Editorial

Dissecting the evolutionary genetics of iron overload in non-alcoholic fatty liver disease

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Hepatic iron accumulation due to primary and secondary iron overload conditions is an important co-factor promoting chronic liver damage in many liver diseases including alcoholic liver disease [1] and chronic hepatitis C [2,3]. In addition to these entities, indicators of increased iron stores are found in approximately one-third of patients with non-alcoholic fatty liver disease (NAFLD) who usually present with increased serum ferritin levels along with normal or only slightly elevated transferrin saturation [4,5] and parenchymal iron deposition on liver histology [6]. The term *insulin resistance-associated hepatic iron overload* (IR-HIO) syndrome has been coined for this association [5] whose pathophysiology, however, is only partly understood. In analogy to hereditary hemochromatosis, consensus exists that iron excess in IR-HIO elicits iron-mediated oxidative stress and lipid peroxidation driving inflammation and fibrosis development [7,8]. Some investigators have identified a role of hemochromatosis gene mutations as promoters of increased iron storage in NAFLD [8,9], while others have not [10,11]. Recently, low copper status was suggested as a modifier of iron storage in NAFLD [12].

In this issue of the Journal, Valenti and co-workers present data from a hypothesis-driven candidate-gene association study in 274 well-characterized Italian subjects with biopsy-proven and graded NAFLD genotyped for the hemochromatosis gene (HFE), ferroportin gene (FPN), and α1-antitrypsin (AAT), and phenotyped for heterozygosity of the β-globin gene mutation associated with thalassemia minor [13]. A control population extracted from a pool of blood donors served as a reference. Major findings of this study include a significant and independent association of the β-thalassemia trait with parenchymal siderosis (OR 2.57, 95% CI 1.49–4.47), and moderate to severe fibrosis (OR 2.5, 95% CI 1.26–5.19). C282Y heterozygosity and H63D homozygosity were also associated with relevant hepatic/hepatocellular siderosis but not with fibrosis, while AAT mutations were neither associated independently with siderosis nor fibrosis.

The finding of the β-globin gene mutation being associated with iron overload and fibrosis in NAFLD is of special interest,

since it exemplifies nicely that certain genetic factors may be important in specific geographical regions and ethnic subgroups who are subjected to environmental factors favouring carriers of genes that confer a selection advantage towards non-carriers. In the present study, this could be true for the β-thalassemia trait: Hemoglobinopathies, including thalassemia render their carriers partially resistant to malarial infections, therefore, thalassemia is frequent where malaria is endemic such as in countries bordering the Mediterranean sea, including Italy where Malaria was wide-spread since the Roman period until 1940 when the Pontine Marshes were successfully drained. Malaria had also been a major health problem in Northern Italy such as in the Po valley which is closer to Milan (where the study was conducted), and thalassemia shows an equally high prevalence in this region. Considering the prominent rural exodus of peasants from the countryside to big cities (such as Milan) during the last two centuries, it is conceivable that this resulted in a high frequency of the β-globin gene mutation among the population under scrutiny. Thus, the β-globin gene mutation which protected carriers against malaria in the past, now increases the risk of progressive NAFLD by promoting iron storage (Fig. 1).

As with all single-center candidate-gene studies, the results of Valenti and co-workers still have to be viewed with some caution. Looking closer at the phenotypes of interest, the study has investigated relatively small numbers: 116 patients had true-iron deposition and only 42 patients had relevant fibrosis greater than stage F1. This might have an impact on the general applicability of these findings since minor changes in numbers could affect the effect-estimates derived. This might especially apply to H63D homozygosity in this study with 13 of 274 patients being carriers of this genotype. In short, independent replication of these findings is needed. It would be fascinating to collect Italian patients with confirmed NAFLD from regions with a high prevalence of thalassemia, and a past history of malaria to assess the impact of β-globin gene mutations in the context of a genome-wide risk profile, for instance, in a genome-wide association study (GWAS).

Globally, the overall genetic risk profile for NASH is indeed emerging, epitomized by the identification of *PNPLA3* as a robust marker of steatosis, liver-enzyme elevation, and fibrosis [14,15] across populations. Despite the advent of GWAS as a very

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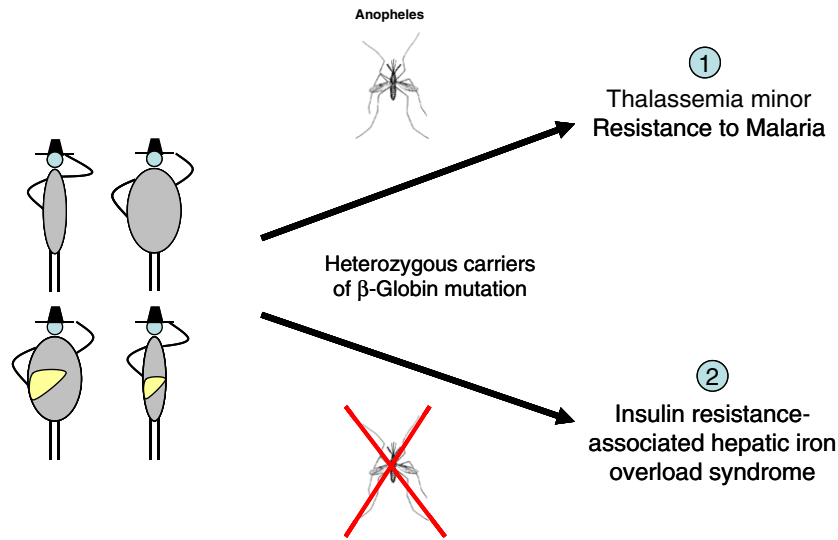
Fig. 1. β-Globin mutations confer protection toward Malaria infections thereby providing a selection advantage over non-carriers. (circle 1) With the eradication of Anopheles populations by draining swamps and by the extensive use of DDT (dichlorodiphenyltrichloroethane), this effect got lost. Instead, in the context of the obesity epidemic β-globin mutations may have become a modifier of iron overload in patients at risk for NAFLD (circle 2) underscoring differential effects of this mutation under different environmental pressure.

powerful and unbiased tool to investigate the genetic susceptibility of complex phenotypes, the study by Valenti et al. underscores the utility of selected, hypothesis-driven candidate studies as this risk factor is likely coupled to a specific population-history. In terms of the general pathogenesis of NASH, this study adds another piece of evidence supporting a central role of iron metabolism in the progression of liver damage that could present a target for therapeutic intervention in future.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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