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Cytochrome P450 (*CYP2D6*) Genotype is Associated with Elevated Systolic Blood Pressure in Preterm Infants Following NICU Discharge

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Abstract

Objective—To determine genetic and clinical risk factors associated with elevated systolic blood pressure (ESBP) in preterm infants following discharge.

Study design—A convenience cohort of infants <32 weeks gestational age was followed after discharge; we retrospectively identified a subgroup of subjects with ESBP (SBP > 90th percentile for term infants). Genetic testing identified alleles associated with ESBP. Multivariable logistic regression analysis was performed for the outcome ESBP with clinical characteristics and genotype as independent variables.

Results—Predictors of ESBP were: *CYP2D6* (rs28360521) CC genotype (OR 2.92; 95% CI 1.48, 5.79), adjusted for outpatient oxygen therapy (OR 4.53, 95%CI 2.23, 8.81) and history of urinary tract infection (OR 4.68, 95% CI 1.47, 14.86). Maximum SBP was modeled by multivariable linear regression analysis: Maximum SBP = 84.8 mmHg + 6.8 mmHg (if *CYP2D6* CC genotype) + 6.8 mmHg (if discharged on supplemental oxygen) + 4.4 mmHg (if received inpatient glucocorticoids) (p=0.0002).

Conclusion—ESBP is common among preterm infants with residual lung disease following NICU discharge. This study reveals clinical factors associated with ESBP, identifies a candidate gene for further testing, and supports the recommendation that BP be monitored sooner than at age 3 years as suggested for term infants.

Keywords

Genetics; Hypertension; Oxygen; Polymorphism; SNP

Both term infants who are small-for-gestational age and preterm infants who have low birth weight by virtue of their prematurity are at an increased risk for hypertension as adults [1-4]. Proposed mechanisms to explain this phenomenon include increased sympathoadrenal

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activity [5], increased arterial stiffness [6], and altered kidney development [7]. Prematurity and low birth weight are among the few conditions in which blood pressure (BP) monitoring is recommended in children less than three years of age [8]. Because of the difficulty in accurately measuring BP in very young children and in defining a normal population of preterm infants little data exist with respect to normal BP values in former preterm infants during the first year of life. One multicenter study has reported the results of monitoring BP in 135 preterm infants during the first year of life [9]. Mean BP was found to rise as postnatal age increased, with a plateau at a post-conceptual age of 40-44 weeks of approximately 92 mmHg. In centers that utilized both Doppler ultrasound and an oscillometric technique (currently the most commonly used method) for comparison, oscillometry tended to overestimate systolic BP when measurements were in a low range. There is currently no universally recognized definition of hypertension in preterm infants at various post- conceptional ages.

Several studies reported an increased risk of elevated BP in preterm infants with bronchopulmonary dysplasia (BPD). The initial report by Abman et al described elevated BP in 13 of 30 infants with BPD and found that the diagnosis often occurred after discharge from the neonatal intensive care unit (NICU) [10]. Anderson et al reported elevated BP in 11 of 87 infants with BPD on home oxygen therapy [11]. Finally, Alagappan and Mallory reported BP elevation in 5 of 41 infants with BPD, with a mean onset 105 days after birth [12]. All of these studies demonstrated an association between BPD and later onset BP elevation, yet the mechanisms linking these conditions are unknown.

We sought to identify genetic and clinical risk factors for ESBP in a cohort of high risk preterm infants born who were monitored in the Neonatology Follow Up Clinic at the University of Iowa Children's Hospital (UICH).

METHODS

The study cohort was assembled from an existing cohort of infants admitted to the NICU at the UICH since 2000. Parents consented on behalf of themselves and their children to the collection of blood and/or buccal swabs for biobanking. This institutional review board-approved program was established to provide biological material for subsequent use in investigations of genetic contributions to diseases of infants (12, 13). We studied a non-random convenience cohort of 305 preterm infants with the following characteristics: 1) born at <32 weeks gestation; 2) seen in the Neonatology Follow Up Clinic at UICH; and 3) had DNA samples available from our Neonatal DNA repository. Approximately 90% of our study population was Caucasian, by parental report. Clinical data were abstracted retrospectively from the infants' medical records.

