OBSTETRICS

Pharmacogenomics of 17-alpha hydroxyprogesterone caproate for recurrent preterm birth prevention

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OBJECTIVE: We hypothesized that genetic variation affects responsiveness to 17-alpha hydroxyprogesterone caproate (17P) for recurrent preterm birth prevention.

STUDY DESIGN: Women of European ancestry with ≥1 spontaneous singleton preterm birth at <34 weeks' gestation who received 17P were recruited prospectively and classified as a 17P responder or nonresponder by the difference in delivery gestational age between 17P-treated and -untreated pregnancies. Samples underwent whole exome sequencing. Coding variants were compared between responders and nonresponders with the use of the Variant Annotation, Analysis, and Search Tool (VAAST), which is a probabilistic search tool for the identification of disease-causing variants, and were compared with a Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway candidate gene list. Genes with the highest VAAST scores were then classified by the online Protein ANalysis THrough Evolutionary Relationships (PANTHER) system into known gene ontology molecular functions and biologic processes. Gene distributions within these classifications were compared with an online reference population to identify over- and under- represented gene sets.

RESULTS: Fifty women (9 nonresponders) were included. Responders delivered 9.2 weeks longer with 17P vs 1.3 weeks' gestation for nonresponders ($P < .001$). A genome-wide search for genetic differences implicated the NOS1 gene to be the most likely associated gene from among genes on the KEGG candidate gene list ($P < .00095$). PANTHER analysis revealed several over-represented gene ontology categories that included cell adhesion, cell communication, signal transduction, nitric oxide signal transduction, and receptor activity (all with significant Bonferroni-corrected probability values).

CONCLUSION: We identified sets of over-represented genes in key processes among responders to 17P, which is the first step in the application of pharmacogenomics to preterm birth prevention.

Key words: pharmacogenomics, progesterone, spontaneous preterm birth

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More than 12% of babies are born preterm, which accounts for >70% of neonatal morbidity and deaths among nonanomalous infants in the United States.[1] Spontaneous preterm birth (SPTB) accounts for 50-80% of all preterm infants. Despite the magnitude of this clinical problem, few preventative or acute therapeutic interventions have proved effective; 17 alpha-hydroxyprogesterone caproate (17P) is one notable exception. When administered weekly beginning in the mid trimester, intramuscular 17P injections are effective prophylaxis against recurrent SPTB.[2] Unfortunately, prophylactic 17P is not always effective, and two-thirds of high-risk women will have a recurrent preterm birth, despite 17P therapy.

There is strong evidence that genes contribute to SPTB susceptibility. SPTB recurs in 35-50% of women and tends to recur at similar gestational ages.[3] Likewise, the probability of SPTB increases with the number of previous SPTB that a woman has experienced, with the most recent birth being the most predictive.[4] Women who themselves were born prematurely at <30 weeks' gestation are more likely to deliver premature infants (odds ratio, 2.38; 95% confidence interval, 1.37−4.16).[5] Population studies have demonstrated a higher rate of SPTB

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among African American women, even when adjustment is made for epidemiologic risk factors, which again suggests genetics as a contributing factor.[6,7] The heritable nature of this complication is further supported by the findings that the risk of SPTB is elevated in women whose sisters have experienced an SPTB (odds ratio, 1.94; 95% confidence interval, 1.26−2.99).[8]

Multiple candidate gene studies have demonstrated associations between several genes and SPTB, with genes involved in inflammation and coagulation pathways most commonly implicated.[9-15] Despite this knowledge, few studies have examined the role of genetic variation in the response to medications that are given for the prophylaxis or treatment of SPTB. An understanding of the reason that some women respond to 17P and others do not is crucial to understanding the cause of SPTB and optimizing prediction and therapeutic strategies.

We hypothesize that genetic variation influences this variability in response to 17P, particularly among women with more severe SPTB phenotypes (early <34 weeks' gestation and/or recurrent SPTB). Specifically, we sought to interrogate the coding regions of the genome and compare genotypes between women with recurrent SPTB despite 17P prophylaxis with those who have a favorable response to 17P. Additionally, we aimed to determine whether there are gene sets that are represented differentially when comparing those genes with the greatest variation between these 2 groups of women.

Materials and Methods

This was a case-control genetic association study. Women of non-Hispanic European ancestry with at least 1 previous documented singleton, nonanomalous SPTB who delivered at <34.0 weeks' gestation who received 17P in at least 1 subsequent pregnancy were recruited prospectively from a consultative Preterm Birth Prevention Clinic from 2008-2010 at Intermountain Medical Center (Salt Lake City, UT). The treatment of women in the prematurity prevention clinic has been described previously.[16] All women provided written informed consent, and this study was approved by the institutional review boards at Intermountain Healthcare and the University of Utah.

Women with a history of either idiopathic spontaneous onset of contractions and cervical dilation or preterm premature rupture of membranes (PPROM) in a previous pregnancy were considered to have a previous SPTB and were included. We excluded women with a known or suspected cause of SPTB, which included women who experienced SPTB after polyhydramnios, within 2 weeks of amniocentesis, because of hypertensive disorders that included preeclampsia or were related to abdominal trauma. Women with known uterine anomalies or a history of treatment for cervical dysplasia with cryotherapy, loop electrosurgical excision procedure, or cervical conization were also excluded.

Women were classified as a 17P responder or nonresponder based on response to 17P. Specifically, the difference between the earliest delivery gestational age because of SPTB without 17P and the delivery gestational age with 17P was calculated and was termed the "17P effect." If a woman had multiple pregnancies that had been treated with 17P after her initial SPTB, the 17P effects from each individual pregnancy were averaged to generate an overall 17P effect. Women with an overall 17P effect of ≥3 weeks (ie, the individual's pregnancy or pregnancies that had been treated with 17P delivered at least 3 weeks later compared with the gestational age of the earliest SPTB without 17P treatment) were considered 17P responders. Women with a negative overall 17P effect and those with an overall 17P effect of <3 weeks were classified as nonresponders. Demographic data were compared between responders and nonresponders with the Student *t* test and Fisher exact test, as appropriate (version 12.1; StataCorp LP, College Station, TX).

DNA was extracted from stored buffy coats. All extracted DNA underwent quality control with a spectrophotometer (NanoDrop Products, Wilmington, DE) reading and evaluation on a 1% agarose gel before genomic library construction. Genomic libraries were then constructed, and samples underwent additional quality control measures that included quantitative polymerase chain reaction quantitation of library concentration with primers (Illumina Inc, San Diego, CA) and evaluation of the library on an Agilent Bioanalyzer DNA 1000 chip (Agilent Technologies Inc, Santa Clara, CA). A PhiX control library (Illumina Inc) was spiked into each lane at a concentration that represented approximately 0.5% of the reads. This platform targeted approximately 180,000 protein-coding exons, in approximately 20,000 genes, for capture. Whole exome sequencing was then performed at The University of Utah Huntsman Cancer Institute's Microarray Core Facility with Illumina HiSeq2000 (Illumina Inc) technology. We indexed 4 samples per lane, with a goal of approximately ×40-50 average depth of coverage per sample.

Sequences were then called simultaneously on all samples with the University of Utah Department of Human Genetics variant-calling software pipeline. Paired-end 101 base pair fastq reads were aligned to the reference genome (b37) with the Burrows-Wheeler aligner software.[17] Additional processing that included sorting, mate-fixing, and duplicate read removal was performed with Samtools and Picard Tools.[18] Insertion and deletion realignment and base recalibration was performed with the Genome Analysis Tool Kit (Broad Institute, Cambridge, MA).[19,20] Processed call-ready BAM files were called jointly with the Unified Genotyper (Broad Institute). Raw genotypes were evaluated and filtered with the Variant Quality Score Recalibrator that is provided in the Genome Analysis Tool Kit package.

