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Subpopulations with Iron Deficiency, Liver Disease, or *HFE* Mutations Revealed by Statistical Mixture Modeling of Transferrin Saturation and Serum Ferritin Concentration in Asians, African Americans, Hispanics, and Whites.

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Abstract

In previous investigations, we modeled the distribution of transferrin saturation (TS) in Caucasians and demonstrated a strong association between *HFE* genotype and TS subpopulations. Extending this approach, we now have analyzed joint population distributions of TS and serum ferritin concentration (SF) measured in the multi-ethnic Hemochromatosis and Iron Overload Screening (HEIRS) Study and examined the association of these distributions with the presence of *HFE* C282Y and H63D mutations, self-reported liver disease, and iron deficiency (defined as SF <15 μg/L). Based on separate models for

each race/ethnicity by gender, four components with successively increasing age-adjusted means for TS and SF were identified in data from 26,832 African Americans, 12,620 Asians, 12,264 Hispanics, and 43,254 Whites. Fig. 1 illustrates age-adjusted values from 16,662 White men. Superimposed 95% confidence ellipses reflect component probability densities and show separation of the 1st and 4th components that had the lowest and highest means for TS and SF, respectively. Table 1 presents the range of estimates from individual models and indicates that the 2nd (largest) component had TS means of 22–26% for women (29–30% for men) and SF means of 43–82 µg/L for women (165–242 µg/L for men). The 3rd and 4th components had progressively smaller proportions and higher mean values of TS and SF, while the 1st component in each model had mean TS <16% for women (<20% for men), and mean SF <28 µg/L for women (<47 µg/L for men). Compared to the 2nd component:

adjusted odds of iron deficiency were significantly higher in the 1st component (15–48 for women, 61–3530 for men); adjusted odds of self-reported liver disease were significantly higher in the 3rd and 4th components for African-American women and all men; and adjusted odds of any *HFE* mutation were increased in the 3rd component (1.4–1.8 for women, 1.2–1.9 for men) and in the 4th component for Hispanic and White women (1.5, 5.2, respectively) and men (2.8, 4.7, respectively).

Joint mixture modeling identifies one component with lower mean SF and TS at risk for iron deficiency and two components with higher mean SF and TS at risk for liver disorders and *HFE* mutations. This approach permits characterization of the aggregate effects of hereditary or acquired factors that influence these serum iron measures in populations, and complements and enhances genetic and phenotypic testing for assessment of disease characteristics.

Table 1

Range of estimates from models.

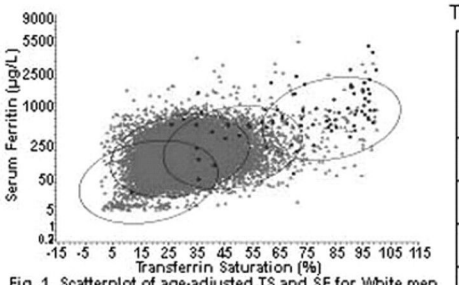

Fig. 1. Scatterplot of age-adjusted TS and SF for White men with 95% confidence ellipses based on a 4-component model. Values from *HFE* C282Y homozygotes shown as blue dots.

Table 1. Range of estimates from models.

Component	Percent of values (Women; Men)	Mean TS (%) (Women; Men)	Mean SF (µg/L) (Women; Men)
1	11-17; 2-5	12-15; 15-19	10-27; 24-46
2	59-73; 69-86	22-26; 29-30	43-82; 165-242
3	10-22; 11-25	35-45; 45-49	64-120; 234-347
4	1-2; 1-1.3	57-80; 79-84	83-266; 503-886

Author notes

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