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*CYP2C9*2* is associated with indomethacin treatment failure for patent ductus arteriosus

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Aims: To identify clinical andgenetic factors associated with indomethacin treatment failure in preterm neonates with patent ductus arteriosus (PDA). **Patients & Methods:** This is a multicenter cohort study of 144 preterm infants (22–32 weeks gestational age) at three centers who received at least one treatment course of indomethacin for PDA. Indomethacin failure was defined as requiring subsequent surgical intervention. **Results:** In multivariate analysis, gestational age (AOR 0.76, 95% CI 0.60–0.96), surfactant use (AOR 9.77, 95% CI 1.15–83.26), and *CYP2C9*2* (AOR 3.74; 95% CI 1.34–10.44) were each associated with indomethacin failure. **Conclusion:** Age, surfactant use, and *CYP2C9*2* influence indomethacin treatment outcome in preterm infants with PDA. This combination of clinical and genetic factors may facilitate targeted indomethacin use for PDA.

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Patent ductus arteriosus (PDA) is a common complication affecting preterm infants in the neonatal intensive care unit [1]. The persistent left-to-right shunt from the PDA is associated with increased risk for pulmonary hemorrhage, congestive heart failure, intracranial hemorrhage, compromised peripheral circulation and development of chronic lung disease [2–4]. The prostaglandin synthase inhibitor indomethacin is routinely used to treat PDA, but clinical response and toxicity from it are highly variable [5,6]. Approximately one in four infants treated with indomethacin for PDA will receive subsequent surgical ligation for definitive ductus closure [6–9]. Potential adverse effects of indomethacin include renal dysfunction, necrotizing enterocolitis, gastrointestinal bleeding and intestinal perforation [10,11].

Identification of clinical and genetic predictors of indomethacin response would allow selective use of indomethacin in infants with the greatest likelihood of therapeutic response, and alternative treatments in those at high risk of indomethacin failure. There are multiple studies examining the clinical factors influencing indomethacin response with mixed and contradictory results [5,12–14]. One genetic study of a small cohort of preterm infants provided evidence for the influence of genes including *TFAP2B* and *EPAS1* in ductus response to indomethacin [11] but has not been replicated. Variants in *CYP2C9* are also hypothesized to potentially influence indomethacin response as the *CYP2C9* gene is important in indomethacin metabolism [12,13]. A recent study identified two *CYP2C9* variants affecting indomethacin response using transmission disequilibrium analysis of parent–child trios [14].

In order to identify risk factors for indomethacin failure, we investigated clinical factors and four candidate genetic variants in a multicenter cohort of preterm infants who received indomethacin to treat PDA. Our main

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objective was to identify factors associated with indomethacin failure, defined as indomethacin treatment followed by surgical ligation of a persistent PDA.

Methods

Study population

This study included individuals from a prospectively collected cohort and from BioVU, the Vanderbilt University Medical Center (VUMC) de-identified biorepository [15]. Individuals in the prospectively collected cohort were recruited as part of a larger study examining genetic factors contributing to preterm PDA ("Genes contributing to patent ductus arteriosus susceptibility in preterm newborns" HL109199). This study includes patients from the neonatal intensive care units at VUMC, University of California, San Francisco (UCSF), and University of Iowa Stead Family Children's Hospital. Each center received Institutional Review Board approval from their home institution. Potential participants were identified at neonatal intensive care unit admission, and parents/guardians were approached for consent. Infants were included if they had an estimated gestational age (EGA) of 22–32 weeks and received at least one treatment course of indomethacin for PDA. Exclusion criteria were: multiple congenital anomalies, significant congenital heart disease, expected mortality prior to initial diagnostic echocardiogram, parents that were unable to provide informed consent or failure of the genotyping assay for the candidate variants. In addition to the prospective cohort, subjects were identified using BioVU, a biorepository that links DNA from discarded blood samples to de-identified electronic health records (EHR) data [15]. EHR and administrative data were used to identify individuals meeting the following inclusion criteria: ICD code for PDA (ICD9-747.0, ICD10-Q25.0) or documentation of PDA in EHR; indomethacin exposure documented in the EHR or extracted by natural language processing by MedEx [16]; DNA available in BioVU. Individuals were excluded from the BioVU cohort if they had complex congenital heart disease, received prostaglandins, were transferred to another healthcare facility <7 days after indomethacin treatment, did not have sufficient information to determine outcome, failed genotyping for the candidate variants or were included in the prospective cohort.

