Risk factors for primary congenital glaucoma in the National Birth Defects Prevention Study

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Abstract

Primary congenital glaucoma (PCG) is a rare but serious birth defect. Genetic mutations have been implicated in the development of PCG, but little is known about nongenetic risk factors. This study investigates potential risk factors for PCG in the National Birth Defects Prevention Study (NBDPS), a large population-based case–control study of major birth defects in the United States. The analysis includes case infants with PCG (N = 107) and control infants without birth defects (N = 10,084) enrolled in NBDPS from birth years 2000–2011. Pregnancy/infant clinical characteristics, demographics, and parental health history were collected through maternal interview. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were computed to examine associations with all PCG cases and isolated PCG cases without other major malformations. Associations with all the cases included term low birth weight (<2,500 g; aOR = 2.80, CI 1.59–4.94), non-Hispanic black maternal race/ethnicity (aOR = 2.42, CI 1.42–4.13), maternal history of seizure (aOR = 2.73, CI 1.25–5.97), maternal antihypertensive use (aOR = 3.60, CI 1.52–8.53), and maternal sexually transmitted infection (aOR = 2.75, CI 1.17–6.44). These factors were also associated with isolated PCG, as was maternal use of nonsteroidal anti-inflammatory drugs (aOR = 2.70, CI 1.15–6.34). This study is among the first to examine a wide array of potential risk factors for PCG in a population-based sample.

KEYWORDS
population-based study, primary congenital glaucoma, risk factors

Primary congenital glaucoma (PCG) is a type of childhood glaucoma that affects approximately 0.5–1 in 10,000 live births per year in the United States and Europe (Mandal & Netland, 2006; Papadopoulos, Cable, Rahi, & Khaw, 2007), with higher prevalence observed in populations with founder effect or with a high rate of consanguinity (Dandona, Williams, Williams, & Rao, 1998; Genčik, Genčikova, & Ferak, 1982; Jaffar, 1988). Though rare, PCG is a leading cause of vision loss in children throughout the world. Approximately 25% of infants with PCG are diagnosed at birth, and over 75% are diagnosed within the first year of life (Allingham et al., 2011). These defects are usually bilateral (65–80%) and have been reported to affect males more often than females (Allingham et al., 2011; Papadopoulos et al., 2007).

The developmental pathogenesis of childhood glaucomas is variable, and several classification systems have been proposed. The 9th Consensus Report of the World Glaucoma Association (Weinreb, Grajewski, Papadopoulos, Grigg, & Freedman, 2013) classifies childhood glaucomas as either primary or secondary. PCG is a primary childhood glaucoma, typically presenting in the absence of cooccurring

ocular abnormalities. It is distinguished from secondary childhood glaucomas, which are pathogenetically heterogeneous and include anterior segment dysgenesis defects (ASDs) such as Axenfeld-Rieger anomaly, Peters anomaly, and aniridia. The pathogenesis of PCG remains unclear but is likely due to developmental abnormalities of the trabecular meshwork resulting in arrest of angle formation and decreased aqueous outflow. PCG is sometimes inherited, but nonfamilial cases are common (60–96%) (Papadopoulos et al., 2007), which suggests multifactorial causation.

Since the late 1990s, our understanding of the genetic basis of PCG has advanced rapidly. The most consistently identified mutated gene in PCG is *CYP1B1*, a member of the cytochrome P450 family of genes (Li, Zhou, Du, Wei, & Chen, 2011; Vasiliou & Gonzalez, 2008). The frequencies of specific *CYP1B1* mutations vary among ethnic groups (Chouiter & Nadifi, 2017; Li, Zhou, et al., 2011). Within the U.S., an ethnically heterogeneous population, *CYP1B1* mutations are much rarer and are found in less than 15% of families with PCG (Lim et al., 2013). Outside of the U.S., two other genes, *MYOC* and *LTBP2*, have also been found to be mutated in families with PCG (Abu-Amero et al., 2011; Ali et al., 2009; Kaur et al., 2005; Zhuo, Wang, Wei, Huang, & Ge, 2006). However, most cases of PCG in the U.S. do not have known genetic causation, and very little is known about nongenetic risk factors. A Hungarian study investigated various demographic and lifestyle factors and revealed that higher birth order, low socioeconomic status, and maternal smoking and alcohol use were positively associated with PCG (Puhó, Vogt, Csáky-Szunyogh, Métneki, & Czeizel, 2008; Vogt, Horváth-Puhó, & Czeizel, 2006), but a high proportion of Hungarian Gypsies in the study population makes extrapolation to other populations tenuous. In fact, most studies of PCG to date are based on cases from multiplex families, many of whom are from highly consanguineous pedigrees, making findings difficult to generalize to other populations (Papadopoulos et al., 2007; Tamçelik, Atalay, Bolukbasi, Çapar, & Ozkok, 2014; Vogt et al., 2006). To advance our current understanding of childhood glaucoma, we investigated a range of potential risk factors for PCG using data collected in a large case–control study in a population generally representative of the U.S. population.

1 | METHODS

1.1 | Study population

This analysis uses data from the National Birth Defects Prevention Study (NBDPS), a large population-based multisite case–control study of major birth defects in the United States (detailed methods reported previously by Reefhuis et al., 2015). Data collection for NBDPS included births occurring from 1997 to 2011. PCG cases were included in the study as of January 1, 2000. Case infants were identified through birth defects surveillance systems in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah); surveillance programs collected clinical information from medical records to ascertain eligible birth defects. Controls were infants without major birth defects who were randomly selected through vital records or birth hospitals from the same source population as cases. Mothers of eligible cases and controls were invited to participate in a telephone interview. Standardized interviews were conducted in English or Spanish and included questions on demographic factors and a wide variety of environmental exposures. Interviews were completed between 6 weeks and 24 months after the infant's estimated date of delivery ("due date"). This analysis also uses available data on eligible cases whose mothers ultimately chose not to participate in the NBDPS interview. States ascertained and classified all eligible cases, including information from medical records and birth certificates on a limited set of factors such as infant sex, gestational age, plurality, maternal age at delivery, and maternal race/ethnicity. The NBDPS was approved by the Institutional Review Board (IRB) at the Centers for Disease Control and Prevention, and each study center also received local IRB approval.

