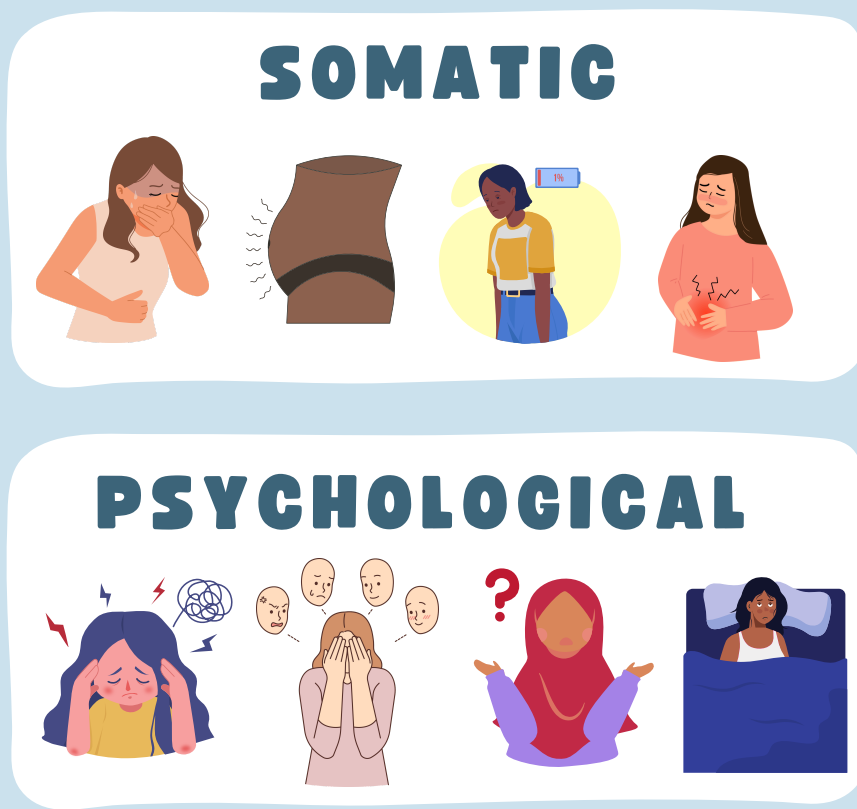


ASSOCIATIONS BETWEEN POLYMORPHISMS IN THE NFKB1 GENE AND PREMENSTRUAL SYMPTOMS

1 INTRODUCTION

Premenstrual symptoms (PMSx) affect 80-90% of women of reproductive age, with 20-32% experiencing significant impairment due to premenstrual syndrome (PMS) (Yonkers et al., 2009; Lete et al., 2017). These symptoms, which range from bloating and fatigue to anxiety and mood swings, vary widely in severity and are not yet fully understood (Biggs & Demuth, 2011). Inflammation has been strongly linked to PMSx, with markers like interleukins and C-reactive protein associated with symptom severity (Bertone-Johnson et al., 2014; Gold et al., 2016).

Central to this inflammatory response is the NF- κ B pathway, regulated by the NFKB1 gene, which plays a critical role in immune responses and inflammation (Goldhirsh et al., 2021; Cartwright et al., 2016). This study explores how variations in the NFKB1 gene may influence PMSx, providing insights into the genetic and molecular factors underlying these symptoms (Glas et al., 2006; Fu et al., 2016).



2 METHODS

The study utilized data from the Toronto Nutrigenomics and Health (TNH) study, a multi-ethnic cross-sectional study conducted between 2004 and 2010, involving 1,640 young, healthy adults aged 20-29 (Nielsen et al., 2023).

For this analysis, only women were included, excluding smokers, hormonal contraceptive users, and those on medications that could influence premenstrual symptoms (Biggs & Demuth, 2011; Jarosz et al., 2021).

Various biomarkers and lifestyle data were collected, including dietary intake and the presence and severity of 15 premenstrual symptoms, assessed via a standardized questionnaire (Jarosz et al., 2021).

