Coincident Two Mutations and One Single Nucleotide Polymorphism of the PTCH1 Gene in a Family with Naevoid Basal Cell Carcinoma Syndrome

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Sir,

Naevoid basal cell carcinoma syndrome (NBCCS, OMIM #109400), also called Gorlin’s syndrome, is an autosomal dominant disease that affects about 1 in 60,000 individuals (1, 2). NBCCS is associated with various skeletal and neurocutaneous abnormalities. Major manifestations are multiple basal cell carcinomas (BCCs), odontogenic keratocysts, palmoplantar dyskeratotic pits and intracranial calcification (3). In addition, rib and vertebral malformations, epidermal cysts, macrocephaly, facial anomalies, ovarian fibromas and medulloblastomas are associated with this syndrome.

It was reported that NBCCS results from germline mutations in the human homologue of the Drosophila segment polarity gene patched (PTCH1) (4, 5). PTCH1 maps to 9q22.3 and contains 23 exons coding for a transmembrane protein with 12 transmembrane regions, two extracellular loops, and a putative sterol-sensing domain. PTCH1 binds the secreted factor sonic hedgehog (SHH) and represses the signalling activity of the co-receptor smoothened that is required for transmission of the hedgehog (Hh) signal to the nucleus (6–8).

Here we report three cases of NBCCS in a family with two mutations and one single nucleotide polymorphism (SNP) in PTCH1.

PATIENTS AND METHODS

A 70-year-old woman (case 1) was referred with multiple tumours on the face and neck. Clinical and histological findings identified them as BCC. The patient also showed frontoparietal bossing, hypertelorism and mental retardation. A computed tomography (CT) scan, X-rays of the skull and an orthopanogram examination revealed odontogenic keratocysts and intracranial calcification. Her daughter was a 36-year-old female (case 2) with similar clinical findings, i.e. odontogenic keratocysts, intracranial calcification, frontoparietal bossing, hypertelorism and palmoplantar pits. The daughter of case 2 was a one-year-old female (case 3) exhibiting frontoparietal bossing, hypertelorism and palmoplantar pits. The findings, i.e. odontogenic keratocysts, intracranial calcification, mental retardation. A computed tomography (CT) scan, X-rays of the skull and an orthopanogram examination revealed them as BCC. The patient also showed frontoparietal bossing, hypertelorism and mental retardation. A computed tomography (CT) scan, X-rays of the skull and an orthopanogram examination revealed odontogenic keratocysts and intracranial calcification. Her daughter was a 36-year-old female (case 2) with similar clinical findings, i.e. odontogenic keratocysts, intracranial calcification, frontoparietal bossing, hypertelorism and mental retardation. A computed tomography (CT) scan, X-rays of the skull and an orthopanogram examination revealed them as BCC. The patient also showed frontoparietal bossing, hypertelorism and mental retardation. A computed tomography (CT) scan, X-rays of the skull and an orthopanogram examination revealed odontogenic keratocysts and intracranial calcification. Her daughter was a 36-year-old female (case 2) with similar clinical findings, i.e. odontogenic keratocysts, intracranial calcification, frontoparietal bossing, hypertelorism and mental retardation.

Since case 2 asked us to perform the genetic analysis, it was anticipated that the truncating PTCH1 mutation reduces the predicted amount of PTCH1 protein by 50%, and that a premature termination in an aberrant mRNA possibly initiates the process of nonsense-mediated decay resulting in reduced protein levels. Therefore, immunohistochemistry could be a candidate for screening NBCCS. However, as shown in Fig 1b, BCC of case

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1 and non-NBCCS (no mutation of *PTCH1* had been confirmed) exhibited an immunohistochemically similar pattern and intensity of PTCH1. The commercially available antibody to PTCH1 protein targets the N-terminus of PTCH. Since the truncating point existed at exon 3 in our case, the N-terminus of PTCH1 produced by the mutated allele could be intact, resulting in the similar staining pattern to the sporadic BCC. It is suggested that the intensity of PTCH1 staining alone cannot predict the existence of *PTCH1* mutation. It is important to bear in mind that the loss of staining depends on the mutational sites, the target regions of antibodies used, and the process of nonsense-mediated decay.

REFERENCES