

Polymorphism in the *ADRB2* Gene Explains a Small Portion of Intersubject Variability in Pain Relative to Cervical Dilation in the First Stage of Labor

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ABSTRACT

Background: Variability in labor pain has been associated with demographic, clinical, and psychological factors. Polymorphisms of the β 2-adrenergic receptor gene (*ADRB2*) influence sensitivity to experimental pain in humans and are a risk factor for chronic pain. The authors hypothesized that polymorphisms in *ADRB2* may influence labor pain.

Methods: After Institutional Review Board approval and written informed consent, the authors prospectively obtained hourly pain reports from 233 nulliparous parturients during the first stage of labor, of which 199 were included in the current analysis. DNA from blood samples was genotyped at polymorphisms in the genes for the β 2-adrenergic receptor, the μ opioid receptor subtype 1, catechol-*O*-methyltransferase, fatty acid amide hydrolase, and the oxytocin receptor. Labor pain as a function of cervical dilation was modeled with previously described methods. Patient covariates, *ADRB2* genotype, and obstetrical and anesthesia treatment were evaluated as covariates in the model.

Results: Labor pain more rapidly became severe in parturients heterozygous or homozygous for the G allele at rs1042714 in the *ADRB2* gene. Labor pain increased more rapidly after artificial rupture of membranes, augmentation with oxytocin, and in younger women. Inclusion of covariates explained approximately 10% of the variability between subjects. *ADRB2* genotype explained less than 1% of the intersubject variability.

Conclusion: *ADRB2* genotype correlates with labor pain but explained less than 1% of the intersubject variance in the model. (ANESTHESIOLOGY 2014; 121:140-8)

THE intensity of labor pain differs substantially among patients.¹ Previous research has identified demographic,² clinical,³ and psychological⁴ factors that influence the intensity of labor pain. However, these variables have only explained a small portion of the variability seen in clinical practice.²

Genetic variation is thought to modulate nociception. Single nucleotide polymorphisms (SNPs) are predictive of differences in pain perception in a variety of clinical and experimental settings.⁵ Polymorphisms in the *ADRB2* gene have been implicated as predisposing factors for the development of chronic pain in a large birth cohort.⁶ Specifically, *ADRB2* SNPs rs12654778 and rs1042713 were associated with chronic pain while other functional haplotypes in *ADRB2* were also associated with the extent and duration of pain. Pharmacological blockade of β -adrenergic receptors has been reported to enhance pain relief in a variety of clinical settings and pain modalities.⁷⁻¹¹

We examined two relatively common, functional polymorphisms within the *ADRB2* (rs1042713 and rs1042714) gene. We hypothesized that the two *ADRB2*

What We Already Know about This Topic

- Polymorphisms of the β 2-adrenoceptor gene (*ADRB2*) influence sensitivity to experimental pain and are associated with development of chronic pain
- Whether polymorphisms in *ADRB2* can explain variability in labor pain is unknown

What This Article Tells Us That Is New

- In modeling hourly labor pain as a function of cervical dilation in nearly 200 women through the course of labor, *ADRB2* explained less than 1% of intersubject variance, considerably less than that of induction of labor

SNPs would be associated with increased labor pain. Additionally, for hypothesis generation we examined other genes that have previously been implicated in pain modulation, including the genes encoding the μ -opioid receptor,¹² catechol-*O*-methyltransferase,¹³ fatty acid amide hydrolase,¹⁴ and the oxytocin receptor.¹⁵ We also evaluated the effects of demographic and clinical factors on the relation between cervical dilation and numerical rating scale for pain (NRS).

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Materials and Methods

After obtaining approval from the Institutional Review Board at King Fahad Medical City, Riyadh, Saudi Arabia, we enrolled subjects between March 2010 and September 2010. Parturients who presented to labor and delivery rooms in the Maternity Hospital in King Fahad Medical City were interviewed by a physician and offered enrollment. Subjects provided written, informed consent.

This is a secondary analysis of these subjects. The primary analysis was the influence of genetics and patient covariates on the time course of cervical dilation, labor progress.¹⁶ Hourly pain scores were gathered in the subjects with the intent to perform this analysis of the genetic determinants, if any, of labor pain. The study methodology, the power analysis for the primary end point (cervical dilation), and the influence of genotype on the rate of cervical dilation are described in the primary article.¹⁶ The study methodology is repeated for completeness.