Individual exomes were analyzed for evidence of population stratification with Eigenstrat software (Harvard School of Public Health, Boston, MA).[21] Single nucleotide polymorphisms with a minor allele frequency of <0.05 and/or a strong deviation from Hardy-Weinberg equilibrium ($P < .00001$) were removed. Single nucleotide polymorphisms were also filtered to remove all single nucleotide polymorphisms with pairwise

linkage disequilibrium of r^2 >0.2. Population stratification was then analyzed among the remaining subjects, and individual outliers were excluded from further analysis.

The remaining exomes were compared between 17P responders and nonresponders using the Variant Annotation, Analysis, and Search Tool (VAAST). VAAST is a publicly available probabilistic search tool for the identification of disease-causing variants. VAAST scores coding variants that are based on the allele and amino acid substitution frequencies differences between case and control genomes have been demonstrated to be effective in the identification of causative disease alleles both in cases of rare variants in rare disease and combinations of rare and common variants in common disease.[22,23] The VAAST analysis produced a "raw" list of genes that was prioritized by the likelihood of allelic differences between 17P responders and nonresponders. We reported raw probability values (uncorrected for multiple comparisons) for our VAAST analysis gene list.

Next, the genes that were obtained from the VAAST analysis were compared with those potential candidate genes. Using the online Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database, we compiled a list of possible candidate genes that we suspected to be involved in either the pathogenesis of prematurity (ie, genes in pathways that affect inflammatory response, myometrial contraction/relaxation, oxidative stress, coagulation, and complement, calcium signaling) or the metabolism of 17P (ie, genes in pathways that involve steroid receptors, drug metabolism, steroid degradation). This list of candidate genes was compared with the raw list of VAAST genes.

In the next step of our pathway analysis, we again used the raw VAAST list of genes and selected the top 2.5% of genes with the highest VAAST scores from that list. Each gene on this raw list was classified by the online Protein Analysis THrough Evolutionary Relationships (PANTHER) system into known gene ontology molecular functions and biologic processes.[24,25] The percentage of genes within each molecular function/biologic process category was compared with an online referent population to search for areas of over- and under-representation with the use of the binomial test that is available through PANTHER tools online.[26] A Bonferroni-corrected probability value $< .05$ for the binomial test was considered significant.

RESULTS

Fifty-six women met initial inclusion criteria. All were of self-reported European ancestry. Of these, sequencing analysis failed in 2 women (average sequencing depth of coverage <1). On initial Eigenstrat analysis, population differentiation between cases and control subjects was not significant ($P >$ .09). However, 4 samples deviated substantially from the main cluster of points. Removal of these 4 samples produced a much less stratified data set with little genome-wide differentiation between cases and control subjects ($P >$ .35). Thus, the final cohort consisted of 50 women (41 responders and 9 nonresponders). All remaining samples met genotype quality filters. The average depth of exome coverage was 51 ± 18 base pairs (range, 13.4−102.6 base pairs).

Demographic and previous pregnancy characteristics were similar between responders and nonresponders with regard to parity, number of preterm births before the studied gestation, cervical insufficiency history, and PPROM history (Table 1). Four women (3 responders, 1 nonresponder) had a history of a cervical laceration that was related to delivery; this was not significantly different between groups ($P = .56$). This group of women was generally healthy. None of the women had a history of type I or II diabetes mellitus or chronic renal disease. Four women (8%) had a history of chronic hypertension; none of the women experienced preeclampsia or required preterm delivery because of worsening hypertension.

Responders delivered an average of +9.2 weeks later (range, +3.8 to +16.9 weeks) with 17P compared with +1.3 weeks (range, −1.9 to +2.9 weeks) for nonresponders ($P < .001$). Two women delivered earlier with 17P: 1 woman delivered 11 days earlier, and the other woman delivered 13 days earlier. There were no indicated preterm deliveries in the study population. Pregnancy management was similar between responders and nonresponders. Nonresponders delivered earlier and were more likely to be preterm (Table 2).

In our VAAST analysis, we allowed for recessive inheritance and locus heterogeneity and tested our genotypes using 1 million permutations. The genes with the greatest difference between responders and nonresponders are listed in Table 3 and represent the raw VAAST list of genes. The probability values that are displayed in Table 3 are unadjusted; none meet genome-wide significance ($P < 2.5 \times 10^{-6}$). Using the KEGG database as described earlier, we generated a list of 518 candidate genes in pathways that potentially are involved with SPTB and/or 17P metabolism (Supplementary Table 1). This list of 518 genes was compared with the raw list of genes from our VAAST analysis. The NOS1 gene was the eighth highest scoring gene on the overall raw VAAST list and was the highest scoring variant from genes on the KEGG candidate gene list (VAAST, $P < .00095$).

Next, the top 2.5% of raw genes (n = 457) that were generated from the initial VAAST analysis were selected for further analysis with the use of PANTHER (Supplementary Table 2). These top 457 genes were compared with the online referent population that was provided by PANTHER. This analysis revealed several differentially expressed biologic processes (Table 4) from our gene list compared with the referent population. The frequencies of genes that were classified by pathway or function in our gene list compared with expected proportions in a general population are also given in Table 4. For example, based on gene distributions within the referent population, the expected frequency of genes in the nitric oxide pathway is 0.002*457 = approximately 1. However, from our list of 457 top genes that were identified by VAAST, the frequency of genes in the nitric oxide pathway was 0.02*457 =

TABLE 1
Demographics and previous pregnancy characteristics

Variable	17P responders (n = 41)	17P nonresponders (n = 9)	*P* value
White, n (%)	41 (100)	9 (100)	—
Married, n (%)	36 (88)	6 (67)	.14
Tobacco use, n	0	0	—
Previous pregnancies, n[a]	2.9 ± 1.8	3.4 ± 1.7	.36
≥1 previous term delivery, n (%)	17 (41.5)	4 (44.4)	> .99
Total number of previous preterm (20.0-36.9 wks' gestation) deliveries, n[a]	1.7 ± 0.8	2.1 ± 0.9	.21
History of preterm premature rupture of membranes, n (%)	16 (39)	2 (25)	.69
Cervical cerclage placed in ≥1 pregnancies, n (%)	11 (27)	2 (22)	> .99
Delivery gestational age of earliest previous preterm birth, wk[a]	28.1 ± 4.0	31.5 ± 2.7	.02

17P, 17-alpha hydroxyprogesterone caproate.

[a] Data are given as mean ± SD.

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approximately 9 (Table 4). We identified 8 genes in the nitric oxide synthase pathway with different allele frequencies between responders and nonresponders; our list included SPTA2, GA2L2, DMD, SYNE1, NOS1, MICA2, SMTL2, and DESP. All statistically significant pathways that are listed in Table 4 were over-represented in our gene list. There were no under- represented biologic processes from among our top gene list.

Comment

Using a novel analytic approach, we have identified over-represented genes in key processes among responders to 17P, which is the first step in applying pharmacogenomics to preterm birth prevention. Our multistep approach identified both new individual candidate genes and general biologic processes (including functions such as cell adhesion and cell communication) that may influence an individual's response to prematurity prevention.