1.2 | Case classification

Nonsyndromic cases of PCG (cases without a known or suspected syndrome) were eligible for the NBDPS if abstracted medical records indicated that PCG was diagnosed by an ophthalmologist within the first 12 months of life, on postnatal ophthalmology exam or autopsy. Birth years 2000–2011 were included in the study. Clinical data were reviewed by clinical geneticists at each study center to confirm that cases met eligibility criteria, and cases with defects of known etiology, including single-gene disorders and chromosomal abnormalities, were excluded. For this analysis, we included only PCG cases without other ASDs (e.g., Peters anomaly, Axenfeld-Rieger anomaly, aniridia, lens coloboma, and aphakia/spherophakia) or cooccurring microphthalmia. Cases were further classified by a clinical geneticist (E.L.) as isolated, multiple, or complex (Rasmussen et al., 2003). PCG cases were considered isolated if there were no other major defects present; other periocular anomalies or anomalies within the globe were not counted as separate major malformations. Cases were considered multiple if two or more unrelated major defects occurred. Complex cases were those with a previously described pattern of major defects that are presumably embryologically related but of unknown cause.

1.3 | Ascertainment of risk factors or data collection

Information on pregnancy and infant characteristics, demographic factors, and maternal health history was collected through the NBDPS maternal interview. Clinical variables examined in this analysis included the following: infant sex, gestational age (<37 weeks or ≥37 weeks), birth weight (restricted to term births only; <2,500 g or ≥2,500 g), small for gestational age (birth weight less than the 10th percentile for gestational age based on previously published race-, sex-, and parity-specific growth curves (Overpeck, Hediger, Zhang, Trumble, & Klebanoff, 1999; Zhang & Bowes, 1995)), plurality (singleton or multiple), gravidity (primigravid or multigravid), parity (number of previous live births and stillbirths; ≤1 or >1), season of conception (spring = March–May, summer = June–August, fall = September–November, or winter = December–February), and maternal use of fertility medications or procedures. Demographic

variables included maternal and paternal age at delivery (<25 years, 25–34 years, or >34 years), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), maternal nativity (US-born or non-U.S.-born), maternal education (<12 years, 12 years, or >12 years), and annual household income (<$10,000, $10,000–$50,000, or >$50,000). For noninterviewed cases, limited demographic and clinical information was obtained from birth certificates and abstracted medical records.

A number of additional variables related to the mother's health status were examined as well: prepregnancy body mass index (BMI) categorized based on the National Institutes of Health recommendations (NHLBI, 1998) (underweight, <18.5; normal weight, 18.5 ≤ BMI < 25; overweight, 25 ≤ BMI < 30; or obese, ≥30), diabetes (gestational diabetes, preexisting type I or type II diabetes, or no diabetes), history of hypertension, history of seizure, thyroid disease, smoking, alcohol use, caffeine intake, folate intake, periconceptional folic acid supplement use (no use, <1/day, or daily use), any X-ray or scan during pregnancy, substance abuse (use of any recreational or street drugs), fever or infection, and medication use. Mothers were asked specific questions concerning history of diabetes, hypertension, seizures, respiratory illness, genitourinary illness (kidney, bladder, or urinary tract infection), sexually transmitted diseases (including pelvic inflammatory disease, human immunodeficiency virus, and human papilloma virus), and fever during pregnancy. Other diseases or illnesses were recorded in open-ended fields. A modified Willett Food Frequency Questionnaire (Willett, Reynolds, Cottrell-Hoehner, Sampson, & Browne, 1987) was used to ascertain consumption of 58 food items for the year prior to pregnancy, and nutrient values were calculated from the USDA National Nutrient Database Standard Reference 16–1 (U.S. Department of Agriculture, 2004). Total folate intake was derived from combining dietary folate and folic acid from fortified foods into a measure of dietary folate equivalents, which takes into consideration the enhanced bioavailability of folic acid. Quartiles of caffeine and folate intake were calculated based on the intake of the control group mothers.

Prescription and nonprescription medications, along with start and stop dates, duration, and frequency of use were recorded during the maternal interview. Reported medications were grouped into predefined classes by their active ingredients using the Slone Epidemiology Drug Dictionary (Kelley, Kelley, Kaufman, & Mitchell, 2003). This analysis included the following medication classes with at least three exposed cases of PCG: antipyretics, anti-infectives, antitussives, cold medicines, antihypertensives, thyroid/antithyroid medications, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, selective serotonin reuptake inhibitors, and antihistamines; and specific medications: acetaminophen, doxylamine, and promethazine.

It is unclear whether exposures during postembryonic development (>8 weeks postconception) may be associated with PCG. Therefore, infections, medication use, and smoking and alcohol use were assessed for the periconceptional period (1 month prior to pregnancy through first trimester), second, and third trimesters. Because reported exposures were highly correlated across trimesters, exposure anytime during pregnancy was used for analysis of these variables. Categorization and exposure window specifications for each variable examined are further detailed in each of the Tables.

1.4 | Analytic methods

First, all eligible cases of PCG (both interviewed and noninterviewed) were compared on clinical and demographic characteristics: gender, gestational age, plurality, maternal age at delivery, maternal race/ethnicity, study center, defect classification (isolated, multiple, or complex), and laterality (unilateral, bilateral, or unknown laterality). Chi-square tests, or Fisher's exact tests for associations with expected cell counts less than five, were used to determine statistical differences. All eligible cases (interviewed and noninterviewed) were also compared by defect classification (isolated or multiple) on the same select clinical and demographic characteristics.

