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Letter to the Editor

Hereditary hemochromatosis: The same old song

To the Editor:

Hereditary hemochromatosis (HH) is a genetically determined disorder characterized by iron overload. The classical biochemical presentation is elevated serum ferritin (SF), increased serum iron (SI) and transferrin saturation (TS%) >45%. If untreated, the disorder evolves to diabetes, heart failure, liver cirrhosis and bronze pigmentation of the skin. HH was classified in four types more than 10 years ago [1]. Type 1 is the most common genetic disorder with mild severity, and it is mainly caused principally by the homozygous mutation p.Cys282Tyr or by compound heterozygous mutations p.Cys282Tyr/p.His63Asp of HFE gene. Type 2, defined juvenile hemochromatosis, is the more severe form of the disorder, with the onset in the first to third decades of life. It is characterized by rare mutations in the HAMP (type 2A) or in the HJV (type 2B) genes [2]. Type 3 has an intermediate severity and early onset and is related to rare mutations in the TFR2 gene [3]. Type IV has some peculiarities in clinical manifestations and is also named ferroportin disease, since determined by rare mutations in the SLC40A1 gene [4]. Furthermore not all hemochromatosis cases are explained by mutations in the above mentioned genes and are classifiable in classical types. In the last years so much has been discovered about the molecular mechanisms involved in HH, mainly characterized by the deregulation of the systemic expression of hepcidin or by a lack of the effect on its receptor ferroportin. The penetrance of type 1 HH among individuals with genetic predisposition is incomplete and heterogeneity in the severity of clinical manifestations are often described. This variability is likely explained by both genetic and environmental factors, which were the object of numerous studies in the past decade. In order to understand the reasons of this heterogeneity, some years ago we studied a population affected by HH type 1, carrying classical HFE mutations, hypothesizing that variations in HAMP and HJV genes could contribute to a more severe pathology. We found some polymorphisms and mutations in those genes (as N196K in HJV gene) that worsened the pathological phenotype, but those mutations resulted rare and not sufficient to explain the presentation variability [5].

Recently, we read an interesting article by Radio et al. [6] who studied the controversial phenotype modifying role of variants in HAMP, BMP2, FTL, TFR2 and SLC40A1 genes in 109 HH type 1 patients. The authors analyzed the impact of the studied polymorphisms on SF, SI, serum transferrin (ST) and TS%, stratifying the results by gender.

We would add some considerations to the remarkable observations of the authors, further analyzing the proposed data and assuming that there were no differences in the distribution of the alleles between females and males (although not clearly specified in the authors' article). Concerning the rs10421768 of the HAMP gene, the statistic significance was obtained for the decrease of ST only in females; while in the male cohort the values did not differ between the genotypes. The whole casuistry was influenced by females, then the speculation of the authors should concern principally females.

BMP2 rs235756 seems to have an effect similar to that observed by Milet et al. [7] on SF in females for TT and CC genotypes. The elevated value of TC genotype could be due to some aberrant data as it appears considering the standard deviation. The CC genotype seems to show a protective trend on SF level, ($P = 0.067$ vs TT).

Considering the SLC40A1 rs1439816 (see Table 6 in the paper), the CC genotype resulted, only in females, in a significant decrease in SI, but also the TS% variation was near to significance ($P = 0.08$) and a trend was also deducible for SF.

The genotype AA of TMPRSS6 rs2111833 evidenced a trend to the decrease of SF ($P = 0.09$ vs GA) in females, while not in males. Therefore these polymorphisms could deserve further studies in a large cohort of female with HH type 1 patients. Possibly the generally less aggressive HH form in females could permit to discern the mild effects of these variations.

In males, only an effect of the BMP2 rs235756 TT vs TC genotype ameliorating TS% and an implication of FTL rs2230267 TC vs CC in lowering SI are reported.

The median value of the biochemical parameters, in addition to the mean and standard deviation, and information about patients' age could be precious to better describe the studied cohort. Considering the distinct effects of the studied polymorphisms, a stratification of their frequencies between males and females could also be informative to exclude eventual differences. The comparison of frequencies of the studied polymorphisms in an equivalent Italian healthy population could further be interesting to verify eventual differences versus HH population.

To fully understand the impact of these polymorphisms it will be indispensable to enlarge the population also to evaluate the additive effects of different genotypes, especially for those highly frequent; for example, in females the trend to protect from HH (decreasing SF) of the SCL40A1 rs1439816 CC (73% in the studied population) and of TMPRSS6 rs2111833 AA (11.9% in the studied population) or in males the effect of BMP2 rs235756 TT (40,4%) in lowering TS% and of the FTL rs2230267 TC (55%) in decreasing SI. The TMPRSS6 rs855791 polymorphism also should be considered in these studies.

Finally we would like to compliment the authors for great deal of work they done and for the rare attention to stratify between males and females. The understanding of the genetic causes of the heterogeneity of clinical manifestations of HH remains difficult although several studies were reported in the last decade [8]. We agree with the thinking of the authors that the Next Generation Sequencing technology will be likely decisive to detect mutations and polymorphisms which will contribute to clarify the impact of genetic background in the modulation of the clinical manifestations of hemochromatosis.

Conflict of interest

The authors declare no conflict of interest.

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