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Genomic aspects of common diseases

Human genome is comprised of about 3×10^9 nucleotide pairs per haploid genome. This was originally thought to be too long to determine the nucleotide sequence of the entire genome in 1970s and 1980s. Human Genome Project for its purpose, however, started in 1990 and successfully acquired and released the draft, complete sequence of human genome in 2000 and 2003, respectively [1]. With this great achievement, most researchers considered that numerous disease-responsible genes would be uncovered much more efficiently than before. Indeed, this accomplishment has strongly facilitated the genomic analyses such as the identification of unique single nucleotide polymorphism (SNP) associated with certain specific diseases. Furthermore, recent next-generation sequencing technology has tremendously accelerated its line of progress. On the contrary, the achievement of Human Genome Project rather restrictively endowed benefits to the field of research on familial diseases with Mendelian inheritance as well as basic genomic researches. There exist a group of diseases that occur rather frequently in population, and these are called "common diseases". Because common diseases have complex architecture, their genetic origin is not usually well defined nor even studied until the achievement of Human Genome Project. Although researchers considered that the entire genome sequence information rendered even such common diseases applicable for the genomic studies, unlike their expectations, these studies let researchers be aware that common disease is much more complex in which each disease phenotype is not usually caused by a sole genomic abnormality, rather a reflection of substantial number of variations in the genome [2]. Moreover, the fact that environmental factor substantially contributes to disease phenotype makes the situation much more complex than previously anticipated. For example, positional cloning strategy developed in 1980s [3] will not give rise to positive hits effectively in case multiple genomic variations equally or combinatorially contribute to a particular disease phenotype, though this method is very effective for identifying a disease-causative gene of monogenic diseases with Mendelian inheritance. Indeed, most tremendous efforts by many researchers for identifying responsible genes of common diseases such as Type 2 diabetes and hypertension did not lead to satisfactory outcomes. However, many new technologies, in particular, Genome Wide Association Study (GWAS) [4] surveying the genome macroscopically, have been developed to overcome such difficulty. GWAS is a strategy for identifying common genetic variants in different individuals with respect to common diseases. GWAS typically focuses on identifying SNPs that are significantly associated with certain disease. That is, these studies compare the DNA of two groups: one is the group with the disease and the other is the control group with normal trait. Variants frequently observed in the first group, but not in the second control group would become the candidate risk of the disease. Unlike the ordinary method for analyzing one particular region of the genome, GWAS covers the entire genome, allowing the identification of many potential risk variations of genome simultaneously. Nevertheless, GWAS is not an almighty strategy, having several limitations. The most obvious limitation is relatively low odds ratios. Usually, numerous SNPs closed-up by the study could account for only a small fraction causing the entire patients. Therefore, a substantial number of SNPs associated with disease trait remain to be identified even after repetitive conduction of this study. Notwithstanding with these limitations, a number of reports of GWAS started to come out from the beginning of this century and these reports probably described over 10,000 SNPs in total, which can be candidates of genomic risk portions with respect to hundreds of common diseases and we can say without any reservation that GWAS will exhibit more power in this field in the future in conjunction with the remarkable progress in next-generation sequencing technology.

This edition shows how GWAS and other new molecular genetic approaches have greatly advanced the understanding of many common diseases in a molecular level with ten review articles covering major common diseases such as Type 2 diabetes and Parkinson's disease. The issue starts with a review of recent progress and future perspective about molecular genetics of Type 2 diabetes mellitus by Hara et al. and is followed by Mitsui and Tsuji who focused on sporadic forms of neurodegenerative diseases including Alzheimer disease, Parkinson's disease and multiple system atrophy as examples. The third article by Sekiyama et al. describes about genomic aspect of Parkinson's disease. In addition, this article also discusses about previously unexpected molecular link between Parkinson's disease and Type 2 diabetes mellitus. The fourth and the fifth articles are about Developmental Dyslexia (Kere) and Autism (Liu and Takumi), respectively. The sixth article is a review of Rheumatoid Arthritis by Kochi et al. and seventh and eighth articles describe about age-related macular degeneration and Chronic Obstructive Pulmonary Disease, respectively. The seventh article discusses not only from genomic aspect but also discusses about non-genetic factors that modulate the genetic effects of the disease, while the eighth article emphasizes on the importance of network-based approaches. The ninth article by Urano and Inoue summarized recent progress on genetic factors that are specifically associated with the pathogenesis of osteoporosis and fractures. Finally, the tenth article by Takahashi and Carninci is a rather unique article in this issue describes about the way of approaches dealing with various aspects of regulation of antisense RNA and the challenges for the application to gene therapy.

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In summary, this special issue covers conspicuous advances in the field of many major common diseases including Type 2 diabetes, Parkinson's disease, Rheumatoid Arthritis and so on. Furthermore, each issue not only describes about the identification of responsible genes, but also explains the biological role of the identified genes in the disease phenotypes. Therefore, we hope that this issue is helpful not only for resource of responsible genes for major common diseases but also for understanding the underlying molecular events or pathways that cause disease phenotypes.

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