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The association of single nucleotide polymorphisms in the oxytocin receptor and G protein-coupled receptor kinase 6 (GRK6) genes with oxytocin dosing requirements and labor outcomes

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Abstract

Background—Oxytocin is a potent uterotonic agent that is widely used for induction and augmentation of labor. Oxytocin has a narrow therapeutic index and the optimal dosing for any individual woman varies widely.

Objective—The objective of this study was to determine if genetic variation in the oxytocin receptor (OXTR) or in the gene encoding G protein-coupled receptor kinase 6 (GRK6), which regulates desensitization of the OXTR, could explain variation in oxytocin dosing and labor outcomes among women being induced near term.

Study Design—Pregnant women with a singleton gestation residing in Durham County, NC were prospectively enrolled as part of the Healthy Pregnancy, Healthy Baby cohort study. Those women undergoing an induction of labor at 36 weeks or greater were genotyped for 18 haplotype tagging (ht) single nucleotide polymorphisms (SNPs) in *OXTR* and 7 htSNPs in *GRK6* using TaqMan assays. Linear regression was used to examine the relationship between maternal genotype and maximal oxytocin infusion rate, total oxytocin dose received, and duration of labor. Logistic regression was used to test for association of maternal genotype with mode of delivery.

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For each outcome, backward selection techniques were utilized to control for important confounding variables and additive genetic models were employed. Race/ethnicity was included in all models due to differences in allele frequencies across populations and Bonferroni correction for multiple testing was used.

Results—DNA was available from 482 women undergoing induction of labor at 36 weeks or greater. 18 SNPs within *OXTR* and 7 SNPs within *GRK6* were examined. Five SNPs in *OXTR* showed nominal significance with maximal infusion rate of oxytocin and two SNPs in *OXTR* were associated with total oxytocin dose received. One SNP in *OXTR* and two SNPs in *GRK6* were associated with duration of labor, one of which met the multiple testing threshold (p=0.0014, rs2731664 [*GRK6*], mean duration of labor 17.7 hours vs. 20.2 hours vs. 23.5 hours for AA, AC and CC genotypes, respectively). Three SNPs, two in *OXTR* and one in *GRK6*, showed nominal significance with mode of delivery.

Conclusions—Genetic variation in *OXTR* and *GRK6* is associated with the amount of oxytocin required, as well as the duration of labor and risk for cesarean delivery among women undergoing induction of labor near term. With further research, pharmacogenomic approaches may potentially be utilized to develop personalized treatment to improve safety and efficacy outcomes among women undergoing induction of labor.

Keywords

desensitization; β-arrestin; G protein-coupled receptor; G protein-coupled receptor kinase 6; GRK6; genotype; induction of labor; labor; pregnancy; single nucleotide polymorphism; oxytocin; oxytocin receptor

INTRODUCTION

Oxytocin is a potent uterotonic agent that is used clinically for induction and augmentation of labor. Oxytocin has a narrow therapeutic range and the optimal effective dose for any given woman cannot currently be predicted.[1–3] Oxytocin initiates uterine contractions by activating the oxytocin receptor (OXTR), which is a G protein-coupled receptor (GPCR) that undergoes rapid desensitization with agonist activation.[4] Desensitization of the OXTR paradoxically leads to decreases in uterine contractions that can present clinically as dysfunctional labor patterns, which increase the risk for cesarean delivery, or as uterine atony following delivery, increasing the risk for postpartum hemorrhage.[2, 5–8]

Oxytocin binding of the OXTR leads to receptor desensitization through a well-established mechanism. Oxytocin binding results in receptor phosphorylation by G protein-coupled receptor kinase 6 (GRK6), a member of the GRK family, allowing for the recruitment of β-arrestin, which leads to receptor internalization and desensitization.[9–12] As an entire class, G protein-coupled receptors (GPCRs) are prone to GRK-mediated, β-arrestin-dependent desensitization.