Phenotyping

Because there are no universally accepted criteria for defining normal BP values in former preterm infants in the first year of life, we defined ESBP as a SBP >90th percentile using term infants values [13]. We calculated the corrected age at which each BP measurement was obtained in a preterm subject for comparison with term infant BP values at various chronologic ages using the equation: Corrected age (in weeks) = chronologic age (in weeks) - (40 - gestational age at birth (in weeks)). Systolic, diastolic and mean BP were measured in the 305 study infants at all follow up clinic visits using a calibrated oscillometric device, Dinamap GE Pro 300 V2 (Dinamap GE Medical Systems Information Technologies, Inc., Milwaukee, WI) following a standard clinic protocol by one of three advanced registered nurse practitioners. BP measurements that were abstracted for this study were obtained in a calm infant, either held in a parent's lap or in a car seat, in the right upper extremity using an appropriately sized cuff. Nearly 82% of the study cohort infants were evaluated on more

than one occasion, as indicated by their clinical condition during infancy. Maximum systolic blood pressure was defined as the highest BP obtained in a calm infant at any follow up clinic visit. Blood pressure measurements were generally obtained between 9 AM and 4 PM and there was no segregation of sicker infants to any specific times of the day.

Gestational age (GA) was determined by the clinical team who initially admitted the infant to the NICU, and was generally based on last menstrual period (LMP), prenatal ultrasound and/or physical exam, in decreasing order of priority.

DNA Processing and Genotyping

DNA was extracted from infant cord blood and from venous blood, buccal swabs or saliva from parents. Allelic variation was determined using the TaqMan genotyping system (Applied Biosystems, Foster City, CA, USA), as previously described [14]. Allele scoring was done using the Sequence Detection Systems software (version 2.2, Applied Biosystems, Foster City, CA, USA). The genotype data were uploaded into a Progeny database (Progeny Software, LLC, South Bend, IN, USA) that also contained phenotype data for the infant cohort.

Analytic Strategy

The first phase of this study was a candidate gene survey using SNP genotype information from a larger on-going study of genetic risk factors for prematurity. The genes included in the initial analysis generally related to one of four biological pathways: xenobiotic metabolism, smooth muscle contraction, inflammation, and folic acid metabolism. Non-random allele inheritance was assessed by transmission disequilibrium test (TDT) as implemented in the Family-Based Association Test software [15-17]. We identified for further study all SNPs associated with ESBP in the first year of life with p-values ≤ 0.001 , recognizing the possibility of identifying false positive signals with this liberal p value. Each SNP identified in this manner was next included as the independent variable in a multivariable logistic regression analysis for the outcome of ESBP, adjusting for clinical covariates that were identified by univariate and multivariable logistic regression analyses to be associated with ESBP.

Statistical Analyses

Means and standard deviations of normally distributed continuous variables were compared using analysis of variance. Distribution frequencies were compared by Chi square or Fisher exact tests. Multivariable logistic regression analysis was performed to determine significant predictors of the event in preterm infants of observing a maximum systolic BP $> 90\%$ percentile for term infants. Both stepwise selection and backward elimination algorithms were employed. Multiple linear regression analysis was used to model significant genetic and clinical predictors of maximum systolic BP. In the models all variables were expressed as categorical, except for the continuous variables maximum SBP and gestational age.

RESULTS

The maximum SBP value for each of the 305 preterm infants included in the study cohort, at the corrected age when measured, is shown in the Figure. Using the defined phenotype of ESBP, we identified 221 of the 305 (72%) preterm infants as having one or more ESBP measurement(s). Table I lists characteristics of the study infants by maximum SBP group. There was no difference between the groups with respect to birth weight; however, the infants with ESBP were born at a slightly earlier gestational age (27.3 vs. 28.1 wk, $p=0.007$). The infants in each group were similar with respect to sex, weight-for-gestational age, maternal steroid administration, and rates of serious intraventricular hemorrhage ($> \text{grade I}$),

patent ductus arteriosus and use of umbilical catheters. There were 9 infants in the ESBP group who had been diagnosed during NICU hospitalization as having an elevated BP and one of these was discharged on antihypertensive medication. Most of these 9 infants were diagnosed with late-onset, borderline elevated BP and were discharged with a plan for outpatient monitoring. There were two infants who did not have ESBP as outpatients who had been diagnosed as inpatients to have elevated BP; both of whom were discharged on antihypertensive medication. Significantly more infants in the ESBP group had previous treatment for a urinary tract infection (UTI) in the NICU (46/221) than among the infants who did not have ESBP (8/82) ($p=0.028$). The relatively high rate of infants discharged home on supplemental oxygen reflects the high survival of extremely preterm infants in our center, our adherence to recommended clinical guidelines regarding the use of home oxygen (oxygen saturations $\geq 95\%$) in NICU graduates with lung disease [18], and selective outpatient follow up of such infants at our institution.