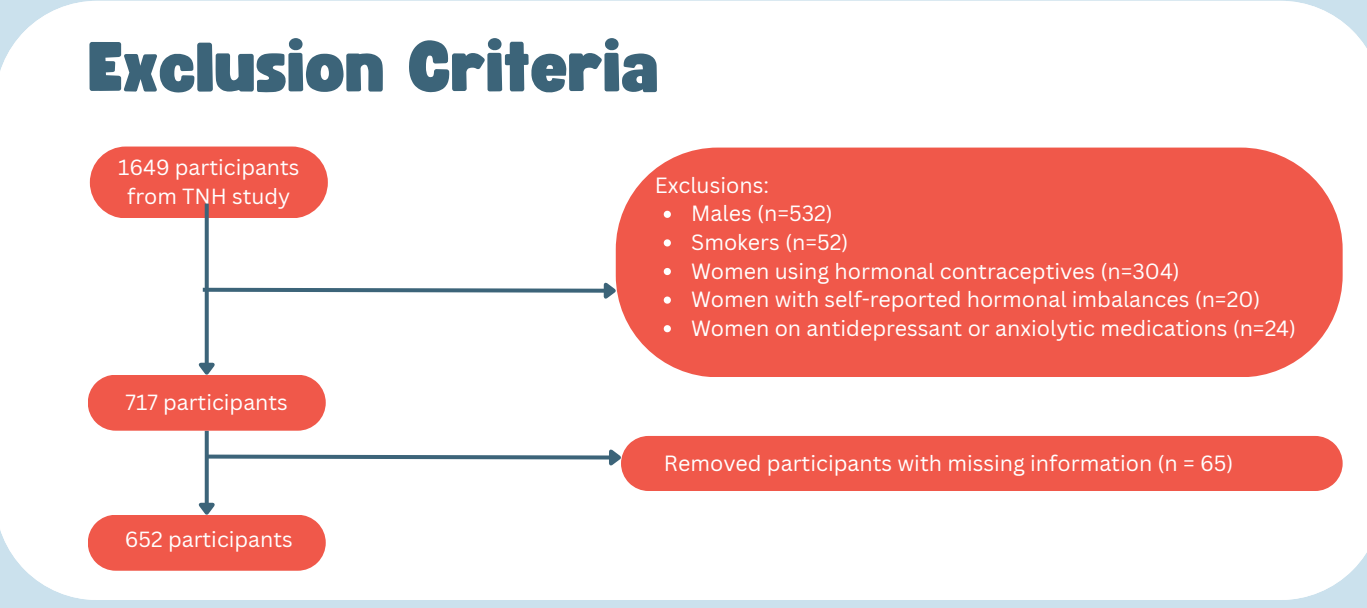
DNA was extracted from blood samples, and 18 SNPs within the NFKB1 gene were genotyped using Sequenom MassARRAY (Merritt et al., 2018).

Logistic regressions were conducted in RStudio to examine associations between these genotypes and premenstrual symptoms, with data stratified into present or absent categories. Preliminary analyses were performed for the two main ethnic groups, and adjustments were made for age, BMI, ethnicity, and physical activity. Statistical significance was set at $p < 0.05$.

