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Nausea and vomiting of pregnancy and HG risk genes associated with blood levels, sleep, stomach pain, and other traits

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INTRODUCTION

Our genome-wide association study (GWAS) and replication studies of nausea and vomiting of pregnancy (NVP) and Hyperemesis Gravidarum (HG) implicate the placenta and appetite hormone gene *GDF15*, its brainstem-restricted receptor gene *GFRAL*, Insulin-like growth factor binding protein 7 (*IGFBP7*), and the progesterone receptor gene, *PGR*.

AIM

The purpose of this study was to determine whether these genes and GWAS summary statistics associated with NVP and HG overlap with other traits.

METHODS

1. The GWAS catalog containing 4220 GWASes was searched for NVP/HG risk genes that have been confirmed in replication studies (GD*F15, GFRAL, IGFBP7, PGR*).

2. All genes (replicated and non-replicated) associated with HG and NVP in the GWAS were searched in the GWAS catalog www.ebi.ac.uk/gwas/ and traits associated with more than 3 genes were highlighted.

3. The database and web interface platform, LD Hub, was used for genetic correlation analysis of summary statistics.

RESULTS

1. NVP/HG RISK GENES *GDF15, GFRAL, IGFBP7,* and *PGR* in GWAS CATALOG of 4220 GWASes

GENES	TRAITS
GDF15	GDF15 protein levels, periodontitis, and lupus
GFRAL	glomerular filtration rate, blood urea nitrogen levels, insomnia, body mass index, periodontal inflammation, blood protein levels, osteoporosis, and HIV-1 infection
IGFBP7	IGFBP7 protein levels, IgG glycosylation, diastolic blood pressure, brain volume in infants, heel bone mineral density, alcohol consumption, itch intensity from mosquitoes, and cotinine glucuronidation
PGR	diastolic blood pressure, endometriosis/endometrial cancer, menstrual cycle length, lung adenocarcinoma, height, and adolescent idiopathic scoliosis

2. Traits Associated With More Than 3 Genes in NVP/HG GWAS

TRAITS	GENES
blood protein measurement	GDF15, LRRC25, IGFBP7, SYN3, GFRAL, NCAM2
NVP severity measurement	LRRC25, PGR, SPECC1L, HCRTR2, GFRAL, TRPC6
diastolic blood pressure	IGFBP7, ZNF462, PGR, TRPC6, USP38, FRMD3
body height	SYN3, ZNF462, PGR, PDGFC, MCHR2, FRMD3
body mass index	HCRTR2, GFRAL, INPP4B, PDGFC, TFAP2B
heel bone mineral density	IGFBP7, SYN3, HCRTR2, GFRAL
alcohol consumption measurement	IGFBP7, SPECC1L, INPP4B, MCHR2
mathematical ability	ZNF462, MAP3K7, TFAP2B, NCAM2
age at menarche	ZNF462, TRPC6, TFAP2B, MCHR2
adolescent idiopathic scoliosis	PGR, TRPC6, MAP3K7, PDGFC

3. USING LD HUB, AMONG 855 PAIRS OF TRAITS, THE TOP FINDING WAS, IN AGGREGATE:

- VARIANTS INCREASING HG ALSO INCREASE STOMACH PAIN (P=0.0004)
- VARIANTS INCREASING NVP ALSO INCREASE SLEEPLESSNESS/INSOMNIA ($P=1.37X10^{-14}$)

CONCLUSIONS

- **The finding that variants in GDF15 and IGFBP7 are associated with blood protein levels supports our study showing abnormal levels of GDF15 and IGFBP7 in women with HG.**
- **Overlap of the genes with other conditions and traits provides biological insight.**
- **Associations with poor sleep and stomach pain may have implications for treatment strategies for NVP/HG.**

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