Inclusion criteria consisted of healthy nulliparous parturients who anticipated vaginal delivery of a singleton infant at term (37 to 42 weeks gestation). Patients were excluded from enrollment if they had preeclampsia, a history of chronic pain, or current use of pain medication. Patients with gestational or essential hypertension were not specifically excluded because of the extremely low incidence within the local population. Patients were excluded if they did not reach full cervical dilation. Pain observations after neuraxial analgesia were censored from the analysis.

As described in the primary article on labor progress,¹⁶ a sample size of 200 had a 90% probability of determining an effect of the primary covariate (*ADRB2* rs1042714) on the rate of cervical dilation at *P* value less than 0.05, assuming the effect of genotype at a single locus could differentiate two populations (*e.g.*, CC vs. CG + GG). Additional details not included in the primary reference¹⁶ are that given a 20% frequency of the interesting allelic combination, a power of 0.9, a one-sided test (given our *a priori* knowledge of the direction of the effect), and 200 subjects, the effect size was calculated in *R** as: *pwr.t2n.test* (*d* = NULL, *n1* = 40, *n2* = 160, *sig.level* = 0.05, *power* = 0.9, *alternative* = less).

The effect size was 0.52 (Cohen's *d* statistic, applied to the difference in *CD*₅₀ estimates in the primary reference), consistent with our intent to only power the study for clinically meaningful effects. As such, we enrolled 233 subjects to have at least 200 subjects who had a vaginal delivery.¹⁶

Parturients were admitted to labor and delivery in spontaneous labor when their cervical dilation was 3 cm or greater unless there was another medical indication such as vaginal bleeding or induction of labor. Before entering the labor and delivery suite, subjects were maintained in a holding area where pain scores were reported to study staff. The patient

was allowed to be accompanied by one family member of her choice. Patients were examined vaginally every 4 h in latent labor and every 2 h in active labor by the obstetrician. Active management of labor included rupture of membranes and oxytocin augmentation. Labor was induced with membrane rupture, misoprostol, and oxytocin as deemed medically appropriate by the obstetrician. The nurse to patient ratio was 1:1. Hourly pain scores were obtained on a form filled out by the patient with encouragement from nursing, obstetrics and anesthesia practitioners. Pain scores did not necessarily coincide with an examination of cervical dilation. Pain scores were only recorded during the first stage of labor, by definition the stage associated with cervical dilation. Meperidine *via* intramuscular injection was offered for analgesia two to three times during labor on maternal request but not after 8 cm cervical dilation.

Genetic data were obtained from a blood sample taken at the time of enrollment in the study. The samples were processed to extract DNA at Columbia University using the PureGene DNA Extraction Kit (Gentra, Minneapolis, MN). The genetic material was analyzed by Sequenom (Danvers, MA). Analysis was performed for the genes encoding the β 2-adrenergic receptor (*ADRB2* rs1042713, rs1042714), the μ -opioid receptor subtype 1 (*OPRM1* rs1799971),¹² catechol-*O*-methyltransferase (*COMT* rs6269, rs4646312, and rs4633),¹³ fatty acid amide hydrolase (*FAAH* rs932816, rs4141964, and rs2295633),¹⁴ and the oxytocin receptor (*OXTR* rs53576, rs2254298, and rs2228485).¹⁵

The demographic and clinical variables included for covariate analysis were age, height, maternal weight on admission, body mass index, birth weight, estimated gestational age, time of self-reported onset of contractions, time of artificial rupture of membranes, time of induction, time of onset of oxytocin administration, type of analgesia (no analgesia or 100 mg intramuscular meperidine every 3 h as needed), number and time of dosage of meperidine if applicable, mode of delivery (spontaneous vaginal delivery, instrumental delivery, or cesarean section after full cervical dilation), and previous medical history. The effect of meperidine was tested, but only on pain scores after the first dose of meperidine was administered to the patient.