We initially screened the infants in the ESBP group for nonrandom allele transmission from their parents for 583 possible candidate gene loci using the Family Based Association Test [19,20]. Two SNPs with a p -value of ≤ 0.001 were considered for further testing in subsequent multivariable logistic regression analyses: rs28360521 in *CYP2D6* ($p=0.0009$) and rs1675414 in *TFAP2B* ($p=0.001$).

Multivariable logistic regression analyses were conducted to test the association of *CYP2D6* and *TFAP2B* genotypes with the ESBP outcome, adjusted for significant clinical predictors. An initial analysis was performed to determine independent clinical predictors of ESBP and included these variables: discharge from the hospital on supplemental oxygen therapy, previous history of a urinary tract infection, left-sided cardiac lesion, umbilical venous catheter, PDA, sex, neonatal glucocorticoid therapy, intraventricular hemorrhage $>$ grade I, and gestational age. Supplemental oxygen therapy and a history of a UTI during prior hospitalization were found to be the only significant clinical variables (Table II, Model 1). We next examined separately each of the two genetic variables for association with the outcome of ESBP, adjusted for the clinical predictors. Similar results were obtained using stepwise selection and backward elimination approaches. When the genotypes for either *CYP2D6* (rs28360521) or *TFAP2B* (rs1675414) were included separately in the analysis, only the *CYP2D6* CC genotype was a significant independent predictor of ESBP, adjusted for the previously identified clinical covariates (Table II, Model 2). These clinical and genetic covariates remained significantly associated independent predictors of ESBP in a sensitivity analysis that excluded 20 patients who were diagnosed with elevated BP prior to discharge and/or treated with outpatient bronchodilators, glucocorticoids or antihypertensive medications (Table II, Model 3). Interaction variables were not significant in these models, suggesting independent effects of *CYP2D6* CC genotype, UTI and discharge on supplemental oxygen on ESBP.

Of the 232 study infants for whom *CYP2D6* (rs28360521) genotyping data was available, the distribution of genotypes for those infants with ESBP was: CC 74.0%, CT 22.5%, and TT 3.5%, which was significantly different than the distribution seen in control infants: CC 52.4%, CT 36.5%, and TT 11.1% ($p=0.003$). The allele distribution was also significantly different between the two groups: infants with ESBP: C 85% and T 15% and control infants: C 71% and T 29% ($p=0.0003$). The C allele frequencies we observed for rs28360521 in our two study groups flanked the reference values (76-78%) reported for Caucasian controls in the National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=28360521).

We next used multivariable linear regression analyses (considering systolic BP as a continuous variable) to model the contribution of the *CYP2D6* genotypes to maximum

systolic BP. The *CYP2D6* CC genotype, referenced to the *CYP2D6* TT genotype, was associated with an increase of 6.8 mmHg, adjusted for the clinical covariates, discharged on supplemental oxygen therapy and a history of neonatal glucocorticoid administration. The significant covariate relative risk coefficients in the equation that describes this relationship are: maximum systolic BP = 84.8 mmHg + 6.8 mmHg (if *CYP2D6* CC genotype) + 6.8 mmHg (if infant was discharged on supplemental oxygen) + 4.4 mmHg (if infant received inpatient glucocorticoid therapy) ($p=0.0001$, $R^2=0.158$). The additional covariates *CYP2D6* CT genotype, gestational age, UTI, intraventricular hemorrhage, left-sided obstructive cardiac lesions (e.g., aortic valve stenosis or aortic coarctation) and patent ductus arteriosus were not significant, but are included in the full model. Finally, additional linear regression analyses demonstrated that the *CYP2D6* CC genotype adjusted for the same clinical covariates was also significantly associated with mean systolic blood pressure in infants who had more than one BP measurement (*i.e.*, multiple clinic visits) ($p=0.003$).

