To the editor:

Fetal origin of the *GATA1* mutation in identical twins with transient myeloproliferative disorder and acute megakaryoblastic leukemia accompanying Down syndrome

GATA1 mutations have been found in almost all cases of transient myeloproliferative disorder (TMD) and acute megakaryoblastic leukemia (AMKL) accompanying Down syndrome (DS).[1-6] The mutations of the *GATA1* gene, which is located on chromosome X, may occur prenatally or perinatally in individuals with TMD. Recently, Rainis et al[4] reported that the same *GATA1* mutation was found in identical twins with AMKL and acquired trisomy 21. This suggested that the mutation occurred in one of the twins in utero, that this twin did not have DS, and that preleukemic cells migrated to the other twin through embryonic blood connections.[4,7] However, no unambiguous evidence has yet been presented for the prenatal timing of the *GATA1* mutation in the patient with TMD and DS. We recently encountered identical twin females who had TMD with DS.

The 34-year-old mother was admitted to our hospital because of threatened premature delivery at 29 weeks of gestation. Because ultrasonography revealed hydrops fetalis in one of the twins, they were delivered by cesarean section at 32 weeks of gestation. Both of the twins showed leukocytosis from birth and were diagnosed as TMD. We analyzed the *GATA1* mutation in peripheral blood samples from both patients. Written informed consent was obtained from their parents. Genomic DNA was extracted and cDNA was constructed, and then polymerase chain reaction (PCR) was performed and the products were sequenced directly, as described previously.[6] Both patients had an identical mutation in the *GATA1* gene. An insertion of 20 nucleotides corresponding to a sequence in exon 2 of the *GATA1* gene was detected, resulting in the introduction of a premature stop codon in the gene sequence encoding the N-terminal activation domain (Figure 1). Both cases evolved to myelodysplastic syndrome after spontaneous resolution 13 months later, and the older twin sister died of pulmonary bleeding because of uncontrolled pulmonary hypertension. The other twin's disease evolved to AMKL at the age of 15 months. The identical mutation was also found in her AMKL blast cells. This unique *GATA1* mutation found in identical twin females provides unequivocal evidence that cases of TMD in identical twins have a common clonal origin. The only plausible explanation is as follows: following initiation of TMD in one twin fetus, clonal progeny spread to the cotwin via vascular anastomoses within a single, monochorionic placenta, like those found in cases of leukemia in infantile identical twins.[8,9] Our results provide definitive evidence that *GATA1* mutations occur in utero in cases of AMKL with DS.

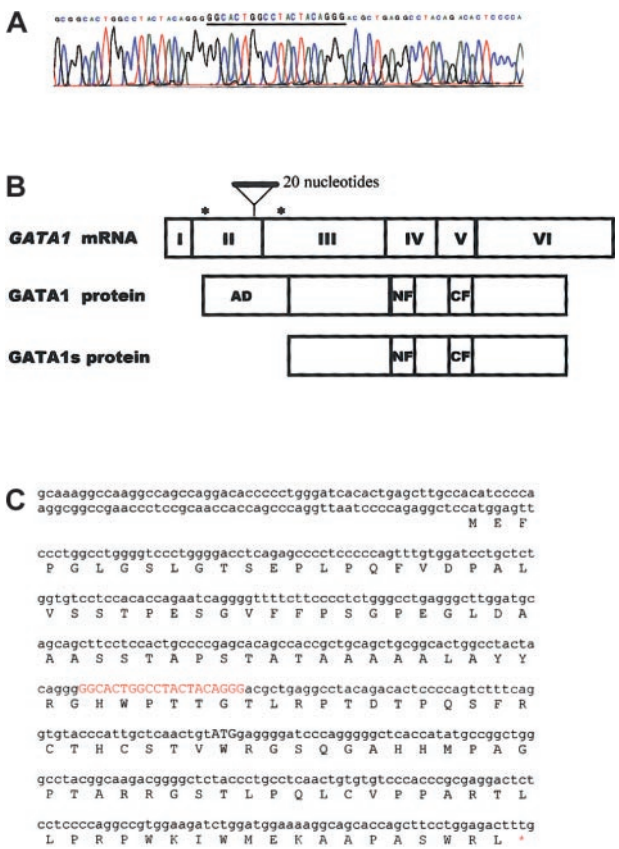

Figure 1. An identical GATA1 mutation in twins with TMD accompanying DS. (A) Direct sequence analysis of cDNA and genomic DNA from TMD blast cells of identical twins with DS showed that 20 nucleotides of the duplicated sequences were inserted in exon 2 of the *GATA1* gene in both patients. (B-C) The mutation resulted in the introduction of a premature stop codon in the gene sequence encoding the N-terminal activation domain. The predicted protein, GATA-1s, lacks the transactivation domain.

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References

1. Wechsler J, Greene M, McDevitt MA, et al. Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. Nat Genet. 2002;32:148-152.
2. Mundschau G, Gurbuxani S, Gamis AS, et al. Mutagenesis of GATA1 is an initiating event in Down syndrome leukemogenesis. Blood. 2003;101:4298-4300.
3. Hitzler JK, Cheung J, Li Y, et al. GATA1 mutations in transient leukemia and acute megakaryoblastic leukemia of Down syndrome. Blood. 2003;101:4301-4304.
4. Rainis L, Bercovich D, Strehl S, et al. Mutations in exon 2 of GATA1 are early events in megakaryocytic malignancies associated with trisomy 21. Blood. 2003;102:981-986.
5. Groet J, McElwaine S, Spinelli M, et al. Acquired mutations in GATA1 in neonates with Down's syndrome with transient myeloid disorder. Lancet. 2003;361:1617-1620.
6. Xu G, Nagano M, Kanezaki R, et al. Frequent mutations in the GATA-1 gene in the transient myeloproliferative disorder of Down's syndrome. Blood. 2003;102:2960-2968.
7. Stark B, Jeison M, Preudhomme C, et al. Acquired trisomy 21 and distinct clonal evolution in acute megakaryoblastic leukaemia in young monozygotic twins. Br J Haematol. 2002;118:1082-1086.
8. Wiemels JL, Cazzaniga G, Daniotti M, et al. Prenatal origin of acute lymphoblastic leukaemia in children. Lancet. 1999;354:1499-1503.
9. Greaves M, Maia AT, Wiemels JL, Ford AM. Leukemia in twins: lessons in natural history. Blood. 2003;102:2321-2333.