Among interviewed cases, we then examined the association between each potential risk factor and all PCG cases using crude odds ratios and 95% confidence intervals (CIs). We used multivariate logistic regression to calculate adjusted odds ratios (aORs) for exposures with at least five cases exposed. Potential confounders were identified using directed acyclic graphs; multivariate models were adjusted for maternal age, maternal race/ethnicity, prepregnancy BMI, and periconceptional folic acid supplementation. Analyses were repeated for isolated PCG cases to explore potential heterogeneity associated with the development of multiple defects. Additionally, we conducted sensitivity analyses excluding infants conceived by donor egg or sperm (1 case, 28 controls); and excluding infants with a reported first-degree family history of childhood glaucoma (1 case, 1 control). Results of the sensitivity analyses (not shown) did not differ appreciably from the main analysis. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

2 | RESULTS

2.1 | Eligible cases

For birth years 2000–2011, there were 217 PCG cases eligible for NBDPS. After excluding cases for this analysis with associated ASDs (n = 32) or microphthalmia (n = 10, including n = 2 with ASDs), 177 eligible PCG cases remained. Of these, 106 (60%) were male and 71 (40%) were female. Defects were unilateral in 61 (34%), bilateral in 114 (64%), and unknown in 2 (1%) of the cases. There were 157 (89%) cases with isolated PCG, 19 (11%) cases with other cooccurring major defects, and 1 complex (0.6%) case. Preterm births and male sex were more common among cases with multiple unrelated major defects (Appendix Table S-1). Among cases with multiple defects, congenital heart defects were most frequently present (37%), followed by central nervous system defects and cataracts (>20%). Gastrointestinal, genitourinary, neural tube, ear, and musculoskeletal defects were recorded as well, but were present in only two or fewer cases.

2.2 | Interviewed cases

A total of 107 (60%) eligible cases and 10,084 (64%) eligible controls completed the maternal interview. The average age at interview was 13 months for cases and 9 months for controls. Interviewed and noninterviewed cases did not differ significantly when compared on infant

TABLE 1 Infant and pregnancy characteristics of primary congenital glaucoma cases and controls (National Birth Defects Prevention Study, 2000–2011)

	Controls (*n* = 10,084)	All cases (*n* = 107)			Isolated cases (*n* = 92)		
	n (%)	*n* (%)	cOR (95% CI)	aOR[a] (95% CI)	*n* (%)	cOR (95% CI)	aOR[a] (95% CI)
Sex							
Female	4,893 (48.6)	47 (43.9)	0.83 (0.57–1.22)	0.81 (0.54–1.21)	44 (47.8)	0.97 (0.64–1.46)	0.94 (0.61–1.45)
Male	5,179 (51.4)	60 (56.1)	1.00 (Ref)	1.00 (Ref)	48 (52.2)	1.00 (Ref)	1.00 (Ref)
Gestational age							
<37 weeks	964 (9.6)	15 (14.0)	1.54 (0.89–2.67)	1.42 (0.79–2.56)	10 (10.9)	1.15 (0.60–2.23)	1.11 (0.55–2.23)
≥37 weeks	9,118 (90.4)	92 (86.0)	1.00 (Ref)	1.00 (Ref)	82 (89.1)	1.00 (Ref)	1.00 (Ref)
Birth weight[b]							
<2,500 g	186 (2.1)	5 (5.8)	2.92 (1.17–7.30)	3.04 (1.20–7.70)	3 (4.0)	1.95 (0.39–6.00)[c]	--
≥2,500 g	8,808 (97.9)	81 (94.2)	1.00 (Ref)	1.00 (Ref)	73 (96.1)	1.00 (Ref)	--
Small for gestational age (≤10%)							
Yes	920 (9.5)	14 (14.0)	1.55 (0.88–2.74)	1.72 (0.95–3.12)	11 (12.6)	1.38 (0.73–2.60)	1.48 (0.76–2.89)
No	8,765 (90.5)	86 (86.0)	1.00 (Ref)	1.00 (Ref)	76 (87.4)	1.00 (Ref)	1.00 (Ref)
Plurality							
Singleton	9,766 (97.1)	102 (95.3)	1.00 (Ref)	1.00 (Ref)	88 (95.7)	1.00 (Ref)	--
Multiple	293 (2.9)	5 (4.7)	1.63 (0.66–4.04)	1.93 (0.77–4.81)	4 (4.4)	1.52 (0.40–4.06)[c]	--
Gravidity							
Primigravid	2,961 (29.5)	35 (33.0)	1.18 (0.78–1.77)	1.03 (0.66–1.62)	32 (35.2)	1.30 (0.84–2.00)	1.25 (0.77–2.01)
Multigravid	7,078 (70.5)	71 (67.0)	1.00 (Ref)	1.00 (Ref)	59 (64.8)	1.00 (Ref)	1.00 (Ref)
Parity							
≤1	7,134 (71.1)	81 (76.4)	1.32 (0.84–2.07)	1.22 (0.74–2.02)	69 (75.8)	1.28 (0.79–2.07)	1.28 (0.75–2.19)
>1	2,905 (28.9)	25 (23.6)	1.00 (Ref)	1.00 (Ref)	22 (24.2)	1.00 (Ref)	1.00 (Ref)
Season of conception							
Spring	2,442 (24.2)	24 (22.4)	1.00 (Ref)	1.00 (Ref)	23 (25.0)	1.00 (Ref)	1.00 (Ref)
Summer	2,550 (25.3)	21 (19.6)	0.84 (0.47–1.51)	0.74 (0.40–1.36)	21 (22.8)	0.87 (0.48–1.58)	0.77 (0.41–1.43)
Fall	2,602 (25.8)	27 (25.2)	1.06 (0.61–1.84)	0.93 (0.53–1.66)	22 (23.9)	0.90 (0.50–1.62)	0.76 (0.41–1.41)
Winter	2,490 (24.7)	35 (32.7)	1.43 (0.85–2.41)	1.34 (0.79–2.29)	26 (28.3)	1.11 (0.63–1.95)	1.05 (0.59–1.87)
Use of fertility medication or procedure							
Yes	487 (4.9)	4 (3.8)	0.77 (0.21–2.04)[c]	--	3 (3.3)	0.67 (0.14–2.03)[c]	--
No	9,540 (95.1)	102 (96.2)	1.00 (Ref)	--	88 (96.7)	1.00 (Ref)	--

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio.
[a]Adjusted for maternal age, maternal race/ethnicity, prepregnancy BMI, and periconceptional folic acid supplement use.
[b]Among term births (≥37 weeks) only.
[c]Exact confidence limits computed.

sex, gestational age, plurality, maternal age at delivery, maternal race/ethnicity, defect classification, and laterality. First-degree family history of childhood glaucoma was reported by one case and one control.