The relation between cervical dilation and NRS pain score was modeled as a sigmoid equation with nonlinear mixed effects modeling (NONMEM), implemented using the graphical user interface PLTTools (PLTsoft.com, San Francisco, CA). NRS score was on an 11 unit score with 0 representing no pain and 10 representing the worst possible pain with contractions. The model was built according to previously published methods.^{2,17} The pain model was described by four parameters: NRS pain score at cervical dilation = 0 (*E*₀), a maximum NRS pain score (*E*_{max}), the cervical dilation (CD) at which 50% of the maximum pain score was reached (*CD*₅₀), and the slope function of the sigmoidal equation, γ , which approximately described the rate of development of labor

* R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: <http://www.R-project.org/>. Version 3. *pwr.t2n.test* is found in the "pwr" package. Accessed February 17, 2014.

pain as a function of increasing cervical dilation. The fit was constrained between 0 and 10 NRS points according to the following equation:

$$\text{NRS} = E_0 + (E_{\text{max}} - E_0) \times \text{CD}^\gamma / (\text{CD}^\gamma + \text{CD}_{50}^\gamma)$$

After construction of the initial model, each demographic, clinical, and genetic factor was tested for significance on each of the model parameters. Each homozygous genetic variable was considered independently. Interindividual error on E_0 and E_{max} was modeled using an additive model. Interindividual error on CD_{50} was modeled using a proportional error model. The residual intraindividual error was modeled using an additive error model.

Factors that improved the model in a statistically significant fashion, defined as P value less than 0.05 (improvement in $-2 \log$ likelihood of >3.84), and tested by chi-square test with 1 degree of freedom, were maintained for inclusion in the multivariable model.

The final model was built by assembling the significant univariate results in order from greatest significance to least significance. They were sequentially added into the model, where they were again tested for statistical significance in the presence of previously added and retained covariates. Covariates that remained significant after correction for the more significant factors were maintained in the model. Covariates that failed to reach significance (by above criteria) when added to the model were discarded.

Once the final model was built, covariates were removed individually to validate their significance independent of other variables. If the model significantly worsened ($-2 \log$ likelihood increased by >3.84) after removal of the covariate, it was maintained in the final model.

CIs for the final model parameters were calculated with likelihood profiles on each parameter using 101 iterations. The prediction error (PE) was calculated as the measured NRS – predicted NRS. Model bias was assessed using median PE. Model inaccuracy was assessed using median absolute PE. Sample variance was calculated as the average squared PE (PE^2).

The graphs were prepared using the R programming language (R Foundation for Statistical Computing, Vienna, Austria).

Results

Data Collection

A total of 233 parturients were enrolled.¹⁶ Of the initial cohort, 206 parturients completed the first stage of labor. Table 1 shows demographic and treatment data. Only two patients received epidural analgesia. The median number of pain scores provided for each patient was 7 with a range of 2 to 22. The median duration of labor was 9 h with a range of 3 to 24 h. All patients were Saudi.

A total of 202 patients were genotyped for rs1042713, and 200 patients were successfully genotyped at

Table 1. Demographic and Clinical Characteristics of the Cohort Included in the Final Model (N = 199)

Demographic Characteristics	Median (Range)
Age (yr)	24 (16–37)
Height (cm)	158 (143–175)
Weight (kg)	71 (45–135)
Body mass index (kg/m ²)	29 (19–58)
Gestational age (days)	278 (259–297)
Birth weight (g)	3,100 (2,030–4,330)
Clinical Characteristics	Number (%)
Intervention	
Artificial rupture of membranes	113 (57)
Induction	26 (13)
Augmentation (oxytocin)	87 (44)
Analgesia	
Meperidine w/o epidural	187 (94)
Meperidine with epidural	2 (1)
No analgesia	10 (5)
Type of delivery	
NSVD	151 (76)
Instrumental	31 (16)
Cesarean Section	17 (9)

NSVD = normal spontaneous vaginal delivery.

Table 2. Population Distribution of Genetic Polymorphisms Examined for Their Effect on Labor Pain

SNP (Total Population)	Genotype	Number (%)
β2-adrenergic receptor rs1042713 (202)	AA	31 (15)
	AG	94 (47)
	GG	77 (38)
rs1042714 (200)	CC	115 (58)
	CG	72 (36)
	GG	13 (6.5)

SNP = single nucleotide polymorphism.

rs1042714 (see table 2 for population frequencies). Among the 200 patients genotyped at rs1042714, a single subject did not have a recorded age. The final analysis cohort consisted of the 199 parturients for which we had age, rs1042714 genotype, and who completed the first stage of labor.

