SMFM
Annual Pregnancy Meeting
February 11-16, 2019
Las Vegas, NV

Hormone receptor genes *PGR* and *GFRAL* linked to Hyperemesis Gravidarum

ABSTRACT 905

MS FEJZO[1,2], KW MACGIBBON[3], PM MULLIN[2]

[1]University of California, Los Angeles, USA
[2]University of Southern California, USA
[3]Hyperemesis Education and Research Foundation, USA

INTRODUCTION

Most pregnancies are complicated by nausea and vomiting of pregnancy (NVP) and 18% of women with NVP require medication. The severest form of NVP, Hyperemesis Gravidarum (HG), occurs in 2% of pregnant women. It accounts for 285,000 hospitalizations in the US annually and can cause brain, renal, and liver dysfunction, esophageal rupture, and post-partum post-traumatic stress. HG is associated with a 4-fold increased risk of adverse fetal outcome including low birth weight, preterm birth, and a 3-fold increased risk of neurodevelopmental delay. It is highly heritable. Our recent genome-wide association (GWAS) and replication study identified the placenta, appetite, and cachexia genes GDF15 and IGFBP7 as being associated with HG.

OBJECTIVE

In our GWAS study, hormone receptor genes *PGR* and *GFRAL* were also found to be significant. We performed a replication study to validate the genome-wide association linking *PGR* and *GFRAL* to HG.

STUDY DESIGN

DNA from 789 women treated for HG and 606 women with normal or no nausea and vomiting of pregnancy were genotyped using a Taqman platform. Genotypes of risk alleles for *PGR* and *GFRAL* were compared between cases and controls using medcalc.org/calc/odds_ratio.php.

RESULTS

TABLE 1. Demographic characteristics of unrelated, individuals from the United States included for REPLICATION

Phenotype for REPLICATION STUDY	Group	Total	Year Born (Average)	Ethnicity
HG	Case	789	1977	90% caucasian
NO HG	Control	606	1975	92% caucasian

TABLE 2. Genotyping results for replication of progesterone receptor gene *PGR*
(N's based on total participants successfully genotyped)

PGR						
rs7948518	N	CC	CT	TT	*P*-value	OR (95% CI)
HG	773	42	333	398		
CONTROL	606	26	178	402	7.82×10^{-07}	0.63 [0.53,0.76]

TABLE 3. Genotyping results for replication of GDF15 receptor gene *GFRAL*
(N's based on total participants successfully genotyped)

GFRAL						
rs7761177	N	TT	CT	CC	*P*-value	OR (95% CI)
HG	759	250	366	143		
CONTROL	593	143	310	140	4.00×10^{-04}	1.31 [1.13,1.53]

CONCLUSIONS

- Evidence suggests abnormal levels of the placenta and appetite hormone GDF15 are associated with HG.
- Validation of the GDF15 receptor gene *GFRAL* as a genetic risk factor for HG provides further support that the GDF15-GFRAL pathway is involved in disease etiology.
- Additionally, the progesterone receptor *PGR*, like GDF15, plays a role in the developing placenta and gastrointestinal mobility.
- Our findings validate *PGR* as a genetic risk factor for HG.

FUTURE DIRECTIONS

- GDF15 inhibitors have proven successful in restoring body weight and appetite in animal models of cachexia, making this a promising strategy for treating NVP and HG.
- Therapeutics targeting GFRAL and PGR should also be investigated.

ACKNOWLEDGEMENTS

- HYPEREMESIS EDUCATION AND RESEARCH FOUNDATION (HELPHER.ORG)
- STUDY PARTICIPANTS
- PAUL AND JANIS PLOTKIN FAMILY FOUNDATION

Contact Information: Marlena S Fejzo, mfejzo@mednet.ucla.edu