The clinical and molecular genetic characteristics of Korean patients with Fabry diseae

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Fabry disease is caused by an alpha-galactosidase A (GLA) deficiency. Thirty-seven unrelated Korean families, comprised of 45 males and 13 females, had been enrolled in the Korean Fabry Registry. The presenting signs were acroparesthesia (23%), proteinuria (19%), hypertrophic cardiomyopathy (HCMP; 8%), angikeratoma (4%), heat stroke (4%) and renal failure (4%). The remaining 38% of the patients were identified by familial screening. The average onset age was 14.3 ± 8.3 yrs, and the age at diagnosis was 28.8 ± 13.3 yrs. At diagnosis, HCMP, hearing difficulty, proteinuria (>300mg/day), and end stage renal failure were noted in 46%, 62%, 23%, 8% of the patients, respectively. Enzyme replacement therapy were commenced at 31.4 ± 13.6 yrs of age. During 47.4 ± 25.1 months of therapy, no patient experienced the aggravation of HCMP or proteinuria, deterioration of renal function, or stroke-like episode.

Thirty distinct mutations in the *GLA* gene including 8 novel mutations (p.W47X, p.D61EfsX32, p.Y86H, p.C90X, IVS4^{-11}T>A, p.G274R, p.D322E and p.W349) have been identified. The GLA activity of each mutant was decreased either in patient's leukocytes or in transiently over-expressed COS-7 cells. Notably, five subjects from four unrelated families carried the p.E66Q variant, previously known as a pathogenic mutation in atypical Fabry disease. Review of their clinical manifestations, measurement of in vivo and in vitro enzymatic activity, assessment of intracellular expression of p.E66Q variant, and the investigation of the allele frequency of p.E66Q variant in normal Korean population, which was high at 1.046% (95% C.I., 0.458 – 1.634%), revealed that p.E66Q is a functional polymorphism rather than a pathogenic mutation.

In conclusion, more efforts are needed to identify more cases with Fabry disease, which shows a wide spectrum of clinical manifestations. The variable molecular genetic heterogeneities of Fabry disese were also noted in this cohort, which might reflect ethnic diversity and affect their correlations to the phenotypes.