Trisomy 21 and Risk of Retinopathy of Prematurity

Tammy Z. Movsas, MD, MPH, Alan R. Spitzer, MD, Ira H. Gewolb, MD

BACKGROUND AND OBJECTIVES: Trisomy 21 is known to decrease the risk of several (nonocular) angiogenic-mediated diseases. The objective of this study was to determine whether trisomy 21 can also be shown to be significantly protective against ocular angiogenic-mediated disorders such as retinopathy of prematurity (ROP).

METHODS: A retrospective analysis of deidentified data from the Pediatrix BabySteps Clinical Warehouse. This large repository of neonatal data is approved for use in research studies by the Western Institutional Review Board. The study population consisted of 99,080 infants with very low birth weights (BW; BW < 1500 g), born between 1996 and 2013, cared for at >300 US NICUs, and who had been discharged alive from hospital. Statistical significance for unadjusted comparisons between groups was determined with Pearson’s χ² test or Student’s t test. Logistic regression models were used to calculate the odds of ROP (of any stage) and advanced ROP (stage 3 or greater) for infants with trisomy 21 compared with all other infants.

RESULTS: The prevalence of trisomy 21 was 0.3% in the study population (321 of 99,080). After adjustment for BW, gestational age, oxygen exposure, and other potential confounders, there was an odds ratio of 0.6 (95% confidence interval: 0.5–0.8) for ROP in infants with trisomy 21 compared with other infants and an odds ratio of 0.4 (95% confidence interval: 0.1–0.9) for advanced-stage ROP.

CONCLUSIONS: Trisomy 21 significantly decreases the odds for ROP in very low BW infant survivors. This study unmasks a potentially identifiable genetic component to ROP risk, paving the way for the development of a laboratory-based ROP screening tool.

WHAT’S KNOWN ON THIS SUBJECT: It is known that trisomy 21 decreases the risk of (nonocular) angiogenic-mediated disorders, such as solid tumors. It is not known whether trisomy 21 decreases the risk of ocular angiogenic-mediated disorders such as retinopathy of prematurity.

WHAT THIS STUDY ADDS: This study shows that trisomy 21 decreases the risk of retinopathy of prematurity (ROP), thus unmasking a potentially identifiable genetic component to ROP risk. This study paves the way for the future development of a laboratory-based ROP screening tool.
Because ∼10% of births worldwide are preterm, 13 million infants per year are potentially at risk of retinopathy of prematurity (ROP). The pathophysiology of ROP involves pathologic ocular angiogenesis, the formation of abnormal blood vessels arising from the retinal vascular tree. The more preterm the infant (ie, the larger the zone of the retina that is not yet vascularized), the higher is the risk of ROP. When ROP was first reported in the 1940s, it was highly associated with unregulated oxygen delivery to preterm infants. However, despite drastic reductions in oxygen delivery to preterm infants, ROP is still a common occurrence. In infants with a birth weight (BW) <1500 g, ROP incidence exceeds 25%, and in preterm infants with a BW <1000 g, ROP incidence exceeds 50%. Several studies have shown that individuals with trisomy 21 have a decreased risk of many nonocular, angiogenic-mediated diseases. For example, it is uncommon for individuals with Down syndrome (DS) to develop solid tumors and vascular anomalies. We propose that individuals with trisomy 21 may have decreased risk of ocular angiogenic-mediated diseases such as ROP. In other words, we hypothesize that the increase in gene expression of HSA21 genes, secondary to increased gene dosage in DS, may be protective against abnormal retinal neovascularization. At this time, the medical literature provides only scant epidemiologic evidence to support our hypothesis. For example, 1 small study found a very low prevalence of diabetic retinopathy (which is also an ocular angiogenic-mediated disease) among adults with DS with longstanding diabetes mellitus. A morbidity study of DS in a very low birth weight (VLBW) population (BW <1500 g) reported a trend toward decreased ROP risk in infants with DS; however, the number of infants with DS who had undergone ROP screening in their cohort was not large enough to provide statistical significance in multivariate analysis.

The objective of this epidemiology study was to determine whether trisomy 21 can be shown to be significantly protective against the angiogenic-associated ocular disorder of ROP in a large, high-risk neonatal population (ie, preterm infants with birth weight <1500 g). To achieve this objective, we used data from Pediatrix BabySteps (Pediatrix Medical Group, Sunrise, Florida) Clinical Data Warehouse (CDW), one of the world’s largest repositories of neonatal data, to examine ROP incidence in nearly 100 000 VLBW infants (of whom >300 of these infants had been diagnosed with DS).