Definitions

Inclusion in this study required documentation of persistent flow through a clinically significant PDA [17–19]. For both the prospective and BioVU cohorts, PDAs were diagnosed by echocardiography and Doppler exams between postnatal days 5 and 7: infants <28 weeks were examined between days 5 and 7 of life, regardless of symptoms; infants ≥28 weeks' gestation were examined between days 5 and 7 if a murmur suggestive of a PDA was present. The decision to treat the PDA was made by the infants' clinical care teams. Every individual in the study received at least one treatment course of indomethacin for PDA, defined as an initial 0.2 mg/kg dose of intravenous indomethacin, followed by two doses between 0.1 and 0.25 mg/kg, depending on patient's age, at 12–24 h intervals. Subjects who received only prophylactic doses of indomethacin were not included. The decision to proceed with surgical ligation after indomethacin was also made by the clinical care teams and not dictated by the study.

The primary outcome was indomethacin treatment failure that resulted in surgical ligation. Indomethacin failure was defined as surgical intervention for PDA after the indomethacin treatment course(s) and before hospital discharge, whereas indomethacin responders were those treated with a treatment-dose course(s) of indomethacin for PDA and who had no surgical ligation during their hospital stay. The use of surgical ligation as a definition for indomethacin treatment failure aligns with previous literature [20,21].

Previously reported risk factors were analyzed for association with indomethacin failure resulting in surgical ligation, including sex, race, EGA, postnatal age at indomethacin treatment, diagnosis of respiratory distress syndrome, surfactant exposure, APGAR score at 5 min, diagnosis of small for gestational age, maternal diagnosis of pre-eclampsia, maternal diagnosis of chorioamnionitis and mode of delivery (vaginal vs cesarean section).

Genotyping

For the prospective cohort, buccal samples were obtained from the infants for DNA extraction and genotyping. For the BioVU cohort, remnant blood samples collected and retained in the biorepository were utilized for the analysis. All DNA samples were genotyped at Vanderbilt Technologies for Advanced Genomics (VANTAGE). Genotyping was completed using the multi-ethnic genotyping array, a high density custom exome chip array (Illumina, CA, USA). The four variants chosen for investigation were pre-selected based on known influence on NSAID metabolism and/or prior evidence in the literature as potentially influencing PDA response (*CYP2C9*2* – rs1799853, *CYP2C9*3* – rs1057910 [22], *TFAP2B* – rs987237 [20], *EPAS1* – rs1867785 [20]).

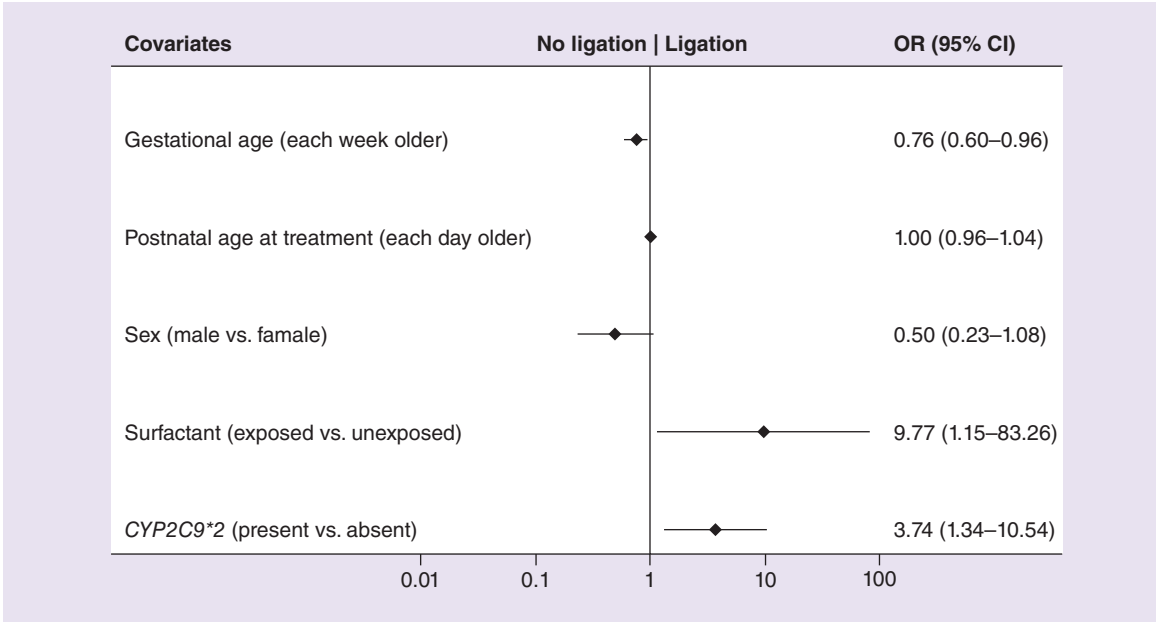

Figure 1. The figure shows a Forest plot with multivariate adjusted odds ratio and 95% CI for indomethacin failure resulting in ligation (OR > 1) for estimated gestational age, postnatal age at treatment, sex, surfactant use and the *CYP2C9*2* variant.

