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Localization of the gene for X-linked calvarial hyperostosis to chromosome Xq27.3–Xqter

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ABSTRACT

X-linked calvarial hyperostosis is a rare disorder characterized by isolated calvarial thickening. Symptoms are prominent frontoparietal bones, a flat nasal root and a short upturned nose, a high forehead with ridging of the metopic and sagittal sutures, and lateral frontal prominences. The mandible is normal, as are the clavicles, pelvis and long bones. The thickened bone in the skull appears to be softer than normal bone. Despite calvarial hyperostosis, increased intracranial pressure and cranial nerve entrapment do not occur. The major disability seems to be cosmetic. The disease segregates with an X-linked recessive mode of inheritance. Female carriers do not show any clinical symptoms.

To date, only one family has been described with X-linked calvarial hyperostosis including three affected individuals. In order to localize the disease causing gene, 31 polymorphic microsatellite markers that spread across the X-chromosome were analyzed. Genotypes were combined in haplotypes to delineate the region. A chromosomal region spanning from Xq27.3 to Xqter cosegregates with the disorder. This region encompasses 23.53 cM or 8.2 Mb according to the deCODE map and contains 165 genes. CNV-analysis did not show small duplications or deletions in this region. Exome sequencing was performed on a male patient in this family. However, this did not reveal any putative mutation. These results indicate that a non-coding regulatory sequence might be involved in the pathogenesis of this disorder.

Introduction

Bone is a dynamic tissue that is continuously remodeled by a balanced process of bone formation and bone resorption. Disturbance of this balance can lead to a wide variety of bone disorders, characterized by either low or high bone mineral density [1]. In the last years, several genes have been identified underlying monogenic diseases with an abnormal bone mineral density [2–5]. These studies provide new insights into bone homeostasis and can be important in the understanding of the pathogenesis of complex diseases, like osteoporosis; they might even lead to therapeutical applications for this condition.

Calvarial hyperostosis is a benign X-linked disorder that affects only the skull. Symptoms are prominent frontoparietal bones, a flat nasal root and a short upturned nose, a high forehead with ridging of the metopic and sagittal sutures, and lateral frontal prominences. The mandible is normal, as are the clavicles, pelvis and long bones. Radiographs of the skull show increased bone thickness at the sagittal suture line and prominent lateral frontal horns. The thickened bone in the skull appears to be softer than normal bone. Despite calvarial hyperostosis, increased intracranial pressure and cranial nerve entrapment do not occur. The disorder appears to be benign and the major disability seems to be cosmetic. The disease segregates with an X-linked recessive mode of inheritance.

Family and methods

Case reports

To date, only one family including three affected individuals with calvarial hyperostosis (Fig. 1) has been described in 1986 by Pagon et al. [6].

The proband (IV.1, Fig. 1) was diagnosed with calvarial hyperostosis at approximately 3 years of age because he showed prominence of the frontoparietal bones (Fig. 2a). He had a flat nasal root, a short upturned nose and a high forehead with ridging of the metopic and sagittal sutures and lateral prominences. His neurologic exam was normal as were his vision and hearing. Radiographs showed thickened diploic spaces, prominent trabeculae and closure of all but the lambdoidal sutures. There was thickening of the diploic spaces and prominent maxillary sinuses. He had normal radiographs of the pelvis and one leg.

At age twenty-four he returned to the genetics clinic for follow-up. His only health complaints at that time were headaches. They were pounding