DISCUSSION

Using a convenience cohort of high risk preterm infants, we demonstrated an association between ESBP following NICU discharge and the CC genotype at rs28360521 in *CYP2D6*. This association was observed using two analytic strategies, allele transmission and regression modeling. The rs28360521 polymorphism is found ~ 2Kb upstream of the *CYP2D6* gene; however the entire gene (as well as 2 other more distant genes: *NDUFA6* and *NAGA*) is in linkage disequilibrium (LD) with this SNP (<http://hapmap.ncbi.nlm.nih.gov/>). Thus, any sequence variation within the ~182 Kb region is statistically linked to variations in rs28360521 and may be considered as potentially etiologic. *CYP2D6* encodes a cytochrome P450 oxidase that has been estimated to metabolize 25% of all medications processed in the human liver (reviewed in [21]). Studies of *CYP2D6* genetics have revealed both qualitative (SNP) and quantitative (insertion/deletion or copy number) polymorphisms that result in a wide range of enzyme activity in any given individual, ranging from poor to ultrarapid metabolizer phenotypes [22]. Most reports linking *CYP2D6* polymorphisms and hypertension in adults have focused on the metabolism of exogenous beta-blockers; effects of *CYP2D6* polymorphisms on risk of hypertension and ischemic heart disease in adults have been suggested [23]. The difference in maximum SBP predicted by the equation above for preterm infants with the CC versus TT genotype of *CYP2D6* (rs28360521) is 6.8 mmHg, a clinically meaningful increment. Reductions in BP of this magnitude have been associated with significant reductions in cardiovascular morbidities in adults [24]. Thus, our study identifies *CYP2D6* as an appropriate candidate gene for further investigations of blood pressure elevation in preterm infants.

In our highly selected cohort, we found that infants discharged home on supplemental oxygen had a > 4- fold risk of ESBP compared with those discharged on ambient air, supporting previous reports linking BPD and elevated BP [10-12]. Although no clear mechanism has been reported to describe the observed relationship between BPD and elevated BP, alveolar and/or blood oxygen levels may have a direct effect on BP. Animal models have demonstrated systemic hypertension in response to either hypoxia [25,26] or hyperoxia [27]. Extremely preterm infants with BPD often experience a wide range of oxygen saturations over time as a result of their lung disease. Interestingly, one of the more distant genes present within the LD block with rs28360521 (*NDUFA6*) encodes a component of the mitochondrial complex I that is a target of oxidative damage [28]. Although quite speculative, this finding may somehow link the environmental (discharge home on supplemental oxygen) and genetic (rs28360521) risk factors identified in this study.

There are several possible explanations for the association seen in our linear regression analysis between the administration of glucocorticoids to preterm infants during the initial NICU admission and subsequent ESBP. The administration of glucocorticoids in the NICU is generally restricted to infants with the most severe BPD, as the use of this therapy has implications with respect to neurodevelopmental outcome [29,30]. Thus, glucocorticoid therapy might be a marker for BPD severity. Alternatively, the administration of glucocorticoids in the neonatal period might have a direct effect on BP later in life. Glucocorticoid administration to sheep, during critical periods of prenatal development, has been shown to be associated with elevated BP in later in life, forming a model of fetal programming [31].

Our study and three prior reports [10-12] demonstrate that the onset of elevated BP associated with residual lung disease in preterm infants is often not seen until after discharge from the NICU. Whether the ESBP would have occurred had the infants in our study remained in the NICU or is related to a change in their environment (NICU versus home) is unclear. A number of significant changes occur around the time of discharge from the NICU. Infants discharged on supplemental oxygen often experience an increase in oxygen concentration upon discharge, a consequence of the lack of home blenders to adjust the fraction of inspired oxygen. In addition, infants who may have had marginal weight gain during their hospitalization often experience increased nutritional intake (commonly referred to as “catch-up” growth) as their condition improves and they become ready for discharge. This situation of early nutritional deprivation, followed by rapid increases in caloric intake and weight, may also result in developmental programming with increased long term cardiovascular risk, including elevated BP (reviewed in [32]).

Strengths of this study include the large number of preterm infants included and the consideration of both clinical and genetic factors. We also employed two distinct analytic strategies to identify the *CYP2D6* gene. In addition, genotyping was performed independently of any knowledge of blood pressure or other phenotypes. The study is limited by the retrospective assembly of a nonrandom cohort, and also by the BP measurements, which were obtained in a clinical setting, rather than in a rigorous research setting, with fewer observations over time than that required for the definition of hypertension in older individuals. Abstracting clinical data for an observational study also results in sampling individuals at different rates, which may lead to an increased probability of observing the outcome in those sampled more frequently. An additional limitation of the study is the absence of long-term follow up of subjects to determine the duration and consequences of ESBP as an infant.

We speculate that developmental programming might play a role in the development of late-onset ESBP. The small, preterm infant with suboptimal nutrition in the perinatal period is at risk for developmental programming, especially with the prospect of improving nutrition over time. These infants may also be treated with glucocorticoids which might further enhance effects of programming. Finally, their lung disease often results in periods of both relative hypoxemia and hyperoxia. It is currently unknown how the *CYP2D6* genotype might play a role in altering BP following NICU discharge in these medically complex individuals. Our study supports the importance of routinely assessing BP in preterm infants following their discharge from the NICU, especially those treated with supplemental home oxygen and/or with a history of UTI. Importantly, it also identifies *CYP2D6* as a candidate gene for further study in prospective investigations of blood pressure in preterm infants following NICU discharge.