Statistical analysis

Summary data are presented as number (percentages) or median (interquartile range [IQR]), as appropriate. We analyzed demographic and clinical variables as well as the four preselected genetic variants using all infants in the combined cohorts meeting our inclusion criteria with successful genotyping. Differences between outcome groups were determined using the Pearson χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables. Sex and covariates with $p < 0.05$ were further analyzed using logistic regression to determine significance after accounting for other variables. Statistical analyses were performed using STATA 15.1.

Results

Data were available for 527 infants enrolled in the prospective cohort during their neonatal intensive care unit stays between 2011 and 2016. UCSF contributed 100 subjects (18.9%), VUMC contributed 189 subjects (35.9%) and University of Iowa Stead Family Children's Hospital contributed 238 subjects (45.2%). Of these, there were 131 infants treated with indomethacin for PDA with successful genotyping and thus eligible for our analysis (29 from UCSF, 40 from VUMC and 62 from Iowa). In addition, 13 infants were identified for inclusion from BioVU. 12 infants from Iowa included in our analysis were part of a previous report investigating parent–child trios [21]. Of the 144 total infants included in the analysis, 52% were males, and there was an indomethacin failure resulting in surgical ligation rate of 35%. Demographic and clinical characteristics analyzed for association with indomethacin failure are shown in Table 1. In univariate analysis of clinical factors, EGA, postnatal age at treatment and surfactant exposure were associated with indomethacin failure with subsequent ligation. Among the study population, there were no differences in indomethacin efficacy based on sex, race, respiratory distress, pre-eclampsia, chorioamnionitis, 5-min APGAR score, small for gestational age status or mode of delivery.

Results of the univariate analyses of the association of candidate genetic variants to indomethacin failure are shown in Table 2. The *CYP2C9*2* variant (T allele of rs1799853) was associated with increased risk of indomethacin failure resulting in ligation. The *CYP2C9*3* variant (rs1057910(C)), *TFAB2B* variant (rs987237) and *EPAS1* variant (rs1867785) were not associated with indomethacin failure. The *CYP2C9*2* variant, significant clinical covariates from the univariate analysis, and sex were included as covariates in the multivariate analysis (Table 3 & Figure 1). Despite sex lacking significance in the univariate analysis, it was included in the multivariate analysis due to its presence as a predictor in previous studies [12]. Estimated gestational age (AOR: 0.76 per week older, 95% CI: 0.60–0.96), surfactant exposure (AOR: 9.77, 95% CI: 1.15–83.26) and the *CYP2C9*2* variant (AOR: 3.74, 95%

Table 1. Association of demographic and clinical factors with ligation after indomethacin.

Characteristic	N nonmissing	No ligation (n = 93)	Ligation (n = 51)	p-value
Sex:	144			0.1
– Males		44/93 (47%)	31/51 (61%)	
– Females		49/93 (53%)	20/51 (39%)	
Race:	129			0.3
– Whites		68/81 (84%)	37/48 (77%)	
– Non-whites		13/81 (16%)	11/48 (23%)	
Weeks gestational age (median, IQR)	144	26.3 (25.3–27.6)	25.4 (24.7–26.9)	0.01*
Postnatal age at treatment (days, median, IQR)	140	8 (7–13)	7 (5–12)	0.02*
Respiratory distress syndrome:	123			0.5
– Yes		77/81 (95%)	41/42 (98%)	
– No		4/81 (5%)	1/42 (2%)	
Surfactant:	143			0.02*
– Yes		79/93 (85%)	49/50 (98%)	
– No		14/93 (15%)	1/50 (2%)	
Pre-eclampsia:	133			0.9
– Yes		11/89 (12%)	5/44 (11%)	
– No		78/89 (88%)	39/44 (89%)	
Chorioamnionitis:	133			0.09
– Yes		18/88 (20%)	4/45 (9%)	
– No		70/88 (80%)	41/45 (91%)	
APGAR score at 5 min:	139			0.4
– 1–6		39/91 (43%)	24/48 (50%)	
– 7–9		52/91 (57%)	24/48 (50%)	
Small for gestational age:	144			0.07
– Yes		7/93 (8%)	9/51 (18%)	
– No		86/93 (92%)	42/51 (82%)	
Mode of delivery:	141			1
– C-section		65/90 (72%)	36/51 (71%)	
– Vaginal delivery		25/90 (28%)	15/51 (29%)	

*Statistical significance < 0.05.