Liggett et al identified a single nucleotide polymorphism in *GRK5*, another member of the GRK family that promotes desensitization of the β-adrenergic receptor. Individuals with a specific genotype in the SNP exhibited enhanced β-adrenergic receptor desensitization that produced a “genetic β-blockade” and improved outcomes in the setting of heart failure.[13]

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Given this precedent where a *GRK* polymorphism results in a phenotype of enhanced GPCR desensitization, we hypothesize that polymorphisms exist within genes encoding the OXTR/GRK6 system that enhance desensitization of the OXTR. Genetic predisposition to enhanced OXTR desensitization could present as a need for higher oxytocin infusion rates during labor and/or need for higher total doses of oxytocin, longer duration of labor, increased risk for cesarean delivery for failed induction or dysfunctional labor, or increased risk for uterine atony. The objective of this study was to determine if polymorphisms in *OXTR* or *GRK6* are associated with oxytocin dosing requirements, duration of labor, or mode of delivery among women being inducted near term.

MATERIALS AND METHODS

To determine if *OXTR* and *GRK6* genotype is associated with oxytocin dosing and labor outcomes among women at term, we genotyped women participating in the Healthy Pregnancy, Healthy Baby study at Duke University Medical Center.[14, 15] The Healthy Pregnancy, Healthy Baby cohort study is a key component of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO), an interdisciplinary center with the goal of understanding how environmental, social, and host factors contribute to disparities in pregnancy outcomes. The Healthy Pregnancy, Healthy Baby cohort study enrolled 1897 pregnant women from Durham County, NC between 2005 and 2011 and the study was reviewed and approved by the Duke University Institutional Review Board (Pro00007633).

Women were recruited at the prenatal clinics of the Duke University Medical Center or the Durham County Health Department between 18 and 28 weeks' gestation. Women were excluded if they were not English-literate, resided outside of Durham County, had a multiple gestation, or had a known fetal genetic or congenital anomaly. Socio-demographic characteristics, medical conditions, and health behaviors were collected by study staff through direct patient interview and review of the medical records. Maternal race and ethnicity was based on self-report. Pregnancy outcomes were obtained from review of the medical record. For this genotyping study, women with a singleton gestation who underwent a labor induction at 36 weeks' gestation or greater were genotyped for haplotype tagging SNPs within the *OXTR* and *GRK6* genes.

Oxytocin dosing was characterized by the maximal infusion rate and the total amount of oxytocin received. Maximal rate of infusion was defined as the highest infusion rate of oxytocin (mU/min) that a subject received at any time during her labor. The total dose of oxytocin received during labor (mU) was calculated by plotting the oxytocin infusion rate versus time (Figure 1) and then computing the area under the curve (AUC) using Microsoft Excel (Microsoft Corporation, Redmond, WA). The duration of induced labor was defined as the time from the start of the first induction agent to delivery. Uterine atony was considered present if recorded in the medical record.

Maternal body mass index (BMI) was calculated using pre-pregnancy weight. Pre-gestational diabetes, gestational diabetes, and preeclampsia were considered present if recorded in the medical record. All subjects were managed at Duke University Hospital

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under a standard oxytocin infusion protocol, that remained constant during the entire study duration. The oxytocin infusion is started at 2 mU/min and increased by 2mU/min every 30 minutes until an adequate contraction pattern is achieved. Adequate contraction patterns are defined by our protocol as uterine contractions occurring every two-to-three minutes.

Maternal blood samples were obtained at 24 to 28 weeks and processed for DNA isolation. Haplotype tagging SNPs within the *OXTR* and *GRK6* genes were identified using LD Select from the Yoruban (YRI) and Caucasian (CEU) populations of the HapMap project (www.hapmap.org).[16] All identified SNPs were genotyped for women who had self-identified as non-Hispanic white, non-Hispanic black, Hispanic, or non-Hispanic Asian. Other racial and ethnic categories were present in too few numbers so were not included in the final analysis. SNP genotyping was performed by the Duke Molecular Physiology Institute's Molecular Genotyping Core Facility using TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA). Blinded duplicates and Centre d'Etude du Polymorphism Humain (CEPH) samples were included as controls. Hardy-Weinberg Equilibrium (HWE) p-values as well as allele and genotype frequencies were calculated by ethnicity using PROC ALLELE in SAS version 9.4 (SAS Institute, Cary, NC).