Infants with PCG born at term were more likely to have low birth weight (aOR 2.92, 95% CI 1.17–7.30) than control infants born at term, but this association was attenuated for isolated cases (Table 1). Cases were also more likely to be born to non-Hispanic black mothers (all cases: aOR 2.42, 95% CI, 1.42–4.13; isolated cases: aOR 2.22, 95% CI 1.25–3.95) (Table 2). Additionally, cases were more likely to be small for gestational age and have a household income between $10,000–$50,000, though these results were not statistically significant.

Mothers of case infants were more likely than controls to have a history of seizure (all cases: aOR 2.73, 95% CI 1.25–5.97; isolated cases: aOR 2.76, 95% CI 1.19–6.41) (Table 3). Sexually transmitted infection was also associated with PCG (all cases: aOR 2.75, 95% CI 1.17–6.44; isolated cases: 3.27, 95% CI 1.39–7.70). Case mothers were less likely to report smoking (all cases: aOR 0.50, 95% CI 0.25–0.98; isolated cases: aOR 0.46, 95% CI 0.22–0.97) and alcohol use during pregnancy (all cases: aOR 0.58, 95% CI 0.37–0.92; isolated cases: aOR 0.61, 95% CI 0.37–0.99). When alcohol use was further categorized into binge drinking (greater than four drinks in one occasion) and drinking but not binge drinking, drinking

TABLE 2 Demographic characteristics of primary congenital glaucoma cases and controls (National Birth Defects Prevention Study, 2000–2011)

	Controls (*n* = 10,084)	All cases (*n* = 107)			Isolated cases (*n* = 92)		
	n (%)	*n* (%)	cOR (95% CI)	aOR[a] (95% CI)	*n* (%)	cOR (95% CI)	aOR[a] (95% CI)
Maternal age at delivery							
≤24 years	3,276 (32.5)	41 (38.3)	1.20 (0.80–1.81)	1.19 (0.76–1.87)	35 (38.0)	1.22 (0.79–1.90)	1.12 (0.68–1.83)
25–34 years	5,385 (53.4)	56 (52.3)	1.00 (Ref)	1.00 (Ref)	47 (51.1)	1.00 (Ref)	1.00 (Ref)
≥35 years	1,423 (14.1)	10 (9.4)	0.68 (0.34–1.33)	0.64 (0.31–1.29)	10 (10.9)	0.81 (0.41–1.60)	0.76 (0.37–1.55)
Paternal age at delivery							
≤24 years	2,111 (21.6)	25 (24.8)	1.23 (0.76–2.00)	1.33 (0.70–2.53)	22 (25.3)	1.26 (0.75–2.12)	1.40 (0.70–2.79)
25–34 years	5,211 (53.4)	50 (49.5)	1.00 (Ref)	1.00 (Ref)	43 (49.4)	1.00 (Ref)	1.00 (Ref)
≥35 years	2,444 (25.0)	26 (25.7)	1.11 (0.69–1.79)	1.39 (0.80–2.41)	22 (25.3)	1.09 (0.65–1.83)	1.23 (0.67–2.27)
Maternal race/ethnicity							
Non-Hispanic white	5,734 (56.9)	51 (47.7)	1.00 (Ref)	1.00 (Ref)	46 (50.0)	1.00 (Ref)	1.00 (Ref)
Non-Hispanic black	1,101 (10.9)	27 (25.2)	2.76 (1.72–4.42)	2.42 (1.42–4.13)	23 (25.0)	2.60 (1.57–4.31)	2.22 (1.25–3.95)
Hispanic	2,546 (25.3)	20 (18.7)	0.88 (0.53–1.48)	0.95 (0.53–1.69)	18 (19.6)	0.88 (0.51–1.52)	0.89 (0.48–1.65)
Other	696 (6.9)	9 (8.4)	1.45 (0.71–2.97)	1.60 (0.78–3.27)	5 (5.4)	0.90 (0.36–2.26)	0.97 (0.38–2.46)
Maternal nativity							
United States	7,685 (78.6)	76 (74.5)	1.00 (Ref)	1.00 (Ref)	67 (76.1)	1.00 (Ref)	1.00 (Ref)
Other	2,089 (21.4)	26 (25.5)	1.26 (0.80–1.97)	1.58 (0.88–2.84)	21 (23.9)	1.15 (0.71–1.89)	1.39 (0.72–2.67)
Maternal education							
<12 years	1,634 (16.7)	17 (16.7)	0.98 (0.57–1.69)	1.01 (0.52–1.97)	15 (17.1)	0.93 (0.52–1.64)	0.83 (0.41–1.70)
12 years	2,277 (23.3)	23 (22.6)	0.95 (0.59–1.54)	0.91 (0.54–1.55)	15 (17.1)	0.67 (0.38–1.18)	0.58 (0.31–1.08)
>12 years	5,855 (60.0)	62 (60.8)	1.00 (Ref)	1.00 (Ref)	58 (65.9)	1.00 (Ref)	1.00 (Ref)
Household annual income							
<$10,000	1,773 (19.1)	19 (19.8)	1.36 (0.75–2.45)	1.48 (0.72–3.01)	15 (18.3)	1.16 (0.61–2.20)	1.19 (0.55–2.60)
$10,000–$50,000	4,107 (44.2)	50 (52.1)	1.54 (0.96–2.47)	1.59 (0.94–2.70)	42 (51.2)	1.40 (0.85–2.30)	1.42 (0.81–2.49)
>$50,000	3,420 (36.8)	27 (28.1)	1.00 (Ref)	1.00 (Ref)	25 (30.5)	1.00 (Ref)	1.00 (Ref)

Abbreviations: aOR, adjusted odds ratio; CI, 95% confidence interval; cOR, crude odds ratio.
[a]Adjusted for maternal age, maternal race/ethnicity, prepregnancy BMI, and periconceptional folic acid supplement use.

but not binge drinking remained associated with PCG (aOR 0.54, 95% CI 0.40–0.93).

