RESULTS: Noninvasive genome-wide screening did not detect the same rate of clinically significant chromosomal abnormalities when compared to a microarray, with a kappa statistic of κ=0.75 (95% confidence interval [CI], 0.61-0.89). Overall clinical sensitivity and specificity for detecting clinically significant findings within this study was 82.1% (95% CI 63.1-93.9%) and 93.7% (95% CI 96.9-97.7%), respectively. Excluding copy number variants < 7Mb, the agreement between noninvasive genome-wide screening and chromosomal microarray was improved with κ=0.88 (95% CI, 0.77-0.98). The agreement between noninvasive genome-wide screening and chromosomal microarray inclusive of all copy number variants was represented by κ=0.51 (95% CI, 0.35-0.67).

CONCLUSION: Although an excellent screening test for the common aneuploidies, noninvasive genome-wide screening misses clinically significant findings that would be detected on a microarray. False positive and false negative cases highlight the importance of the underlying biologic and technologic difference between the two tests. Discrepancies in the results emphasize the importance of counseling regarding the tests' design and associated limitations.

82 Additional risk variant in GDF15 and a stronger maternal genetic influence linked to Hyperemesis Gravidarum

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OBJECTIVE: Our recent genome-wide association (GWAS) and replication studies validated the placenta, appetite, and cachexia gene GDF15 and the GDF15 receptor, GFRAL, to be associated with Hyperemesis Gravidarum (HG). A second unlinked (r2< 0.01) SNP located in the 3'UTR of GDF15 (rs1054221) was also identified in the GWAS. Herein, we performed a replication study to validate the GWAS finding which linked rs1054221 to HG. Maternal versus paternal inheritance of nausea and vomiting of pregnancy (NVP) was also evaluated.

STUDY DESIGN: DNA from 893 women with HG and 635 women with normal or no NVP were genotyped using a Taqman platform for rs1054221. Genotype rs1054221 and a previously identified risk allele in *GDF15*, rs16982345, were compared between cases requiring tube feeding and controls reporting no NVP using medcalc.org/calc/odds_ratio.php. Additionally, using an online survey from 2007 to 2017 of women with and without HG, severity of NVP was compared between participants' sisters and sisters-in-law.

RESULTS: Women with HG were significantly more likely to carry a T allele in rs1054221 compared to women who did not have HG (OR,1.44, P=0.001). Women with no NVP were 12 times more likely to have the genotype AA in rs16982345 or CC in rs1054221 than women with HG requiring tube feeding. 793 women with HG and 572 women with normal or no NVP self-reported on the NVP level of their sisters and sisters-in-law. Sisters of women with HG were significantly more likely to have HG themselves (OR, 5.91; P = .0001) compared to their sisters-in-law. Conversely, sisters of women with little to no NVP were significantly more likely to have little or no NVP (OR, 1.84; P = .0002), compared to their sisters-in-law.

CONCLUSION: Evidence suggests abnormal levels of the hormone GDF15 are associated with HG. The validation of a second risk variant, rs1054221, provides further support for GDF15's role in the etiology of HG. Additionally, maternal genes appear to play a more significant role than paternal DNA in contributing to the severity of NVP.

83 HyDROPS study: Exome sequencing identifies genetic disorders causing non-immune hydrops fetalis

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OBJECTIVE: A substantial proportion of non-immune hydrops fetalis (NIHF) cases remain of unknown etiology despite standard evaluations with karyotype and chromosomal microarray. This aim of this study is to investigate the genetic disorders underlying prenatally-diagnosed NIHF through trio exome sequencing (ES).

STUDY DESIGN: HyDROPS (Hydrops: Diagnosing and Re-defining Outcomes with Precision Study) is an ongoing prospective cohort study that has enrolled NIHF cases since 2018. Cases of NIHF are referred from institutions within the UC Fetal-Maternal Consortium as well as other sites in the U.S. Inclusion criteria are NIHF with a non-diagnostic karyotype or chromosomal microarray. Exclusion criteria are alloimmunization, clear evidence of an infectious etiology, and twin-twin transfusion syndrome. Robust clinical data are collected for each case, and trio ES (samples from fetus or neonate, and both biological parents) is performed through the UCSF Genomic Medicine Laboratory.

RESULTS: A total of 36 NIHF cases have been enrolled to date. Median maternal age was 32 years; 42% (15/36) were nulliparous; ethnicities included 61% (22/36) White, 14% (5/36) Latina/Hispanic, 14% (5/36) mixed, 8% (3/36) Asian, and 3% (1/36) unknown. Six percent (2/36) had a history of NIHF in a prior pregnancy. Results have returned for 22 cases to date, and in 36% (8/22), trio ES yielded clinically useful data to inform counseling regarding diagnosis, prognosis, and recurrence risk. Table 1 displays the genetic variants found, as well as the associated coding change, inheritance, gene-disease relationship, and variant classification.

CONCLUSION: Trio ES yields clinically useful information to inform counseling about diagnosis, prognosis, and recurrence risk in over one-third of NIHF cases. Given the high risk of morbidity and mortality associated with NIHF, a more expansive approach to the genetic evaluation through ES is essential for cases not explained by standard testing in order to optimize care for fetuses and neonates with this heterogeneous diagnosis.