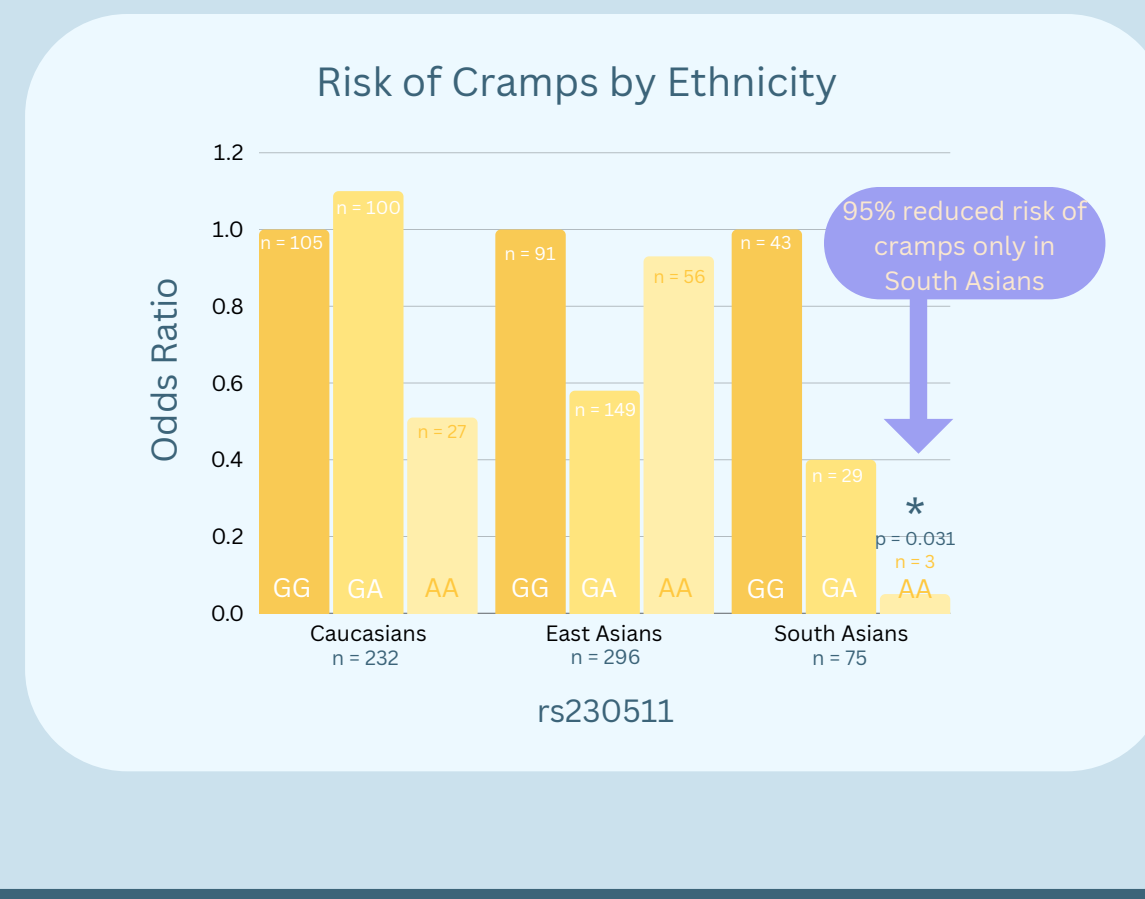
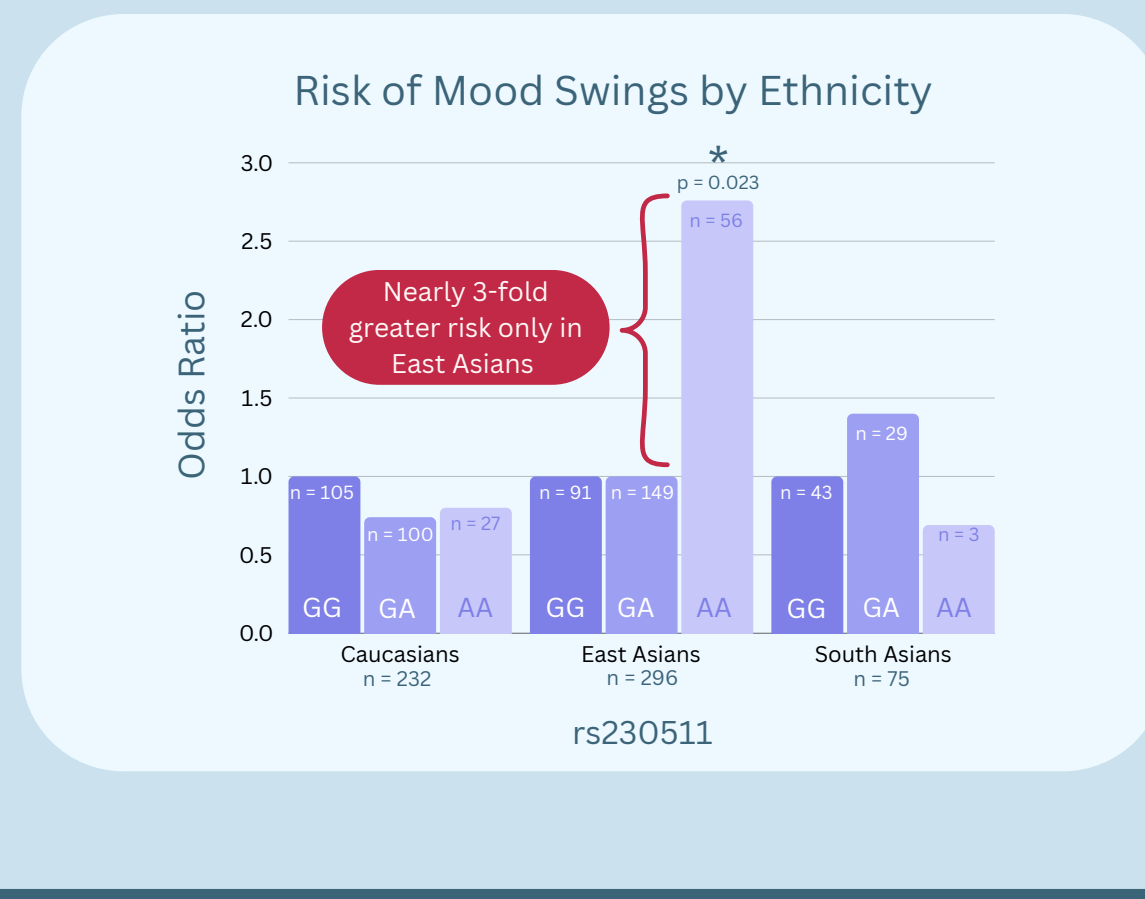
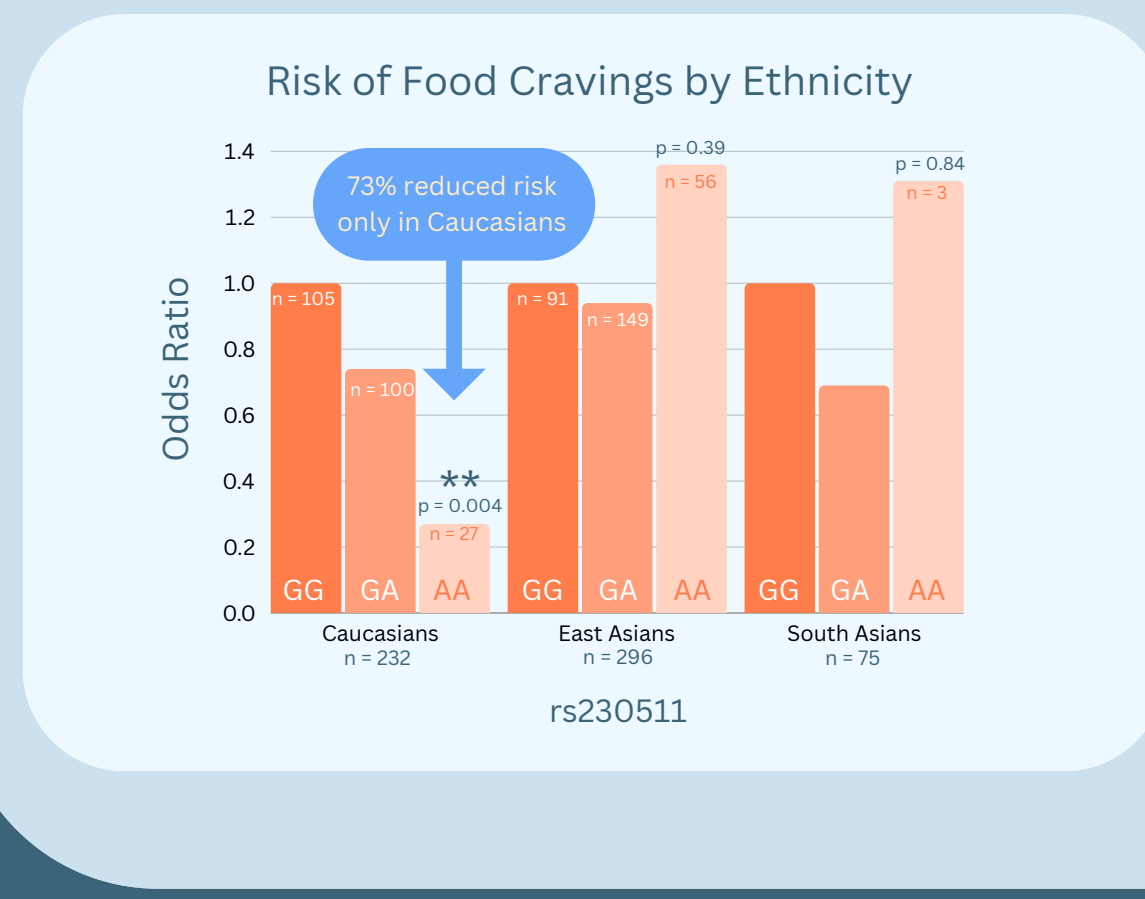
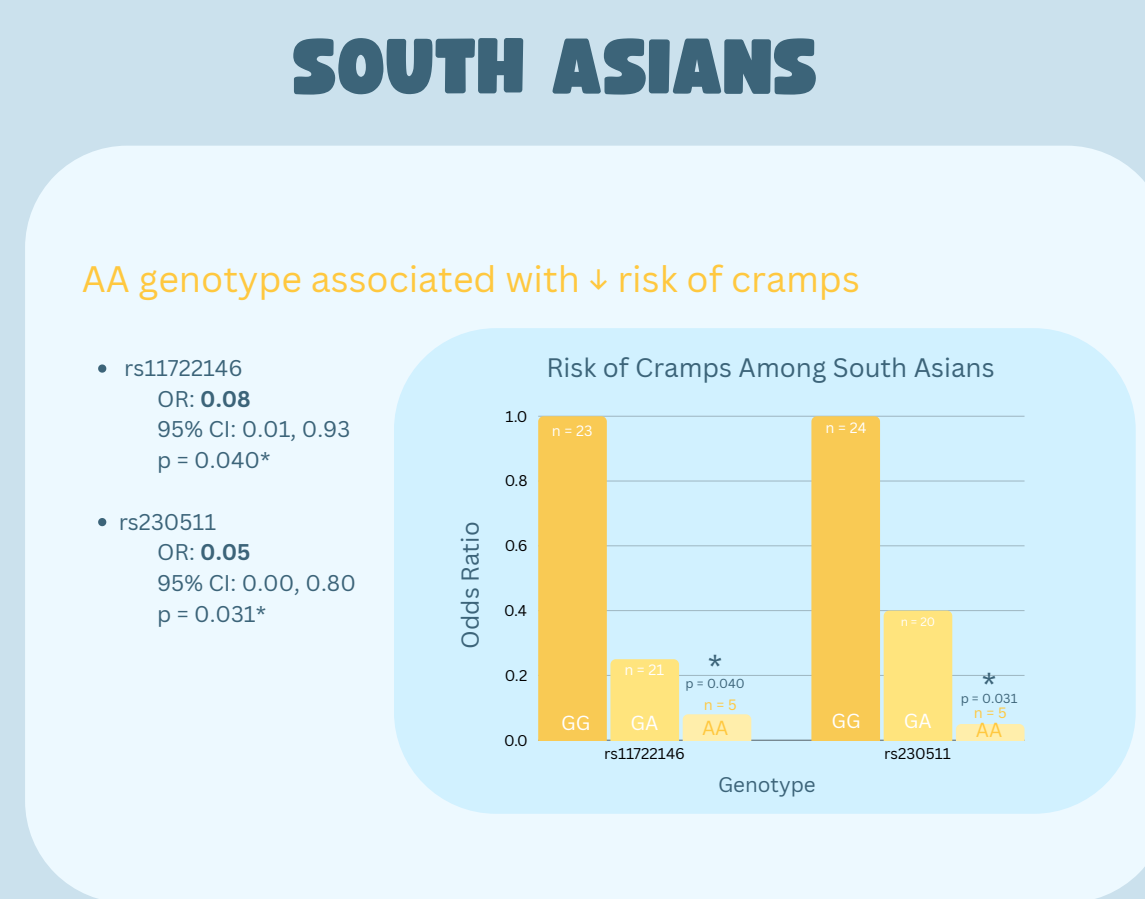
