Brief report

Incidence and clinical implications of GATA1 mutations in newborns with Down syndrome

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Somatic mutations in the GATA1 gene are present in almost all cases of Down syndrome (DS)-associated acute megakaryoblastic leukemia (AMKL) and transient leukemia (TL). An in utero origin of the GATA1 mutation suggests it is an early leukemogenic event. To determine the detectable incidence and clinical relevance of GATA1 mutations in DS newborns, we screened Guthrie cards from 590 DS infants for mutations in the GATA1 gene. Twenty-two (3.8%) of 585 evaluable infants harbored a predicted functional GATA1 mutation; 2 were identified exclusively within intron 1. Hispanic newborns were 2.6 times more likely to have a mutated GATA1 gene than non-Hispanics (P = .02). Two newborns with a GATA1 mutation subsequently developed AMKL, and none of the infants without a functional GATA1 mutation were reported to have developed leukemia. In addition, GATA1 mutations were detected in 2 of 21 neonatal blood-spot samples from DS children.10 GATA1 mutations were also found at birth in DS infants who later developed AMKL, including cases that did not have diagnosed TL,10 suggesting that either the TL was subclinical or that GATA1 mutations in the absence of TL still participate in leukemia development. To determine the incidence of GATA1 mutations in a large cohort of DS newborns, we screened 590 blood spots from DS neonates. We then examined the association between the GATA1 mutations and risk of developing AMKL in the study population.

Introduction

Newborns with Down syndrome (DS) are at an increased risk of being diagnosed with transient leukemia (TL), or transient myeloproliferative disorder, which is characterized by an accumulation of immature clonal megakaryoblasts in the peripheral blood and liver. The disease usually spontaneously resolves within 3 months, although in rare cases it is fatal due to hepatic fibrosis or liver failure.1-3 Children with DS have a 1 in 500 chance of developing acute megakaryoblastic leukemia (AMKL),4-6 and 19% of DS (or trisomy 21) neonates are diagnosed with TL develop AMKL within 4 years.3,7

Somatic mutations of GATA1 are found in almost all cases of DS or mosaic trisomy 21–associated TL and AMKL.8 GATA1 mutations have not been detected in healthy children without DS, in DS children with other types of leukemia, or in AMKL cells of non-DS/non–trisomy 21 mosaic children, with the exception of a single case of adult AMKL without DS or acquired trisomy 21.3,9 This suggests that GATA1 mutations play an important role in TL and AMKL development in the DS/mosaic trisomy 21 setting. We and others have shown that the GATA1 mutation is cleared after resolution of TL or AMKL,10-13 and therefore the GATA1 mutation appears to be restricted to the blast cells. All reported mutations occur in the 5’ end of the gene, mostly within exon 2. Mutations either introduce a premature stop codon, a frameshift, or the loss of exon 2 from altered splicing, resulting in the expression of a shortened GATA1 protein, termed GATA1s, that lacks exon 2 and its N-terminal transactivation domain.14

The overall incidence of GATA1 mutations in DS infants and their clinical relevance for predicting development of AMKL is uncertain. GATA1 mutations were detected in 2 of 21 neonatal blood-spot samples from DS children.10 GATA1 mutations were also found at birth in DS infants who later developed AMKL, including cases that did not have diagnosed TL,10 suggesting that either the TL was subclinical or that GATA1 mutations in the absence of TL still participate in leukemia development. To determine the incidence of GATA1 mutations in a large cohort of DS newborns, we screened 590 blood spots from DS neonates. We then examined the association between the GATA1 mutations and risk of developing AMKL in the study population.

Patients, materials, and methods

Guthrie cards from 590 DS infants born in New York State between January 1997 and December 1999 were obtained from the New York Congenital Malformation Registry. Infants were matched to the New York State Cancer Registry (Albany, New York State Department of Health). The institutional review boards of New York Medical College, Westchester Medical Center, and the New York State Department of Health approved this project. Informed consent was obtained in accordance with the Declaration of Helsinki.

DNA samples were screened for GATA1 mutations by single-strand conformation polymorphism (SSCP) and sequencing of polymerase chain reaction (PCR) products, as described.11 Sixty samples were randomly chosen and analyzed in an independent assay. Potential single-nucleotide polymorphisms (SNPs) were compared with known SNPs.15,16 Potential splicing aberrations were analyzed by using GENSCAN17,18 and NNSPLICE version 0.9.19

Calculations were performed using STATA software v.9.0 (Stata, College Station, TX) using 2-tailed χ2 or Fisher exact tests or analysis of variance (ANOVA).