In both pathway analysis approaches, genes that were involved with nitric oxide were identified as potential mediators of 17P response. Nitric oxide synthase catalyzes the synthesis of nitric oxide from L-arginine. Animal model studies have shown that nitric oxide has a potent relaxant effect on uterine smooth muscle cells.[27,28] Nitric oxide metabolites have been found in higher concentrations among women in labor (both at term and preterm) compared with nonlaboring women.[29] Additionally, nitric oxide is thought to work synergistically with progesterone to inhibit uterine contractility. In humans, a functional withdrawal of progesterone (through changes in progesterone receptor expression) combined with decreased synthesis of nitric oxide is associated with the initiation of term and preterm parturition.[29-31] In 1 study, treatment of pregnant rats with a combination of an antiprogestin and a nitric oxide inhibitor induced preterm labor significantly faster than treatment with an antiprogestin alone.[32]

We have found that genotype nitric oxide pathway genes differ among women who do not respond to 17P for prematurity prevention, which provides additional insight into the possible mechanism of action of 17P. Transdermal nitroglycerin (a nitric oxide donor) has received some recent attention as a possible acute tocolytic, with

TABLE 2
Pregnancy management and outcomes during the most recent pregnancy

Variable	17-alpha hydroxyprogesterone caproate responders (n = 41)	17-alpha hydroxyprogesterone caproate nonresponders (n = 9)	*P* value
Cervical cerclage placed, n (%)	10 (24)	2 (22)	> .99
Vaginal cervical length assessed at least once during pregnancy, n (%)	35 (92)	8 (89)	> .99
Delivery gestational age, wk[a]	37.3 ± 1.8	32.9 ± 3.7	< .001
Delivered <37 weeks' gestation, n (%)	16 (39)	8 (89)	.009
Delivered <32 weeks' gestation, n (%)	0	3 (33)	.004
Birthweight, g[a]	3001 ± 544	2094 ± 755	< .001

[a] Data are given as mean ± SD.

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TABLE 3
Top VAAST genes with greatest difference between responders and nonresponders

Rank	Gene	Gene name	*P* value[a]	Variant Annotation, Analysis, and Search Tool score	Gene function (if known)[b]
1	CUBN	Cubilin	7.32e-5	23.3	Receptor for intrinsic factor-vitamin B12 complexes
2	TMTC1	Transmembrane and tetra-tricopeptide repeat containing 1	9.40e-5	17.1	
3	TMEM158	Transmembrane protein 158	.00035	23.8	Surface receptor proposed to function in neuronal survival pathway
4	ATMIN	ATM interactor	.00041	6.1	
5	MYOG	Myogenin	.00056	13.0	
6	NLRP10	NLR family pyrin domain containing 10	.00057	13.4	Multifunctional negative regulator of inflammation and apoptosis
7	ENP1	Essential nuclear protein 1	.00094	13.8	
8	NOS1	Nitric oxide synthase 1	.00094	11.2	Synthesizes nitric oxide from L-arginine
9	PRMT6	Protein arginine methyltransferase 6	.0011	8.5	Stimulates polymerase activity by enhancing DNA binding and processivity
10	ZFP28	Zinc finger protein	.0023	10.7	
11	CASZ1	Castor zinc finger 1	.00298	15.3	Tumor suppression, blood pressure variation
12	VPS13C	Vacuolar protein sorting 13 homolog C	.00301	11.4	
13	FCGR2A	Fc fragment of IgG, low affinity IIa receptor	.00305	14.6	Found on phagocytic cells and involved with clearing of immune complexes
14	OR56A5	Olfactory receptor family 56 subfamily A member 5	.00318	13.0	Smell perception
15	RPA4	Replication protein A4	.00337	5.5	DNA double-strand break repair, inhibition of viral replication
16	ZNF853	Zinc finger protein 853	.00352	5.3	
17	TSKS	Testis specific serine kinase substrate	.00373	8.0	Tumorigenesis pathways and progression
18	MICAL2	Microtubule associated monooxygenase, calponin and LIM domain containing 2	.00384	10.2	
19	CCDC50	Coiled-coil domain containing 50	.00401	11.1	Hearing loss, effector of epidermal growth factor—mediated cell signaling
20	ANP32D	Acidic nuclear phosphoprotein 32 family member D	.00408	7.5	Tumor suppressor
21	RALGAPA1	Ral GTPase activating protein alpha subunit 1	.00409	8.1	
22	C16orf46	Chromosome 16 open reading frame	.00409	5.9	
23	ATP6V0A2	ATPase lysosomal V0 subunit A2	.00425	7.4	Cutis laxa type II and wrinkly skin syndrome
24	SPRR1A	Small proline-rich protein 1A	.0457	4.9	
25	PIH1D1	PIH1domain containing 1	.00464	2.1	

[a] Unadjusted for multiple comparisons; [b] Gene functions per National Center for Biotechnology Information gene database (ncbi.nlm.nih.gov).

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TABLE 4
Pathway analysis results

Biologic process or molecular function	Frequency in referent group	Frequency among top Variant Annotation, Analysis, and Search Tool genes	*P* value[a]
Cell adhesion	0.06	0.12	.0004
Cell communication	0.21	0.30	.0015
Signal transduction	0.20	0.28	.0021
Nitric oxide signal transduction	0.002	0.02	.0037
Receptor activity	0.09	0.15	.0110

Protein ANalysis THrough Evolutionary Relationships gene ontology pathway analysis results compared the distribution of the leading genes that were identified by the Variant Annotation, Analysis, and Search Tool within known molecular functions with the biologic processes to evaluate for over- and under-representation.

[a] After Bonferroni correction for multiple testing.

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mixed results. In one small randomized controlled trial of 158 women, it was found to reduce the risk of severe neonatal morbidity and death, although it was not associated with a prolongation of gestation.[33] In another study, it was not found to be effective.[34] To our knowledge, the role of nitroglycerin in preterm prevention or as an adjunct to 17P has not been investigated.

Our study has several strengths. This cohort included women with more severe SPTB phenotypes who were more likely to have a recurrent preterm birth compared with those with a single preterm birth or a preterm birth at a later gestational age. Additionally, our cohort was ethnically homogeneous, because all women were of European ancestry, which was confirmed by our population stratification analysis. Because preterm birth is a complex phenotype and is likely the final common pathway that results from a variety of different initial causes or triggers and the relationship between genotype and clinical response is equally complex, it is unlikely that a single gene will be responsible for SPTB or for response to tocolysis. Therefore, our exhaustive interrogation of the coding regions of the genome was more comprehensive than previous candidate-gene studies and genome-wide association studies. Our pathway analysis also allowed for some refinement of results by considering genes that were involved in suspected SPTB pathways and 17P metabolic pathways.

Our classification of women into responder and nonresponder groups was objective and clinically relevant. Neonates who were delivered by women who gained at least 3 weeks gestation with 17P would be expected to have a clinically significant decrease in morbidity. One major limitation of our study was the small sample size. Unfortunately, because of sample size limitations, we were unable to conduct subgroup analyses of women with and without specific SPTB phenotypes, such as PPROM. Although the overall sample size was relatively small, our exome sequencing provided information regarding all coding regions of the genome. No single gene in our raw VAAST list results reached formal genome wide significance, but this was expected, given our relatively small sample size. However, the pathway analysis provides broad insight into this complex phenotype; our raw VAAST results and PANTHER pathway analysis did not rely on investigator assumptions regarding possible causative pathways. To date, few studies have undertaken a comprehensive, unbiased analysis of the genome to search for variants that are involved with obstetric pharmacogenomics.

Our study, like any sequencing study, was also limited by the genotyping depth of coverage, because samples with lower depths of coverage are more prone to genotyping errors. As genotyping technology continues to improve and the depth of coverage increases in the future, this will become less of a concern. Furthermore, functional data that are obtained through databases such as PANTHER depend on general genetic knowledge that is unrelated to pregnancy or preterm birth. The genes that are identified have functions that are cell and tissue specific, and the environment of pregnancy alone may alter function. It is beyond the scope of this investigation to study the pharmacokinetics and pharmacodynamics of 17P thoroughly. For example, it is possible that genotype alters response only in the presence of a certain critical threshold or serum level of 17P, but 17P concentration levels were not available for this cohort.

Physiologic changes during pregnancy result in the alteration of many processes, which include drug metabolism. Sharma et al[35] found that 17P metabolism is mediated by the cytochrome p450 enzyme system, specifically the CYP3A family. Genes that are involved in progesterone metabolism were not among the "top hits" from our VAAST analysis. Previous studies suggest that significant interindividual variability exists and that metabolic activity of these cytochromes varies throughout pregnancy.[35] Previous exploratory research in the area of preterm birth pharmacogenomics suggests that progesterone receptor polymorphisms may contribute to variable responsiveness to 17P but that known genetic variation in this receptor accounts for only a small percentage of the clinical variation that was seen in response to this medication.[36] The results from this study suggest a role for both receptor genotypes and other biologic processes. However, quantification of the response to 17P based on metabolic enzyme polymorphisms, progesterone receptor polymorphisms, or variation in other genetic factors remains difficult and is an area for further research.