Study subject demographic variables were summarized for the population. The primary study outcome was maximal rate of oxytocin infusion during labor. The secondary study outcomes included total oxytocin dose received in labor, duration of labor, cesarean delivery rate, cesarean for failed induction, and rate of uterine atony. Linear regression was used to test for association between SNPs and the continuous outcome variables (maximal oxytocin infusion rate, total oxytocin dose received, and duration of induced labor). Logistic regression was used to test for association between SNPs and the binary outcome variables (mode of delivery, failed induction, and uterine atony). An additive genetic model was employed. Clinically important covariates were selected *a priori*. These included parity, cervical dilation at start of induction, modified

Bishop score, pre-pregnancy BMI, gestational age at delivery, indication for induction, chorioamnionitis, diabetes (pre-gestational or gestational), chronic hypertension, preeclampsia and exposure to magnesium sulfate during labor. Cervical dilation at start of induction was found to be highly correlated with modified Bishop score, therefore only cervical dilation at start of induction was included in the models (Supplemental Figure 1). For each of the studied outcomes, backwards selection was used to choose the covariates that independently correlated with each outcome and would remain in the final model. Race/ethnicity was included in all models due to differences in allele frequencies across populations. Total oxytocin dose received and duration of labor were log-transformed for analysis to achieve a more normal distribution but untransformed means of these values are presented for interpretability. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). There were twenty-five maternal SNPs studied for each outcome. To account for multiple testing, a Bonferroni correction was made and statistical significance was defined as a p-value <0.002 (Bonferroni correction as alpha = 0.05 /25 tests). Each outcome of interest was analyzed separately and corrections for multiple comparisons were not made across each outcome as the outcomes were highly correlated with one another. As this was a pilot discovery project, genotype-outcome associations with a p-value < 0.05 that

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did not meet the conservative level of significance determined by Bonferroni correction ($p<0.002$) were defined as nominally significant.[14]

RESULTS

DNA was available from 482 women from the Non-Hispanic white, Non-Hispanic black, Hispanic, and Non-Hispanic Asian groups for analysis. The racial and ethnic breakdown of the included subjects is listed in Table 1. The mean age of the population was 26.9 years (SD=6.4) and the mean pre-pregnancy BMI was 30.1 kg/m^2 (SD=9.4). The most common indications for induction were post-dates (n=116, 24.1%), gestational hypertension or preeclampsia (n=90, 18.7%), chronic hypertension (n=66, 13.7%), other maternal medical conditions (n=52, 10.8%), and oligohydramnios (n=23, 4.8%). Other indications for induction included elective/maternal request, spontaneous rupture of the membranes without onset of labor, polyhydramnios, and macrosomia. The mean gestational age at delivery was 38.9 weeks (SD=1.5) and the mean cesarean delivery rate was 30.0% (Table 1). Other subject characteristics are listed in Table 1. The distribution of the maximal oxytocin infusion rate received during labor induction is presented in Figure 2.

Table 2 describes the 25 htSNPs chosen for the study, with base pair location, SNP type, and minor allele frequency for the entire studied population listed. One SNP (rs11131149 [*OXTR*], $p<0.0001$) deviated from Hardy-Weinberg equilibrium (HWE) in the non-Hispanic black population only. Three SNPs in *OXTR* are located in the three prime untranslated region (3'-UTR), while the remainder of the *OXTR* and *GRK6* SNPs were intronic.

Five SNPs in *OXTR* showed nominal significance with maximal oxytocin infusion rate while controlling for race/ethnicity, cervical dilation at start of induction, pre-pregnancy BMI, gestational age at delivery, chronic hypertension, and magnesium treatment in labor (Table 3). Two SNPs in *OXTR* showed nominal significance with total dose of oxytocin received in labor while controlling for race/ethnicity, cervical dilation at start of induction, pre-pregnancy BMI, gestational age at delivery, chronic hypertension, and magnesium treatment during labor (Table 4). Both SNPs (rs1042778 and rs4686301) also showed nominal significance with maximal infusion rate of oxytocin required in labor.

Table 5 shows the associations of SNPs with duration of induced labor while controlling for race/ethnicity, nulliparity, cervical dilation at the start of induction, pre-pregnancy BMI, and diabetes. One SNP in *OXTR* showed nominal significance with duration of labor, while two SNPs in *GRK6* showed significance with duration of labor, with one (rs2731664) surpassing the multiple testing threshold of $p=0.002$ (Bonferroni correction; 25 tests, alpha=0.05). Women with genotype AA at rs2731664 had a mean duration of induced labor of 17.7 ± 13.7 hours compared to women with the AC and CC genotypes who had a mean duration of labor of 20.2 ± 14.3 and 23.5 ± 16.5 hours, respectively ($p=0.001$).

