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REPLY TO LETTER

Reply to: MIDN locus structural variants and Parkinson's disease risk

Yutaro Obara[1], Hidenori Sato[2], Takahiro Nakayama[3], Takeo Kato[4] & Kuniaki Ishii[1]

[1]Department of Pharmacology, Yamagata University School of Medicine, Yamagata, Japan
[2]Genome Informatics Unit, Institution for Promotion of Medical Science Research, Yamagata University School of Medicine, Yamagata, Japan
[3]Research Institute of Bio-system informatics, Tohoku Chemical Co., LTD, Morioka, Japan
[4]Yamagata City Institute of Public Health, Yamagata, Japan

Correspondence
Yutaro Obara, Department of Pharmacology, Yamagata University School of Medicine. Tel: +81-23-628-5233; Fax: +81-23-628-5235; E-mail: obaray@med.id.yamagata-u.ac.jp

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Dear Editor,

We thank Billingsley et al. for their interest in our study that showed a genetic association of *MIDN* deletions with Parkinson's disease (PD) in a British population.[1] In their letter to the editor, they noted that they could not identify any PD-associated deletions within 100 kb of *MIDN* in 3868 individuals analyzed by whole-genome sequencing (WGS) and raised issues regarding using SNP genotyping to identify structural variants.[2]

We respect their analyzed data. However, as we obtained consistent results in British and Japanese cohort studies, our results may be reproduced in other cohorts if analyzed by array-based technology. In fact, a variety of deletions or multiplications within the *MIDN* locus have been identified in a general population and shown in public databases analyzed mainly by microarrays (Database of Genomic Variants; http://dgv.tcag.ca/dgv/app/home or UCSC Genome Browser; https://genome.ucsc.edu)[3,4] (Fig. S1). Additionally, we examined the physiological functions of MIDN in neuronal cells using genome editing and RNA interference methodologies and demonstrated that MIDN is responsible for neurite outgrowth and expression of Parkin E3 ubiquitin ligase, which is associated with PD phenotypes.[5]

High-resolution array-based analysis is widely used in basic research and clinical practice. For example, deletions at 22q11.2 in idiopathic PD have been identified using an analytical method very similar to ours (the same datasets from UK Wellcome Trust Case Control Consortium 2 and the same analysis algorithms).[6] Recently, duplications in 19p13.3, including *MIDN* and other adjacent genes, were demonstrated to be associated with male infertility according to array-based analysis.[7] However, because genome-wide copy number variation (CNV) detection power varies depending on platforms and analysis software,[8,9] we recognize the necessity of multiple analysis algorithms and independent experimental validation for array-based CNV detection studies. As in the case of array-based analysis, each different sequencing-based method (algorithms, experimental methods) has different strengths and weaknesses for detection, depending on the variant type or properties, and unique and common CNVs are often discovered using various approaches.[9] Furthermore, more than 90% of the lengths of discovered variants were less than 1 Kbp in sequence-based analysis, and the median length of deletions detected by sequencing was 742 bp, whereas that by SNP microarray was 50,265 bp.[9] In our analysis of the PD case group, the so-called CNV length was 42.6 Kbp (mean)/12.1 Kbp (median) in a British population and 169 Kbp (mean)/103 Kbp (median) in a Japanese population. Such large CNVs spanning the *MIDN* locus have been identified, suggesting that these

deletion or multiplication sizes are relatively insensitive range to identify efficiently by WGS-based analysis.[9] Long-read sequencing is assumed to be more preferable for detection of segmental duplications, gene loss, and fusion events in this case rather than short-read DNA (<1 Kbp) sequencing.[10]

Under these circumstances, it is assumed that the discrepancy in the conclusions between Billingsley et al.'s and our studies mainly results from methodologies used for CNV analysis. Both sequence- and array-based methods have advantages and limitations, and it cannot be easily concluded which method is superior.

In summary, regardless of the use of WGS or array-based analysis, we consider the necessity of additional approaches to validate the conclusion noted by Billingsley et al. For example, copy number analysis by array CGH or digital PCR is a preferred method in this case. Furthermore, using *Midn* knockout mice is an alternative approach to this issue to determine the pathophysiological roles of MIDN.

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Conflict of Interest

Takahiro Nakayama is an employee of Tohoku Chemical Co., LTD. (Hirosaki, Japan).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Diagram of the MIDN locus generated by the Database of Genomic Variants. A variety of copy number variations including deletions and duplications within the MIDN locus have been identified in a general population. Gain (blue); Loss (red); Both loss and gain (brown).