Initial Model

Covariates were individually tested in the model. Covariates significantly associated with labor pain were *ADRB2* (rs1042714 genotype CC, the common allele), μ -opioid receptor type 1 (rs1799971, genotype AA, the common allele), fatty acid amid hydrolase (rs2295633, genotype AA, the minor allele), catechol-*O*-methyltransferase (*COMT*, rs6269, genotype AA, the minor allele), oxytocin receptor (*OXTR* rs2228485 genotype TT and *OXTR* rs53576 genotype GG, both the minor allele), cesarean delivery, maternal height, weight, body mass index, oxytocin administration, induction of labor, and

Table 3. Initial, Intermediate, and Final Models, Together with Metrics of Model Performance

Models	Objective Function	Delta	P Value	MPE (NRS Units)	MAPE (NRS Units)	Variance (NRS Units ²)	Variance Change from Prior Model (NRS Units ²)	Percentage of Explainable Variance*
Initial model	2,098.7			0.063	1.12	3.316		
Oxytocin on C ₅₀	2,055.5	-43.1	<0.00005	0.086	1.08	3.141	0.174	6.73
AROM on C ₅₀ (only for OXY=0)	2,048.3	-7.3	0.00696	0.047	1.04	3.073	0.068	2.62
IND on E0	2,040.2	-8.0	0.00463	0.078	1.06	3.049	0.025	0.96
Age as an additive factor on γ	2,032.4	-7.9	0.00500	0.086	1.08	3.054	-0.005	-0.20
β 2AR-27 type on γ	2,017.7	-14.7	0.00013	0.055	1.04	3.042	0.012	0.47

* Explainable variance is the intersubject variance that could be explained if all of model parameters were known for each patient. In the initial model, the population variance calculated assuming that all subjects have the same model parameters is 3.316 NRS units². However, NONMEM also calculates *post hoc* predictions, estimating the parameters for each subject. The variance for the *post hoc* individual fits was 0.722 units². The difference between these, 2.594 NRS units², represents the potentially explainable intersubject variance if the model parameters were known for each subject. The numbers in the last column are the change in variance between two models, divided by 2.594 NRS units², the potentially explainable variance.

AROM = artificial rupture of membranes; C₅₀ = cervical dilation at which pain is half maximal (cm); Delta = change in objective function; E0 = Extrapolated pain score at 0 cm dilation (NRS units); IND = induced labor; MAPE = median absolute prediction error (NRS units, measure of accuracy); MPE = median prediction error (NRS units, measure of bias); NRS = numerical rating score for pain; β 2AR-B27 = *ADRB2* genotype; γ = steepness of the relationship between cervical dilation and NRS score.

Table 4. Model Parameters

Parameters	Value (95% CI)
Initial model	
E ₀	3.47
E _{max}	9.55
CD ₅₀	5.06
γ	5.43
Final model	
E ₀ (without induction)	3.75* (3.28–4.16)
E ₀ (induction)	4.99* (4.08–5.54)
E _{max}	9.59 (9.43–9.77)
CD ₅₀ (oxytocin)	4.66 (4.35–4.97)
CD ₅₀ (no oxytocin, AROM)	5.28 (4.93–5.61)
CD ₅₀ (no oxytocin, no AROM)	5.74 (5.34–6.14)
Effect size of age on γ (yr ⁻¹)	-0.18 (-0.26 to -0.094)
γ (<i>ADRB2</i> rs1042714 CG or GG)	6.29 (5.25–7.47)
γ (<i>ADRB2</i> rs1042714 CC)	4.59 (3.98–5.30)

* Both E0 values in the final model are larger than the E0 value without covariates because induction is a time-varying covariate.

AROM = artificial rupture of membranes; CD₅₀ = cervical dilation at which pain is half maximal (cm); E₀ = pain score at cervical dilation = 0 (NRS units); E_{max} = maximal pain (NRS units); NRS = numerical rating scale for pain; γ = slope function representing increase of pain across cervical dilation (unitless).

artificial rupture of membranes. Meperidine administration did not influence the pain reported in labor.

Final Model

Table 3 shows the iterative improvement in objective function, the P value associated with the change in objective function, the median prediction error, the median absolute prediction error, variance, and change in variance with each additional parameter. The values for parameters that remained significant in the final model are shown in table 4.

Patients who expressed at least one G allele at the *ADRB2* SNP rs1042714 (β 2AR-27) have a more rapid transition to

severe pain with increasing cervical dilation than parturients homozygous for the common allele (CC; fig. 1A). Older mothers had more gradual progression to maximal pain compared with younger women (fig. 1B). Their value of the γ slope function decreased by 0.18 (unitless) for each additional year of maternal age.