Three SNPs showed nominal significance with mode of delivery, two in *OXTR* and one in *GRK6* (Table 6). Adjusted odds ratios (OR) for cesarean delivery were calculated while controlling for race/ethnicity, nulliparity, cervical dilation at start of induction, pre-pregnancy BMI, gestational age at delivery, chorioamnionitis, diabetes, and magnesium

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treatment during labor. The rate of failed induction was only 3.5% for the entire population so the association of this outcome with *OXTR* or *GRK6* genotype was not able to be determined. Similarly, uterine atony only occurred in 2.9% of the entire study population so the association of SNP genotype with this planned outcome was also not able to be determined. Figure 3 demonstrates the location of each of the significantly and nominally significantly associated SNPs within the *OXTR* and *GRK6* genes.

COMMENT

In this study, we demonstrate that maternal genotype in the *OXTR* and *GRK6* genes are associated with oxytocin dosing and labor outcomes among women undergoing induction of labor near term. These findings are significant as they demonstrate that variation in maternal genes is important in oxytocin receptor function, and that desensitization may influence the amount of oxytocin required for induction, the duration of labor, and overall cesarean delivery rates. With further research, this work could potentially be translated into a personalized management of labor induction and augmentation for women near term.

The optimal oxytocin infusion rate for women undergoing induction or augmentation of labor cannot be accurately predicted and the narrow therapeutic range of oxytocin hampers its use. There is a wide distribution in the optimal infusion rate of oxytocin across a population of laboring women. Our findings suggest that there may be genetic influences that affect this distribution of optimal oxytocin dosing in the population. Furthermore, genetics may affect OXTR desensitization, thereby explaining why not all women who are exposed to prolonged infusions of oxytocin experience paradoxical decreases in uterine contractility associated with OXTR desensitization such as dysfunctional labor or uterine atony.[2, 5–7] Genetic predisposition to GPRC desensitization may allow for enhanced OXTR desensitization such as seen with the GRK5/β-adrenergic receptor system.[13] Liggett et al demonstrated that subjects with a specific GRK5 genotype have enhanced β-adrenergic receptor desensitization resulting in a “genetic β-blockage” and improved outcomes in the setting of heart failure.[13] The corollary for the GRK6/OXTR system may be that specific *OXTR* or *GRK6* genotypes enhance OXTR desensitization resulting in the need for higher maximal infusion rates of oxytocin, higher total doses of oxytocin, longer duration of infusion, long duration of induction, or contribute to higher overall cesarean delivery rates during labor induction as was seen in our study. Without functional studies, we cannot prove that the observed association of maternal *OXTR* and *GRK6* genotype with oxytocin dosing and labor outcomes was the direct result of enhanced OXTR desensitization, but future work may elucidate these mechanisms.

Terkawi et al have shown that nulliparous women in spontaneous labor with the GG genotype at rs53576 in *OXTR* have a two hour longer duration of the latent phase of labor than women with the AA genotype.[17] rs53576 is a widely studied common variant in the third intron of *OXTR* and genetic variation at this SNP has been associated with differences in social behavior.[18] The haplotype tagging SNPs chosen in our study were all in the 3’-UTR or intronic regions of the genes, thus it is not known if they directly affect protein structure or function. Sequencing studies to identify coding variants in *OXTR* and *GRK6*

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may be necessary to learn more about how genetic variation in these genes are affecting protein function and/or structure.

Agonists binding GPCRs can activate the receptor in a biased fashion.[19, 20] A GCPR agonist can therefore recruit β-arrestin to the receptor in varying amounts such that it is possible that an OXTR-G protein biased agonist could result in little β-arrestin recruitment to the receptor, resulting in a non-desensitizing OXTR agonist. Such an agent could then potentially benefit women with a genetic predisposition to OXTR desensitization. A non-desensitizing OXTR agonist may overcome the genetic influence that leads to enhanced OXTR desensitization, resulting in lower oxytocin utilization and improved labor outcomes. Currently, we utilize a “one-size fits all” approach to oxytocin dosing for labor induction and augmentation. Future research based on our study’s findings may be an initial step to improve labor outcomes through a more personalized approach.