Maternal medications used during pregnancy among cases and controls are presented in Table 4. Compared with controls, mothers of case infants were more likely to report using antihypertensive medications (all cases: aOR 3.60, 95% CI 1.52–8.53; isolated cases: aOR 3.55, 95% CI 1.39–9.10). Additionally, NSAID use was more prevalent among mothers of isolated cases compared with controls (aOR 1.58, 1.02–2.46).

3 | DISCUSSION

In this national population-based case–control study, we analyzed a spectrum of clinical and demographic characteristics and potential risk factors for PCG in a large sample of infants generally representative of the U.S. population. Most cases of PCG that were eligible for the NBDPS (both interviewed and noninterviewed) were isolated, though some differences in potential risk factors were observed between isolated cases and cases with multiple defects. In particular, male sex and preterm birth were more common in cases with multiple defects. Consistent with previous reports, the majority of cases in our analytic sample were bilateral, and there was a preponderance of males (Allingham et al., 2011; Tamçelik et al., 2014). In addition, similar to some previous findings, infants with PCG in our study were more likely to have low birth weight at term compared with controls (Vogt et al., 2006), though this association was not statistically significant when examining isolated cases only.

Other findings in our study differed from those of previous reports. Reports using earlier data from the NBDPS found statistically significant positive associations between use of antibacterial medications and opioid analgesics and PCG/other ASDs (Broussard et al., 2011; Crider et al., 2009), whereas we found null associations with these exposures in the present study. Both the Crider et al. (2009) and Broussard et al. (2011) studies, however, used a smaller subset of cases than ours, and included ASDs, which could explain the different findings. Vogt et al. (2006) found that higher birth order, smoking,

TABLE 3 Maternal health conditions and behaviors among primary congenital glaucoma cases and controls (National Birth Defects Prevention Study, 2000–2011)

	Controls (*n* = 10,084)	All cases (*n* = 107)			Isolated cases (*n* = 92)		
	n (%)	*n* (%)	cOR (95% CI)	aOR[a] (95% CI)	*n* (%)	cOR (95% CI)	aOR[a] (95% CI)
Prepregnancy BMI (kg/m^2)							
Underweight (<18.5)	500 (5.2)	2 (2.0)	0.37 (0.04–1.42)[b]	–	2 (2.4)	0.45 (0.05–1.73)[b]	–
Normal weight (18.5–24.9)	5,044 (52.6)	54 (54.6)	1.00 (Ref)	1.00 (Ref)	45 (53.6)	1.00 (Ref)	1.00 (Ref)
Overweight (25.0–29.9)	2,220 (23.1)	23 (23.2)	0.97 (0.59–1.58)	0.92 (0.55–1.51)	20 (23.8)	1.01 (0.60–1.71)	0.99 (0.58–1.70)
Obese (> = 30.0)	1,830 (19.1)	20 (20.2)	1.02 (0.61–1.71)	0.99 (0.58–1.67)	17 (20.2)	1.04 (0.59–1.82)	0.99 (0.56–1.76)
Diabetes							
Gestational diabetes	717 (7.1)	7 (6.5)	0.94 (0.43–2.02)	1.14 (0.52–2.51)	5 (5.4)	0.77 (0.31–1.91)	0.95 (0.38–2.38)
Prepregnancy diabetes	71 (0.7)	3 (2.8)	4.05 (0.80–12.67)[b]	–	3 (3.3)	4.68 (0.92–14.69)[b]	–
No diabetes	9,296 (92.2)	97 (90.7)	1.00 (Ref)	1.00 (Ref)	84 (91.3)	1.00 (Ref)	1.00 (Ref)
History of hypertension							
Yes	1,391 (13.9)	18 (17.1)	1.28 (0.77–2.14)	1.34 (0.79–2.28)	16 (17.8)	1.34 (0.78–2.31)	1.40 (0.80–2.45)
No	8,622 (86.1)	87 (82.9)	1.00 (Ref)	1.00 (Ref)	74 (82.2)	1.00 (Ref)	1.00 (Ref)
History of seizure							
Yes	277 (2.8)	7 (6.7)	2.51 (1.16–5.45)	2.73 (1.25–5.97)	6 (6.7)	2.51 (1.09–5.79)	2.76 (1.19–6.41)
No	9,729 (97.2)	98 (93.3)	1.00 (Ref)	1.00 (Ref)	84 (93.3)	1.00 (Ref)	1.00 (Ref)
Thyroid disease							
Yes	242 (2.4)	4 (3.7)	1.58 (0.42–4.22)[b]	–	3 (3.3)	1.37 (0.28–4.19)[b]	–
No	9,842 (97.6)	103 (96.3)	1.00 (Ref)	–	89 (96.7)	1.00 (Ref)	–
Smoking[c]							
Yes	1,735 (17.7)	10 (9.8)	0.51 (0.26–0.97)	0.50 (0.25–0.98)	8 (9.1)	0.47 (0.23–0.96)	0.46 (0.22–0.97)
No	8,071 (82.3)	92 (90.2)	1.00 (Ref)	1.00 (Ref)	80 (90.9)	1.00 (Ref)	1.00 (Ref)
Alcohol[c]							
Yes	3,779 (38.6)	27 (26.5)	0.57 (0.37–0.89)	0.58 (0.37–0.92)	24 (27.3)	0.60 (0.37–0.95)	0.61 (0.37–0.99)
No	6,005 (61.4)	75 (73.5)	1.00 (Ref)	1.00 (Ref)	64 (72.7)	1.00 (Ref)	1.00 (Ref)
Periconceptional folic acid supplement[d]							
No use	2,273 (23.1)	21 (20.6)	1.00 (Ref)	1.00 (Ref)	21 (23.9)	1.00 (Ref)	1.00 (Ref)
<1/day	4,714 (47.9)	51 (50.0)	1.17 (0.70–1.95)	1.23 (0.72–2.10)	42 (47.7)	0.96 (0.57–1.63)	0.97 (0.56–1.70)
Daily use	2,853 (29.0)	30 (29.4)	1.14 (0.65–1.99)	1.37 (0.73–2.57)	25 (28.4)	0.95 (0.53–1.70)	1.06 (0.55–2.05)
Caffeine intake[e] (quartiles)							
Q1	2,448 (25.0)	30 (29.7)	1.00 (Ref)	1.00 (Ref)	27 (31.0)	1.00 (Ref)	1.00 (Ref)
Q2	2,444 (25.0)	24 (23.8)	0.80 (0.47–1.37)	0.75 (0.43–1.31)	21 (24.1)	0.78 (0.44–1.38)	0.72 (0.40–1.30)
Q3	2,446 (25.0)	25 (24.8)	0.83 (0.49–1.42)	0.81 (0.46–1.41)	20 (23.0)	0.74 (0.42–1.33)	0.69 (0.37–1.27)
Q4	2,445 (25.0)	22 (21.8)	0.73 (0.42–1.28)	0.79 (0.44–1.39)	19 (21.8)	0.70 (0.39–1.27)	0.73 (0.40–1.34)
Total folate intake[e] (quartiles)							
Q1	2,476 (25.0)	30 (29.1)	1.00 (Ref)	1.00 (Ref)	24 (27.0)	1.00 (Ref)	1.00 (Ref)
Q2	2,477 (25.0)	21 (20.4)	0.70 (0.40–1.23)	0.72 (0.41–1.27)	20 (22.5)	0.83 (0.46–1.51)	0.86 (0.47–1.58)
Q3	2,477 (25.0)	22 (21.4)	0.73 (0.42–1.27)	0.72 (0.40–1.27)	19 (21.4)	0.79 (0.43–1.45)	0.77 (0.41–1.46)
Q4	2,477 (25.0)	30 (29.1)	1.00 (0.60–1.66)	1.00 (0.59–1.70)	26 (29.2)	1.08 (0.62–1.89)	1.10 (0.61–1.97)
Any X-ray/scan[f]							
Yes	1,303 (13.1)	17 (16.4)	1.30 (0.77–2.19)	1.31 (0.76–2.26)	17 (19.1)	1.57 (0.92–2.67)	1.59 (0.92–2.77)
No	8,667 (86.9)	87 (83.7)	1.00 (Ref)	1.00 (Ref)	72 (80.9)	1.00 (Ref)	1.00 (Ref)

