Bigenome (Nuclear GWAS and Mitochondrial Haplogroup) Analysis to Provide Genetic Evidence for Divergent Features of Heart Failure and Metabolic Syndrome

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Summary

Both heart failure (HF) and metabolic syndrome (MeS) show symptomatic overlap, ethnic diversity, ambiguous therapeutics and variable prognosis, impacting sociomedical circumstances worldwide (1, 2). Recent huge (>100,000 cases *vs.* control) Caucasian-main GWAS reports on MeS trilogy (blood pressure, body mass index and blood lipids) commonly revealed leading SNPs (3-5) and suggest that MeS shares the genetic background in part. Our on-going GWAS project for HF (6-8) with 600k SNP microarray identified four independent Japanese pedigrees with HF (NYHA class II~IV), intractable arrhythmias or sudden death, carrying the same SNP as Caucasians with MeS. This non-synonymous SNP encoding a cation/anion co-transporter at the transmembrane domain conceivably controls intracellular ion homeostasis and development of multiple organs (9). Gene expression has been restricted to Caucasians (MAF 0.034~0.18) and no report in East-Asians so far. The expression of transgene-family is regulated by cAMP-CREB system, as was confirmed by beneficial outcome of patients after α/β1-adrenoblocker treatment. Furthermore, full-length mitochondrial sequence of these 4 cases revealed East-Asian specific mt-haplogroup with the highly discrete power ($p<10^{-8}$). The 2D or 3D structures of both nuclear and mt-mutants predicted distorted construction of the transgene. Electron microscopy of cardiac samples demonstrated marked accumulation of small-sized mitochondria (mitochondriosis) at perinuclear~subsacolemmal regions. Intriguingly, the same nuclear gene mutation caused no clinical sign of HF in Caucasian carriers without the mt-gene mutation. These genetic analyses and multidisciplinary approaches present a novel concept of BWAS (bigenome-wide association study) unifying nuclear and mt-genomes to substantiate the ethnicity-dependent and haplogroup-specific access to HF and MS. BWAS provide hierarchy of mitochondrial haplogroup-dominant phenotype exceeding the nuclear genotype *per se* and molecular biology-based relevancy for the therapeutics, as well.

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Notice

This short monograph dealt with the proposal of our emerging concept on the pathogenesis and the progression of HF to the advanced stage. It is under reviewing for the publication elsewhere and we should refrain from duplicated submission. We declare no conflicts of interest. The current study was financially supported by grant-in-aid from the Ministry of Education, Culture, Science and Sports, the Ministry of Health, Welfare and Labor, and the Motor Vehicle Foundation, Japan.