Our study is limited by its relatively small sample size, though we were able to identify a number of nominally significant associations with oxytocin dosing and labor outcomes as well as one genetic association with duration of labor that met our strict criteria for multiple testing of several genetic markers. Importantly, as stated in the Methods, we did not correct for testing across multiple outcomes. This is because the four outcomes examined are not independent of one another. Total oxytocin dose and maximal oxytocin infusion rate have the highest correlation ($r=0.81$, $p<0.0001$); total oxytocin dose and duration of induced labor, and maximal oxytocin infusion rate and duration of induced labor have more moderate correlations ($r=0.60$ and 0.40, respectively, p’s<0.0001). Those who underwent a cesarean delivery had significantly higher total oxytocin dose ($p=0.0002$), higher maximal oxytocin infusion rate ($p=0.001$), and higher duration of induced labor ($p<0.0001$). Nonetheless, we presented the results for all four outcomes because they each may impact future research related to personalization of labor management. In addition, our population was racially and ethnically diverse, though approximately 71% of the studied subjects were non-Hispanic blacks. The relatively small sample size prevented us from analyzing data separately for each racial and ethnic group, but race/ethnicity was included as a covariate in our analysis that was controlled for in all models. Our findings will need to be repeated in another population to determine if the results are largely being driven by a North Carolina non-Hispanic black population or if the findings persist in other groups. Furthermore, validation in an independent cohort is needed.

In summary, specific genotype at SNPs in *OXTR* and *GRK6* demonstrated a significant association with oxytocin dosing and labor outcomes among a cohort of women residing in Durham, North Carolina who underwent induction of labor near term. The observed genotypes may affect OXTR desensitization or some other aspect of OXTR signaling which then leads to the observed phenotypes. With further research, pharmacogenomic approaches may potentially be utilized to improve labor outcomes among women undergoing induction of labor and future research focusing on OXTR biased ligands may be one potential avenue in which to better personalize labor management.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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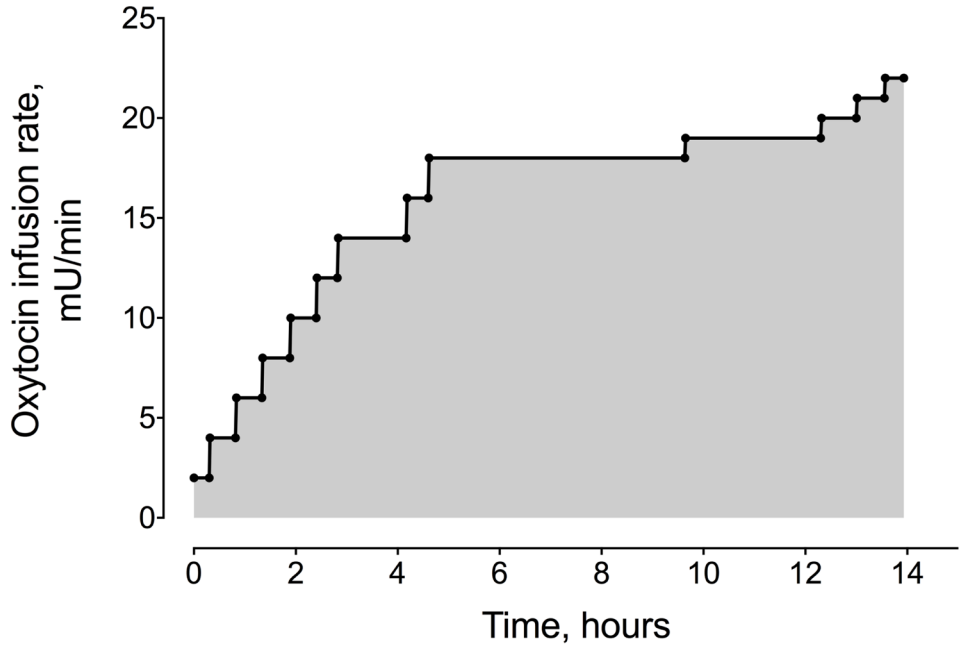

Figure 1. Graphical representation of total oxytocin dose received from a single subject

In order to calculate the total dose of oxytocin received during labor, for each woman a plot was constructed of oxytocin infusion rate by time. The shaded region, or the area under the curve (AUC), represents the total dose of oxytocin received during labor.

