Methods

Genetic correlation between TS and iron-related traits were evaluated by LD score (LDSC) regression analysis (Bulik-Sullivan et al., 2015). LDSC regression analysis uses the summary statistics from genome-wide association studies (GWAS) of two traits of interest to estimate the heritability and genetic correlation of these traits. TS summary statistics were derived from the most recent TS GWAS of 4819 European ancestry TS cases and 9488 population-matched controls (Yu, et al., 2019). GWAS summary statistics for two iron-related traits, ferritin and transferrin, are available at LD Hub, a web interface for LD score regression analysis (<http://ldsc.broadinstitute.org/ldhub/>) (Zheng, et al., 2017). GWAS studies of both iron-related traits were performed on 23,986 European ancestry samples collected by the Genetics of Iron Status Consortium (GISC) (Benyamin, et al., 2014). The genetic correlations between ferritin, transferrin, and TS were evaluated at LD Hub, and Bonferroni correction was applied for multiple testing.

Results

In order to investigate whether the observed inverse (linear) relationship between serum ferritin levels and tic severity is indicative of shared pathophysiology, we tested whether TS and iron-related traits have overlapping genetic risk by evaluating the genetic correlation between GWAS summary statistics of ferritin, transferrin, and TS using LDSC regression (Bulik-Sullivan et al., 2015). We found a significant negative genetic correlation between ferritin and TS (rg = -0.34; SE = 0.13; P = 0.0087), indicating that shared genetic variants contribute both to increased TS risk and decreased ferritin levels. A similar genetic correlation between higher TS risk and higher transferrin levels (rg = 0.28; SE = 0.13; P = 0.036), though the finding did not surpass a Bonferroni correction threshold (P = 0.025).

Bulik-Sullivan. et al. An atlas of genetic correlations across human diseases and traits. Nat. Genet. 2015 47, 1236–1241.

Yu, et al. [Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies.](https://www.ncbi.nlm.nih.gov/pubmed/30818990) Am J Psychiatry. 2019 Mar 1;176(3):217-227

[Zheng, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2017 Jan 15;33(2):272-279.](http://bioinformatics.oxfordjournals.org/content/early/2016/09/22/bioinformatics.btw613.abstract)

Benyamin, et al. [Novel loci affecting iron homeostasis and their effects in individuals at risk for hemochromatosis.](https://www.ncbi.nlm.nih.gov/pubmed/25352340) Nat Commun. 2014 Oct 29;5:4926