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Abbreviations

BPD	bronchopulmonary dysplasia
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6
ESBP	elevated systolic blood pressure
NICU	neonatal intensive care unit
SNP	single nucleotide polymorphism
UICH	University of Iowa Children's Hospital

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Figure 1.

Maximum systolic blood pressure of study infants. The maximum systolic blood pressure of each study infant is plotted at the corrected age. Black diamonds (◆) represent infants whose maximum systolic blood pressure is > the 90th percentile for corrected age, and the gray squares (■) represent those whose maximum systolic blood pressure is ≤ the 90th percentile.

Table 1

Characteristics of study population

Characteristic	Outpatient Elevated Systolic BP (n= 221)	Control (n= 84)	p-value
Birth weight, mean (SD)	1056 (388)	1078 (430)	0.66
Gestational age, mean (SD)	27.3 (2.2)	28.1 (2.4)	0.007
Fetal growth, SGA ^a , n (%)	34 (16.7)	14 (15.5)	0.97
Fetal growth, AGA ^b , n (%)	173 (78.6)	65 (77.4)	
Fetal growth, LGA ^c , n (%)	13 (5.9)	5 (6.0)	
Maternal antenatal steroids, n (%)	195 (88.2)	75 (89.3)	0.78
Male gender, n, (%)	132 (58.7)	42 (50)	0.13
Umbilical venous catheter, n (%)	165 (78.2)	55 (67.9)	0.07
Umbilical arterial catheter, n (%)	161 (75.9)	55 (67.9)	0.16
Percutaneous central catheter, n (%)	196 (89.1)	71 (84.5)	0.28
Intraventricular hemorrhage Gr 2-4, n (%)	20 (9.4)	11 (13.4)	0.10
Neonatal urinary tract infection	46 (20.8)	8 (9.5)	0.028
Patent ductus arteriosus (PDA), n (%)	90 (41.5)	28 (33.3)	0.19
PDA treated with indomethacin, n (%)	67 (30.3)	22 (26.2)	0.76
Left-sided cardiac lesion, n (%)	4 (1.8)	3 (3.6)	0.40
Inhaled nitric oxide therapy, n (%)	15 (7.7)	5 (6.2)	0.80
Neonatal steroid therapy, n (%)	72 (33.3)	16 (19.5)	0.02
Outpatient oxygen therapy, n (%)	168 (76)	45 (53.6)	0.001
Outpatient bronchodilator therapy, n (%)	33 (14.9)	10 (11.9)	0.50
Inpatient diagnosis of elevated BP, n (%)	9 (4.3)	2 (2.3)	0.47
Outpatient antihypertensive therapy, n (%)	1 (0.5)	2 (2.4)	0.26

^aSmall for gestational age (<10th percentile)

^bAppropriate for gestational age (10th to 90th percentile)

^cLarge for gestational age (>90th percentile)

Table 2

Significant odds ratio coefficients in multivariable logistic regression analyses for the event of elevated systolic BP in preterm infants after NICU discharge

Model Variables ^a	OR	95% CI	p value
Model 1: Only clinical predictors			
Supplemental home oxygen therapy	2.88	1.65, 5.03	0.0002
History of treated UTI as inpatient	2.71	1.14, 6.42	0.024
Model 2: Genetic and clinical predictors			
<i>CYP2D6</i> genotype (CC)	2.92	1.48, 5.79	0.0021
Supplemental home oxygen therapy	4.53	2.33, 8.81	<0.0001
History of treated UTI as inpatient	4.68	1.47, 14.86	0.0089
Model 3: Genetic and clinical predictors excluding 20 subjects treated with bronchodilators, steroids and/or antihypertensive medications when elevated systolic BP was observed			
<i>CYP2D6</i> genotype (CC)	3.17	1.64, 6.13	0.0006
Supplemental home oxygen therapy	4.23	2.21, 8.09	<0.0001
History of treated UTI as inpatient	3.64	1.27, 10.45	0.016

^a Other non-significant variables included in the model are left-sided cardiac lesion, umbilical venous catheter, PDA, sex, neonatal glucocorticoid therapy, intraventricular hemorrhage > grade I, and gestational age.