PLA1a variant rs2692622 associates with red blood cell phospholipid fatty acid composition and blood pressure of pregnant women of African descent: The NUPED study

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Introduction

Pregnancy is a well-adapted, physiologically altered state with continuous anatomical and physiological adaptations occurring. Remodelling of the cardiovascular system is one of the major adaptations happening during pregnancy. Increased circulating maternal blood volume, increased foetal nutrient requirements and the addition of the new placental circulatory system increase the cardiovascular load (Vinturache and Khalil, 2021). Hypertensive disorders are the most common risk factor for maternal and perinatal morbidity and mortality and affect 10% of pregnancies (Barton et al., 2001). Arterial stiffness has proven to be an important prognostic factor, and possibly a therapeutic target in patients diagnosed with high blood pressure (Zieman et al., 2005, Kim et al., 2013). Total phospholipid fatty acid composition dictates cellular flexibility, rigidness, and evidence for fluidity (Stillwell and Wassall, 2003). The fatty acid composition of the two lipid chains have been characterised as predominantly saturated fatty acids located at the sn-1 position where as mono- and polyunsaturated fatty acids are predominantly located at the sn-2 position of the phospholipid molecule (Filkin et al., 2020). The enzyme Phospholipase A1 (PLA1), encoded by the *PLA1A* gene, is involved with the mobilisation of functional n-3 PUFAs from phospholipids. Genetic determinants of *PLA1A* and its implication on lipid mediator metabolism is still poorly understood. The objective for this study was to characterise and associate genetic variations of the *PLA1A* gene with lipid mediators of urban African pregnant women in the Nutrition during Pregnancy and Early Development (NUPED) study

Methodology

Here, we characterized the genetic variation in the PLA1A gene of 247 pregnant women of African descent and studied the associations with red blood cell total phospholipid fatty acid composition, inflammatory markers, brachial blood pressure and heart rate during pregnancy, and there for contributing to a better understanding the multifactorial aetiology for an increased likeliness for the development of preeclampsia observed in pregnant women of African descent. Whole blood was collected at 18 weeks gestation. Genomic DNA was isolated followed by targeted exome sequencing of *PLA1a* for 32 pregnant (18wks) participants, 16 with low n-3 LCPUFA and 16 with high n-3 LCPUFA status. The variant rs2692622 was validated in the entire NUPED cohort (n=247). Data was scrutinized through statistical analysis to identify genetic associations. *In silico* structure modelling was done for the PLA1 gene. Red blood cell total phospholipid FA were extracted and analysed using GC/GC/MS.

Results

In total, 26 variants were identified through NGS in the selected 32 participant samples. The variant rs2692622, located in a disulphide bond, substitutes a serine for an asparagine at position 284. In total, 247 eligible African women were included in this study to investigate the associations between red blood cell phospholipid levels and high blood pressure. The median age of the participants was 27 and median gestational age at enrolment was 14.25 weeks. A total of 53 participants harboured the variant rs2692622$_{GA/AA}$. At entry of pregnancy, i.e <18 weeks gestation, higher stearic acid and lower DGLA total phospholipids were observed in the A-allele carriers. Using the recessive rs2692622 model, at <18 weeks gestation, an association was seen in CRP, where A-allele carriers had higher levels.

Discussion

We hypothesized that this variant in the *PLA1a* gene results in a discrimination (due to activated response to inflammation) against saturated fatty acids, specifically stearate, in favour of unsaturated fatty acids, specifically DGLA. We have evidence of a significant association between rs2692622 and an anomalous phospholipid composition (saturated vs unsaturated) at <18 weeks' gestational period. CRP levels were 14.76 and
31.59 respectively for participants with no genetic change and participants harbouring the variant suggesting inflammation. Furthermore, higher heart rate levels were observed in A-allele carriers. In conclusion, we have found significant evidence which suggests a genetic predisposition in African women to address inflammation during pregnancy.

Keywords

Saturated fatty acids, unsaturated fatty acids, genetic associations, inflammation

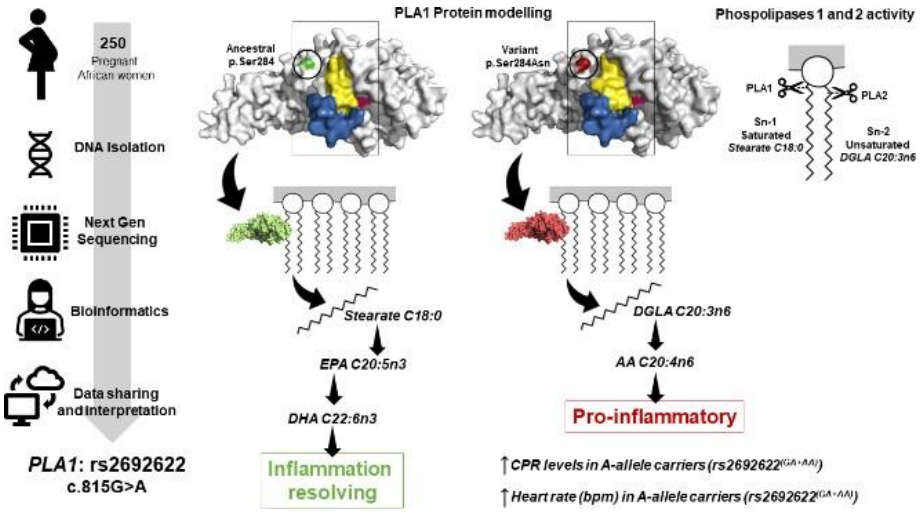

Figure 1: Suggested mechanism for the altered Pla1 protein activity. It is hypothesized that Pla1's catalytic triad is altered due to the variant and therefor have a higher affinity for DGLA than for Stearate.