CI: 1.34–10.44) were all associated with indomethacin failure resulting in ligation. Postnatal age at treatment was not associated with indomethacin failure in multivariate analysis.

Discussion

The major findings of this study are that younger gestational age, use of surfactant and the common polymorphism *CYP2C9*2* are each associated with indomethacin failure requiring subsequent surgical ligation in preterm infants with PDA. Indomethacin failure was common (35%), consistent with previous studies [6–8,10,12]. While numerous studies have reported an association between younger gestational age, need for surfactant and poor indomethacin response [12,14,23–25], our finding of an association between the *CYP2C9*2* allele and poor indomethacin response has only recently been observed [21,26].

The *CYP2C9*2* allele was present in 16.7% of our cohort, which aligns with current literature [26]. Indomethacin therapy failed to successfully close the PDA and surgical ligation was required in the majority (54.2%) of these individuals. *CYP2C9* variants were originally chosen for this analysis due to their known effects on the metabolism and, ultimately, plasma concentration of drugs this enzyme metabolizes [27,28]. One previous study examining how *CYP2C8* and *CYP2C9* variants affect PDA responsiveness to ibuprofen found that wild-type genotypes were more likely to respond successfully in univariate but not in multivariate analysis [26]. The finding that wild-type CYP2C9 genotypes are more likely to respond to ibuprofen is consistent with our finding that CYP2C9*2 was associated with indomethacin failure. A more recent study showed a significant effect of *CYP2C9*2* in transmission disequilibrium

Table 2. Association of candidate genetic variants with ligation after indomethacin.

Characteristic	No ligation (n = 93)	Ligation (n = 51)	p-value
CYP2C9*2 **(rs1799853(T))**			0.03*
0 allele	81 (88%)	37 (73%)	
1 allele	11 (12%)	13 (25%)	
2 alleles	0	0	
Unknown	1 (1%)	1 (2%)	
CYP2C9*3 **(rs1057910(C))**			0.6
0 allele	84 (91%)	46 (90%)	
1 allele	8 (9%)	3 (6%)	
2 alleles	0	0	
Unknown	1 (1%)	2 (4%)	
TFAP2B **(rs987237(G))**			0.1
0 allele	50 (54%)	36 (71%)	
1 allele	36 (38%)	13 (25%)	
2 alleles	6 (6%)	1 (2%)	
Unknown	1 (1%)	1 (2%)	
EPAS1 **(rs1867785(G))**			1
0 allele	33 (35%)	18 (35%)	
1 allele	40 (44%)	22 (43%)	
2 alleles	18 (19%)	10 (20%)	
Unknown	2 (2%)	1 (2%)	

*Statistical significance < 0.05.

Table 3. Multivariate analysis of genetic and clinical associations with ligation after indomethacin.

Characteristic	Odds ratio (95% CI)	p-value
Gestational age (each additional week)	0.76 (0.60–0.96)	0.02*
Postnatal age at treatment (days, median, IQR)	1.0 (0.96–1.04)	0.91
Sex (males vs females)	0.50 (0.23–1.08)	0.08
Surfactant use (yes vs no)	9.77 (1.15–83.26)	0.04*
*CYPC2C9*2* (rs1799853)	3.74 (1.34–10.44)	0.01*

*Statistical significance < 0.05.

analysis of parent–child trios in infants who responded to indomethacin [21]. The direction of effect in that study suggested that *CYP2C9*2* was associated with successful response to indomethacin, in contrast to our study. This may be due to differences in the study design (case–control analysis vs family-based transmission disequilibrium test).

