PREMATURITY

Abstracts 9 – 17

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9 Genetic variation in key biologic processes may influence response to 17-alpha hydroxyprogesterone caproate (17P) for recurrent preterm birth (PTB) prevention

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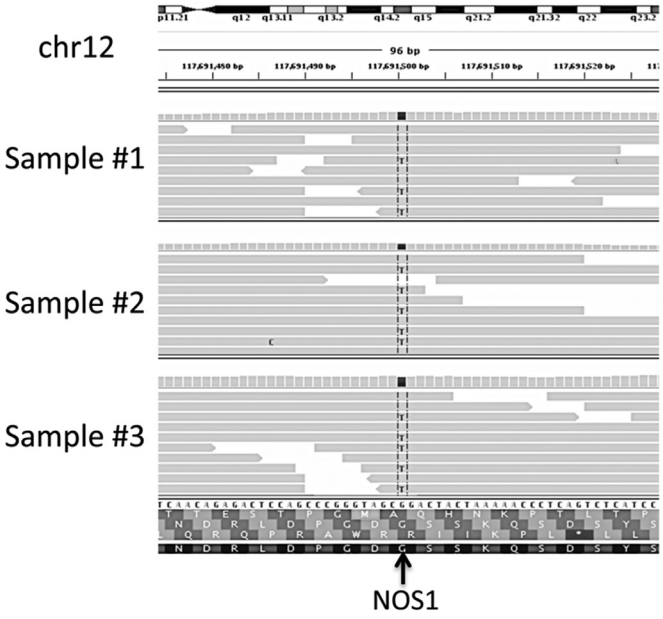
OBJECTIVE: We hypothesized that genetic variation affects variable response to 17P for recurrent PTB prevention.

STUDY DESIGN: Women with ≥1 spontaneous singleton PTB <34 wks who received 17P were recruited prospectively and classified as a 17P responder (RES) or non-responder (NRES) by the difference in delivery gest. age (GA) between 17P treated & untreated pregnancies. Illumina HiSeq2000 whole exome sequencing technology genotyped each woman for ~180,000 protein-coding exons. Exomes were compared between RES and NRES women using the Variant Annotation, Analysis & Search Tool (VAAST), a probabilistic search tool for identifying disease-causing variants, & compared to a KEGG pathway candidate gene list. The top 2.5% of genes (n=470) with the highest VAAST scores were then selected for pathway analysis. Genes were classified by the online Protein ANalysis THrough Evolutionary Relationships (PANTHER) system into known gene ontology molecular functions & biologic processes. Gene distributions within these classifications were compared to an online referent population to search for areas of over- and under- representation. Bonferroni-corrected p-values are reported.

RESULTS: 50 women (41 RES, 9 NRES, all European ancestry) were included. RES and NRES did not differ with regards to parity, CI hx, or PPROM hx. RES delivered, on avg, +9.2 wks longer with 17P vs. +1.3 wks for NRES (p<0.001). All samples met genotype quality filters, and the avg depth of exome coverage was 51 +/- 18. Our VAAST analysis allowed for recessive inheritance & locus heterogeneity. The NOS1 gene scored highest in VAAST among the KEGG-pathway identified candidate genes (Figure). PANTHER analysis revealed several over- represented biologic processes (Table).

CONCLUSION: Using a novel analytic approach, we have identified over-represented genes in key processes (incl. the biologically plausible NO signal pathway) among RES to 17P, the 1st step in applying pharmacogenomics to PTB prevention.

3 representative samples corresponding to women who are heterozygotes for the NOS1 gene on chr 12



The NOS1 gene was the top hit among KEGG candidate genes and was in the top 10 hits on the overall VAAST gene list.

NOS, nitric oxide synthase 1.

Biologic Process or Molecular Function	Freq. Among Referent Group	Freq. Among Top VAAST Genes	p-value*
Cell Adhesion	0.06	0.12	0.0004
Cell Communication	0.21	0.30	0.0015
Signal Transduction	0.20	0.28	0.0021
Nitric Oxide (NO) Signal Transduction	0.002	0.02	0.0037
Receptor Activity	0.09	0.15	0.0110

PANTHER gene ontology pathway analysis results comparing the distribution of the leading genes identified by VAAST within known molecular functions and biologic processes to evaluate for over- and under- representation. All statistically significant pathways were over-represented in our gene list.

*After Bonferroni correction for multiple testing.