ACKNOWLEDGMENT

Supported by grants from the Medical Research Council of Canada and the National Cancer Institute of Canada.

Trena Sutcliffe
Loning Fu
Jacinthe Abraham
Homayoun Vaziri
Samuel Benchimol
Division of Cellular/Molecular Biology
Ontario Cancer Institute
Princess Margaret Hospital
Department of Medical Biophysics
University of Toronto
Toronto, Ontario, Canada

REFERENCES


Juvenile Genetic Hemochromatosis Is Clinically and Genetically Distinct From the Classical HLA-Related Disorder

To the Editor:

Genetic hemochromatosis (GH) is a common HLA-linked recessive disorder characterized by progressive parenchymal iron loading and the appearance of clinical manifestations in the fifth decade of life, predominantly in males. HFE has been recently identified as the candidate gene, with most patients being homozygous for a Cys-282 → Tyr (C282Y) mutation and others being compound heterozygotes for C282Y and a second mutation, His-63 → Asp (H63D). Homozygosity for C282Y is found in more than 90% of North European patients, but in only 64% of severely iron-loaded Italian individuals. This finding may suggest that various genetic iron overload syndromes exist in addition to the HFE-related one.

Fifteen years ago, we described cases of juvenile GH suggesting that this was a distinct disease entity. In the juvenile condition, males and females appear to be equally affected. Patients present with hypogonadotropic hypogonadism and, unless proper treatment is started, die early because of cardiac dysfunction. We now provide further evidence that the juvenile condition is clinically and genetically distinct from the classical adult disorder.

The pedigrees of our two Italian families with juvenile GH are shown in Fig 1. The clinical features of family 1 were reported in 1983, whereas family 2 has never been described. Of the four affected individuals, three presented with hypogonadotropic hypogonadism at 14 to 21 years of age. The affected male of family 2 presented with cardiac failure at 20 years of age and died at 21 years of age of congestive cardiomyopathy.

From www.bloodjournal.org by guest on April 11, 2017. For personal use only.
There is no relationship in family 1 between HLA-A antigens and iron overload. In fact, although the two probands are HLA identical, the youngest sibling has the same HLA constellation, but a fully normal body iron status at 30 years of age. Family 2 is not informative with respect to HLA linkage, but helps to exclude any interaction between hemochromatosis and \( \beta \)-thalassemia.

All of the family members we examined using the approach of Lynas\(^5\) were found to be negative for the C282Y and H63D mutations in the HFE gene (Fig 1). In a study on 7 Italian patients belonging to 5 unrelated families with juvenile GH, Camaschella et al\(^6\) have independently excluded the HFE gene as responsible for this condition. Segregation analysis of 6p markers closely associated with HFE showed, in fact, that juvenile GH is unlinked to 6p and thus genetically distinct from HFE.

Both patients of family 1 and the young lady of family 2 underwent regular phlebotomies. Based on the amount of iron mobilized by bleedings, we estimated that these subjects had body iron stores ranging from 220 to 329 mg/kg of body weight at the time of diagnosis at 17 to 21 years of age. Once the three patients became iron deficient at the end of the intensive phlebotomy program, they underwent regular venesec-
Hypermethylation of p15\(^{INK4B}\) Gene in a Patient With Acute Myelogenous Leukemia Evolved From Paroxysmal Nocturnal Hemoglobinuria

To the Editor:

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disease resulting from somatic mutations in the PIG-A gene involving primitive hematopoietic stem cells. The PNH clones may have growth or survival advantages relative to normal clones that may promote their expansion, resulting in the development of overt PNH. However, little is known about how PNH clones gain growth advantage. Recent studies demonstrated preferential hematopoiesis by PNH clones in vivo.\(^1,2\) However, proliferation may be affected similarly in PIG-A–deficient clones and in normal clones,\(^3\) suggesting that PIG-A abnormalities alone may not be sufficient to confer a growth advantage on PNH clones.

A proportion of PNH patients terminate in severe pancytopenia with dysplasia, ie, myelodysplastic syndrome (MDS), and rarely progress to acute leukemia. We previously reported in BLOOD that specific p15\(^{INK4B}\) gene inactivation by promoter hypermethylation may be associated with the development of MDS,\(^4\) because it may confer a growth advantage on cells. One overt leukemia patient analyzed in this study in whom PNH evolved through MDS (PNH/MDS-OL) showed intense hypermethylation of the p15\(^{INK4B}\) gene. Surface marker analysis of his leukemic blasts showed low levels of expression of CD59, suggesting that leukemic blasts were derived from the PNH clone. So, to clarify at what point the p15\(^{INK4B}\) gene was densely methylated and inactivated in this PNH/MDS-OL patient and whether this p15\(^{INK4B}\) gene methylation is related to the expansion of PNH clones, we analyzed this patient and an additional 17 PNH patients.

We obtained clinical samples after receiving informed consent from a total of 18 patients (4 men and 14 women) who were positive for sugar water test and/or acidic serum (Ham) test and were diagnosed as PNH based on clinical manifestations. They included 12 female patients (unique patient no. [UPN] 1 through 12) analyzed in our previous study in which we demonstrated the existence of monoclonal populations with PNH phenotype by clonality analysis using X-chromosome restriction fragment length polymorphism method for the detection of the HLA-H gene mutations occurring in hereditary hemochromatosis.\(^5\) Blood 90:4235, 1997


REFERENCES


Juvenile Genetic Hemochromatosis Is Clinically and Genetically Distinct From the Classical HLA-Related Disorder

Mario Cazzola, Paola Cerani, Andrea Rovati, Angioletta Iannone, Giovanni Claudiani and Gaetano Bergamaschi