医学セミナー・第 19 回分子遺伝疫学セミナー
“Seminars in Medical Sciences” Lecture

ゲノム医科学リサーチユニット　難治性免疫疾患・アレルギーリサーチユニット

Identification of genomic structural variations and analysis of their functional roles

Speaker: **Dr. Akihiro Fujimoto** (Professor, Department of Human Genetics, Graduate School of Medicine, The University of Tokyo)

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Date: September 19, 2019 (Thurs)

Time: 17:30-18:45

Venue: Clinical Lecture Room B 臨床講義室 B

This seminar is one of the seminars for the subject “Seminar in Medical Sciences” in Doctoral Programs in Biomedical Sciences and Clinical Sciences. The seminar will be given in English, but discussion in Japanese is also welcome.

Next generation sequencing has allowed the identification of genetic variations known to contribute to diseases. Insertions and deletions are the second most abundant types of variations in the genome, but their biological importance or disease association are not well-studied, especially for deletions of intermediate-sizes.

We identified intermediate-sized deletions from whole-genome sequencing data from Japanese subjects with a novel deletion calling method. These deletions were used to construct a reference panel for use in imputation. Imputation was then conducted using the data from publicly-available 82 Japanese subjects with gene expression data. We also conducted an expression quantitative trait loci (eQTL) association analysis using the deletions to infer their functional impacts on genes.

We obtained a set of polymorphic 4,378 high-confidence deletions and constructed a reference panel. The deletions were successfully imputed into the Japanese samples with high accuracy (97.3%). The eQTL analysis identified 181 deletions (4.1%) suggested as causal for gene expression level changes. The causal deletion candidates were significantly enriched in promoters, super-enhancers and transcription elongation chromatin states. Generation of deletions in a cell line with the CRISPR-Cas9 system confirmed that they were indeed causative variants for gene expression change. Furthermore, one of the deletions was observed to affect expression levels of a gene in which the deletion was not located.

This study reports an accurate deletion calling method for genotype imputation at the whole genome level, and shows the importance of intermediate-sized deletions in the human population.

References

1. Wong JH, et al. (2019) Identification of intermediate-sized deletions and inference of their impact on gene expression in a human population. Genome Medicine 11:44.
2. Shigemizu D, et al. (2018) IMSindel: An accurate intermediate-size indel detection tool incorporating de novo assembly and gapped global-local alignment with split read analysis. Sci Rep 8: 10367
3. Fujimoto A, et al. (2010) Whole-genome sequencing and comprehensive variant analysis of a Japanese individual using massively parallel sequencing. Nat Genet 42: 931–936

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