Management of labor significantly affected labor pain. As expected, treatments associated with the active management of labor were associated with more painful labor. Labor induction was associated with more pain in early in the first stage of labor (fig. 2A). Augmentation of labor with oxytocin was associated with development of maximum labor pain at an earlier cervical dilation, as was artificial rupture of membranes. Among subjects who were not treated with oxytocin, those who had artificial rupture of membranes reached maximal labor pain more than 1 cm of cervical dilation earlier than those who had no intervention (fig. 2B). Among those who were treated with oxytocin, rupture of membranes did not add to labor pain. Patients who were treated with meperidine had more rapidly increasing pain before they were treated with meperidine but after treatment they were not different from those who had not been treated. Figure 3 shows the goodness-of-fit of final model for the population (A) and *post hoc* individual (B) fits. The shaded regions represent prediction errors that cannot exist because numerical rating score is bounded by 0 and 10.

Model Performance

Table 3 shows the median prediction error, median absolute prediction error, and sample variance for initial model (no covariates), intermediate models, and the final model. The last two columns, the change in sample variance from the previous model, and the percentage of the potentially explainable variance, are described below.

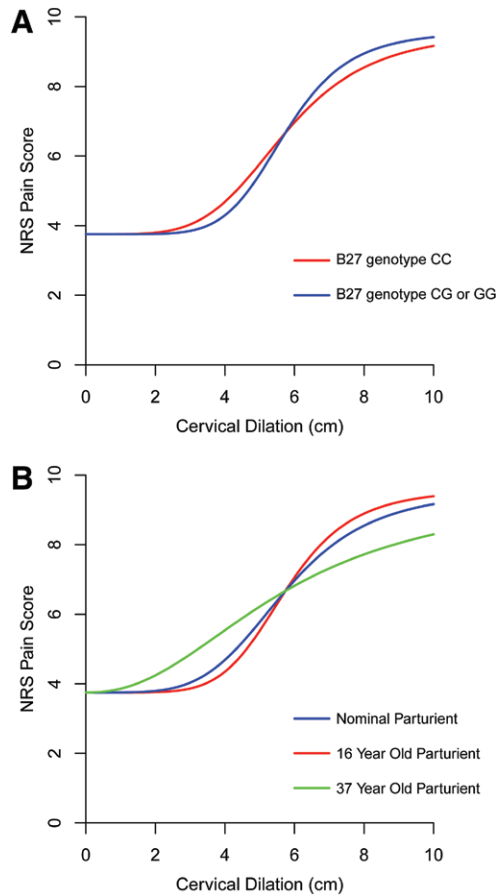


Fig. 1. Intrinsic patient-related factors. (A) Effect of *ADRB2* genotype (rs1042714). Subjects who express at least G allele at rs1042714 have more rapid development of pain with increasing cervical dilation. The pain response of subjects who carry the common allele (CC) is shown in *red* and for those who carry at least G allele in *blue*. The simulations were calculated for 24-yr-old parturients (median age) without oxytocin, artificial rupture of membranes, or induction of labor. (B) Effect of age. Labor pain develops more slowly with increasing cervical dilation in older parturients. The pain response for the youngest subject (aged 16 yr) is depicted in *red* and that of the oldest subject (aged 37 yr) in *green*. The relation between pain and cervical dilation for the nominal patient (median age 24 yr) is shown in *blue*. The simulations were calculated for the common *ADRB2* genotype (rs1042714) allele (CC), for parturients without oxytocin, artificial rupture of membranes, or induction of labor. NRS = numerical rating scale for pain.

All models were unbiased, with median prediction errors less than 0.1 NRS units. The typical miss, measured as the median absolute prediction error, ranged from 1.12 NRS units for the initial model to 1.04 NRS units for the final model. Thus, the accuracy of the prediction of the NRS decreased from only 1.12 to 1.04 NRS units during the course of model development. The median absolute prediction error for the individual *post hoc* predictions was 0.54 NRS units for the initial model, and 0.51 NRS units for the final model.

