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What Color Are Newborns' Eyes? Prevalence of Iris Color in the Newborn Eye Screening Test (NEST) Study

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Abstract

Purpose—The birth prevalence of iris color among newborns has not been assessed in a prospective, healthy, full-term newborn cohort.

Methods—The Newborn Eye Screening Test (NEST) study is a prospective cohort study conducted at Lucile Packard Children's Hospital at Stanford University School of Medicine. A pediatric vitreoretinal specialist (DMM) reviewed images sent to the Byers Eye Institute telemedicine reading center and recorded eye color for every infant screened. Variables were graphed to assess for normality, and frequencies per subject were reported for eye color, sex, ethnicity, and race.

Results—Among 192 subjects screened in the first year of the NEST study with external images of appropriate quality for visualization of the irides, the birth prevalence of iris color was 63.0% brown, 20.8% blue, 5.7% green/hazel, 9.9% indeterminate and 0.5% partial heterochromia. The study population was derived from a quaternary care children's hospital. We report the birth prevalence of iris color among full-term newborns in a diverse prospective cohort.

Conclusion—The study demonstrates a broad range of iris color prevalence at birth with a predominance of brown iris coloration. Future studies with the NEST cohort will assess the change in iris color over time and whether the frequencies of eye color change as the child ages.

Keywords

eye color; newborns; prevalence; universal newborn screening; pediatric ophthalmology

INTRODUCTION

The Newborn Eye Screening Test (NEST) study is a universal newborn ophthalmic screening initiative utilizing retinal imaging photography to assess newborns for ophthalmic disease and report the birth prevalence of disease. During the first year of screening, parents consistently asked the research team the same questions after their child was screened: 1) Are my baby's eyes healthy? and 2) What color are his or her eyes? The answer to the first

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question is still being investigated, but the second question we could answer in the examination room.

A review of the literature by these authors revealed that no published study reports the prevalence of iris color among a large prospective cohort of newborns assessed shortly after birth. In this study we aimed to answer the following question: What is the prevalence of iris color shortly after birth among newborns?

MATERIALS AND METHODS

Ethics

This study was approved by the Institutional Review Board and Ethics Committee at Stanford University School of Medicine. Informed consent was obtained from a parent of an infant participating in NEST screening and the study was conducted in a HIPAA-compliant fashion. All research adhered to the tenets of the Declaration of Helsinki.

Study Design

The NEST study is a prospective cohort study conducted at Lucile Packard Children's Hospital (LPCH) at Stanford University School of Medicine. Screening was offered to all infants born at the children's hospital who did not receive retinopathy of prematurity (ROP) screening. This study includes participants screened during the first year of enrollment (July 25th, 2013 to July 25th, 2014). Exclusion criteria were patients who were bilaterally anophthalmic, lacked images or medical charts for review, had infectious conjunctivitis, or were deemed too unstable for exam.

Data Acquisition

Digital images were taken by a NICU-certified nurse and stored on the RetCam III (Clarity Medical Systems, Pleasanton, CA) computer hard drive as well as input into the NEST telemedicine database management system. The research nurse recorded baseline demographic characteristics for each infant. Study data were collected and managed using REDCap electronic data capture tools (Harris et al. 2009). All image acquisition and transmittal was handled in a HIPAA-compliant fashion with strict attention to the confidentiality of personal data.

Image Review

A pediatric vitreoretinal specialist (DMM) reviewed images sent to the Byers Eye Institute telemedicine reading center. The reviewing ophthalmologist recorded eye color and ophthalmic examination findings for every infant screened.

Intraobserver Reliability

The intraobserver reliability was assessed using a random subset of 40 consecutive infants whose images were re-graded one year following the initial grading. We found an overall agreement of 87.5% with an unweighted kappa of 0.742 (95% CI: 0.550 to 0.934) indicating substantial agreement.

Statistical Analysis

Variables were graphed to assess for normality and frequencies per subject were reported for eye color, sex, ethnicity, and race. Groups were compared using crude bivariate statistical tests appropriate for the variable of interest with statistical significance set as a two-tailed alpha of <0.05 .

RESULTS

We screened 202 subjects during the first year of enrollment with 192 subjects (95.0%) with external images of appropriate quality for visualization of the irides (Fig. 1). The overall prevalence of eye color is shown in Fig. 2 with brown being the most common iris color (63.0%, 121/192). We found one case of partial heterochromia and no cases of complete heterochromia. The reviewing vitreoretinal specialist chose standard iris color images (Fig. 1) to compare images for color assessment. Any images that did not appear close to these color photographs were deemed “indeterminate” color (9.9%, 19/192).

Table 1 compares the frequency of eye color by sex, race, and ethnicity. There was no significant difference in color by sex. By ethnicity, significantly more newborns identified by parents as Not Hispanic or Latino had blue irides compared to those identified as Hispanic or Latino ($p<0.0001$, chi-squared test). A comparison of iris color by self-identified race was limited because race was missing a significant portion of the data (37.6% missing). All other variables had less than 5% missing values. Crude bivariate methods were used to compare eye color by race. Newborns whose parents identified them as White/Caucasian more often had blue irides compared to those identified as Asian ($p<0.0001$, Fisher’s exact test) or Native Hawaiian or Pacific Islander ($p=.0032$, Fisher’s exact test). In contrast, significantly more newborns identified as Asian ($p<0.0001$, Fisher’s exact test) and Native Hawaiian or Pacific Islander ($p=.0104$, Fisher’s exact test) had brown irides than newborns identified by parents as White/Caucasian.