Drug response in preterm neonates is multifactorial and depends on environmental, ontogenic and genetic factors which contribute to variability in absolute drug exposure and drug response. Indomethacin is metabolized via multiple competing pathways (cytochrome P450 and UDP-glucuronosyltransferase), and the relative contribution of these pathways will determine the amount of active drug available for drug action [29]. The postnatal age at which these infants were treated (22–32 weeks) is likely to be associated with reduced *CYP2C9* expression, and thus genetically 'poor metabolizers' may not be clinically distinguishable from normal metabolizers. The conflicting results of the direction of rs1799853 effect between our cohort and the Smith *et al.* cohort may relate to differences in enzyme expression at the time of treatment, the currently unknown relative contribution of other metabolic pathways for each preterm infant, and possibly genetic variation in the drug target for these infants. Furthermore, the significant effects were derived from different methodologies – case–control analysis in the present study versus transmission disequilibrium testing in parent–child trios in the previous study. Although our cohort overlapped slightly with that of Smith *et al.*, the number of infants common to both studies was small (<9% of each cohort). The absolute effect of a single SNP which likely decreases CYP2C9 enzyme kinetics cannot be fully understood without knowledge of other important variables. It is important for future prospective research to account for

developmental pharmacology (developmental enzyme expression of multiple pathways) and quantification of drug exposures in order to fully interpret genetic associations.

Although polymorphisms in *TFAP2B* have previously been shown to be associated with failure of spontaneous ductus closure after birth and the presence of a PDA [20], our study suggests that these *TFAP2B* polymorphisms are not associated with PDA treatment failure. We also did not find a significant association with indomethacin failure and *CYP2C9*3*-rs1057910(C) or *EPAS1*-rs1867785. Though *CYP2C9*3* is thought to act similarly to *CYP2C9*2* and increase drug plasma concentrations due to reduced indomethacin metabolism, this allele was present in <10% of our cohort, making it harder to assess its effect with certainty. The variants of *TFAP2B* and *EPAS1* studied were previously suggested to have a borderline association with PDA response to medical management [30]. That, however, was a subanalysis of a larger study looking at genetics of PDA predisposition, and the authors acknowledged that the number of infants requiring surgical ligation was small. It should be noted that if we dichotomized the TFAP2B (rs987237) polymorphism by combining those with one or more G alleles, it is significantly associated with surgical ligation in univariate ($p = 0.04$), but not multivariate analysis ($p = 0.24$). Further study of these variants and their role in PDA and indomethacin response may be warranted.

Our study has several limitations. Inclusion in our cohort required echocardiographic documentation of a PDA and subsequent indomethacin treatment, but the degree of PDA patency (small, moderate, large) was not always documented. Practice pattern variations among centers may influence the data on indomethacin response. One center had a 45% indomethacin failure rate, compared with 21 and 25% failure rate at the other sites, indicating the potential for site-to-site differences in indications for ligation or recruitment to the parent study. This does, however, increase generalizability as current management of PDA is highly variable with surgical ligation rates ranging from 0 to 54% across children's hospitals in the Pediatric Hospital Information System database [9]. Surgical PDA ligation serves as a suitable proxy for indomethacin failure, but absence of surgical ligation does not necessarily indicate indomethacin response. We chose this as the primary outcome as it is a consistently documented and unambiguous phenotype and has been used as a surrogate for indomethacin failure in many previous studies [20,21,31,32]. However, it is important to note that indomethacin treatment resulting in surgical ligation is not necessarily due to failure of the ductus to constrict but may also be due to an infant's inability to tolerate the need for ongoing ventilatory, nutritional or inotropic support in the presence of a persistent moderate-to-large shunt. In such cases, a clinician may resort to surgical closure in order to alleviate worsening respiratory or circulatory symptoms caused by concurrent treatments used to offset the hemodynamic consequences of the shunt. Therefore, the outcome of ligation may be dependent on the magnitude of the shunt, but it also may be due to other factors that make one infant more susceptible to the hemodynamic consequences of the shunt [3]. In addition to the variability in surgical ligation, it is important to note that surfactant administration, one of the variables determined to be significant in determining indomethacin response, likely varies across centers. However, it is not something we would expect to be associated with genotype, so it is unlikely to confound our results. It is possible that a true association with respiratory distress syndrome is not observed due to missing data in our cohort. Although we examined multiple clinical factors, additional variables that were not accounted for may contribute to indomethacin response, including variability in serum indomethacin concentrations which are not available in this cohort and are not routinely performed in most NICUs. In order to validate the genetic association, our work suggests, replication in an independent cohort is required.

In conclusion, younger gestational age, use of surfactant and the *CYP2C9*2* polymorphism are each independently associated with indomethacin failure and the need for subsequent surgical ligation in preterm infants with PDA. Clinical and genetic predictors of indomethacin response can be useful to tailor treatment of PDA in preterm infants. Future advances in personalized medicine permitting *CYP2C9* variant detection at the bedside would allow for further study of this variant and its effect on indomethacin exposure and response.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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