If the subset of women most likely to respond to 17P can be identified, women with SPTB could receive individualized treatment that would maximize benefit

and limit side-effects. Additional advances in the prevention of SPTB with 17P can be made if women most likely to respond to 17P can be identified prospectively by genotype and if an appropriate individualized prevention regimen can be outlined. If this strategy is applied to nulliparous women with other risk factors for preterm birth (such as a personal history of Müllerian anomalies or a family history of preterm birth), those women with a high-risk genotype could be studied to determine whether treatment with 17P during their first pregnancy could reduce the risk of primary SPTB.

Future studies should confirm these findings in a larger cohort and further refine the role of genetic variation in response to 17P through identification of a specific set of genes that demonstrate the greatest relationship between genotype and response to medications. This has the potential to individualize preterm birth interventions and to lower the overall rate of both primary and recurrent SPTB and its corresponding neonatal morbidity and mortality rates.

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APPENDIX

SUPPLEMENTARY TABLE 1

List of 518 potential candidate genes identified from Kyoto Encyclopedia of Genes and Genomes database

Gene name	Ensembl gene	Description
A2M	ENSG00000175899	Alpha-2-macroglobulin
ACTA1	ENSG00000143632	Actin, alpha 1, skeletal muscle
ACTA2	ENSG00000006071	Actin, alpha 2, smooth muscle, aorta
ACTB		Actin, beta
ACTC1	ENSG00000204574|ENSG00000206410|ENSG00000206490	Actin, alpha, cardiac muscle 1
ACTG1	ENSG00000184009	Actin, gamma 1
ADCY1	ENSG00000164742	Adenylate cyclase 1 (brain)
ADCY2	ENSG00000078295	Adenylate cyclase 2 (brain)
ADCY3	ENSG00000138031	Adenylate cyclase 3
ADCY4		Adenylate cyclase 4
ADCY5	ENSG00000173175	Adenylate cyclase 5
ADCY6	ENSG00000174233	Adenylate cyclase 6
ADCY7	ENSG00000121281	Adenylate cyclase 7
ADCY8	ENSG00000155897	Adenylate cyclase 8 (brain)
ADCY9	ENSG00000162104	Adenylate cyclase 9
ADM		Adrenomedullin
AGT	ENSG00000135744	Angiotensinogen (serpin peptidase inhibitor, clade A, member 8)
AKT1	ENSG00000142208	V-akt murine thymoma viral oncogene homolog 1
AKT2	ENSG00000105221|ENSG00000134249	V-akt murine thymoma viral oncogene homolog 2
AKT3	ENSG00000117020	V-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)
ANXA1	ENSG00000135046	Annexin A1
ANXA2	ENSG00000182718	Annexin A2
ANXA3		Annexin A3
ANXA4	ENSG00000104964	Annexin A4
ANXA5	ENSG00000164111	Annexin A5
ANXA6	ENSG00000197043	Annexin A6
ANXA8L2	ENSG00000075340	Annexin A8-like 2
APAF1	ENSG00000120868	Apoptotic peptidase activating factor 1
ARRB2	ENSG00000141480	Arrestin, beta 2
ATF1	ENSG00000123268	Activating transcription factor 1
ATF2	ENSG00000115966|ENSG00000175544	Activating transcription factor 2
ATF3		Activating transcription factor 3
ATF4	ENSG00000128272	Activating transcription factor 4 (tax-responsive enhancer element B67)
ATF5	ENSG00000169136	Activating transcription factor 5

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SUPPLEMENTARY TABLE 1

List of 518 potential candidate genes identified from Kyoto Encyclopedia of Genes and Genomes database

(continued)

Gene name	Ensembl gene	Description
ATP2A2		ATPase, Ca++ transporting, cardiac muscle, slow twitch 2
ATP2A3	ENSG00000116194	ATPase, Ca++ transporting, ubiquitous
BAD		BCL2-antagonist of cell death
BAX	ENSG00000087088|ENSG00000166313	BCL2-associated X protein
BCL2	ENSG00000171791	B-cell CLL/lymphoma 2
BCL2L1	ENSG00000084234	BCL2-like 1
BDKRB1	ENSG00000100739	
BID	ENSG00000015475	BH3 interacting domain death agonist
BIRC2	ENSG00000110330|ENSG00000188157	Baculoviral IAP repeat-containing 2
BIRC3	ENSG00000023445	Baculoviral IAP repeat-containing 3
BRAF	ENSG00000157764	V-raf murine sarcoma viral oncogene homolog B1
BTRC	ENSG00000166167	Beta-transducin repeat containing

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis

Gene name	Ensembl gene	Description
ABCA4	ENSG00000198691	Retinal-specific ATP-binding cassette transporter
ABCA7	ENSG00000064687	ATP-binding cassette sub-family A member 7
ABCB5	ENSG00000004846	ATP-binding cassette sub-family B member 5
ACHA5	ENSG00000169684	Neuronal acetylcholine receptor subunit alpha-5
ACV1C	ENSG00000123612	Activin receptor type-1C
ADC	ENSG00000142920	Arginine decarboxylase
ADCK2	ENSG00000133597	Uncharacterized aarF domain-containing protein kinase 2
ADRB2	ENSG00000169252	Beta-2 adrenergic receptor
AEBP1	ENSG00000106624	Adipocyte enhancer-binding protein 1
AGAP4	ENSG00000188234	Arf-GAP with GTPase, ANK repeat and PH domain-containing protein 4
AGFG1	ENSG00000173744	Arf-GAP domain and FG repeat-containing protein 1
AHDC1	ENSG00000126705	AT-hook DNA-binding motif-containing protein 1
AJAP1	ENSG00000196581	Adherens junction-associated protein 1
AL1L1	ENSG00000144908	Cytosolic 10-formyltetrahydrofolate dehydrogenase
ALMS1	ENSG00000116127	Alstrom syndrome protein 1
AN32D	ENSG00000139223	Acidic leucine-rich nuclear phosphoprotein 32 family member D
ANGL4	ENSG00000167772	Angiopoietin-related protein 4
ANM6	ENSG00000198890	Protein arginine N-methyltransferase 6
ANO1	ENSG00000131620	Anoctamin-1
ANPRA	ENSG00000169418	Atrial natriuretic peptide receptor 1
ANX11	ENSG00000122359	Annexin A11
AP1G1	ENSG00000166747	AP-1 complex subunit gamma-1
APBB2	ENSG00000163697	Amyloid beta A4 precursor protein-binding family B member 2
ARI3C	ENSG00000205143	AT-rich interactive domain-containing protein 3C
ARI4B	ENSG00000054267	AT-rich interactive domain-containing protein 4B
ARVC	ENSG00000099889	Armadillo repeat protein deleted in velo-cardio-facial syndrome
ASPX	ENSG00000134940	Acrosomal protein SP-10
AT8B3	ENSG00000130270	Probable phospholipid-transporting ATPase IK
ATL4	ENSG00000143382	ADAMTS-like protein 4
ATM	ENSG00000149311	Serine-protein kinase ATM
ATMIN	ENSG00000166454	ATM interactor
ATPB	ENSG00000110955	ATP synthase subunit beta, mitochondrial
ATS8	ENSG00000134917	A disintegrin and metalloproteinase with thrombospondin motifs 8
B3GNL	ENSG00000175711	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase-like protein 1
BAMBI	ENSG00000095739	BMP and activin membrane-bound inhibitor homolog
BCAT2	ENSG00000105552	Branched-chain-amino-acid aminotransferase, mitochondrial
BEST3	ENSG00000127325	Bestrophin-3
BOK	ENSG00000176720	Bcl-2-related ovarian killer protein
BST1	ENSG00000109743	ADP-ribosyl cyclase 2