DISCUSSION

We report the birth prevalence of newborn eye color shortly after birth as determined by retinal image photography in a universal newborn screening initiative. Newborn iris color at birth is brown in 63.0% (121/192) of infants, blue in 20.8% (40/192) of infants, green/hazel in 5.7% (11/192) of infants, indeterminate in 9.9% (19/192) of infants and partially heterochromic in 0.5% (1/192) of infants. The study cohort represents a diverse patient population presenting to a quaternary care children’s hospital and enrolled in the Newborn Eye Screening Test (NEST) study at Stanford University aimed to detect ophthalmic pathology at birth. Not surprisingly, the study also confirmed ethnic and racial predispositions to select eye colors with significantly more brown-eyed Asian and Native Hawaiian/Pacific Islander infants and significantly more blue-eyed Caucasian infants. No statistically significant correlations between sex and eye color were seen and no significant relationships between green/hazel eyes and race were revealed in this study, however, the sample size remains too small for these categories at this time.

A newborn's iris color holds significance for both families and clinicians. Families are curious and eager to learn more about the newest member of their family. Clinicians, on the other hand, monitor iris color as the child ages because iridial discoloration may be a sign of pathology. Genetic, biochemical, and infectious lesions such as Downs syndrome, neurofibromatosis, albinism, pigment dispersion, and even herpetic infections can present with iris discoloration (Mackey et al. 2011).

At least sixteen different genes influence iris color (White & Rabago-Smith 2011). Nevertheless, two adjacent genes on chromosome 15 control the majority of iris color variation: the oculocutaneous albinism type II gene (OCA2) and the hect domain and RCC1-like domain-containing protein 2 gene (HERC2) (White & Rabago-Smith 2011). Specifically, polymorphisms in one intron of the OCA2 gene that is regulated by a promoter region in the intron of HERC2 correlate with blue/non-blue iris color variation (Duffy et al. 2007). Likewise, blue-brown iris color variation corresponds to a single SNP in the HERC2 intron (Sturm et al. 2008).

At the biochemical level, iris color appears to vary by the quantity of melanin within the iris, with brown irides simply possessing more melanin than blue irides (White & Rabago-Smith 2011, Wielgus & Sarna 2005). Lighter features provide evolutionary advantage to those at higher latitudes by aiding in vitamin D production at low levels of ultra violet (UV) radiation (Sanfilippo et al. 2014, Roberts 1977). Conversely, darker features provide evolutionary advantage to those at lower latitudes by protecting against high levels of UV radiation (Sanfilippo et al. 2014, Roberts 1977).

Changes in melanin production over time can yield changes in iris color from infancy and may explain the popular myth that all infants are born with blue eyes. The Louisville Twin Study demonstrated that 10% to 20% of children experienced a change in iris color between 3 months and 6 years of age (Bito et al. 1997). Furthermore, a subpopulation of 10–15% of Caucasian subjects in the study had changes up until adulthood (Bito et al. 1997). However, the study lacks prevalence of iris color at birth as infants were first screened at 3 months. Furthermore, the study has restricted generalizability because it was limited to twins. Given the lack of information regarding iris color at birth, our team developed this study to prospectively evaluate the birth prevalence of eye color among universally screened infants drawn from a diverse patient population in hopes of alleviating this gap in the literature.

The strength of this study is that it is a large, population-based, prospective study enrolling infants of all races, sexes, and socioeconomic classes into a universal newborn screening initiative with images documenting the examination findings. One reviewer used standard color photographs to compare new iris photos and determine eye color. Thus, the study results are likely generally applicable to the population. The low number of Black or African American and American Indian or Alaska Native families limited the generalizability of this study to these groups. Furthermore, eye color is an inherently subjective assessment and thus prone to the bias of the single image reviewer. The use of standardized color images for borderline cases aimed to standardize the classification process, however, the potential for reviewer bias remains. We do not anticipate there was any differential misclassification of the eye color, and thus any bias would likely not affect the overall results of the study. Of

note, it is possible that better scoring of eye color may have been achieved through use of a brighter flash system.

To these authors' knowledge this study is the first, large-scale universal newborn study that reports the prevalence of eye color among newborns within the first few days of birth. Future studies of the NEST cohort will assess the change in iris color over time and whether the frequencies of eye color change as the child ages.