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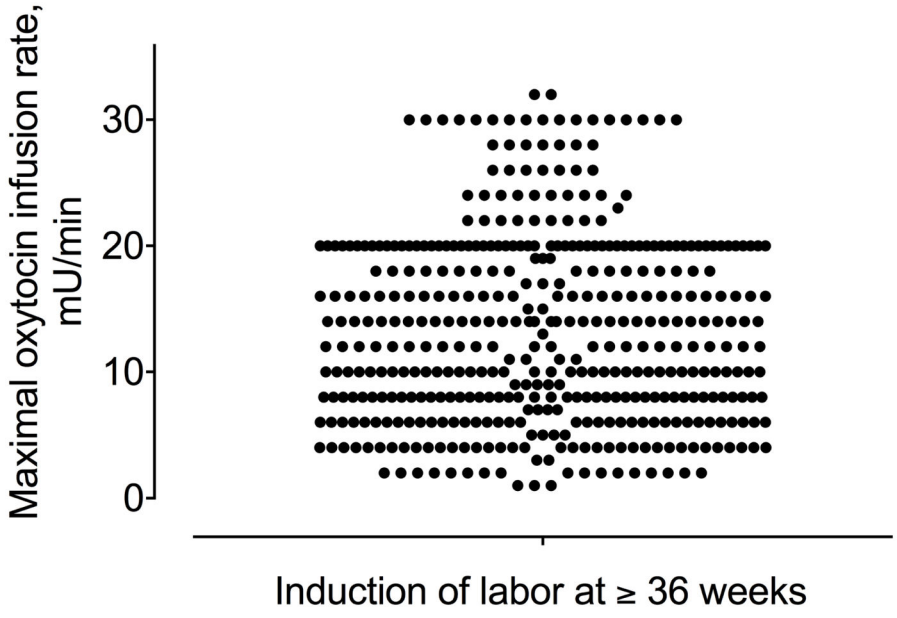

Figure 2. Distribution of maximal oxytocin infusion rate in the study population

The mean (± SD) and median (quartile) maximal rate of oxytocin infusion in the study population was 13.3 (± 7.5) mU/min and 12 (8, 20) mU/min, respectively.

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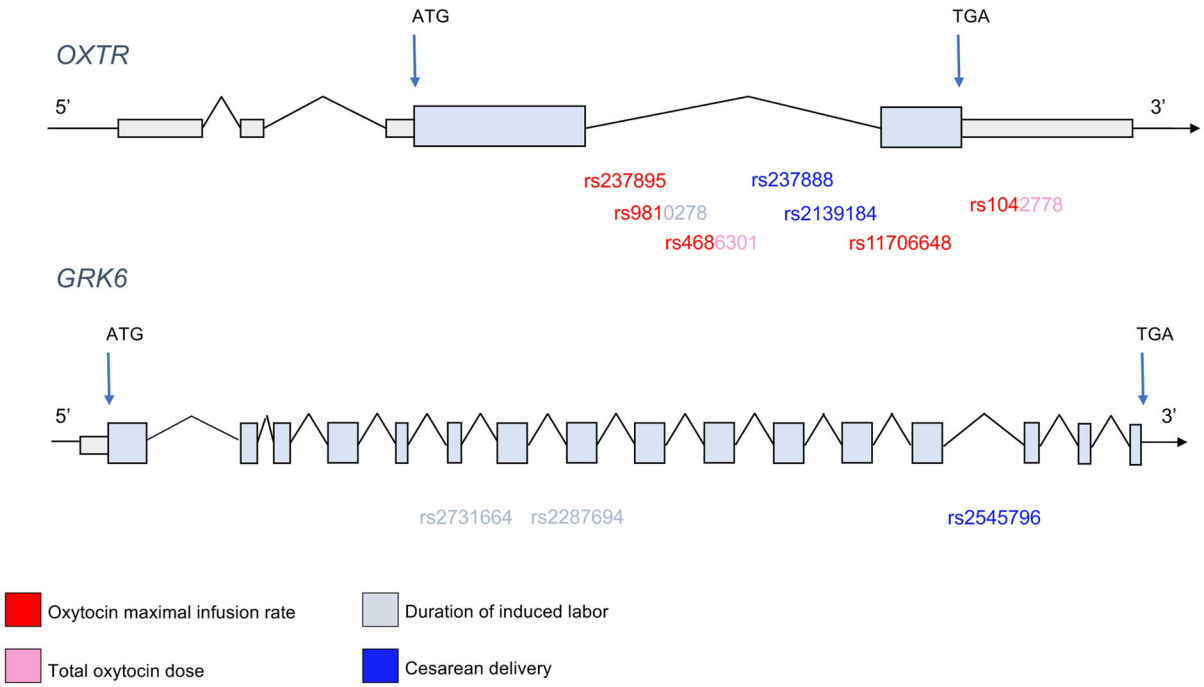

