Variables Related to Iron Status and Genetic Background Among Korean Populations: Ironing Out the Differences

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Laboratory evidence of elevated iron stores can be an important predictor of cardiovascular diseases, diabetes, neurodegenerative diseases, and cancers [1–3]. Iron status is routinely evaluated by biochemical assays such as serum iron (SI), total iron-binding capacity (TIBC), and serum ferritin (SF). Although SF has high sensitivity for iron overload, it has low specificity, since inflammatory processes, liver diseases, and alcohol consumption can elevate SF. Transferrin saturation (TS), which is calculated by dividing SI by TIBC, identifies iron overload as well, with $TS \geq 50\%$ for females or $\geq 60\%$ for males suggestive of genetic disease [4].

TS is elevated in many studies of Korean populations [5–7] although the most commonly reported genetic predisposition to iron overload, the hereditary hemochromatosis (HH)-associated p.Cys282Tyr homozygous or compound heterozygous (p.Cys282Tyr/p.His63Asp) genotypes, is rare in Korean populations. In this issue of *Digestive Diseases and Sciences*, Oh et al. [7] thus sought, using an epidemiological approach based on the Fifth Korea National Health and Nutrition Examination Survey (KNHANES V-1 2010), to determine whether an alternative genetic basis for the observed elevated TS exists. They reported whether TS patterns cluster within families, concluding that a greater percentage of Koreans had increased TS compared to European populations [7].

Oh et al. included 260 families with 370 children in their analysis. Parents and children were classified into groups based on TS values. The mean TS value of the offspring differed according to the parental groups, whereas age, daily iron intake, and aspartate and alanine transaminases did not affect TS [7], even though aging, daily iron intake, and liver tests are reportedly influential [8–10]. The absence of association of these factors with TS might have been due to the inclusion criteria used, since subjects were excluded if they were anemic, if they had serum transaminase concentrations >40 U/L, or if the specimens used for SI measurements were not obtained at a standardized time. Although these criteria minimized the variability of their data, the authors might have chosen some of these inclusion criteria to evaluate the possibility that those variables were not the cause of the high TS in Koreans. Furthermore, to evaluate the relationship between iron status and the studied variables, additional iron status tests such as the SF and soluble transferrin receptor should have been measured to further define iron status.

The authors concluded that the findings suggest unidentified genetic variations underlie high TS in Koreans beyond the gene encoding the human hemochromatosis protein (*HFE*) p.Cys282Tyr and p.His63Asp polymorphisms. The p.His63Asp variant, frequent in many countries (allelic frequency of approximately 15 %), has been associated with iron status measurements in individuals from general population [11–13]. These significant associations were not associated with iron overload, but with slightly higher mean values. Although the authors did not genotype the population for *HFE*, these *HFE* variants as stated previously are rare in Korean populations. Thus, one can assume that *HFE* variants did not affect the iron status of Koreans, at least no more so than in populations of European ancestry. The authors concluded that iron status

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is based on a polygenic profile, which contributes 20–30 % of the variation of blood iron measures [14].

Genome-wide association, familial, and exome sequencing studies reported significant correlations between polymorphisms and iron status or the severity of the HH phenotype [15, 16]. For example, Benyamin et al. [15] analyzed the genetic data and biochemical iron status published in 11 European population-based studies in 48,972 subjects, identifying genome-wide significant loci including several well-known iron-related genes (i.e., *HFE*, *SLC40A1*, *TF*, *TFR2*, *TFRC*, *TMPRSS6*) and other novel genes (i.e., *ABO*, *ARNTL*, *FADS2*, *NAT2*, *TEX14*). In another study, the *PCSK7* rs236918 variant was reported as a risk factor for the development of liver cirrhosis in patients with HH carrying the homozygous genotype for *HFE* p.Cys282Tyr [16].

In conclusion, the authors present a compelling case that iron load observed in Korean populations is likely genetically based due to several gene *loci* besides *HFE*. Which genes are involved in which combinations, and the clinical consequences of their polymorphism or mutation await further studies.

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