(Continues)

TABLE 3 (Continued)

	Controls (*n* = 10,084)	All cases (*n* = 107)			Isolated cases (*n* = 92)		
	n (%)	*n* (%)	cOR (95% CI)	aOR[a] (95% CI)	*n* (%)	cOR (95% CI)	aOR[a] (95% CI)
Any illicit substance abuse[f]							
Yes	536 (5.3)	5 (4.7)	0.87 (0.35–2.15)	0.84 (0.34–2.11)	5 (5.4)	1.02 (0.41–2.53)	1.00 (0.40–2.51)
No	9,548 (94.7)	102 (95.3)	1.00 (Ref)	1.00 (Ref)	87 (94.6)	1.00 (Ref)	1.00 (Ref)
Fever[c]							
Yes	2,015 (20.1)	23 (21.9)	1.11 (0.70–1.77)	1.26 (0.78–2.02)	19 (21.1)	1.06 (0.64–1.77)	1.20 (0.72–2.01)
No	8,003 (79.9)	82 (78.1)	1.00 (Ref)	1.00 (Ref)	71 (78.9)	1.00 (Ref)	1.00 (Ref)
Respiratory infection[c]							
Yes	4,913 (52.7)	46 (49.5)	0.88 (0.59–1.32)	1.02 (0.66–1.57)	40 (51.3)	0.95 (0.61–1.48)	1.14 (0.71–1.84)
No	4,418 (47.4)	47 (50.5)	1.00 (Ref)	1.00 (Ref)	38 (48.7)	1.00 (Ref)	1.00 (Ref)
Genitourinary infection[c]							
Yes	1,738 (17.5)	19 (18.1)	1.04 (0.63–1.72)	1.03 (0.61–1.73)	17 (18.9)	1.10 (0.65–1.87)	1.08 (0.62–1.88)
No	8,191 (82.5)	86 (81.9)	1.00 (Ref)	1.00 (Ref)	73 (81.1)	1.00 (Ref)	1.00 (Ref)
Sexually transmitted infection[c]							
Yes	219 (2.2)	6 (5.6)	2.68 (1.16–6.16)	2.75 (1.17–6.44)	6 (6.5)	3.14 (1.36–7.27)	3.27 (1.39–7.70)
No	9,865 (97.8)	101 (94.4)	1.00 (Ref)	1.00 (Ref)	86 (93.5)	1.00 (Ref)	1.00 (Ref)

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index, CI, 95% confidence interval; cOR, crude odds ratio.
[a]Adjusted for maternal age, maternal race/ethnicity, prepregnancy BMI, and periconceptional folic acid supplement use.
[b]Exact confidence limits computed.
[c]Beginning 1 month prior to pregnancy through delivery.
[d]Beginning 1 month prior to pregnancy through the end of the first trimester.
[e]Reported during the year prior to pregnancy.
[f]Beginning 3 months prior to pregnancy through delivery.

regular alcohol use, and low folic acid intake were associated with PCG. We did not observe these associations, although differences between the two study populations (predominately Hungarian Gypsy versus U.S. infants) make comparison of the findings difficult. For instance, Vogt and colleagues note that compared with the non-Gypsy female population in Hungary, Hungarian Gypsies tend to have more children at earlier ages, are more likely to smoke and drink heavily, and are less likely to use nutritional supplements during pregnancy.

