A glucocorticoid receptor gene haplotype is associated with increased risk for low birth weight infants among Kenyan mothers

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Background and objectives: Inflammatory pathway components play critical roles in mediating preterm and low birth weight births in response to malaria infection. The glucocorticoid receptor gene, also known as *NR3C1*, mediates cross-talk between the inflammatory response and endocrine pathways. Glucocorticoid receptor polymorphisms in this study were selected based on their previous association with glucocorticoid activity, which may be a factor contributing to low birth weight. The gene is located on chromosome 5q31.3.

Methods: This study utilized the retrospective (1992-1999) longitudinal population-based cohort study on mothers within the Asembo Bay Cohort Project (ABCP) of Western Kenya. Three SNPs in the glucocorticoid receptor gene were included in this study design: 3669A>G (rs6198), *Bcl*I (intron 2) and *Tth111*I (5' flanking region, rs10052957). A total of 735 mothers were included in this study: 61 delivered a low birth weight (<2500g) infant (cases) and 674 delivered a normal weight (≥2500g) infant (controls). Genotyping was performed with the Sequenom high throughput iPLEX assay. Using SAS 9.1 for Windows, biologically significant covariates as well as the three SNP genotypes were examined univariately for an association with low birth weight. Statistically significant variables as well as those with biological significance were later used in the multivariate analysis. Haploview 4.0 was used to construct and determine population haplotypes. PHASE 2.1 was used to generate individual haplotypes which went into a logistic regression model along with the significant covariates.

Results: Among the glucocorticoid receptor polymorphisms analyzed, only the 3669A>G SNP showed significantly increased odds for delivering a low birth weight infant. In univariate analysis, GGA was the only significant haplotype. After adjusting for potential confounders of parity, placental malaria parasitemia (PNPL) and height, the GG/GA genotype of the 3669A>G polymorphism was no longer significantly associated with the odds of delivering of a low birth weight infant. The GGA haplotype remained significantly associated with increased odds for delivering a low birth weight infant after adjusting for parity, PNPL, and height.

Discussion/Conclusion: In this Kenyan maternal population, having the GGA haplotype of the glucocorticoid receptor gene SNPs 3669A>G, *Bcl*I (intron 2) and *Tth111*I increases the odds of delivering a low birth weight infant [OR=4.58 (1.94, 10.82)]. These results may suggest that endocrine pathway genes are associated with low birth weight. Further research is necessary to determine the mechanisms of these genes and other pathways which might be involved in low birth weight.