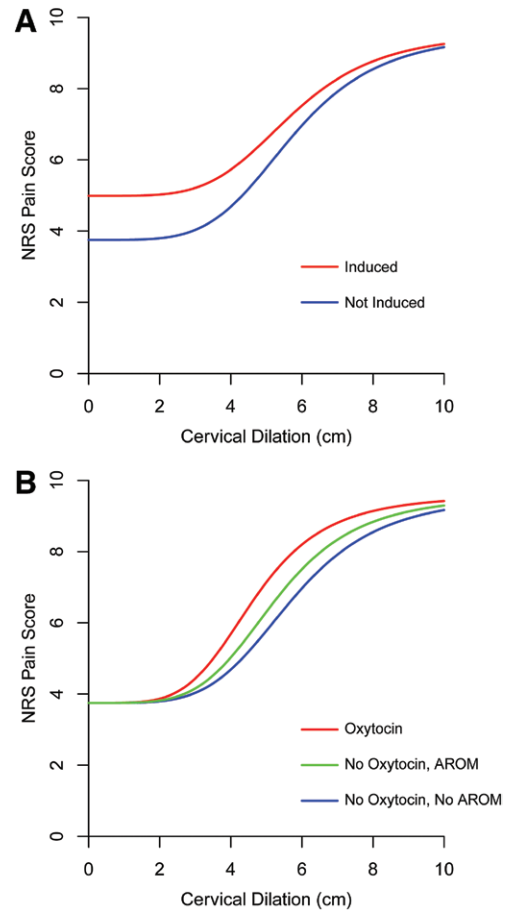


Fig. 2. Treatment-related factors. (A) Labor induction. Induced labor is associated with more pain in early labor. The simulations were calculated for 24-yr-old parturients (median age) with the common *ADRB2* genotype (rs1042714) allele (CC), without oxytocin or artificial rupture of membranes. (B) Augmentation and rupture of membranes. Labor that is augmented with oxytocin becomes painful more quickly. Rupture of membranes is also associated with more rapid development of pain. The simulations were calculated for 24-yr-old parturients (median age) with the common *ADRB2* genotype (rs1042714) allele (CC), without induction of labor. AROM = artificial rupture of membranes; NRS = numerical rating score for pain.

As shown in table 3, the sample variance (average squared error) of the initial model for the population fit was 3.316 NRS units.² The sample variance of the initial model for the *post hoc* individual fits was 0.722 NRS units² (not shown in table 3). The difference between these, 2.594 NRS units,² represents the variance that could be explained if each subject's parameters (E_0 , E_{max} , CD_{50} , and γ) could be calculated from known covariates (*e.g.*, age, genotype, oxytocin, induction, artificial rupture of membranes). As such, 2.594 NRS units² is the potentially explainable variance.

As shown in table 3, as the log likelihood decreased with inclusion of additional covariates, the model variance decreased to 3.042 NRS units.² This represents a reduction in sample variance of 0.274 NRS units² from the initial model, a decrease of 10.6%. The effect of oxytocin accounted for