**METHODS**

To populate our study, we used data from the Pediatrix BabySteps CDW, which contains information on >1 025 000 infants who had been cared for by Pediatrix Medical Group providers at hospitals all over the United States since 1996. At the current time, the Pediatrix Medical Group cares for nearly 25% of neonates in NICUs across the United States. The CDW captures diagnostic and procedure coding data from the Pediatrix Medical Group electronic health record, which strictly adheres to the American Academy of Pediatrics (AAP) Perinatal Section Coding Committee Guidelines. Data are automatically extracted from the daily medical record notes on each child admitted by Pediatrix physicians. All data entry is verified on an ongoing basis by the Pediatrix CDW information technology team and by a database manager.

The data from the Pediatrix BabySteps CDW is annually certified as deidentified and approved for use in research studies by the Western institutional review board (IRB). In addition, an exemption for any additional IRB approval for use of the deidentified data set in this study was granted by The Michigan State University IRB.

The following 3 inclusion criteria were used for the VLBW population for this study: (1) BW <1500 g, (2) hospitalization survival (ie, discharged from hospital alive), and (3) ophthalmomic ROP examination results recorded in medical record.

BW <1500 g was chosen as an inclusion criteria, because infants with a BW <1500 g are routinely screened for ROP per AAP and American Academy of Ophthalmology (AAO) guidelines. Hospitalization survival was chosen as an inclusion criterion because death before retinal maturation is complete can preclude the occurrence or progression of ROP. Because of this inclusion criterion, a higher percentage of VLBW infants with trisomy 21 (14.5%) were excluded from our study population because of the higher mortality rate for VLBW infants with trisomy 21 (14.5%) compared with the other VLBW infants (8.3%).

The Pediatrix BabySteps CDW repository was queried for infants meeting the criteria. Data from 99 080 deidentified infant entries from the CDW repository satisfied all 3 inclusion criteria; thus, data from these entries were used to compile the study data set. Of these 99 080 infants, 321 (0.3%) were diagnosed with trisomy 21. The study participants were born between 1996 and 2013 and had been NICU inpatients at 306 different hospitals across the United States. Trisomy 21 status was coded as positive for both partial (translocation) or complete HSA21 trisomy.

The diagnosis and stage of ROP were assigned by the board-certified ophthalmologists who performed the retinal ROP examinations for the
study participants. The retinal findings were standardized by classifying the examination results according to the International Classification of Retinopathy of Prematurity. The diagnosis and stage (as assigned by the ophthalmologist) were recorded in each study participant’s electronic medical record. In most cases, multiple ROP examinations had been performed for each infant; the most advanced stage of ROP noted in the medical record was recorded as the infant’s ROP stage. Although infants may have received additional ROP follow-up after hospital discharge, no postdischarge examination results were available for this study. However, given that the average age at discharge was at a postmenstrual age close to term, it is highly probable that ROP severity would have reached its peak for the vast majority of the study participants before being discharged from the hospital.

Infant characteristics, ROP, and neonatal comorbidities were compared between infants with trisomy 21 and all other infants (ie, infants without trisomy 21). Statistical significance for unadjusted comparisons between groups was determined with Pearson’s χ² test or Student’s t test. Logistic regression models were used to calculate odds of ROP (of any stage) and advanced ROP (stage 3 or greater) for infants with trisomy 21 compared with all other infants. Unadjusted and adjusted models were conducted for the cohort of VLBW infants as well as for a subcohort of infants with extremely low BW (BW <750 g). The trisomy 21 effect on odds of ROP incidence and 95% confidence intervals were calculated for each model. Analyses were performed by using SAS (SAS Institute, Cary, NC).

The final multivariate models were adjusted for the major known risk factors for ROP (BW, gestational age [GA], variables related to oxygen exposure) as well as for additional characteristics/morbidities that had been found to be significantly different between groups (eg, Apgar scores, congenital heart disorders [CHDs], and patent ductus arteriosus). Despite some collinearity, both BW and GA were included in the final model because these are known to be independent ROP risk factors, even within the VLBW population. 14,15 The variables related to oxygen exposure/ventilation included in the model were as follows: (1) number of days that fraction of inspired oxygen was >0.21, (2) number of days of high-flow nasal cannula administration, (3) number of days receiving ventilation, and (4) number of days receiving continuous positive airway pressure. The variable CHDs included any of the following: atrial septal defect, ventricular septal defect, pulmonary stenosis, and tetralogy of Fallot. The variables year of birth, hospital facility, and transfer status were examined in univariate and multivariate models but did not have any significant effect on odds of ROP; thus, they were not included in the final multivariate model.