Our study identified several associations that have not been previously reported. We found that infants of non-Hispanic black mothers had increased odds of PCG compared to infants of non-Hispanic whites, after controlling for potential confounders. PCG prevalence is known to vary geographically and among different ethnic groups. Our study is the first to demonstrate a higher risk among non-Hispanic blacks in the U.S.

In our analyses, smoking and alcohol use were unexpectedly found to be negatively associated with PCG. While smoking and alcohol are considered risk factors for many birth defects and other adverse pregnancy outcomes, findings of negative association have been reported for some specific birth defects in other analyses based on case–control data in the U.S. (Carmichael, Ma, Shaw, & the National Birth Defects Prevention Study, 2017; Caspers Conway et al., 2014; Grewel, Carmichael, Ma, Lammer, & Shaw, 2008; Zhu et al., 2015). These findings could reflect true associations; potential mechanisms cited include vasoactive effects, endocrine effects, or antiangiogenic factors (Carmichael et al., 2017). Alternatively, underreporting or nonparticipation of smokers and alcohol users might bias results. More research is needed to understand these findings, and we advise women to continue to follow public health policy recommendations regarding abstinence from smoking and alcohol during pregnancy.

We also found associations between certain medications and PCG. Maternal use of antihypertensive medications was associated with significantly increased odds of PCG. Previous studies have examined the association between use of antihypertensive medications and various birth defects, with mixed findings (Bateman et al., 2017; Caton et al., 2009; Li, Yang, Andrade, Tavares, & Ferber, 2011). It is possible that the positive findings in some studies are due to the underlying maternal hypertension rather than to the medications themselves. In our study, odds of PCG were not significantly associated with a history of hypertension. We also found that women who reported using NSAIDs during pregnancy were more likely to have an infant with isolated PCG compared with women reporting no use. NSAIDs are commonly used to treat symptoms of pain, cold, and flu in early pregnancy. Findings from other studies suggest that NSAID use is not a major risk factor for birth defects. On the other hand, a study using NBDPS data reported small-to-moderate increased risks for some specific birth defects, including anophthalmia/microphthalmia (Hernandez, Werler, Romitti, Sun, & Anderka, 2012), but PCG was not included in that analysis.

TABLE 4 Maternal medication during pregnancy[a] among primary congenital glaucoma cases and controls (National Birth Defects Prevention Study, 2000–2011)

	Controls (*n* = 10,084)	All cases (*n* = 107)			Isolated cases (*n* = 92)		
	n (%)	*n* (%)	cOR (95% CI)	aOR[b] (95% CI)	*n* (%)	cOR (95% CI)	aOR[b] (95% CI)
Antipyretic use							
Yes	7,389 (74.2)	79 (75.2)	1.06 (0.68–1.65)	1.02 (0.64–1.63)	68 (75.6)	1.08 (0.66–1.74)	1.04 (0.63–1.74)
No	2,571 (25.8)	26 (24.8)	1.00 (Ref)	1.00 (Ref)	22 (24.4)	1.00 (Ref)	1.00 (Ref)
Anti-infective use							
Yes	2,595 (26.2)	26 (25.2)	0.95 (0.61–1.49)	0.89 (0.56–1.42)	23 (25.8)	0.98 (0.61–1.59)	0.92 (0.56–1.51)
No	7,330 (73.9)	77 (74.8)	1.00 (Ref)	1.00 (Ref)	66 (74.2)	1.00 (Ref)	1.00 (Ref)
Antitussive use							
Yes	1,333 (13.5)	11 (10.7)	0.77 (0.41–1.44)	0.80 (0.43–1.50)	11 (12.4)	0.91 (0.48–1.71)	0.97 (0.51–1.83)
No	8,574 (86.5)	92 (89.3)	1.00 (Ref)	1.00 (Ref)	78 (87.6)	1.00 (Ref)	1.00 (Ref)
Cold medicine use							
Yes	1,315 (13.3)	17 (16.5)	1.29 (0.77–2.18)	1.31 (0.77–2.22)	16 (18.0)	1.43 (0.83–2.47)	1.47 (0.85–2.56)
No	8,591 (86.7)	86 (83.5)	1.00 (Ref)	1.00 (Ref)	73 (82.0)	1.00 (Ref)	1.00 (Ref)
Antihypertensive use							
Yes	164 (1.7)	6 (5.8)	3.67 (1.59–8.49)	3.60 (1.52–8.53)	5 (5.6)	3.53 (1.41–8.82)	3.55 (1.39–9.10)
No	9,730 (98.3)	97 (94.2)	1.00 (Ref)	1.00 (Ref)	84 (94.4)	1.00 (Ref)	1.00 (Ref)
Thyroid/antithyroid use							
Yes	230 (2.3)	4 (3.9)	1.70 (0.45–4.55)[c]	--	3 (3.4)	1.47 (0.29–4.49)[c]	--
No	9,669 (97.7)	99 (96.1)	1.00 (Ref)	--	86 (96.6)	1.00 (Ref)	--
NSAID use							
Yes	3,057 (30.8)	38 (36.9)	1.31 (0.88–1.96)	1.35 (0.89–2.04)	36 (40.5)	1.53 (1.00–2.33)	1.58 (1.02–2.46)
No	6,863 (69.2)	65 (63.1)	1.00 (Ref)	1.00 (Ref)	53 (59.6)	1.00 (Ref)	1.00 (Ref)
Acetaminophen use							
Yes	6,686 (67.2)	72 (68.6)	1.07 (0.70–1.61)	1.07 (0.69–1.66)	61 (67.8)	1.03 (0.66–1.60)	1.04 (0.65–1.67)
No	3,266 (32.8)	33 (31.4)	1.00 (Ref)	1.00 (Ref)	29 (32.2)	1.00 (Ref)	1.00 (Ref)
Opioid use							
Yes	454 (4.6)	5 (4.9)	1.06 (0.43–2.62)	1.07 (0.43–2.65)	5 (5.6)	1.24 (0.50–3.07)	1.25 (0.50–3.12)
No	9,446 (95.4)	98 (95.2)	1.00 (Ref)	1.00 (Ref)	84 (94.4)	1.00 (Ref)	1.00 (Ref)
SSRI use							
Yes	419 (4.2)	8 (7.8)	1.91 (0.92–3.95)	1.89 (0.86–4.15)	7 (7.9)	1.93 (0.89–4.21)	1.86 (0.80–4.34)
No	9,479 (95.8)	95 (92.2)	1.00 (Ref)	1.00 (Ref)	82 (92.1)	1.00 (Ref)	1.00 (Ref)
Antihistamine use							
Yes	1,824 (18.4)	24 (23.1)	1.33 (0.84–2.11)	1.31 (0.81–2.11)	20 (22.5)	1.29 (0.78–2.12)	1.35 (0.81–2.24)
No	8,084 (81.6)	80 (76.9)	1.00 (Ref)	1.00 (Ref)	69 (77.5)	1.00 (Ref)	1.00 (Ref)
Doxylamine use							
Yes	212 (2.1)	4 (3.9)	1.85 (0.49–4.95)[c]	--	4 (4.5)	2.15 (0.57–5.79)[c]	--
No	9,685 (97.9)	99 (96.1)	1.00 (Ref)	--	85 (95.5)	1.00 (Ref)	--
Promethazine use							
Yes	483 (4.9)	8 (7.8)	1.64 (0.79–3.40)	1.59 (0.76–3.31)	8 (9.0)	1.93 (0.93–4.00)	1.89 (0.90–3.97)
No	9,414 (95.1)	95 (92.2)	1.00 (Ref)	1.00 (Ref)	81 (91.0)	1.00 (Ref)	1.00 (Ref)