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
C2D1B	ENSG00000154222	Coiled-coil and C2 domain-containing protein 1B
C4BPA	ENSG00000123838	C4b-binding protein alpha chain
C9J7L3	ENSG00000173200	Poly [ADP-ribose] polymerase 15
C9JGD5	ENSG00000204851	PNMA-like protein 2
C9JHY1	ENSG00000260119	Transient receptor potential cation channel subfamily V member 6
C9JHY2	ENSG00000257382	Uncharacterized protein
CABIN	ENSG00000099991	Calcineurin-binding protein cabin-1
CAC1F	ENSG00000102001	Voltage-dependent L-type calcium channel subunit alpha-1F
CAC1G	ENSG00000006283	Voltage-dependent T-type calcium channel subunit alpha-1G
CAC1S	ENSG00000081248	Voltage-dependent L-type calcium channel subunit alpha-1S
CAN13	ENSG00000162949	Calpain-13
CAPS2	ENSG00000081803	Calcium-dependent secretion activator 2
CASP8	ENSG00000064012	Caspase-8
CASZ1	ENSG00000130940	Zinc finger protein castor homolog 1
CB071	ENSG00000179270	Uncharacterized protein C2orf71
CC85A	ENSG00000055813	Coiled-coil domain-containing protein 85A
CC88B	ENSG00000168071	Coiled-coil domain-containing protein 88B
CCD50	ENSG00000152492	Coiled-coil domain-containing protein 50
CCD63	ENSG00000173093	Coiled-coil domain-containing protein 63
CCL11	ENSG00000172156	Eotaxin
CCL25	ENSG00000131142	C-C motif chemokine 25
CD033	ENSG00000151470	UPF0462 protein C4orf33
CD3G	ENSG00000160654	T-cell surface glycoprotein CD3 gamma chain
CDHR3	ENSG00000128536	Cadherin-related family member 3
CDYL2	ENSG00000166446	Chromodomain Y-like protein 2
CEL2A	ENSG00000142615	Chymotrypsin-like elastase family member 2A
CERK1	ENSG00000100422	Ceramide kinase
CH045	ENSG00000178460	MCM domain-containing protein C8orf45
CI079	ENSG00000177992	FAM75-like protein C9orf79
CI131	ENSG00000174038	Uncharacterized protein C9orf131
CI174	ENSG00000197816	Uncharacterized protein C9orf174
CLC7A	ENSG00000172243	C-type lectin domain family 7 member A
CLCC1	ENSG00000121940	Chloride channel CLIC-like protein 1
CLCF1	ENSG00000175505	Cardiotrophin-like cytokine factor 1
CLGN	ENSG00000153132	Calmegin
CLM6	ENSG00000167850	CMRF35-like molecule 6
CLM8	ENSG00000167851	CMRF35-like molecule 8
CLN5	ENSG00000102805	Ceroid-lipofuscinosis neuronal protein 5
CLNK	ENSG00000109684	Cytokine-dependent hematopoietic cell linker

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
CLRN3	ENSG00000180745	Clarin-3
CO4A2	ENSG00000134871	Canstatin
CO9A1	ENSG00000112280	Collagen alpha-1(IX) chain
COGA1	ENSG00000084636	Collagen alpha-1(XVI) chain
CP2B6	ENSG00000197408	Cytochrome P450 2B6
CQ056	ENSG00000167302	Uncharacterized protein C17orf56
CREG2	ENSG00000175874	Protein CREG2
CSAD	ENSG00000139631	Cysteine sulfinic acid decarboxylase
CSF3R	ENSG00000119535	Granulocyte colony-stimulating factor receptor
CST9L	ENSG00000101435	Cystatin-9-like
CTF18	ENSG00000127586	Chromosome transmission fidelity protein 18 homolog
CTND2	ENSG00000169862	Catenin delta-2
CUBN	ENSG00000107611	Cubilin
CX057	ENSG00000147231	Uncharacterized protein CXorf57
CYTSB	ENSG00000128487	Cytospin-B
D2HDH	ENSG00000180902	D-2-hydroxyglutarate dehydrogenase, mitochondrial
DB125	ENSG00000178591	Beta-defensin 125
DB127	ENSG00000088782	Beta-defensin 127
DCHS	ENSG00000140287	Histidine decarboxylase
DCP1B	ENSG00000151065	mRNA-decapping enzyme 1B
DESP	ENSG00000096696	Desmoplakin
DHDDS	ENSG00000117682	Dehydrodolichyl diphosphate synthase
DHSA	ENSG00000073578	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
DISP2	ENSG00000140323	Protein dispatched homolog 2
DLEC1	ENSG00000008226	Deleted in lung and esophageal cancer protein 1
DMD	ENSG00000198947	Dystrophin
DMRTB	ENSG00000143006	Doublesex- and mab-3-related transcription factor B1
DNAI1	ENSG00000122735	Dynein intermediate chain 1, axonemal
DOCK6	ENSG00000130158	Dedicator of cytokinesis protein 6
DP13A	ENSG00000157500	DCC-interacting protein 13-alpha
DRD5	ENSG00000169676	D(1B) dopamine receptor
DRGX	ENSG00000165606	Dorsal root ganglia homeobox protein
DTX2	ENSG00000091073	Protein deltex-2
DUS3L	ENSG00000141994	tRNA-dihydrouridine(47) synthase [NAD(P)(+)]-like
DYH12	ENSG00000174844	Dynein heavy chain 12, axonemal
E2AK1	ENSG00000086232	Eukaryotic translation initiation factor 2-alpha kinase 1
E7EPJ1	ENSG00000132669	Ras and Rab interactor 2
E7EQL6	ENSG00000100033	Proline dehydrogenase 1, mitochondrial
E9PDY6	ENSG00000145113	Mucin-4

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
E9PHH6	ENSG00000138759	Extracellular matrix protein FRAS1
E9PI22	ENSG00000255251	Uncharacterized protein
EBP2	ENSG00000117395	Probable rRNA-processing protein EBP2
EGFLA	ENSG00000164318	Pikachurin
ELAF	ENSG00000124102	Elafin
ELP1	ENSG00000070061	Elongator complex protein 1
EMR2	ENSG00000127507	EGF-like module-containing mucin-like hormone receptor-like 2
EP400	ENSG00000183495	E1A-binding protein p400
EPN1	ENSG00000063245	Epsin-1
ERBB3	ENSG00000065361	Receptor tyrosine-protein kinase erbB-3
ERMP1	ENSG00000099219	Endoplasmic reticulum metallopeptidase 1
EVC	ENSG00000072840	Ellis-van Creveld syndrome protein
EXO5	ENSG00000164002	Probable exonuclease V
EXOS3	ENSG00000107371	Exosome complex component RRP40
EYA4	ENSG00000112319	Eyes absent homolog 4
F107A	ENSG00000168309	Protein FAM107A
F125A	ENSG00000141971	Multivesicular body subunit 12A
F164C	ENSG00000119703	Protein FAM164C
F5H5U3	ENSG00000135100	Hepatocyte nuclear factor 1-alpha
F8W7C3	ENSG00000104218	Centrosome and spindle pole-associated protein 1
F8W7D1	ENSG00000160111	C3 and PZP-like alpha-2-macroglobulin domain-containing protein 8
F8WAI1	ENSG00000163395	Immunoglobulin-like and fibronectin type III domain-containing protein 1
F8WAN1	ENSG00000258555	Uncharacterized protein
F8WAT0	ENSG00000176406	Regulating synaptic membrane exocytosis protein 2
FA40B	ENSG00000128578	Protein FAM40B
FA71C	ENSG00000180219	Protein FAM71C
FA83A	ENSG00000147689	Protein FAM83A
FA83C	ENSG00000125998	Protein FAM83C
FANCE	ENSG00000112039	Fanconi anemia group E protein
FBX5	ENSG00000112029	F-box only protein 5
FCG2A	ENSG00000143226	Low affinity immunoglobulin gamma Fc region receptor II-a
FCRLB	ENSG00000162746	Fc receptor-like B
FHR2	ENSG00000080910	Complement factor H-related protein 2
FLT3	ENSG00000122025	Receptor-type tyrosine-protein kinase FLT3
FNIP2	ENSG00000052795	Folliculin-interacting protein 2
FRITZ	ENSG00000143951	WD repeat-containing and planar cell polarity effector protein fritz homolog
FSCN3	ENSG00000106328	Fascin-3
FUT2	ENSG00000176920	Galactoside 2-alpha-L-fucosyltransferase 2
FUT7	ENSG00000180549	Alpha-(1,3)-fucosyltransferase