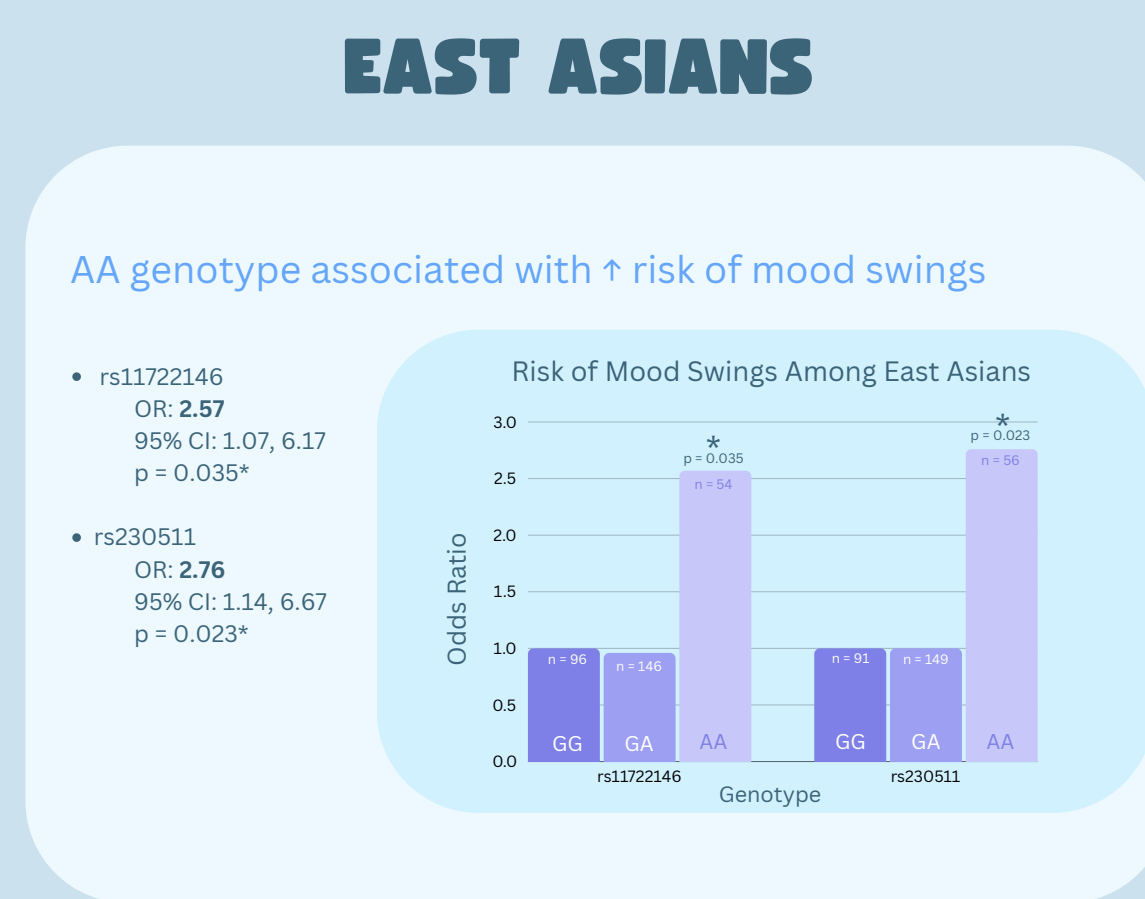
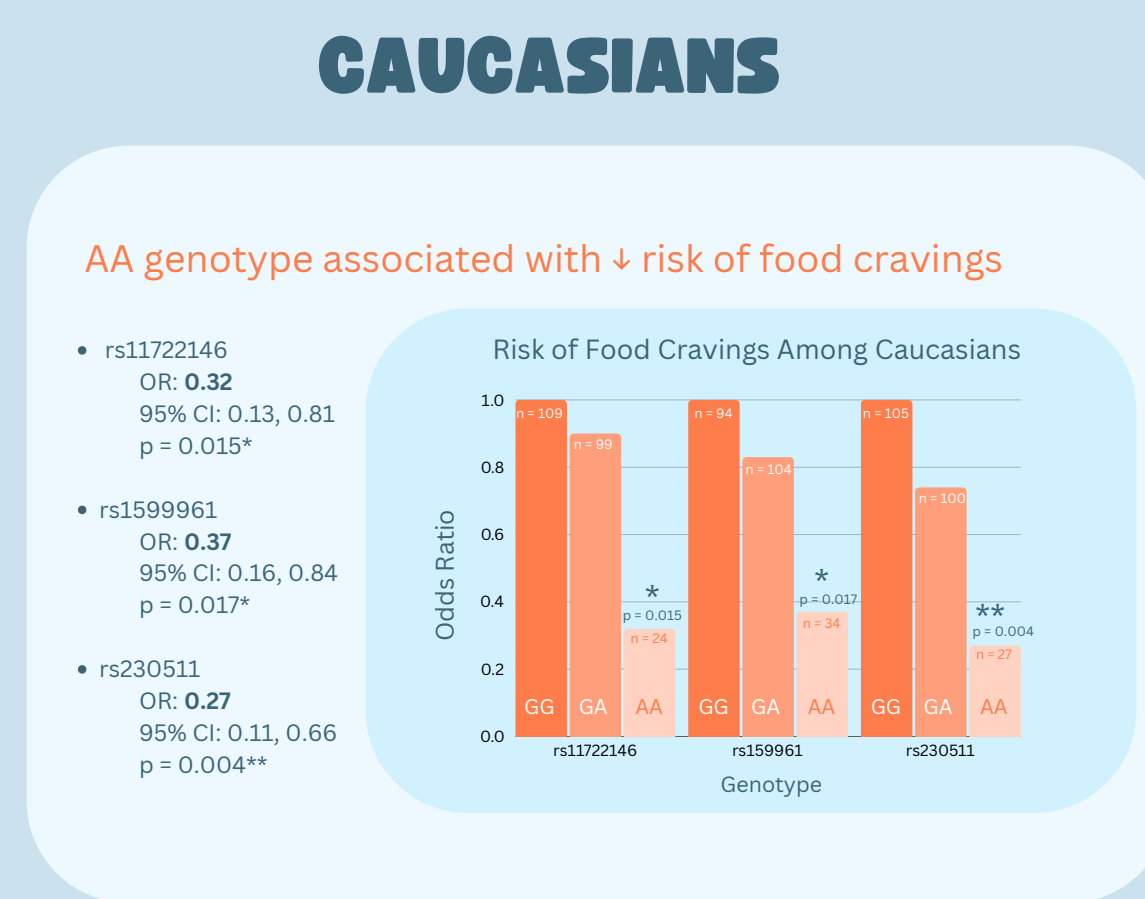
Symptoms	Absent				Present			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Acne, skin blemish								
Bloating, swelling, breast tenderness								
Cramping								
Mood swings, crying easily, irritability, angry outbursts								
Increased appetite, food cravings								
Fatigue								
Headaches								
Anxiety, tension, nervousness								
Clumsiness								
Confusion, difficulty concentrating, forgetfulness								
Sexual desire/activity change								
Insomnia								
Nausea								
Depression								
Desire to be alone								
Other (specify)								