**RESULTS**

Table 1 compares the characteristics of neonates with trisomy 21 with the other VLBW neonates in the study population. The prevalence of trisomy 21 was 0.3% in the study population (321 of 99 080). The infants with trisomy 21 were generally larger at birth (mean BW, GA, and Apgar scores at 1 minute and 5 minutes) compared with those without trisomy 21. However, adjustment for ROP risk factors and other significant group differences, there was 0.6 times the odds of any ROP for VLBW infants with trisomy 21 compared with other VLBW infants and 0.4 times the odds of advanced ROP for trisomy 21. In the subpopulation of neonates with a BW <750 g, there was 0.3 times the odds of ROP for infants with trisomy 21 compared with other VLBW infants in this subpopulation. Hospital, birth year, and transfer status yielded no significant effect on odds of ROP (results not shown).

**DISCUSSION**

In general, the more preterm the infant (and/or the lower the BW), the more likely that the infant is more ill (and thus requires more procedures, medications, oxygen administration, etc) and is more likely to spend more time in the NICU before discharge. It is not possible to adjust for all factors. However, the major ROP risk factors of BW, GA, and oxygen exposure as well as any other significant differences that we found between the groups with and without trisomy 21 were adjusted for in our analyses. Our multivariate analysis affirmed our hypothesis that trisomy 21 significantly decreases the odds of the incidence of any stage of ROP in VLBW survivors. In addition, multivariate analysis also revealed that trisomy 21 significantly decreases the odds of advanced-stage ROP (stages 3–5) in the same population.

Every few years, the AAO and the AAP review and discuss current ROP data and issue a joint policy statement with regard to screening.
recommendations for ROP. Their goal is to screen infants at significant risk of ROP so that treatment can be initiated (if needed). The most recent policy statement of the AAO and AAP (issued in 2013) continues to recommend ROP screening for all infants with either a BW <1500 g or a GA of <30 weeks.13 Thus, all infants in our study (ie, all study participants had BWs <1500 g) were considered to be at risk of significant ROP (ie, ROP that may need treatment).13

Nevertheless, both BW and GA are independent ROP risk factors and thus they were included (as continuous variables) in our multivariate analyses.3,4 We also performed a subanalysis of infants with BWs <750 g (all of whom had a GA of <30 weeks), because these infants are most vulnerable for ROP. Our analysis of this subgroup revealed that the protective effect of trisomy 21 on the incidence of ROP is magnified for this subgroup. We also found a trend toward an increasing protective effect of trisomy 21 against advanced-stage ROP in the infants with BWs <750 g; however, significance was most probably lost secondary to the much smaller numbers of infants with trisomy 21 in this group.

Consistent with findings from a previous trisomy 21 VLBW study,10 the mortality rate for VLBW infants with trisomy 21 from the Pediatrix database (which was used in this study) is much higher than for other VLBW infants (14.5% vs 8.3%). This higher mortality rate is probably due to the much higher rate of CHD in the trisomy 21 population. It is specifically because of this higher mortality rate that we chose to examine ROP incidence only in VLBW survivors. If we had included all VLBW infants, we would not have known whether the decreased incidence in ROP had been a result of the increased mortality rate in infants with trisomy 21 (ie, less opportunity to develop the disease). Thus, by choosing to examine ROP in VLBW survivors, we have intentionally eliminated death as a competing outcome with ROP. In other words, because all of the infants in our study survived, all of them had “equal opportunity” for the disease to either develop or progress. (Note that we did adjust for CHD in our analyses.)

There has been growing support for the role of genetic factors accounting for the liability of ROP. Twin studies suggest that genetic factors may account for as high as 70% of the variance in ROP development.16 In addition, several single nucleotide polymorphisms associated with ROP have been identified.17,18 However, because it is not fully known which mutations are expressed, caution needs to be exercised in associating single nucleotide polymorphisms with ROP risk.17,18 The most critical result of our study is the unmasking of a new, potentially identifiable genetic component to ROP risk. In the case of trisomy 21, increased gene

