Screening for c-mpl mutations in patients with congenital amegakaryocytic thrombocytopenia identifies a polymorphism [letter]

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DOI
10.1182/blood.V97.11.3675

Publication date
2001

Published in
Blood

2. Woods WG, Sanders JE, Neudorf S. Treatment of acute myeloid leukemia [letter]. New Engl J Med. 1999;340:1437-1438.
3. Stevens RF, Hann IM, Wheatley K, Gray RG. Marked improvements in outcome with chemotherapy alone in paediatric acute myeloid leukaemia: results of the United Kingdom Medical Research Council's 10th AML trial. Br J Haematol. 1998;101:130-140.
4. Woods, WG, Kobrinsky N, Buckley JD, et al. Timed-sequential induction therapy improves postremission outcome in acute myeloid leukemia: a report from the Children's Cancer Group. Blood. 1996;87:4979-4989.
5. Thomas ED, Buckner CD, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission. New Engl J Med. 1979;301:597-599.
6. Clift RA, Buckner CD, Thomas ED, et al. The treatment of acute nonlymphoblastic leukemia by allogeneic marrow transplantation. Bone Marrow Transplantation. 1987;2:243-258.
7. Davies SM, Wagner JE, Shu XO, et al. Unrelated donor bone marrow transplantation for children with acute leukemia. J Clin Oncol. 1997:15:557-565.
8. Creutzig U, Ritter J, Zimmerman M, et al. Idarubicin improves blast cell clearance during induction therapy in children with AML: results of the study AML-BFM 93. Leukemia. 2001;15:348-354.
9. Creutzig U, Zimmermann M, Ritter J, et al. Definition of a standard-risk group in children with AML. Br J Haematol. 1999;104:630-639.
10. Cantu-Rajnoldi A, Biondi A, Jankovic M, et al. Diagnosis and incidence of acute promyelocytic leukemia (FAB M3 and M3 variant) in childhood. Blood. 1993;81: 2209-2210.
11. Davies SM, Robison LL, Buckley JD, et al. Glutathione-S transference polymorphisms and outcome of chemotherapy in childhood AML. J Clin Oncol. 2001;19:1279-1287.
12. Creutzig U, Ritter J, Zimmerman M, Schellong G. Does cranial irradiation reduce the risk for bone marrow relapse in acute myelogenous leukemia? unexpected results of the childhood acute myelogenous leukemia study BFM-87. J Clin Oncol. 1993;11:279-286.
13. Jankovic M, Brouwers P, Valsecchi MG, et al. Association of 1800 cGy cranial irradiation with intellectual function in children with acute lymphoblastic leukaemia. Lancet. 1994;344:224-227.

To the editor:

Screening for *c-mpl* mutations in patients with congenital amegakaryocytic thrombocytopenia identifies a polymorphism

Congenital amegakaryocytic thrombocytopenia (CAMT) is an uncommon disorder, characterized by an isolated thrombocytopenia and the almost complete absence of megakaryocytes in the bone marrow. Several studies have indicated that the origin of CAMT is an intrinsic stem cell defect.[1-3] Recently, we and others have demonstrated the presence of mutations in the thrombopoietin-receptor gene, *c-mpl*, as a possible cause of CAMT.[4-7] Although some mutations directly predict loss of Mpl function, it has not been established that others, notably those that lead to an amino acid substitution, also directly predict this loss.

To exclude that the mutations we found in our patients represent non–disease-related polymorphisms, we screened 50 healthy donors (100 alleles) for the presence of the different mutations by either sequence analysis or allele-specific restriction analysis.[4] None of the healthy donors were carriers of our reported CAMT-associated mutations. In one new CAMT patient, 3 heterozygous mutations were observed: a G-to-C substitution at nucleotide 305 in exon 3, predicting an arginine-to-proline substitution at codon 102; a G-to-A transition at position 340, also in exon 3, leading to valine-to-methionine replacement at codon 114 (Mpl-114V/M); and a G-to-C substitution in the fifth nucleotide of intron 3, which leads to loss of the splice site 3′ of exon 3. Screening of 50 healthy donors revealed that 4 were heterozygous carriers of the G340A mutation. The other mutations were not observed in this population. The *c-mpl-340A* gene thus seems to have a frequency of 0.04 in a white Dutch population. Functional studies should reveal whether this Mpl-114V/M polymorphism influences the function of Mpl.

Recently, Ballmaier et al[7] reported *c-mpl* mutations in another series of patients with CAMT. One of their patients was a homozygous carrier for 2 different point mutations. One mutation predicted a stopcodon in exon 3. The second mutation was the G340A mutation, which we also found in healthy donors. Therefore, we propose that the first mutation plays a role in the development of CAMT in this patient. The G340A may not be involved in CAMT, and its presence in 2 CAMT patients may be incidental.

In conclusion, mutations that predict amino-acid substitutions found by genetic screening of patients with CAMT can be due to polymorphisms of the *c-mpl* gene. The relation of such mutations to disease should be proven by functional studies with the mutated protein.

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References

1. Muraoka K, Ishii E, Tsuji K, et al. Defective response to thrombopoietin and impaired expression of c-mpl mRNA of bone marrow cells in congenital amegakaryocytic thrombocytopenia. Br J Haematol. 1997;96:287-292.
2. Freedman MH, Estrov Z. Congenital amegakaryocytic thrombocytopenia: an intrinsic hematopoietic stem cell defect. Am J Pedriatr Hematol Oncol. 1990;12: 225-230.
3. Scarlett JD, Williams NT, McKellar WJ. Acquired amegakaryocytic thrombocytopaenia in a child. J Paediatr Child Health. 1992;28:263-266.
4. van den Oudenrijn S, Bruin M, Folman CC, et al. Mutations in the thrombopoietin receptor, Mpl, in children with congenital amegakaryocytic thrombocytopenia. Br J Haematol. 2000;110:441-448.
5. Ihara K, Ishii E, Eguchi M, et al. Identification of mutations in the c-mpl gene in congenital amegakaryocytic thrombocytopenia. Proc Natl Acad Sci U S A. 1999;96:3132-3136.
6. Tonelli R, Scardovi AL, Pession A, et al. Compound heterozygosity for two different amino-acid substitution mutations in the thrombopoietin receptor (c-mpl gene) in congenital amegakaryocytic thrombocytopenia (CAMT). Hum Genet. 2000;107:225-233.
7. Ballmaier M, Germeshausen M, Schulze H, et al. c-mpl mutations are the cause of congenital amegakaryocytic thrombocytopenia. Blood. 2001;97:139-146.