Homozygosity for a novel nonsense mutation (G66X) of the HJV gene causes severe juvenile hemochromatosis with fatal cardiomyopathy

Juvenile hemochromatosis (JH) is a rare autosomal recessive disorder of iron metabolism. The early onset of severe iron overload and the frequent occurrence of cardiomyopathy, reduced glucose tolerance, and hypogonadism distinguish JH from the more common HFE-related hereditary hemochromatosis.1 JH is genetically heterogeneous: most families are related to the recently cloned hemوجuelin (HJV) gene,2-5 and a small subset of JH patients was shown to harbor mutations in the HAMP gene encoding hepcidin.6-7

A 25-year-old man, originating from a small village in Transylvania, Romania, presented with abdominal pain and hepatomegaly, later supraventricular tachycardia and dyspnea. Echocardiography revealed reduced ejection fraction (21%), pericardial fluid, increased end diastolic left ventricular diameter (60 mm), and grade 2 mitral and tricuspidal insufficiency. Coronary angiography and myocardial biopsy were performed for the identification of the possible cause(s) of the heart failure (eg, myocardial inflammation or primary dilatative cardiomyopathy), and histology revealed hemochromatosis. Laboratory findings and other phenotypic characteristics confirmed the heavy iron overload of the patient, whereas his mother and one of his healthy brothers were unaffected (Table 1). As a treatment for the iron overload–related cardiomyopathy, heart transplantation was considered. Two days after the diagnosis of JH, the patient’s circulatory status deteriorated and the patient died. Autopsy confirmed the diagnosis of hemochromatosis. By histology, large amounts of iron pigment were detected in the heart, the liver, the pancreas, the lymph nodes, the testes, and the pituitary and adrenal glands. In the liver, a typical gradient hepatocyte iron accumulation was observed with prominent involvement of perportal hepatocytes, as well as mild fibrosis and lack of cirrhosis. In the testes, no mature sperms were observed.

DNA from peripheral blood was isolated from the patient, parents, and one of his healthy brothers. The patient was negative for HFE C282Y, H63D, and S65C mutations. Mutation screening of the HJV and HAMP genes was performed by di-deoxy chain termination sequencing. Primer sequences were provided by Papanikolaou et al2 and Roetto et al.7 In the patient sample, we detected a homozygous mutation previously not described (196G>T; cDNA sequence first described by Papanikolaou et al2) in exon 3 of HJV, resulting in a truncation mutation (G66X), whereas no other sequence alteration in the coding and the noncoding regions were observed in HJV and HAMP genes. Both parents and the healthy brother showed heterozygous genotypes at the same HJV position. Sequencing results were confirmed by polymerase chain reaction–restriction fragment-length polymorphism (PCR-RFLP), in which amplification was performed by the sequencing primers giving rise to a PCR product of 743 base pairs. Upon FokI restriction cleavage, fragments of 671 + 72 and 502 + 169 + 72 base pairs were observed for the wild-type and the mutant alleles, respectively. The independent de novo formation of such a base substitution is extremely unlikely, therefore, we suppose consanguinity between the parents. However, the family was unaware of such relatedness.

The identified mutation G66X is located upstream from the initiation codons of transcripts 2-5, thus the putative polypeptides (of 313 or 200 amino acids from transcript 2-5) may normally be expressed in the presence of G66X homozygosity. Based on the above observation, it is unlikely that polypeptides of transcripts 2-5 are capable of complementing the deficiency of the 426 amino acid protein (transcript 1). The novel mutation presented here extends the mutation spectrum of the HJV gene.

References

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András Jánosi, Hajnalka Andrikovics, Katalin Vas, András Bors, Márta Hubay, Zoltán Sápi and Attila Tordai