### TABLE 1 Comparison of Characteristics of Neonates With and Without Trisomy 21 in a VLBW Cohort (BW <1500 g)

<table>
<thead>
<tr>
<th></th>
<th>Trisomy 21 (N = 321)</th>
<th>Non-Trisomy 21 (N = 98759)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, % (n)</td>
<td>52 (169)</td>
<td>51 (48972)</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Race/ethnicity, % (n)</td>
<td></td>
<td></td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>White</td>
<td>50 (159)</td>
<td>47 (46423)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>17 (53)</td>
<td>26 (25619)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4 (14)</td>
<td>3 (3201)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>30 (95)</td>
<td>24 (23516)</td>
<td></td>
</tr>
<tr>
<td>GA, wk</td>
<td>30.1 ± 2.5</td>
<td>28.1 ± 2.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>BW, g</td>
<td>1140 ± 250</td>
<td>1040 ± 271</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Apgar score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 minute</td>
<td>6.1 ± 2.2</td>
<td>5.4 ± 2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 5 minutes</td>
<td>7.8 ± 1.5</td>
<td>7.5 ± 1.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chronological age at hospital discharge, wk</td>
<td>10.0 ± 5.1</td>
<td>9.6 ± 4.9</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>FiO2 &gt;0.21, number of days</td>
<td>32.5 ± 30.2</td>
<td>32.7 ± 32.9</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Receiving high-fresh nasal cannula, number of days</td>
<td>11.8 ± 19.6</td>
<td>9.7 ± 14.9</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Receiving ventilation, number of days</td>
<td>10.2 ± 21.9</td>
<td>13.9 ± 24.7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Receiving CPAP, number of days</td>
<td>5.6 ± 10.8</td>
<td>8.8 ± 12.9</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Data are presented as means ± SDs unless otherwise indicated. CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen.

### TABLE 2 Comparison of ROP and Other Comorbidities of Neonates With Trisomy 21 to Neonates Without Trisomy 21 in a VLBW Cohort (BW <1500 g)

<table>
<thead>
<tr>
<th></th>
<th>Trisomy 21 (N = 321)</th>
<th>Non-Trisomy 21 (N = 98759)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROP, % (n)</td>
<td>19.3 (62)</td>
<td>37.8 (38915)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Advanced ROP (stages 3–5)</td>
<td>2.2 (7)</td>
<td>6.5 (6429)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treated for ROP (cryo, laser; surgery)</td>
<td>1.3 (4)</td>
<td>3.6 (3593)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Other disorders, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHDs (ASD, VSD, pulmonary stenosis, tetralogy of Fallot)</td>
<td>37.4 (120)</td>
<td>9.8 (9700)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PDA</td>
<td>48.9 (157)</td>
<td>40.5 (40029)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Brain hemorrhage (any type)</td>
<td>0.9 (3)</td>
<td>0.3 (330)</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>8.8 (22)</td>
<td>7.0 (6649)</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>29.6 (95)</td>
<td>25.5 (25222)</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>Sepsis</td>
<td>11.5 (37)</td>
<td>14.0 (13833)</td>
<td>Nonsignificant</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; cryo, cryotherapy; VSD, ventricular septal defect; cryo, cryotherapy; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
Extremely low BW subcohort (agents or as potential ROP investigated as either antiangiogenic already independently being dismutase, and regulator of genes (endostatin, superoxide least 3 proteins encoded by HSA21 targets ROP protection. Indeed, at may include a set of genes that explain some of the variability in ROP risk for these infants. However, even if they all did have a complete extra dosage, attributable to an extra copy of HSA21, appears to result in an increase in gene expression for a number of HSA21 genes.19,20 Because trisomy 21 significantly decreases the odds of ROP, HSA21 may include a set of genes that targets ROP protection. Indeed, at least 3 proteins encoded by HSA21 genes (endostatin, superoxide dismutase, and regulator of calcineurin 1 [RCAN 1]) are already independently being investigated as either antiangiogenic agents or as potential ROP protectants.16,19,21 Endostatin has been shown to inhibit endothelial cell proliferation, migration, and retinal angiogenesis in vitro and in vivo.22,23 Superoxide dismutase, an essential enzyme in the metabolism of free radicals, has been shown to ameliorate oxygen-induced retinopathy in transgenic mice.24 RCAN1 has been shown to inhibit pathologic angiogenesis via a vascular endothelial growth factor (VEGF)–mediated negative-feedback loop mechanism.25–27 Of note, our trisomy 21 data do not distinguish between the presence of a complete additional chromosome versus partial translocations. Thus, not all infants with trisomy 21 in our study have increased gene dosage for all HSA21 genes. This deficiency may explain some of the variability in ROP risk for these infants. However, even if they all did have a complete extra chromosome, we would still not expect all infants with trisomy 21 (with equal HSA21 gene dosage) to have equivalent gene expression profiles. Gene dosage is only one of many factors impacting gene expression; additional factors, such as developmental and tissue-specific differences to name a few, dynamically interplay to create a gene expression profile at a given point in time. Along the same line of reasoning, we would not expect all infants with normal gene dosage (ie, infants without trisomy 21) to have equal expression of genes targeted for ROP risk. Furthermore, increases in HSA21 gene expression have global transcriptional consequences for genes on other chromosomes as well.28,29 However, by analyzing and comparing the gene expression profiles of VLBW infants with trisomy 21 (with and without ROP) with other VLBW infants (with and without ROP) at a time period coincident with ROP development (ie, 4–8 weeks after preterm birth), a unique genetic signature associated with ROP risk may be able to be identified.