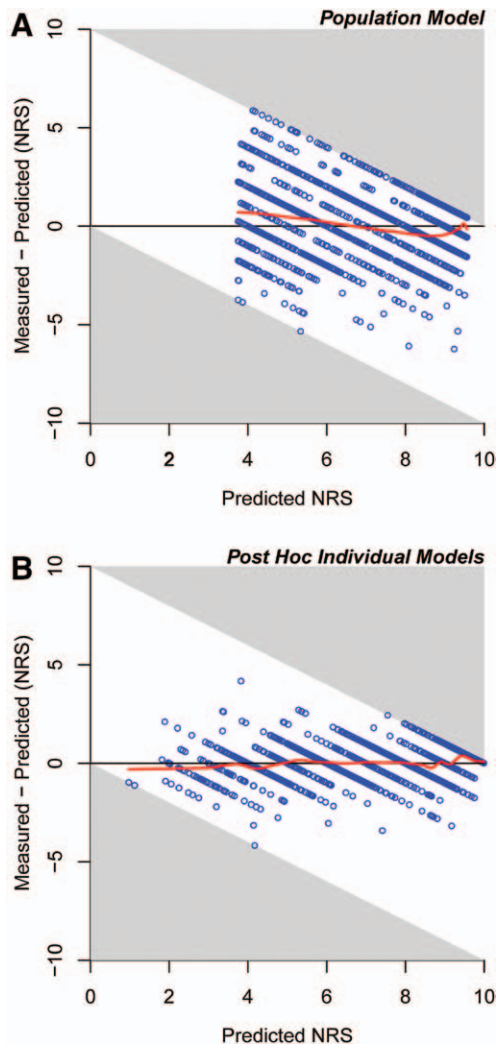


Fig. 3. Model goodness of fit. (A) The figure shows the error in NRS prediction (y axis) as a function of the predicted NRS score (x axis) for the population fit, reflecting the effects of covariates known to the model. The *red line* is Friedman SuperSmoother. The *shaded regions* show the portions of the figures where prediction errors cannot occur because both measured and predicted NRS are bounded by 0 and 10. (B) The figure shows the error in NRS prediction (y axis) as a function of the predicted NRS score (x axes) for the individual fit, reflecting the effects of covariates known to the model as well as random intersubject differences estimated by NONMEM (NONlinear Mixed Effects Modeling program). The *red line* is Friedman SuperSmoother. The *shaded regions* show the portions of the figures where prediction errors cannot occur, because both measured and predicted NRS are bounded by 0 and 10. The fit shows how well the model could work, given the limitations of the measurements and the model structure, if all of the intersubject variability could be explained by patient or treatment characteristics. NRS = numerical rating score for pain.

nearly two thirds of the 0.274 NRS units² of explained variance. The effect of artificial rupture of membranes accounted for a quarter of the explained variance. Induction, age, and *ADRB2* genotype all accounted for less of the potentially

explainable variance (*i.e.*, had small effects on model performance). Even with the best possible model, approximately 90% of the potentially explainable variance in the relation of pain to cervical dilation remained unexplained.

Discussion

Mixed effects models provide a technique for the analysis of complex, multifactorial processes, such as labor pain. Because of relatively low rates of cesarean section and neuraxial analgesia in the current study population, we were able to obtain rich pain data relevant to nulliparous delivery. This cohort is unique in providing hourly pain scores collected for the purpose of this study. As such this population provided the ability to evaluate, in great detail, how pain progresses as the cervix dilates during the first stage of labor.

The high level of unexplained variability is not surprising. The NRS pain score is anchored at no pain and maximal pain. There is no reason to expect nulliparous parturients to approach labor and delivery with consistent expectations for maximal pain. NONMEM can capture this subject to subject difference in scale as unexplained intersubject variability, demonstrated by the difference between the median absolute prediction error of 1.12 NRS units for the population fit, and 0.54 NRS units for the *post hoc* individual fits with the initial model. This tells us that intersubject variability and residual noise each explain about half of the residual unexplained variability.

Thus, calculation of the role of each covariate based simply on numerical evaluation of residual error, as shown in table 3, is complicated by the high levels of residual noise in the NRS measurement, and the lack of a means of standardizing the NRS scale among subjects. Another approach to calibrating these results is to anchor the effects to clinical observation. For example, the increase in pain associated with oxytocin only accounted for 6.73% of the potentially explainable variance, but it is clinically obvious that oxytocin substantially increases the pain of labor to the clinician who has followed the patient throughout labor. It might not be evident to a clinician who knew the pain score without knowing the patient's previous pain trajectory. Similarly, artificial rupture of membranes clearly increases the pain and intensity of labor after the procedure. Although it accounted for only 2.62% of the potentially explainable variance, it causes a clinical evident change in labor pain. The same is true for induction of labor.

ADRB2 genotype accounts for less than 0.5% of the potentially explainable intersubject variability, about half of the effect of labor induction. The clinical interpretation is that the effect will be less than labor induction. Thus, although *ADRB2* genotype *might* be clinically noticeable, the overall effect on labor pain will be small.

We confirmed our hypothesis that parturients who express at least one G allele at rs1042714 (β 2AR-27) progress to severe pain more rapidly with increasing cervical dilation. *ADRB2* genotype was not found to be a significant predictor of pain in

a cohort of 250 women who delivered at Columbia University in New York.¹⁸ However, the study by Reitman *et al.* did not have the ability to evaluate the full course of labor in most parturients because epidural analgesia was used frequently in that population after which point they were censored for analysis. It is likely that patients with more rapidly progressive labor pain would request neuraxial analgesia at an earlier point in labor. Although we have confirmed that the G allele is associated with more rapid development of labor pain, this explains just a modest portion of intersubject variability.

The β 2AR is the primary adrenergic receptor involved in relaxation of human uterine myometrium.¹⁹ Stimulation of the β 2AR by endogenous catecholamines, which circulate at high levels during labor,²⁰ results in relaxation of myometrial cells through a cyclic adenosine monophosphate-related mechanism.²¹ The two *ADRB2* SNPs that we studied result in changes to the extracellular domain of the protein: an Arg->Gly mutation at amino acid 16, and a Gln->Glu mutation at amino acid 27. We found that parturients homozygous for the C polymorphism at position 27 had slower development of maximum labor pain. Previous work by Reitman *et al.*¹⁸ found an association between this same genotype and a slower progress of the first stage of labor. Our finding of a correlation between parturients homozygous for this polymorphism and slower development of maximum labor pain could be related to the slower development of coordinated contractions that occur during the first stage of labor.

