Abstract title:
The impact of common TMPRSS6 gene variants on iron status of pregnant women from rural Gambian

Authors:
Momodou W. Jallow¹,², Amat Bah¹,³, Alasana Saidykhan¹, Carla Cerami¹ and Andrew Prentice¹

Affiliations:
1. MRC Unit The Gambia at LSHTM, Atlantic boulevard Fajara, Banjul The Gambia.
2. Regeneron Genetic Center, 777 Old Saw Mill River Road, Tarrytown, NY 10591.

Background
Anaemia is a global health problem that has a significant impact on women of reproductive age in low-and middle-income countries. Nutritional deficiencies, infection and genetic risk factors are the major drivers. However, the role of genetic factors particularly in settings where the prevalence of anaemia is high, has not been fully investigated. Genome-wide association studies have identified numerous single nucleotide polymorphisms in the TMPRSS6 gene which are linked to impaired iron status in non-African populations. However, the impact of these SNPs on the risk of anaemia in West African populations have not been fully investigated.

Objectives
To investigate the effects of TMPRSS6 rs2235321, rs4820268 and rs855791 on iron status biomarkers in pregnant Gambian women.

Methods
We analyse data from a cohort of pregnant (18 to 49 years, N=364), with genotype data on TMPRSS6 rs2235321, rs855791 and rs4820268, and on iron biomarkers (serum iron, unsaturated iron binding capacity (UIBC), transferrin, ferritin soluble transferrin receptor (sTfR), transferrin saturation (TSAT) and total iron binding capacity (TIBC) and hepcidin) and hematology traits. We investigated the effects of genotype on these iron status indicators.

Results
The TMPRSS6 rs223521 is associated significantly with reduced hepcidin levels (F ratio = 6.16, P=0.00235). The carriers of the minor allele (A) had decreased hepcidin concentration compared to GG carriers; AA vs GG = [mean (SE) 3.28 ng/mL (1.11) vs 5.44 ng/mL (0.62), P=0.0004]. Similarly, TMPRSS6 rs4820268 significantly influenced serum iron levels (F = ratio = 3.58, P = 0.0289). Carriers of the rs4820268 minor alleles (GG) had decreased serum iron concentrations compared to AA
genotype carriers; GG vs AA = [mean (SE) 10.77 \( \mu \text{mol/L} \) (1.40) vs 13.56 \( \mu \text{mol/L} \) (3.13)]. No other iron phenotype was influenced by any of these two SNPs and no effect of rs855791 was observed on any phenotype.

**Conclusion**

*TMPRSS6* rs2235321 may modulate hepcidin levels in pregnancy, whereas rs2235321 may predispose pregnant women to low iron status. Analysis of a larger dataset with more genetic markers associated with iron status may provide further insight into the functional effects of genetic variants within the iron regulatory genes on the risk of anaemia in African women of reproductive age. This may enable the development of genomic medicine approaches for the treatment and prevention of anaemia and iron related pathologies.

Keywords:

*TMPRSS6* SNPs, Iron biomarkers, Pregnant women, Anemia