Abbreviations: aOR, adjusted odds ratio; CI, 95% confidence interval; cOR, crude odds ratio; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

[a]Beginning 1 month prior to pregnancy through delivery.

[b]Adjusted for maternal age, maternal race/ethnicity, prepregnancy BMI, and periconceptional folic acid supplement use.

[c]Exact confidence limits computed.

Other maternal factors associated with PCG in our multivariate analyses included maternal history of seizure and sexually transmitted infection. Mothers of PCG cases were more than twice as likely to report a history of seizure compared with controls. Many anticonvulsant medications have well-established associations with birth defects, but the contribution of seizure history is more controversial (Fried, Kozer, Nulman, Einarson, & Koren, 2004). A study examining these relationships in the NBDPS found no evidence of an association between untreated epilepsy and birth defects (Werler et al., 2011), but this and other previous studies did not examine PCG specifically.

Women reporting a history of sexually transmitted infection during pregnancy were 2.75 times as likely to have an infant with PCG, and over three times as likely to have an infant with isolated PCG, compared with those reporting no infection. Other maternal infections are known to cause ocular defects in the exposed fetus, including toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus (Mets & Chhabra, 2008). This finding of an association between sexually transmitted infections and PCG has not been previously reported. An earlier study of genital tract infections and birth defects using NBDPS data found two-and-a-half-fold increased odds of PCG and ASDs, combined, in infants of mothers reporting first trimester chlamydia, gonorrhea, or PID, based on only two exposed cases (Carter et al., 2011).

Our study has several strengths. The study subjects are drawn from a large, geographically and racially/ethnically diverse base population of mothers and infants in 10 states across the U.S. The multisite, multiyear study design provides a unique opportunity to describe the epidemiology of rare birth defects such as PCG, and to examine a variety of potential risk factors that have not been previously studied. Demographic characteristics of subjects participating in the maternal interview did not differ substantially from the noninterviewed subjects, providing further support of the representativeness of the study sample. In addition, careful and consistent clinical review and classification of NBDPS case infants, including exclusion of cases with known chromosomal syndromes, provided a more homogeneous case sample for this study. To further reduce heterogeneity in our sample, we also excluded cases with ASDs from our analysis. Clinical information on glaucoma diagnoses was obtained from medical records and included verbatim diagnostic descriptions with supporting documentation such as surgical reports or clinical ophthalmologic findings.

This study also has some limitations. Our sample size was reasonably large, but because of the rarity of PCG, this study was not able to precisely estimate effects for certain exposures, or to perform additional analyses within phenotypic subgroups such as laterality and clinical disease severity. Although we were able to analyze isolated cases separately, there were too few cases with multiple defects to analyze potential risk factors separately for this group. The retrospective exposure assessment, based primarily on maternal self-report, presents limitations regarding the accuracy of maternal recall for exposures that occurred many months prior to interview. Inaccurate recall among study participants, if similar among cases and controls, would tend to bias odds ratios toward the null. Differential recall is a possibility, but there is little evidence to suggest this form of bias for many exposures in birth defect case–control studies (Werler, Louik, & Mitchell, 2011). Other limitations are that we did not have specific exposure information about sexually transmitted infections and we had incomplete information on family history of PCG for case infants. This information was solicited in the maternal questionnaire and was also occasionally obtained from medical records when available, but it was inconsistently reported and nonspecific. In our study population, family history of PCG was infrequently reported compared with some other studies, possibly because our study subjects were ascertained from a population-based sample rather than one with a high prevalence of PCG. Finally, NBDPS cases were limited to infants diagnosed within the first year of life. Because some infants with PCG are diagnosed after age one (Allingham et al., 2011), our case sample may be incomplete and more representative of infants with more severe forms of the disease or those diagnosed early for other reasons (e.g., better access to health care).

In summary, this study examined a wide array of potential risk factors for PCG and identified several possible associations that may provide leads for further investigation. Future studies should also consider how the presence of genetic mutations known to be associated with PCG may interact with the associations observed in this study. Improved knowledge of the epidemiology of this rare birth defect may be useful for clinicians to help improve early detection and long-term outcomes for these infants and their families.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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