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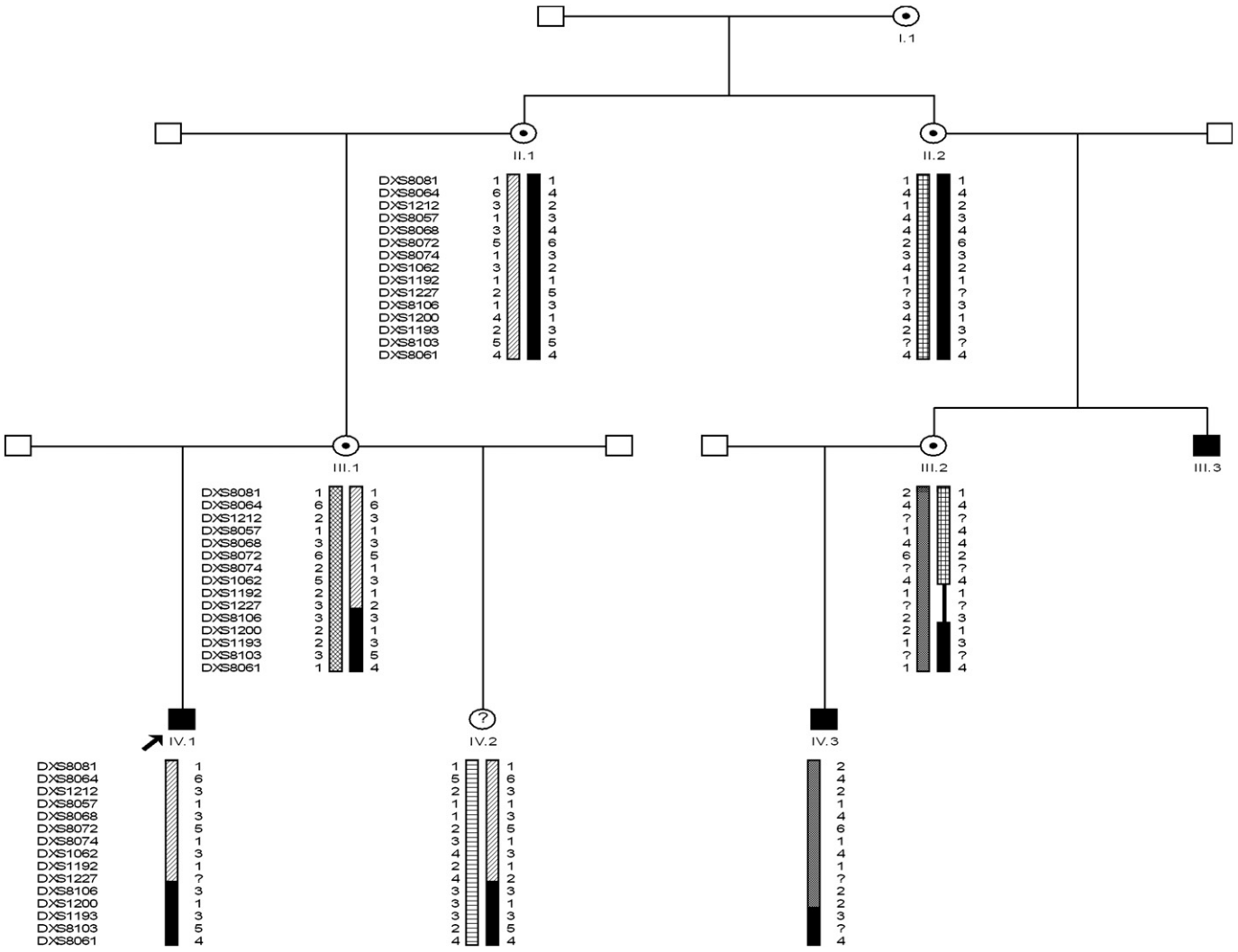

Fig. 1. Pedigree of a family with X-linked calvarial hyperostosis. Black symbols indicate affected individuals, white symbols indicate unaffected individuals, white symbols with a dot are carriers. The haplotypes are zoomed in on the long arm of chromosome X. The black haplotype is present in all carriers and affected individuals. Arrow: proband.

in nature and appeared to be in the mid occipital region. They only occurred during waking hours and were not associated with nausea or vomiting, visual disturbance, weakness or paralysis. His facial appearance showed fullness to the right face and in mid-to-lower aspects. However, the eyes themselves were not distorted. There was bony thickening overlying the lateral right frontal prominence and supraorbital region. The mid part of the frontal skull was depressed and there was a flat region overlying the formal sagittal suture. The extremities were normal, there was no sign of nerve entrapment. The disease showed no obvious progression.

A maternal cousin (III.3, Fig. 2b) and a maternal second cousin (IV.3) were also diagnosed with calvarial hyperostosis. Patient III.12 was diagnosed at the age of one. Skull radiographs showed calvarial hyperostosis which involved bones that originate from membranous bone. At age two 8/12 radiographs showed prominent lateral horns (Fig. 3) and increased thickness of the bone in the region of the closed sagittal suture line. There was presumed intracranial pressure with slight Luckenschadel appearance to the entire skull. The mandible was normal, as were the clavicles, the pelvis and the long bones. A craniectomy and morcellation of the coronal, lambdoidal and sagittal sutures with excision of the frontal protuberances were performed. At the age of eighteen his face had a normal appearance [6].

Patient IV.3 was diagnosed at eighteen months of age when unusual frontoparietal bony prominences were noted and skull radiographs showed thickening of the diploic space, lateral and frontal horns and a Luckenschadel appearance in the frontal and occipital areas [6].

Obligate gene carriers (II.1, II.7, and III.1) show no unusual cranial configuration. However, radiographs were not obtained.

Genotyping

Peripheral blood was collected from 7 family members (two patients, four obligate carriers and one with unknown status). Genomic DNA was isolated from these blood samples using standard procedures.

31 polymorphic markers that spread across the X chromosome were analyzed. These markers were selected from the deCODE genetic map and were analyzed by a Taq DNA polymerase mediated PCR, using fluorescently labeled primers [7]. Fragment analysis of amplified products was performed by an ABI PRISM® 3130 XL Genetic Analyzer (Applied Biosystems). Allele identification was done with Gene mapper v3.7 software (Applied Biosystems).

CNV analysis

The Illumina iScan system was used with the Human OmniExpress-12 v1.0 DNA Analysis BeadChip (Illumina, San Diego, CA) for CNV analysis. Resulting data were analyzed using the CNV-Webstore tool [8].