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REFERENCES

- Bitto LZ, Matheny A, Cruickshanks KJ, Nondahl DM, Carino OB. Eye color changes past early childhood. The Louisville Twin Study. *Arch Ophthalmol*. 1997; 115:659–663. [PubMed: 9152135]
- Duffy DL, Montgomery GW, Chen W, Zhao ZZ, James MR, Hayward NK, Martin NG, Sturm RA. A three-single-nucleotide polymorphism haplotype in intron 1 of OCA2 explains most human eye-color variation. *Am J Hum Genet*. 2007; 80:241–252. [PubMed: 17236130]
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42:377–381. [PubMed: 18929686]
- Mackey DA, Wilkinson CH, Kearns LS, Hewitt AW. Classification of iris colour: review and refinement of a classification schema. *Clin Exp Ophthalmol*. 2011; 39:462–471.
- Roberts DF. Human pigmentation: its geographical and racial distribution and biological significance. *J Soc Cosmet Chem*. 1977; 28:329–342.
- Sanfilippo PG, Wilkinson CH, Ruddle JB, Zhu G, Martin NG, Hewitt AW, Mackey DA. Don't it make your brown eyes blue? A comparison of iris colour across latitude in Australian twins. *Clin Exp Optom*. 2014;1–5. [PubMed: 24345028]
- Sturm RA, Duffy DL, Zhao ZZ, Leite FP, Stark MS, Hayward NK, Martin NG, Montgomery GW. A single SNP in an evolutionary conserved region within intron 86 of the HERC2 gene determines human blue-brown eye color. *Am J Hum Genet*. 2008; 82:424–431. [PubMed: 18252222]
- White D, Rabago-Smith M. Genotype-phenotype associations and human eye color. *J Hum Gen*. 2011; 56:5–7.
- Wielgus AR, Sarna T. Melanin in human irides of different color and age of donors. *Pigment Cell Res*. 2005; 18:454–464. [PubMed: 16280011]

Fig. 1. Iris color photographs of a A) brown B) blue C) green/hazel D) indeterminate* & E) partially heterochromic eye

Eye color was determined by one reviewing pediatric vitreoretinal specialist (DMM). The photographs were taken by RetCam III by a NICU-nurse trained in retinal image photography as a part of the Newborn Eye Screening Test (NEST). The images displayed in this figure represent the classic image for the eye color description.

*In some cases a subject's iris color did not easily fit these categories and was deemed indeterminate (panel D).

Fig. 2. Frequency of iris color among newborns detected after birth via retinal image photography screening

The majority of newborns had brown eyes at birth, with blue being the next most common eye color. One pediatric ophthalmologist reviewed the images and assessed eye color for each eye independently. 9.4% of infants had colors that did not clearly match the pre-assigned eye color templates and were deemed "Indeterminate". One case of partial heterochromia was identified, no cases of complete heterochromia were observed. Data are given as the percentage of newborns with count noted circumferentially.

Table 1

Prevalence of Iris Color of Newborns in the Newborn Eye Screening Test (NEST) study by Sex, Ethnicity and Race

Characteristic	No.	% (n)				
		Brown	Blue	Indeterminate	Green/Hazel	Partial Heterochromia
Overall	192	63.0 (121/192)	20.8 (40/192)	9.9 (19/192)	5.7 (11/192)	0.5 (1/192)
Sex						
Female	89	65.2 (58/89)	19.1 (17/89)	11.2 (10/89)	4.5 (4/89)	0.0 (0/89)
Male	103	61.1 (63/103)	22.3 (23/103)	8.7 (9/103)	6.8 (7/103)	1.0 (1/103)
Race/Ethnicity						
Hispanic or Latino	82	74.4 (61/82)	7.3 (6/82)*	11.0 (9/82)	7.3 (6/82)	0.0 (0/82)
Not Hispanic or Latino	109	54.1 (59/109)	31.2 (34/109)*	9.2 (10/109)	4.6 (5/109)	0.9 (1/109)
Race***						
Did Not Answer	73	76.1 (56/73)	5.5 (4/73)	9.6 (7/73)	8.2 (6/73)	0.0 (0/73)
White/Caucasian	64	34.4 (22/64)	54.7 (35/64)**	7.8 (5/64)	1.6 (1/64)	1.6 (1/64)
Asian	45	80.0 (36/45)	2.2 (1/45)**	13.3 (6/45)	4.4 (2/45)	0.0 (0/45)
Native Hawaiian or Pacific Islander	9	77.8 (7/9)	0.0 (0/9)	0.0 (0/9)	22.2 (2/9)	0.0 (0/9)
Black or African American	1	0.0 (0/1)	0.0 (0/1)	100.0 (1/1)	0.0 (0/1)	0.0 (0/1)

Note- Percentages may not add up to 100 due to rounding. The NEST study is a universal newborn screening initiative at Lucile Packard Children's Hospital where universal RetCam III screening is offered to all infants who otherwise did not meet retinopathy of prematurity screening criteria. The table above reports the one-year birth prevalence of iris color. Overall, brown was the most common eye color in the cohort.

* Significantly more newborns identified by parents as Not Hispanic or Latino had blue irides compared to those identified as Hispanic or Latino ($p < 0.0001$, chi-squared test).

** Infants whose parents identified as White/Caucasian were more likely to have blue irides when compared to infants whose parents identified them as Asian ($p < 0.0001$, Fisher's exact test) or Native Hawaiian or Pacific Islander ($p = 0.0032$, Fisher's exact test).

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Self-identified race was the only variable missing a significant portion (37.6%). All other variables had less than 5% missing values.