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Updated understanding of *WRN* variants using the Japanese whole-genome reference panel 3.5KJPNv2

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Dear Editor,

Werner syndrome (WS), an autosomal recessive disorder that causes deficiency of the WRN protein,[1] presents clinical features suggestive of accelerated aging.[2] This progeroid syndrome was originally described in 1904, and more than 1200 patients were reported from 1904 to 1996, with 845 from Japan.[3] The WRN protein plays a role in DNA replication, transcription, repair, and recombination; thus, genetic instability has been observed in WS patients and *WRN* heterozygous mutation carriers.[4] Recently, an international research group, including the Japanese Werner Consortium (Chiba, Japan), reported a total of 83 novel *WRN* mutations among WS patients, as well as 75 mutations already reported in the literature,[5] suggesting that the genetic diversity of *WRN* heterozygous mutation carriers is greater than expected.

The combination of data science and biobank sample collection has the potential to clarify the frequencies of disease-related genetic variants in a given population.[6] To investigate the diversity of *WRN* gene variants, we used the 3.5K Japanese whole-genome reference panel "3.5KJPNv2," allele frequencies from 3,552 individuals, which is a part of the Japanese Multi Omics Reference Panel (jMorp, available at https://jmorp.megabank.tohoku.ac.jp/201806/) released from Tohoku University's Tohoku Medical Megabank Organization (ToMMo).[7] The two large-scale prospective studies of ToMMo, Tohoku Medical Megabank Project Community-Based Cohort Study (TMM CommCohort Study) and Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study (TMM BirThree Cohort Study), were performed in Miyagi and Iwate Prefectures in Japan after the 2011 Great East Japan Earthquake and Tsunami.[8] As of 2018, these projects have collected biospecimens, such as blood and urine, from more than 150,000 Japanese participants who have given informed consent.

As shown in Figure 1, we confirmed a total of 4,632 allele variants in the *WRN* gene, including 1,133 (24%) novel variants that have not yet been assigned reference SNP ID numbers (RefSNP). Furthermore, we found 12 novel missense variants in the *WRN* gene that could change the expression and function of the WRN protein. Next, we investigated the 10 pathogenic variants in the *WRN* gene reported by the ClinVar archive (available at https://www.ncbi.nlm.nih.gov/clinvar/): rs267607008(A>G), rs775802030(A>G), rs17847577(C>T), rs121908448(A>T), rs281865157(A>G), rs113993961(G>C), rs281865159(A>C), rs121908447(C>T), rs369158322(A>T), and rs121908446(C>T). We found one DNA sample with heterogenous mutation rs17847577(C>T) (0.0001), 15 samples with heterogenous mutation rs113993961(G>C) (0.0021), and one sample with heterogenous mutation rs121908446(C>T) (0.0001). Our data analysis of the whole-genome reference panel, 3.5KJPNv2, demonstrates that, with the assumption of the Hardy-Weinberg equilibrium, a large number of healthy individuals have “likely pathogenic” or “pathogenic” heterogenous variants in the *WRN* gene, indicating that the genetic diversity of WS patients and *WRN* heterozygotes is greater than previously reported[5].

The combination of data science and biobank collections will lead to a better understanding of the genetic basis of Werner syndrome. Population-based whole-genome reference panels, including 3.5KJPNv2, have the great potential for future innovations in the research fields of geriatric medicine and gerontology.

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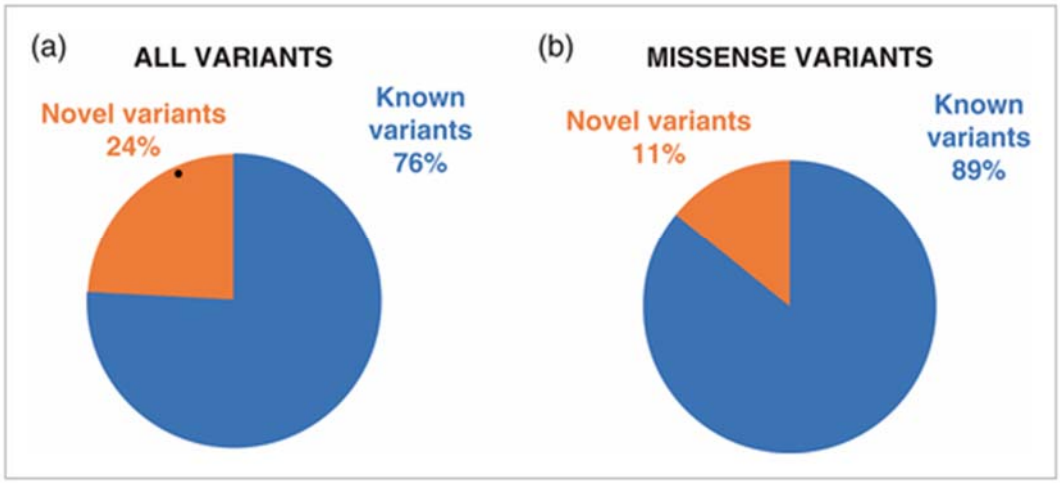

Figure 1. Variants in the *WRN* gene.

(a) 4,632 allele variants in the *WRN* gene have been confirmed, including 1,133 (24%) novel variants that have not yet been assigned reference SNP ID numbers (RefSNP).

(b) 108 missense *WRN* variants that could change the expression or function of the WRN protein have also been confirmed, including 12 (11%) novel variants.