The importance of the quest for an ROP genetic signature resides in the need for an ROP screening test that does not rely on ocular examination. Ocular ROP examinations are far from benign for fragile neonates. Examination-induced neonatal distress is evidenced by changes in pulse rate and oxygen saturation.30 Retinal hemorrhages have been reported from ocular manipulation and dilating eye drops can have adverse systemic effects.31 Most worrisome is the increase in apneic events that occur in the 24- to 48-hour postexamination period.30,31 In addition, there is a shortage of ophthalmologists willing to perform ROP examinations secondary to limited reimbursement, time constraints, and liability risks.32 Thus, an ROP screening tool, such as one based on HSA21 gene expression profile, could limit the need for ophthalmic assessment, thereby conserving resources and preventing exposure to harm.

Limitations of this study included the large number of different ophthalmologists who performed the ROP examinations in >300 NICUs over a 15-year period. However, to account for examiner differences and any changes in secular trends regarding ROP over time, the variables of birth year, hospital facility, and hospital transfer status were examined in univariate and multivariate analyses and eliminated as potential confounders. In addition, our data were limited to results of ROP examinations performed before hospital discharge. Given that the mean age at discharge was ~10 weeks old (chronological age), the majority of the ROP examinations would have occurred before discharge.

For many years, the neonatal mouse model of oxygen-induced retinopathy has been the cornerstone of ROP animal investigations. In this model, retinopathy is induced in 7-day-old mice by a 5-day exposure to 75% oxygen.33 The protective mechanism of DS for ROP may be able to be studied in an animal model by following a similar oxygen-induced retinopathy protocol but by using neonatal "DS" mice (instead of wild-type mice as are usually used).

### Table 3

<table>
<thead>
<tr>
<th>Trisomy 21 Effect on Odds of ROP Incidence in a VLBW (BW &lt;1500 g) Cohort and in an Extremely Low BW (BW &lt;750 g) Subcohort</th>
<th>Trisomy 21 Effect on Odds of ROP Incidence, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLBW cohort (N = 99 080)</td>
<td>Univariate Logistic Regression</td>
</tr>
<tr>
<td>With ROP (of any stage)</td>
<td>0.4 (0.3–0.5)</td>
</tr>
<tr>
<td>With advanced ROP (stages 3–5)</td>
<td>0.5 (0.1–0.8)</td>
</tr>
<tr>
<td>Extremely low BW subcohort (N = 16 549)</td>
<td>Multivariate Logistic Regression</td>
</tr>
<tr>
<td>With ROP (of any stage)</td>
<td>0.3 (0.1–0.6)</td>
</tr>
<tr>
<td>With advanced ROP (stages 3–5)</td>
<td>0.5 (0.1–0.5)</td>
</tr>
</tbody>
</table>

Multivariate logistic regression adjusted for GA, BW, CHDs, patent ductus arteriosus, Apgar scores, and oxygen exposure (FiO2 [fraction of inspired oxygen] and number of days receiving ventilation, high-flow nasal cannula, and continuous positive airway pressure) CI, confidence interval; OR, odds ratio.
CONCLUSIONS
The demonstration that trisomy 21 is protective against the angiogenic-associated ocular disorder of ROP opens up avenues for future research. These findings support the possibility that trisomy 21 may also be protective against other angiogenic-associated ocular disorders such as diabetic retinopathy. Most important, it opens the door for an HSA21 gene expression profile to be potentially incorporated into an ROP screening tool, which may, in turn, translate into new therapies.

ACKNOWLEDGMENTS
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REFERENCES

ABBREVIATIONS
AAO: American Academy of Ophthalmology
AAP: American Academy of Pediatrics
BW: birth weight
CDW: Pediatrix BabySteps Clinical Data Warehouse
CHD: congenital heart disorder
DS: Down syndrome
GA: gestational age
IRB: institutional review board
ROP: retinopathy of prematurity
VLBW: very low birth weight
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