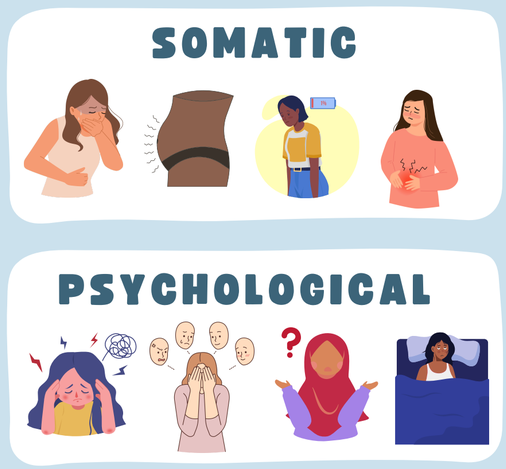
ASSOCIATIONS BETWEEN POLYMORPHISMS IN THE NFKB1 GENE AND PREMENSTRUAL SYMPTOMS

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-κB 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).

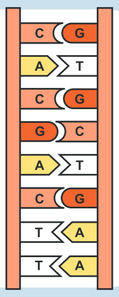
DNA was extracted from blood samples, and 18 SNPs within the NFKB1 gene were genotyped using Sequenom MassARRAY (Merritt et al., 2018).

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 $p < 0.05$.

	Absent	Present		
Symptoms	**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



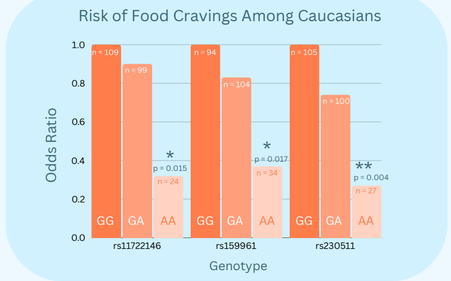
Exclusion Criteria

3 RESULTS

CAUCASIANS

AA genotype associated with ↓ risk of food cravings

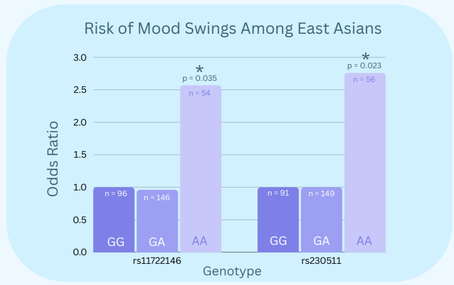
- rs11722146
  OR: **0.32**
  95% CI: 0.13, 0.81
  p = 0.015*
- rs1599961
  OR: **0.37**
  95% CI: 0.16, 0.84
  p = 0.017*
- rs230511
  OR: **0.27**
  95% CI: 0.11, 0.66
  p = 0.004**



EAST ASIANS

AA genotype associated with ↑ risk of mood swings

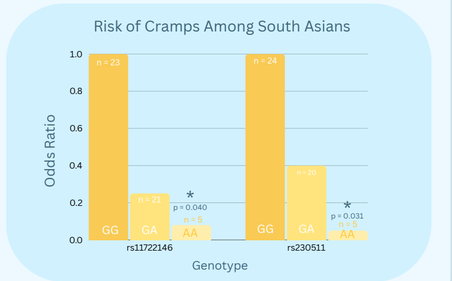
- rs11722146
  OR: **2.57**
  95% CI: 1.07, 6.17
  p = 0.035*
- rs230511
  OR: **2.76**
  95% CI: 1.14, 6.67
  p = 0.023*

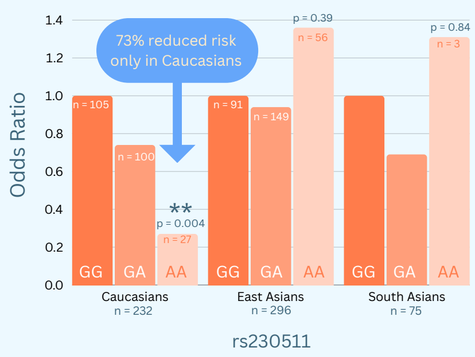


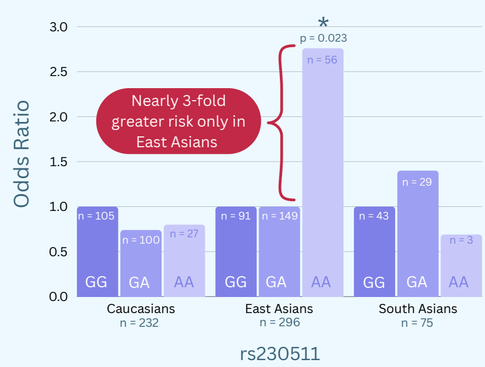
SOUTH ASIANS

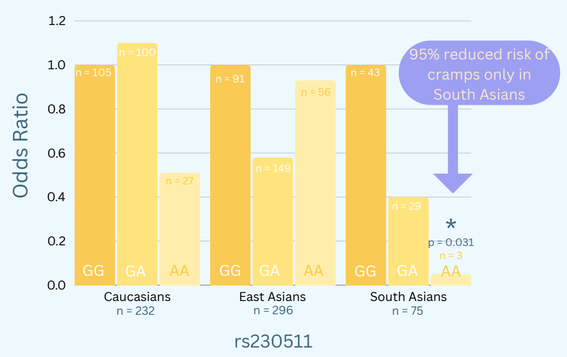
AA genotype associated with ↓ risk of cramps

- rs11722146
  OR: **0.08**
  95% CI: 0.01, 0.93
  p = 0.040*
- rs230511
  OR: **0.05**
  95% CI: 0.00, 0.80
  p = 0.031*



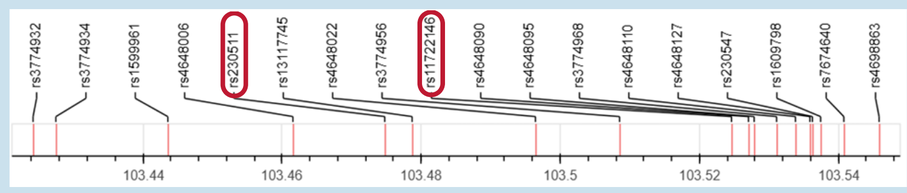






4 DISCUSSION & CONCLUSION

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.

5 AKNOWLEDGEMENT

I am deeply grateful to my research advisor Dr. Ahmed El-Sohemy for his invaluable guidance and support. My thanks also go to Dr. Sara Mahdavi, Isabella Monasterios, Victoria Chen, Mahaylia Datars, and the El-Sohemy Lab team for their encouragement and feedback.

I appreciate the Laidlaw Foundation for enabling this research, and my Laidlaw supervisor, You Jia Lee, for her essential guidance. I also thank the University of Toronto Laidlaw Scholars Programme team for their support and training.

Finally, I thank my Deep Dive group members for their camaraderie and insights, which provided motivation throughout this journey.

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