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
G3V1M9	ENSG00000251655	HCG26567, isoform CRA_b
G3V1Q7	ENSG00000118557	Polyamine modulated factor 1 binding protein 1, isoform CRA_b
G3V325	ENSG00000248919	Pentatricopeptide repeat-containing protein 1
GA2L2	ENSG00000132139	GAS2-like protein 2
GAG2A	ENSG00000189064	G antigen 2A
GALP	ENSG00000197487	Galanin-like peptide
GATD1	ENSG00000157259	GATA zinc finger domain-containing protein 1
GD1L1	ENSG00000124194	Ganglioside-induced differentiation-associated protein 1-like 1
GDF3	ENSG00000184344	Growth/differentiation factor 3
GG6LA	ENSG00000205281	Putative golgin subfamily A member 6-like protein 10
GG6LB	ENSG00000178115	Putative golgin subfamily A member 6-like protein 11
GIMA5	ENSG00000196329	GTPase IMAP family member 5
GLRX3	ENSG00000108010	Glutaredoxin-3
GLTL1	ENSG00000100626	Putative polypeptide N-acetylgalactosaminyltransferase-like protein 1
GLTL2	ENSG00000131386	Polypeptide N-acetylgalactosaminyltransferase-like protein 2
GLYL2	ENSG00000156689	Glycine N-acyltransferase-like protein 2
GOG6D	ENSG00000140478	Putative golgin subfamily A member 6D
GOGB1	ENSG00000173230	Golgin subfamily B member 1
GP124	ENSG00000020181	G-protein coupled receptor 124
GPR35	ENSG00000178623	G-protein coupled receptor 35
GPR78	ENSG00000155269	G-protein coupled receptor 78
GRD2I	ENSG00000215045	Delphilin
GRHL2	ENSG00000083307	Grainyhead-like protein 2 homolog
GRHL3	ENSG00000158055	Grainyhead-like protein 3 homolog
GRM2	ENSG00000164082	Metabotropic glutamate receptor 2
GRM6	ENSG00000113262	Metabotropic glutamate receptor 6
GRM7	ENSG00000196277	Metabotropic glutamate receptor 7
GSDMB	ENSG00000073605	Gasdermin-B
GTPB5	ENSG00000101181	GTP-binding protein 5
GTSFL	ENSG00000124196	Gametocyte-specific factor 1-like
H3BLS7	ENSG00000048707	Vacuolar protein sorting-associated protein 13D
HACL1	ENSG00000131373	2-hydroxyacyl-CoA lyase 1
HAUS3	ENSG00000214367	HAUS augmin-like complex subunit 3
HDC	ENSG00000112406	Headcase protein homolog
HHATL	ENSG00000010282	Protein-cysteine N-palmitoyltransferase HHAT-like protein
HMCN1	ENSG00000143341	Hemicentin-1
HUNK	ENSG00000142149	Hormonally up-regulated neu tumor-associated kinase
IDI2	ENSG00000148377	Isopentenyl-diphosphate Delta-isomerase 2
IFT46	ENSG00000118096	Intraflagellar transport protein 46 homolog

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
IGFL4	ENSG00000204869	Insulin growth factor-like family member 4
IGS22	ENSG00000179057	Immunoglobulin superfamily member 22
IL17F	ENSG00000112116	Interleukin-17F
INAR2	ENSG00000159110	Interferon alpha/beta receptor 2
IPIL1	ENSG00000198885	Inositol 1,4,5-trisphosphate receptor-interacting protein-like 1
IPO11	ENSG00000086200	Importin-11
IQCB1	ENSG00000173226	IQ calmodulin-binding motif-containing protein 1
IRX2	ENSG00000170561	Iroquois-class homeodomain protein IRX-2
ITB6	ENSG00000115221	Integrin beta-6
K0614	ENSG00000173064	Probable E3 ubiquitin-protein ligase C12orf51
K0889	ENSG00000149639	Uncharacterized protein KIAA0889
K0895	ENSG00000164542	Uncharacterized protein KIAA0895
K1024	ENSG00000169330	UPF0258 protein KIAA1024
K2C3	ENSG00000186442	Keratin, type II cytoskeletal 3
KCC2B	ENSG00000058404	Calcium/calmodulin-dependent protein kinase type II subunit beta
KCNG4	ENSG00000168418	Potassium voltage-gated channel subfamily G member 4
KCNK4	ENSG00000182450	Potassium channel subfamily K member 4
KCNU1	ENSG00000215262	Potassium channel subfamily U member 1
KDEL2	ENSG00000178202	KDEL motif-containing protein 2
KDM4D	ENSG00000186280	Lysine-specific demethylase 4D
KI20B	ENSG00000138182	Kinesin-like protein KIF20B
KIBRA	ENSG00000113645	Protein KIBRA
KLC4	ENSG00000137171	Kinesin light chain 4
KLF12	ENSG00000118922	Krueppel-like factor 12
KLHL8	ENSG00000145332	Kelch-like protein 8
KR132	ENSG00000182816	Keratin-associated protein 13-2
L2HDH	ENSG00000087299	L-2-hydroxyglutarate dehydrogenase, mitochondrial
LCAT	ENSG00000213398	Phosphatidylcholine-sterol acyltransferase
LCTL	ENSG00000188501	Lactase-like protein
LEG3	ENSG00000131981	Galectin-3
LGR6	ENSG00000133067	Leucine-rich repeat-containing G-protein coupled receptor 6
LIPG	ENSG00000182333	Gastric triacylglycerol lipase
LIRB2	ENSG00000131042	Leukocyte immunoglobulin-like receptor subfamily B member 2
LMA1L	ENSG00000140506	Protein ERGIC-53-like
LMNB2	ENSG00000176619	Lamin-B2
LOXH1	ENSG00000167210	Lipoxygenase homology domain-containing protein 1
LR16B	ENSG00000186648	Leucine-rich repeat-containing protein 16B
LRBA	ENSG00000198589	Lipopolysaccharide-responsive and beige-like anchor protein
LRCC1	ENSG00000133739	Leucine-rich repeat and coiled-coil domain-containing protein 1

