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***TINF2* Mutations in Children With Severe Aplastic Anemia**

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To the Editor: Dyskeratosis congenita (DC), a bone marrow failure (BMF) syndrome associated with skin abnormalities, dystrophic nails, and leukoplakia, has been linked to mutations in genes that encode components of telomerase (dyskerin, *TERC*, *TERT*, *NHP2*, and *NOP10*). Recently, one of the components of the shelterin complex, *TIN2*, which is encoded by the *TINF2* gene, was found to be mutated in some patients with autosomal dominant DC and in sporadic cases of DC [1,2]. Autosomal dominant forms of DC caused by mutations in *TERT* or *TERC* are often mild; many of these patients present with only BMF and are indistinguishable from individuals with idiopathic severe aplastic anemia (SAA) or myelodysplastic syndrome (MDS).

In a recent issue of the journal, Pigullo et al. [3] hypothesized that mutations in *NOLA1* (also known as *GARI*), which encodes another component of the telomerase complex, might account for some cases of aplastic anemia (AA) in children. Of 108 patients with AA screened, none had a pathogenic mutation [3].

We postulated that *TINF2* mutations might underlie some cases of idiopathic AA in childhood. To address this, we analyzed DNA samples from an anonymous registry [4] of pediatric patients who underwent unrelated donor hematopoietic stem cell transplantation (UD-HSCT) for SAA (n = 109) or MDS (n = 137). We focused our mutational analysis on exon 6 of the gene, the site of all known *TINF2* mutations linked to DC [1,2]. We identified potentially pathogenic mutations in 6 of 109 patients with SAA. A 2-year-old Caucasian male and a 10-year-old Caucasian male were heterozygous for *TINF2* G845A (R282H), a mutation previously shown to cause DC with early onset AA [1,2]. A 6-year-old Caucasian female and a 17-year-old Caucasian male were heterozygous for C844T (R282C), another missense mutation linked to DC [2]. A 7-year-old Hispanic boy was heterozygous for a single nucleotide insertion that alters the *TIN2* sequence beginning at residue 290 and introduces a stop codon (F²⁹⁰R²⁹¹N²⁹² → P²⁹⁰L²⁹¹X). The remaining patient, a 4-year-old

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Hispanic girl, was heterozygous for the missense mutation T862C (F288L). The phenylalanine residue at position 288 of human TIN2 is conserved in chimpanzee, rat, and dog, whereas mouse and cow have a leucine residue at this position [1]. Therefore, it is unclear whether the F288L substitution is deleterious. No *TINF2* mutations were detected in patients with MDS ($P < 0.01$). Previously, 298 healthy control individuals of diverse ethnicities were screened for *TINF2* mutations [1]; none had a TIN2 sequence change near amino acid 282 ($P < 0.001$). We conclude that a significant proportion of patients who underwent UD-HSCT for SAA harbored mutations in *TINF2* and may have had occult DC.

Among pediatric patients with SAA in the registry, *TINF2* mutations were more common than *TERC* mutations (5.5% vs. 0%, $P < 0.01$) [4]. In pedigrees with DC due to mutation of *TERC*, signs and symptoms of the disease usually present in adulthood. Our findings, coupled with those of other investigators [1,2], suggest that mutation of *TINF2* is more likely to manifest during childhood as SAA. In contrast, *TERC* and *TERT* gene mutations are associated with MDS and possibly acute myelogenous leukemia later in life.

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