The β 2 adrenergic receptor has also been implicated in several pain syndromes that are unrelated to labor. Agonist autoantibodies against the β 2AR have been found in patients with Complex Regional Pain Syndrome.²² The β 2AR has been implicated in the mechanism of tricyclic antidepressant alleviation of neuropathic pain.^{23–25} One study found a correlation between two variants of the β 2AR and chronic widespread body pain.⁶ Also, manipulation of the β 2AR has also been shown to affect inflammation.^{26,27} Inflammation is well known to be important in cervical ripening in preparation for labor^{28,29} and has been associated with arrest of descent,³⁰ and presumably a difficult and more painful labor course. Thus, inherited differences in the β 2AR could contribute to differences in pain from contraction, intrinsic sensitivity to pain, and inflammatory processes, resulting in a more painful course of labor for parturients with polymorphic receptors.

In this study, maternal age was inversely associated with the rate of development of maximum labor pain. In one study, older age was associated with less use of epidural or spinal analgesia, probably reflecting lower request for such treatment.³¹ Labor pain is also influenced by psychological and social factors. For example, younger women tend to catastrophize the experience of labor pain more than older women, leading to greater difficulty in emotional adjustment after childbirth.³² This difficulty with psychological adjustment could lead to higher perceived and thus reported pain during labor.

Induction of labor with intravaginal prostaglandins is a relatively common intervention for women who would benefit from an expedited onset of labor for a variety of indications. Vaginal prostaglandins are administered to hasten the inflammatory processes that ripen the highly innervated cervix,³³ which in combination with estrogens, may cause peripheral sensitization.^{34,35} Prostaglandins also promote uterine contractions.^{33,36} Greater labor pain in patients induced with prostaglandin could result from peripheral sensitization or stronger contractions against an unripened cervix. This correlation bolsters the findings of Paech,³⁷ who found an association between induction and a greater-than-expected level of pain. However, several sources in the literature, including several of our own studies from cohorts of patients who delivered in the United States found no such association.^{2,17,18,38} Another recent study found no difference in overall pain intensity between women who were induced and women who were not induced but did note an increased use of neuraxial analgesia in the induction group.³⁹

Many of the aforementioned studies did not examine labor pain throughout the first stage of labor. This is an important distinction because our models show that once women reach a certain cervical dilation, most women report pain near maximal pain. Thus, without the intervention of neuraxial analgesia, one could expect that there are relatively small and probably clinically indistinguishable differences in pain as women approach the second stage of labor, regardless of demographics or genetic characteristics or previous clinical intervention. The majority of the population variability is in the pain response to early labor and during transition to active labor. Therefore, it is valuable to observe the early stages of labor for substantial differences in labor pain.

Oxytocin augmentation is associated with a longer time to full dilation in nullipara,⁴⁰ which may be indicative of a more difficult labor. Yet there is some indication that oxytocin itself may enhance the pain associated with labor progress. In support of this supposition, in two randomized, controlled trials, Hemminki *et al.*⁴¹ reported more painful contractions earlier in labor with the use of oxytocin. Read *et al.*⁴² found that women administered oxytocin were more likely to have increased pain during labor. In a previous study, we found more pain in early labor in women who were treated with oxytocin.¹⁷

Our study has important limitations. An intrinsic limitation to the model is that it can only consider women who labor to full cervical dilation and thus is only relevant in this population. The low incidence of neuraxial analgesia in the study population could be considered a limitation in that it unmasks the more subtle pain effects related to the active management of labor, which perhaps would not be clinically important in centers where epidural analgesia is the primary pain control method.

These data shed new light on identified genetic differences and confirm previously documented effects of demographic and clinical differences because they relate to pain

experienced during labor. They also highlight how much we do not understand. Even with the genetics and sophisticated modeling, we were only able to account for 11% of the potentially explainable intersubject variance. The tested polymorphisms accounted for less than 1% of the potentially explainable intersubject variance after adjustment for treatment differences including active management of labor.

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Competing Interests

The authors declare no competing interests.

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