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
LRFN3	ENSG00000126243	Leucine-rich repeat and fibronectin type-III domain-containing protein 3
LRP1B	ENSG00000168702	Low-density lipoprotein receptor-related protein 1B
LRRK2	ENSG00000188906	Leucine-rich repeat serine/threonine-protein kinase 2
LRRN3	ENSG00000173114	Leucine-rich repeat neuronal protein 3
LTBP2	ENSG00000119681	Latent-transforming growth factor beta-binding protein 2
LYL1	ENSG00000104903	Protein lyl-1
LYRIC	ENSG00000147649	Protein LYRIC
LZTS1	ENSG00000061337	Leucine zipper putative tumor suppressor 1
MA1C1	ENSG00000117643	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IC
MAP6	ENSG00000171533	Microtubule-associated protein 6
MEGF8	ENSG00000105429	Multiple epidermal growth factor-like domains protein 8
MFS2B	ENSG00000205639	Major facilitator superfamily domain-containing protein 2B
MGRN1	ENSG00000102858	E3 ubiquitin-protein ligase MGRN1
MIA3	ENSG00000154305	Melanoma inhibitory activity protein 3
MICA2	ENSG00000133816	Protein-methionine sulfoxide oxidase MICAL2
MIRO2	ENSG00000140983	Mitochondrial Rho GTPase 2
MK12	ENSG00000188130	Mitogen-activated protein kinase 12
MKNK1	ENSG00000079277	MAP kinase-interacting serine/threonine-protein kinase 1
MO2R2	ENSG00000206531	Cell surface glycoprotein CD200 receptor 2
MORN2	ENSG00000188010	MORN repeat-containing protein 2
MP2K3	ENSG00000034152	Dual specificity mitogen-activated protein kinase kinase 3
MPI	ENSG00000178802	Mannose-6-phosphate isomerase
MPP10	ENSG00000124383	U3 small nucleolar ribonucleoprotein protein MPP10
MRGX1	ENSG00000170255	Mas-related G-protein coupled receptor member X1
MRGX4	ENSG00000179817	Mas-related G-protein coupled receptor member X4
MRM1	ENSG00000129282	rRNA methyltransferase 1, mitochondrial
MSTRO	ENSG00000134042	Protein maestro
MYH15	ENSG00000144821	Myosin-15
MYO5C	ENSG00000128833	Unconventional myosin-Vc
MYOG	ENSG00000122180	Myogenin
MYOME	ENSG00000178104	Myomegalin
NAAA	ENSG00000138744	N-acylethanolamine-hydrolyzing acid amidase
NACA2	ENSG00000253506	Nascent polypeptide-associated complex subunit alpha-2
NAL10	ENSG00000182261	NACHT, LRR and PYD domains-containing protein 10
NALP3	ENSG00000162711	NACHT, LRR and PYD domains-containing protein 3
NAT8	ENSG00000144035	Probable N-acetyltransferase 8
NCOA3	ENSG00000124151	Nuclear receptor coactivator 3
NCTR2	ENSG00000096264	Natural cytotoxicity triggering receptor 2
NDUB9	ENSG00000147684	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
NETO1	ENSG00000166342	Neuropilin and tolloid-like protein 1
NEUR3	ENSG00000162139	Sialidase-3
NLRC5	ENSG00000140853	Protein NLRC5
NOS1	ENSG00000089250	Nitric oxide synthase
NOTC1	ENSG00000148400	Neurogenic locus notch homolog protein 1
NOTC2	ENSG00000134250	Neurogenic locus notch homolog protein 2
NPC1	ENSG00000141458	Niemann-Pick C1 protein
NPS	ENSG00000214285	Neuropeptide S
NPSR1	ENSG00000187258	Neuropeptide S receptor
NUDC3	ENSG00000015676	NudC domain-containing protein 3
O10A2	ENSG00000170790	Olfactory receptor 10A2
O10J3	ENSG00000196266	Olfactory receptor 10J3
O2T29	ENSG00000182783	Olfactory receptor 2T29
O51A4	ENSG00000205497	Olfactory receptor 51A4
OLA1	ENSG00000138430	Obg-like ATPase 1
OLFL1	ENSG00000183801	Olfactomedin-like protein 1
OLM2A	ENSG00000185585	Olfactomedin-like protein 2A
OR1J2	ENSG00000197233	Olfactory receptor 1J2
OR1J4	ENSG00000239590	Olfactory receptor 1J4
OR1L4	ENSG00000136939	Olfactory receptor 1L4
OR2G2	ENSG00000177489	Olfactory receptor 2G2
OR2L3	ENSG00000198128	Olfactory receptor 2L3
OR2M3	ENSG00000228198	Olfactory receptor 2M3
OR2T5	ENSG00000203661	Olfactory receptor 2T5
OR5K2	ENSG00000231861	Olfactory receptor 5K2
OR5R1	ENSG00000174942	Olfactory receptor 5R1
OR6Y1	ENSG00000197532	Olfactory receptor 6Y1
OR8H1	ENSG00000181693	Olfactory receptor 8H1
OR8H2	ENSG00000181767	Olfactory receptor 8H2
OR8H3	ENSG00000181761	Olfactory receptor 8H3
P121A	ENSG00000196313	Nuclear envelope pore membrane protein POM 121
P4K2B	ENSG00000038210	Phosphatidylinositol 4-kinase type 2-beta
P85B	ENSG00000105647	Phosphatidylinositol 3-kinase regulatory subunit beta
PAK4	ENSG00000130669	Serine/threonine-protein kinase PAK 4
PAMR1	ENSG00000149090	Inactive serine protease PAMR1
PAPP2	ENSG00000116183	Pappalysin-2
PARD3	ENSG00000148498	Partitioning defective 3 homolog
PCCB	ENSG00000114054	Propionyl-CoA carboxylase beta chain, mitochondrial
PCDB1	ENSG00000171815	Protocadherin beta-1

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
PCDB5	ENSG00000113209	Protocadherin beta-5
PCDC1	ENSG00000248383	Protocadherin alpha-C1
PDLI2	ENSG00000120913	PDZ and LIM domain protein 2
PDPR	ENSG00000090857	Pyruvate dehydrogenase phosphatase regulatory subunit, mitochondrial
PDZD8	ENSG00000165650	PDZ domain-containing protein 8
PERT	ENSG00000115705	Thyroid peroxidase
PEX26	ENSG00000215193	Peroxisome assembly protein 26
PIGQ	ENSG00000007541	Phosphatidylinositol N-acetylglucosaminyltransferase subunit Q
PIHD1	ENSG00000104872	PIH1 domain-containing protein 1
PK1L1	ENSG00000158683	Polycystic kidney disease protein 1-like 1
PKHG1	ENSG00000120278	Pleckstrin homology domain-containing family G member 1
PKHN1	ENSG00000187583	Pleckstrin homology domain-containing family N member 1
PKN1	ENSG00000123143	Serine/threonine-protein kinase N1
PL8L1	ENSG00000173261	PLAC8-like protein 1
PLBL2	ENSG00000151176	Putative phospholipase B-like 2
PLXA1	ENSG00000114554	Plexin-A1
PPAL	ENSG00000134575	Lysosomal acid phosphatase
PPIL2	ENSG00000100023	Peptidyl-prolyl cis-trans isomerase-like 2
PRIP1	ENSG00000088899	ProSAP-interacting protein 1
PSG6	ENSG00000170848	Pregnancy-specific beta-1-glycoprotein 6
PTC1	ENSG00000185920	Protein patched homolog 1
PTCA	ENSG00000213402	Protein tyrosine phosphatase receptor type C-associated protein
PTCD1	ENSG00000106246	Pentatricopeptide repeat-containing protein 1
PZRN4	ENSG00000165966	PDZ domain-containing RING finger protein 4
Q1ZZB8	ENSG00000142002	Dipeptidyl peptidase 9
R3HD1	ENSG00000048991	R3H domain-containing protein 1
REPI1	ENSG00000214022	Replication initiator 1
RFA4	ENSG00000204086	Replication protein A 30 kDa subunit
RGDSR	ENSG00000159496	Ral-GDS-related protein
RGPA1	ENSG00000174373	Ral GTPase-activating protein subunit alpha-1
RGS19	ENSG00000171700	Regulator of G-protein signaling 19
RGS22	ENSG00000132554	Regulator of G-protein signaling 22
RHG12	ENSG00000165322	Rho GTPase-activating protein 12
RIMKA	ENSG00000177181	N-acetylaspartyl-glutamate synthetase A
RL28	ENSG00000108107	60S ribosomal protein L28
RMND1	ENSG00000155906	Required for meiotic nuclear division protein 1 homolog
RN157	ENSG00000141576	RING finger protein 157
RPA1	ENSG00000068654	DNA-directed RNA polymerase I subunit RPA1
RSPH3	ENSG00000130363	Radial spoke head protein 3 homolog

