

## Obscure pathogenesis of primary iron overload in Indians warrants more focused research

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Received: 20 April 2011 / Accepted: 22 July 2011 / Published online: 17 August 2011  
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Cirrhosis of liver is one of the common clinical conditions encountered in gastroenterology and hepatology practice, and is associated with significant morbidity and mortality. A varied etiology of the condition necessitates detailed history taking, thorough clinical examination as well as a set of laboratory investigations for confirmation. An uncommon etiology of cirrhosis is primary iron overload, generally due to hereditary hemochromatosis for which a high index of suspicion amongst physicians is required for diagnosis. Hereditary hemochromatosis is commonly inherited as an autosomal recessive disorder, leading to progressive iron overload in several organs and eventual iron toxicity. It is caused by an inappropriate increase in iron absorption in the duodenum and upper small intestine due to malfunction of one of the proteins in iron homeostasis. The disease is relatively commonly encountered in the Caucasians and is associated with mutations in the locus, Histone Family E1 (*HFE*). Among populations of north European origin, two mutations have been identified in the *HFE* gene, viz. substitution of cysteine for tyrosine at position 282 (C282Y, nucleotide 845) in the alpha 3-domain of the HFE protein and aspartate replacing histidine at amino acid 63 (H63D, nucleotide 187) [1]. The mutation C282Y is the predominant Caucasian mutation with over

90% of patients in north Europe being homozygous for this mutation [2].

In this issue of the *Journal*, Jain et al. from a center in northern India, report their experience of the common *HFE* gene mutation in primary iron overload and liver cirrhosis in adult Indian subjects [3]. In their study comprising 496 patients with cirrhosis of various etiologies, they found only 13 with primary iron overload with near absence of C282Y mutation, and only two of them with heterozygous H63D mutation in *HFE* gene. Frequency of the risk allele at H63D was similar in patients and normal subjects. Neither the patients with heterozygous H63D mutation, nor the lone compound heterozygote individual (C282Y/H63D) had primary iron overload. These observations are in concordance with previous studies from India where C282Y has not been identified except for a single individual from Punjab in northern India, and a more widespread distribution of H63D mutation has been reported [4–8]. The H63D mutation is widely distributed in nearly all populations with a variable allele frequency and haplotype analysis suggests that it has occurred earlier to the C282Y mutation. Its frequency varies from 9.1% to 13.9% in different studies from India [5–8] and several studies have showed that even H63D homozygotes have no evidence of iron overload. An independent role of H63D mutation in causing hereditary hemochromatosis is not established yet. It is therefore difficult to propose any important role for this mutation in Indians as the frequency is similar to the reported frequency in the western population, and the overall frequency of 63D allele in patients and controls is also similar.

This raises the question, “what is the pathogenesis of primary iron overload in Indians”. Though it is a much under-rated problem locally, in the few well-characterized patients, it is difficult to understand why and how the increased iron absorption fails to correct despite the patients being put on a

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diet very low in iron. There is a growing concern in monitoring these patients as alcoholic liver disease can aggravate the disease manifestations and hepatocellular carcinoma is one of the long-term complications in hereditary hemochromatosis. Since iron deficiency anemia is common in our population, patients have a later age of presentation and most of the women present after menopause being partially protected by iron losses associated with menstrual blood loss and child-bearing. Hence, the variable presentation of primary iron overload and its consequences is another cause of concern.

In the background of the above mentioned observations in various Indian studies, it may not be inappropriate to propose that the pathogenesis and the genetic basis of primary iron overload in Indians may be different compared to the same in Europeans. This proposition becomes more tenable since the common mutations in *HFE* gene prevalent in Caucasians are lacking in Indians. Newer players involved in iron homeostasis are gathering importance; one such being hepcidin, which is emerging as a central player in the iron homeostasis and studies are underway to develop assays to quantitate hepcidin levels [9]. Role of other mutations in the *HFE* gene and mutations in other iron metabolism regulatory genes such as the transferrin receptor 2 (*TfR2*), hemojuvelin (*HJV*) and hepcidin (*HAMP*), ferroportin (*FPN*), etc. in explaining primary iron overload in Indians is an attractive idea. It is also known that mutations in these genes are mostly private in nature and hence, unique, novel mutations in these genes could explain the disease in Indians. In fact, a preliminary study on iron overload in the Asian community has identified private mutations in the *HJV* and *HAMP* genes in patients from Pakistan, Sri Lanka and Bangladesh [10]. However, this creates a difficult situation of screening several genes in Indians in contrast to Europeans who benefit from the screening of predominantly two mutations in *HFE* gene. Thus, mechanism of primary iron overload in the Indians

needs more focused studies in the future, so that proper diagnosis and management can be extended to them.

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