Blood samples genotyped for 18 SNPs in the NFKB1 gene:

- rs11722146
- rs13117745
- rs1599961
- rs1609798
- rs230511
- rs230547
- rs3774932
- rs3774934
- rs3774956
- rs3774968
- rs4648006
- rs4648022
- rs4648090
- rs4648095
- rs4648110
- rs4648127
- rs4698863
- rs7674640

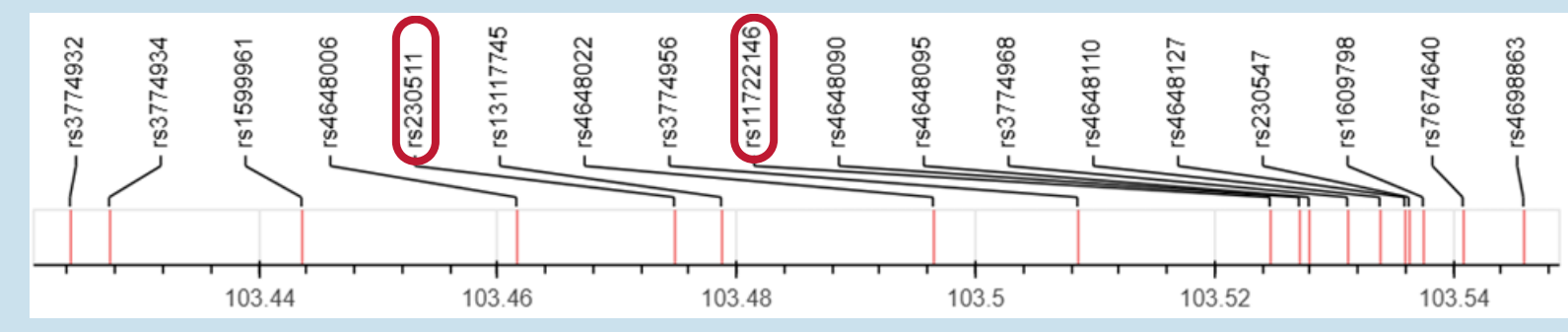


3 RESULTS



4 DISCUSSION AND CONCLUSION

We can conclude that variation in NFKB1 genotypes impacts some premenstrual symptoms, suggesting that endogenous levels of inflammation may be important. This study highlights ethnic-specific susceptibilities to PMSx, with variations in NFKB1 gene polymorphisms linked to both somatic and psychological symptoms. Notably, SNPs rs11722146 and rs230511 showed strong linkage disequilibrium in the East Asian cohort ($D' = 0.972$; $R^2 = 0.921$), suggesting their co-inheritance may contribute to mood swings. These genetic variations influenced PMSx differently across ethnic groups, underscoring the need for personalized approaches to managing these symptoms.



This research, the first to examine NFKB1 genotypes in relation to PMSx, provides important insights but is limited by its cross-sectional design and potential recall bias. Despite these limitations, the findings suggest that genetic markers could guide personalized therapies, potentially improving treatment efficacy and minimizing side effects. Further research is needed to explore these genetic mechanisms and develop tailored management strategies considering ethnic and genetic differences.

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