Figure 3.

Location of significantly and nominally significant-associated SNPs with studied clinical outcomes within the *OXTR* and *GRK6* genes

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Table 1

Subject demographic and pregnancy characteristics

Characteristic	Value (n=482)
Age, years[a]	26.9 ± 6.4
Race/ethnicity, n (%)	
Non-Hispanic white	91 (18.9)
Non-Hispanic black	341 (70.7)
Hispanic	24 (5.0)
Non-Hispanic Asian	26 (5.4)
Pre-pregnancy BMI, kg/m^2 [a]	30.1 ± 9.4
Nulliparous, n (%)	230 (47.7)
Chronic hypertension, n (%)	66 (13.7)
Preeclampsia, n (%)	163 (34.0)
Magnesium exposure, n (%)	37 (7.7)
Pre-gestational or gestational diabetes, n (%)	43 (8.9)
Chorioamnionitis, n (%)	18 (3.8)
Duration of induced labor, hours[b]	17 (9.9, 27.2)
Maximal oxytocin infusion rate, mU/min[b]	12 (8, 20)
Total oxytocin dose, mU[b]	5754 (2290, 14427)
Gestational age at delivery, weeks[a]	38.9 ± 1.5
Cesarean delivery, n (%)	143 (30.0)
Birthweight, g [a]	3203 ± 552
Uterine atony, n (%)	14 (2.9)
Failed induction, n (%)	17 (3.5)

[a]Mean ± SD

[b]Median (interquartile range)

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Table 2

Studied haplotype tagging single nucleotide polymorphisms (SNPs) in *OXTR* and *GRK6*

SNP	Gene	Base pair location	SNP type	Minor allele (all subjects)	Minor allele frequency (n=482)
rs2324728	*OXTR*	8792728	3'UTR	T	0.45
rs9872310	*OXTR*	8793381	3'UTR	G	0.24
rs1042778	*OXTR*	8794545	3'UTR	G	0.45
rs2139184	*OXTR*	8795494	intron	A	0.15
rs237886	*OXTR*	8795587	intron	T	0.42
rs11706648	*OXTR*	8796547	intron	C	0.20
rs237887	*OXTR*	8797042	intron	G	0.31
rs2268490	*OXTR*	8797085	intron	T	0.23
rs237888	*OXTR*	8797095	intron	C	0.28
rs9840864	*OXTR*	8798477	intron	C	0.41
rs4686301	*OXTR*	8798586	intron	T	0.17
rs9810278	*OXTR*	8799773	intron	T	0.07
rs2254295	*OXTR*	8802292	intron	C	0.19
rs11131149	*OXTR*	8802851	intron	G	0.34
rs237894	*OXTR*	8806531	intron	C	0.15
rs237895	*OXTR*	8807423	intron	T	0.21
rs2268495	*OXTR*	8807535	intron	A	0.27
rs237899	*OXTR*	8808515	intron	A	0.36
rs13177732	*GRK6*	176856925	intron	G	0.10
rs2731665	*GRK6*	176857270	intron	C	0.32
rs867755	*GRK6*	176858049	intron	T	0.27
rs2731664	*GRK6*	176859848	intron	A	0.48
rs2287694	*GRK6*	176860293	intron	C	0.06
rs2545796	*GRK6*	176864269	intron	C	0.33
rs189193	*GRK6*	176866006	intron	T	0.08

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Table 3

Nominally significant *OXTR* and *GRK6* genotype associations with *maximal oxytocin infusion rate*

