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SCIENTIFIC LETTER

Mutational Analysis of Exostosin 1 and 2 Genes in Multiple Osteochondroma

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To the Editor: Multiple Osteochondroma (MO) or Multiple Exostosis is a skeletal disorder characterized by out-growth of benign cartilage-capped bone tumors arising from the metaphyses of long tubular bones or from the surface of flat bones like scapula. MO is an autosomal dominant disorder associated with mutations in tumor suppressor genes, Exostosin-1 (*EXT1*) or Exostosin-2 (*EXT2*) in upto 95% of the patients [1]. The two genes affect heparin sulfate synthesis and thus chondrocyte proliferation and differentiation. We report the discovery of a non-sense mutation in *EXT2* in an 11-y-old boy diagnosed with MO. The patient also had bilateral Madelung deformity of wrist.

EXT1(Ref seq: NG_007455.2) and *EXT2* (Ref cDNA Seq: NM_207122.1) were sequenced from peripheral blood lymphocyte DNA with informed consent and known methods [2]. We found c.67C>T heterozygous substitution in *EXT2*-exon-1 (Fig. 1) that converts p.Arg23 encoding CGA codon into TGA stop codon.

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About 355 unique mutations in *EXT1* and about 184 unique mutations in *EXT2* have been reported [1]. Most of these mutations (~77%) are sporadic but for few exceptions (5 in case of *EXT1* and 7 in case of *EXT2*). Recurrent non-sense mutations seen in *EXT2* are c.67C>T (5%), c.544C>T (4%) and c.514C>T (4%). Higher frequencies of these substitutions have led to the hypothesis that these loci are mutational hotspots [3, 4]. However, subsequent review found that the reports on c.67C>T and c.544C>T were from patients predominantly of Italian origin [1]. Seventy seven percent of the patients with c.67C>T were of Italian ancestry and the remaining cases involved patients of Caucasian and/or European/North American origin [1, 5]. Ethnic concentration of these mutations has led to the speculation that their increased frequency is probably due to a common ancestor and founder effect rather than mutational sensitivity of the loci [1]. Similar controversy surrounds c.544C>T as all reports involve patients of Caucasian/European origin [1]. c.514C>T has been reported from multiple geoethnic groups *viz.*, Belgium, China, France, Italy, Germany and Taiwan [5] and therefore, the locus is considered as a mutational hotspot [1]. Discovery of c.67C>T in an Indian patient who is ethnically and geographically distinct from the Italian population argues in favour of the mutational hotspot hypothesis.

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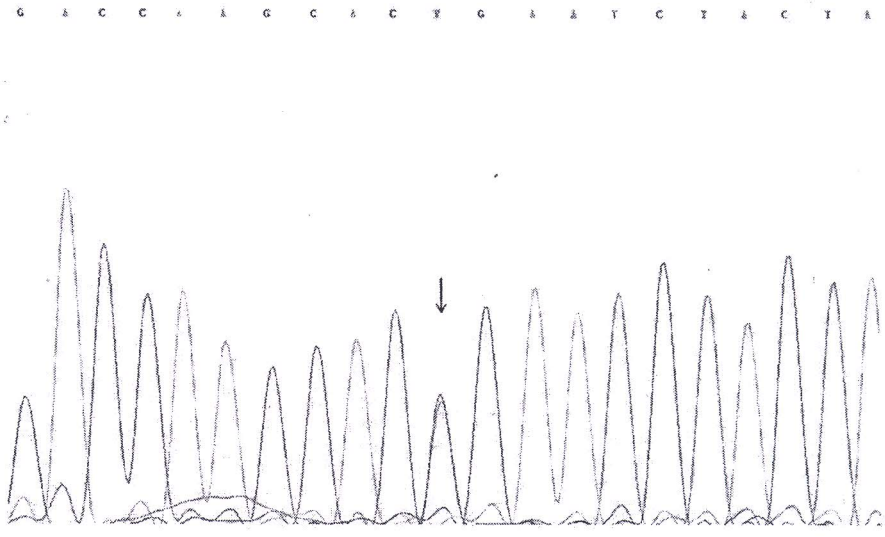

Fig. 1 DNA sequence chromatogram showing heterozygous c.67 C>T substitution (*arrow*) in *EXT2* exon 1

Conflict of Interest None.

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