

# Is Ferroportin Q248H polymorphism protective against clinical manifestations of Malaria during pregnancy?

**Author:** Dr. med. Katja C. Greutelaers  
**Profession:** MD, specialized in Anaesthesiology  
**Submission Date:** September 2015  
**Supervisor:** Prof. Dr. med. Frank P. Mockenhaupt  
Institute for Tropical Medicine and International Health, Charité  
Universitätsmedizin Berlin, Germany

**Key words:** Ferroportin, Q248H polymorphism, iron, hepcidin, malaria, pregnancy

**Background:** Malaria remains a global health problem with the main burden in sub-Saharan Africa. Pregnant women represent a particular risk group with increased susceptibility and clinical manifestation of the disease. Malaria, but also asymptomatic infections can cause low birth weight, preterm delivery, maternal anaemia and consequently high infant mortality.

Risk and manifestation of malaria is influenced by iron status and host genetics. Ferroportin operates as iron exporter transporting  $\text{Fe}^{2+}$  from the cell to the body's circulation. The prevalence of a common FPN mutation, the Q248H polymorphism, ranges from 2.2 to 13.4% in SSA. The polymorphism influences the iron homeostasis and is associated with altered immune responses. The influence of the polymorphism on malaria susceptibility was not explored so far.

**Methods:** The present study is a secondary analysis of a cross-sectional clinical study of 893 Ghanaian women undertaken between January 2000 and January 2001 in the Ashanti region, an area of holoendemic malaria transmission. In the initial study, women presenting at the Agogo District Hospital for delivery were invited to participate in the study. Demographic data including age, socio-economic data, the number of ante natal care visits and parity were documented; peripheral venous and intervillous placental blood samples were taken and analysed with different diagnostic tools for *Plasmodium* infection; chloroquine and pyrimethamine levels in the maternal blood were checked. The women were clinically examined and parameters including temperature and haemoglobin concentrations were measured. The newborns were assessed within 24 hours after delivery for the crude birth weight and the gestational age.

In the current analysis, all 304 primiparous women with live, singleton delivery out of the 893 women of the primary study were included. PCR assays with subsequent endonuclease digestion producing restriction fragment length polymorphisms were carried out to detect the FPN Q248H polymorphism in January 2011.

**Findings:** From the included 304 primiparous women, 68% had evidence of past or present placental *P. falciparum* infection. Typing of the Q248H FPN polymorphism was successful in 290 women. 8.2% had the mutation, which was associated with less *P. falciparum* infection in peripheral and placental blood samples. The association was significant for present and past placental infection (OR 0.33, 95%CI 0.15-0.76,  $P = 0.01$ ) and for *Plasmodium* detection in placental blood via PCR (OR 0.39, 95%CI 0.17-0.89,  $P = 0.02$ ). After adjusting for factors previously identified as being associated with placental malaria, women with FPN polymorphism had substantially reduced OR of placental *P. falciparum* infection (adjusted OR 0.27, 95%CI 0.12-0.71,  $P = 0.01$ ). Association of the mutation with maternal anaemia was not significant ( $P = 0.28$ ), but anaemia was less in women without polymorphism compared to women with Q248H polymorphism (39% versus 28% respectively). The polymorphism was not significantly associated with LBW, PTD and neonatal measures.

**Interpretation and conclusion:** The FPN Q248H polymorphism is significantly and negatively associated with past and present placental malaria. This finding suggests, that the mutation protects against placental malaria and could influence the susceptibility for *P. falciparum* infection in pregnancy. An altered interaction between hepcidin and the single-nucleotide polymorphism (SNP) could influence iron shifts and could withhold iron from the hepatocytes, which is necessary for the *Plasmodium* development. With a prevalence of 10% in SSA, the Q248H polymorphism should also be considered in settings, where iron supplementation is recommended, as it increases the iron absorption in the gut and can elevate serum iron levels.