

Mutations at arginine residues in two Asian hemophilia B patients

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Defects in the factor IX gene which cause hemophilia B can be delineated by direct sequencing methods. We have used one such method, genomic amplification with transcript sequencing (GAWTS) (1), to sequence the factor IX gene in a Chinese and an Indian patient (HB56 and HB60, respectively) with severe hemophilia B. The regions sequenced were those anticipated to be of functional significance including the coding regions, exon-intron splice junctions, the putative promoter, the 5′ untranslated region and portions of the 3′ untranslated region (1). The only sequence change found in patient HB56 was a G→A transition at base 6365, substituting a glutamine for arginine^{-4} in the pre-pro leader sequence of factor IX. The only sequence change found in patient HB60 was a C→T transition at base 30863, substituting the stop codon TGA for arginine ^{248} in the catalytic domain.

Restriction fragment length polymorphism (RFLP) analysis was uninformative for carrier testing in the families of these two patients as all the haplotypes were *TaqI*(−), *HinfI*(−), *XmnI*(−), Malmo(thr). The lack of informative intragenic polymorphisms is common for hemophilia B, particularly in non-Caucasian families. However, genomic sequencing allowed direct carrier testing to be performed for seven at-risk females in these two families.

The two mutations found in patients HB56 and HB60 occurred at the dinucleotide CpG which accounts for about one-third of all mutations in Caucasian hemophiliacs (1, 2). For Asians, the data on point mutations is much more limited (3−7). If the current data are added, four out of seven point mutations are transitions at the dinucleotide CpG. Since these events are expected to account for less than 1% of all mutations at random, this small sample is adequate to determine that CpG is also a dramatic hotspot of mutation in orientals. However, more data is needed to determine if transitions at CpG are of similar relative frequencies in Caucasians and Orientals.

Since 71% of the transitions that alter amino acids in the factor IX coding regions occur at arginines (four of arginine's codons are CGN), one might expect that mutated arginines would account for one in four mutations in Caucasian hemophiliacs (0.71×0.33) (8). This indeed has been observed in two large samples of consecutively sequenced mutations (1, 2). In Asians, the four reported transitions at CpG altered arginine residues indicating that such mutations also account for a substantial fraction of hemophilia B in Orientals.

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