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
RTBDN	ENSG00000132026	Retbindin
RTN3	ENSG00000133318	Reticulon-3
RTP2	ENSG00000198471	Receptor-transporting protein 2
S17A4	ENSG00000146039	Putative small intestine sodium-dependent phosphate transport protein
SART3	ENSG00000075856	Squamous cell carcinoma antigen recognized by T-cells 3
SE1L2	ENSG00000101251	Protein sel-1 homolog 2
SE6L2	ENSG00000174938	Seizure 6-like protein 2
SEMG2	ENSG00000124157	Semenogelin-2
SENP2	ENSG00000163904	Sentrin-specific protease 2
SFI1	ENSG00000198089	Protein SFI1 homolog
SH2B3	ENSG00000111252	SH2B adapter protein 3
SHPK	ENSG00000197417	Sedoheptulokinase
SI1L2	ENSG00000116991	Signal-induced proliferation-associated 1-like protein 2
SIG12	ENSG00000254521	Sialic acid-binding Ig-like lectin 12
SIK2	ENSG00000170145	Serine/threonine-protein kinase SIK2
SIK3	ENSG00000160584	Serine/threonine-protein kinase SIK3
SKIL	ENSG00000136603	Ski-like protein
SLNL1	ENSG00000171790	Schlafen-like protein 1
SMG1	ENSG00000157106	Serine/threonine-protein kinase SMG1
SMTL2	ENSG00000188176	Smoothelin-like protein 2
SO4A1	ENSG00000101187	Solute carrier organic anion transporter family member 4A1
SOAT	ENSG00000145283	Solute carrier family 10 member 6
SPAST	ENSG00000021574	Spastin
SPAT7	ENSG00000042317	Spermatogenesis-associated protein 7
SPEM1	ENSG00000181323	Spermatid maturation protein 1
SPG16	ENSG00000144451	Sperm-associated antigen 16 protein
SPR1A	ENSG00000169474	Cornifin-A
SPRR3	ENSG00000163209	Small proline-rich protein 3
SPTA2	ENSG00000197694	Spectrin alpha chain, brain
SPTC1	ENSG00000090054	Serine palmitoyltransferase 1
SRRM4	ENSG00000139767	Serine/arginine repetitive matrix protein 4
SRRT	ENSG00000087087	Serrate RNA effector molecule homolog
STX17	ENSG00000136874	Syntaxin-17
SYNE1	ENSG00000131018	Nesprin-1
SYNRG	ENSG00000006114	Synergin gamma
SYPM	ENSG00000162396	Probable proline–tRNA ligase, mitochondrial
SYT9	ENSG00000170743	Synaptotagmin-9
SYTC	ENSG00000113407	Threonine–tRNA ligase, cytoplasmic
SYYM	ENSG00000139131	Tyrosine–tRNA ligase, mitochondrial

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
T106C	ENSG00000134291	Transmembrane protein 106C
TARA	ENSG00000100106	TRIO and F-actin-binding protein
TCF7	ENSG00000081059	Transcription factor 7
TCOF	ENSG00000070814	Treacle protein
TCP10	ENSG00000203690	T-complex protein 10A homolog
TCPQM	ENSG00000198445	Putative T-complex protein 1 subunit theta-like 2
TCRGL	ENSG00000176769	Transcription elongation regulator 1-like protein
TECT1	ENSG00000204852	Tectonic-1
TENA	ENSG00000041982	Tenascin
TESK1	ENSG00000107140	Dual specificity testis-specific protein kinase 1
TEX11	ENSG00000120498	Testis-expressed sequence 11 protein
TFE2	ENSG00000071564	Transcription factor E2-alpha
TGM5	ENSG00000104055	Protein-glutamine gamma-glutamyltransferase 5
TITIN	ENSG00000155657	Titin
TLE2	ENSG00000065717	Transducin-like enhancer protein 2
TLR10	ENSG00000174123	Toll-like receptor 10
TM109	ENSG00000110108	Transmembrane protein 109
TMTC1	ENSG00000133687	Transmembrane and TPR repeat-containing protein 1
TNC18	ENSG00000182095	Trinucleotide repeat-containing gene 18 protein
TNR19	ENSG00000127863	Tumor necrosis factor receptor superfamily member 19
TPO	ENSG00000090534	Thrombopoietin
TRAF1	ENSG00000056558	TNF receptor-associated factor 1
TRAK2	ENSG00000115993	Trafficking kinesin-binding protein 2
TRAP1	ENSG00000126602	Heat shock protein 75 kDa, mitochondrial
TRH	ENSG00000170893	Prothyroliberin
TRPC5	ENSG00000072315	Short transient receptor potential channel 5
TRPV4	ENSG00000111199	Transient receptor potential cation channel subfamily V member 4
TRPV6	ENSG00000165125	Transient receptor potential cation channel subfamily V member 6
TSKS	ENSG00000126467	Testis-specific serine kinase substrate
TXK	ENSG00000074966	Tyrosine-protein kinase TXK
TXND8	ENSG00000204193	Thioredoxin domain-containing protein 8
UBE4B	ENSG00000130939	Ubiquitin conjugation factor E4 B
UBP19	ENSG00000172046	Ubiquitin carboxyl-terminal hydrolase 19
UPAR	ENSG00000011422	Urokinase plasminogen activator surface receptor
URP2	ENSG00000149781	Fermitin family homolog 3
USH2A	ENSG00000042781	Usherin
VILI	ENSG00000127831	Villin-1
VIPR1	ENSG00000114812	Vasoactive intestinal polypeptide receptor 1
VP13C	ENSG00000129003	Vacuolar protein sorting-associated protein 13C

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SUPPLEMENTARY TABLE 2

List of 457 top genes identified from Variant Annotation, Analysis, and Search Tool analysis *(continued)*

Gene name	Ensembl gene	Description
VPP2	ENSG00000185344	V-type proton ATPase 116 kDa subunit a isoform 2
VPREB	ENSG00000169575	Immunoglobulin iota chain
WFDC5	ENSG00000175121	WAP four-disulfide core domain protein 5
WFS1	ENSG00000109501	Wolframin
WNK1	ENSG00000060237	Serine/threonine-protein kinase WNK1
WSCD2	ENSG00000075035	WSC domain-containing protein 2
XBP1	ENSG00000100219	X-box-binding protein 1
XYLT1	ENSG00000103489	Xylosyltransferase 1
YYAP1	ENSG00000163374	YY1-associated protein 1
ZAR1	ENSG00000182223	Zygote arrest protein 1
ZBT37	ENSG00000185278	Zinc finger and BTB domain-containing protein 37
ZBT39	ENSG00000166860	Zinc finger and BTB domain-containing protein 39
ZDHC4	ENSG00000136247	Probable palmitoyltransferase ZDHHC4
ZFP28	ENSG00000196867	Zinc finger protein 28 homolog
ZFR2	ENSG00000105278	Zinc finger RNA-binding protein 2
ZHX2	ENSG00000178764	Zinc fingers and homeoboxes protein 2
ZN154	ENSG00000179909	Zinc finger protein 154
ZN442	ENSG00000198342	Zinc finger protein 442
ZN492	ENSG00000229676	Zinc finger protein 492
ZN620	ENSG00000177842	Zinc finger protein 620
ZN642	ENSG00000187815	Zinc finger protein 642
ZN644	ENSG00000122482	Zinc finger protein 644
ZN677	ENSG00000197928	Zinc finger protein 677
ZN837	ENSG00000152475	Zinc finger protein 837
ZN853	ENSG00000236609	Zinc finger protein 853
ZNF76	ENSG00000065029	Zinc finger protein 76
ZO1	ENSG00000104067	Tight junction protein ZO-1
ZSWM5	ENSG00000162415	Zinc finger SWIM domain-containing protein 5

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