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Table 1. Characteristics of Down syndrome infants and incidence of GATA1 mutations

<table>
<thead>
<tr>
<th></th>
<th>Wild-type GATA1</th>
<th>Mutated GATA1</th>
<th>P</th>
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<tbody>
<tr>
<td>n</td>
<td>563</td>
<td>22</td>
<td>—</td>
</tr>
<tr>
<td>Sex, no.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>284</td>
<td>15</td>
<td>—</td>
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<tr>
<td>Female</td>
<td>279</td>
<td>7</td>
<td>.10†</td>
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<td></td>
</tr>
<tr>
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<td>439</td>
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<td>—</td>
</tr>
<tr>
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<td>97</td>
<td>1</td>
<td>.15‡</td>
</tr>
<tr>
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<td>24</td>
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<td>0</td>
<td>—</td>
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<td></td>
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<tr>
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</tr>
<tr>
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<td>409</td>
<td>12</td>
<td>.02†</td>
</tr>
<tr>
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<td>72</td>
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<td>44</td>
<td>1</td>
<td>—</td>
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<tr>
<td>Mean age of mother, y</td>
<td>33.0</td>
<td>34.5</td>
<td>.31§</td>
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<tr>
<td>Developed AMKL, no.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>2</td>
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</tr>
<tr>
<td>No</td>
<td>563</td>
<td>20</td>
<td>.001‡</td>
</tr>
</tbody>
</table>

— indicates not applicable
*Compared with those with a Hispanic ethnicity with any race.
†χ² test.
‡Fisher exact test.
§ANOVA test.
| One patient developed leukemia of unspecified phenotype.

Results and discussion

Frequency and spectrum of GATA1 mutations in DS infants

Table 1 summarizes the selected demographic characteristics of the infants. There was a 99.2% completion rate (585 samples) and a 100% concordance rate (3/60 duplicated samples harbored a mutation). Twenty-eight (4.8%) of 585 DS infants had mutations within intron 1 or exon 2 (Table 2). The sensitivity of detection was 5% (data not shown).

Twenty-one GATA1 mutations from 20 patients were within exon 2 and predicted to express only the GATA1s isoform (Table 2). Functional expression of only the GATA1s isoform (Table 2). Functional analysis is required to confirm that the splicing site was abolished. The mutations in patients 21 and 22 were both Hispanic males who developed AMKL at the ages of 11 and 17 months, respectively. The mutation in patient 22 was located within intron 1. Unfortunately, DNA was not available from the time of AMKL diagnosis, so it is unknown if this mutation was present in the AMKL blasts. Of the 563 DS infants who had only a wild-type GATA1 detected, there were no cases of leukemia reported. Based on estimates from migration data from the United States Census Bureau, approximately 56 (9.6%) children in our study population moved outside New York State and thus were lost to follow-up of cancer. Because 1 in 500 DS children will develop AMKL, it is possible, but unlikely, that a child in our study population who moved out of New York State developed AMKL.

Concordance of GATA1 mutations in twins

Three sets of twins were revealed after the analyses were completed. Two sets were African-American females who carried wild-type GATA1. The third set, Hispanic males (pts 12 and 13), carried identical GATA1 exon 2 mutations. This finding is consistent with previous reports of the same GATA1 mutation being present in twins with AMKL.22 and confirms the prenatal origin of GATA1 mutations.

Subsequent leukemia in DS infants

Two of the patients with a known functional GATA1 mutation were reported to subsequently develop leukemia. Patients 10 and 22 were both Hispanic males who developed AMKL at the ages of 11 and 17 months, respectively. The mutation in patient 22 was located within intron 1. Unfortunately, DNA was not available from the time of AMKL diagnosis, so it is unknown if this mutation was present in the AMKL blasts. Of the 563 DS infants who had only a wild-type GATA1 detected, there were no cases of leukemia reported. Based on estimates from migration data from the United States Census Bureau, approximately 56 (9.6%) children in our study population moved outside New York State and thus were lost to follow-up of cancer. Because 1 in 500 DS children will develop AMKL, it is possible, but unlikely, that a child in our study population who moved out of New York State developed AMKL.

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**Authorship**

Contribution: S.R.P. designed and supervised research and wrote the manuscript; Q.G. performed research and analyzed data; C.Y. performed research and analyzed data; S.J. designed research and reviewed the manuscript; C.M.D. contributed patients and data; and C.S. designed and supervised research and reviewed the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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