. (A) Predicted means of PVT-R and 95% CI using the model for the whole sample. (B) Predicted means of PVT-R and 95% CI using the model for the ASD group. (C) Predicted means of PVT-R and 95% CI using the model for the TD group. The asterisks indicate statistically significant differences ($P < 0.05$). CEM, coarsened exact matching; CI, confidence interval; PVT-R, Picture Vocabulary Test-Revised

Considering our findings, the rs2710102 genotype may help in the early detection of the receptive language delays in children with ASD, which may improve the prognosis by providing timely, tailored educational support. Further studies are required to clarify the mechanism contributing to the delay in receptive language in ASD, which could provide better means for effective early support.

AUTHOR CONTRIBUTIONS

Conceptualization: Yuka Shiota. **Data curation:** Yuka Shiota, Tetsu Hirose. **Formal analysis:** Yuka Shiota, Tetsu Hirose. **Funding acquisition:** Yuka Shiota, Tetsu Hirose, Mitsuru Kikuchi. **Investigation:** Yuka Yoshimura, Sanae Tanaka, Chiaki Hasegawa. **Methodology:** Yuka Shiota, Tetsu Hirose. **Project administration:** Yuka Shiota, Tetsu Hirose. **Resources:** Yuka Yoshimura, Chiaki Hasegawa, Sumie Iwasaki, Kyung-min An, Shigeru Yokoyama. **Software:** Yuka Shiota, Tetsu Hirose. **Supervision:** Shigeru Yokoyama, Mitsuru Kikuchi. **Writing—original draft:** Yuka Shiota. **Writing—review and editing:** Tetsu Hirose, Masuhiko Sano, Shigeru Yokoyama, Mitsuru Kikuchi.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available as Supporting Information. Raw datasets of subjects' condition (ASD or TD), age, sex, Type, scores of IQ, scores of SRS, and scores of PVTR are available in the raw_datasets.csv of Supporting Information.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

All methods and procedures were approved by the Ethics Committee of Kanazawa University Hospital and carried out in accordance with the Declaration of Helsinki. See the Appendix S1 and S2 for further methodological details.

INFORMED CONSENT

All parents agreed to the participation of their children in the study. Written informed consent for participation and publication was acquired.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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