SNP (gene)	Genotype (n): Maximal oxytocin infusion rate (mU/min)	p-value[a]
rs1042778 (*OXTR*)	GG (n=91): 10.9 ± 6.6 GT (n=187): 13.8 ± 7.6 TT (n=140): 14.0 ± 7.6	0.004
rs11706648 (*OXTR*)	AA (n=272): 12.7 ± 7.3 AC (n=132): 14.0 ± 7.5 CC (n=16): 16.4 ± 8.6	0.021
rs4686301 (*OXTR*)	CC (n=297): 12.7 ± 7.3 CT (n=111): 14.3 ± 7.6 TT (n=12): 17.6 ± 9.4	0.016
rs9810278 (*OXTR*)	CC (n=354): 12.9 ± 7.4 CT (n=64): 15.4 ± 7.7 TT (n=2): 11.0 ± 1.4	0.022
rs237895 (*OXTR*)	CC (n=270): 13.8 ± 7.6 CT (n=125): 12.0 ± 7.2 TT (n=24): 12.9 ± 7.6	0.027

[a]The adjusted p-value is for the association of genotype with maximal rate of oxytocin infusion rate while controlling for race/ethnicity, cervical dilation at start of induction, pre-pregnancy BMI, gestational age at delivery, chronic hypertension and magnesium treatment during labor.

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Table 4

Nominally significant *OXTR* and *GRK6* genotype associations with *total oxytocin dose received*

SNP (gene)	Genotype (n): Total oxytocin dose (mU)	p-value[a]
rs1042778 (*OXTR*)	GG (n=94): 6,852 ± 7,871 GT (n=196): 10,159 ± 9,787 TT (n=143): 10,425 ± 10,658	0.015
rs4686301 (*OXTR*)	CC (n=308): 8,961 ± 9,377 CT (n-114): 10,874 ± 10,682 TT (n=13): 11,426 ± 10,092	0.034

[a]The adjusted p-value is for the association of genotype with total oxytocin dose received while controlling for race/ethnicity, cervical dilation at start of induction, pre-pregnancy BMI, gestational age at delivery, chronic hypertension and magnesium treatment during labor.

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Table 5

Significant and nominally significant *OXTR* and *GRK6* genotype associations with *duration of induced labor*

SNP (gene)	Genotype (n): Duration of labor (hours)	p-value[a]
rs9810278 (*OXTR*)	CC (n=406): 20.2 ± 14.5 CT (n=68): 22.6 ± 16.9 TT (n=2): 14.4 ± 2.8	0.041
rs2731664 (*GRK6*)	AA (n=114): 17.7 ± 13.7 AC (n=223): 20.2 ± 14.3 CC (n=132): 23.5 ± 16.5	0.001
rs2287694 (*GRK6*)	CC (n=0): no subjects CT (n=55): 26.2 ± 18.9 TT (n=421): 19.7 ± 14.1	0.009

[a]The adjusted p-value is for the association of genotype with duration of induced labor while controlling for race/ethnicity, nulliparity, cervical dilation at start of induction, pre-pregnancy BMI, and diabetes (pre-gestational or gestational).

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Table 6

Nominally significant *OXTR* and *GRK6* genotype associations with *cesarean delivery*

SNP (gene)	Genotype (n): Cesarean delivery rate	p-value[a] (aOR, [95% CI])
rs2139184 (*OXTR*)	AA (n=6/16): 37.5% AC (n=35/110): 31.8% CC (n=101/355): 28.4%	(aOR 0.55 [95% CI 0.33, 0.92])
rs237888 (*OXTR*)	CC (n=10/47): 21.3% CT (n=46/174): 26.4% TT (n=87/261): 33.3%	0.025 (aOR 1.68 [95% CI 1.07, 2.66])
rs2545796 (*GRK6*)	CC (n=19/54): 35.2% CT (n=57/203): 28.1% TT (n=66/224): 29.5%	0.032 (aOR 0.64 [95% CI 0.43, 0.96])

[a]The adjusted OR and p-value is for the association of genotype with cesarean delivery rate while controlling for race/ethnicity, nulliparity, cervical dilation at start of induction, pre-pregnancy BMI, gestational age at delivery, chorioamnionitis, diabetes (pre-gestational and gestational) and magnesium treatment during labor.