Dear Editor,

Fibroblast growth factor receptor 3 (FGFR3) is a member of the receptor tyrosine kinase family, which is involved in embryogenesis, angiogenesis, and homeostasis of multiple tissues, such as bone and lung. FGFR3 gene mutations in the germline are well-known causes of skeletal syndromes. Interestingly, the same mutations were also found as somatic mutations in various cancers and benign skin disorders, such as multiple myeloma, cervical carcinomas, and seborrheic keratosis (SK).

SK is one of the most common benign human skin tumors, which originates from proliferating keratinocytes and can be found anywhere on the skin surface with the exception of palms and soles. Acanthosis nigricans (AN), also a benign skin tumor, shares many similar histopathological features with SK, such as acanthosis, papillomatosis, hyperkeratosis, and hyperpigmentation. It has been found in some skeletal syndromes associated with germinal activating mutations of FGFR3, which also strongly suggested that the occurrence of AN observed in these human disorders results directly from the expression of mutated FGFR3 in epidermis. To analyze the association between mutations of FGFR3 and benign skin tumor, we screened both SKs and ANs.

After written informed consent was signed, 48 SKs, 30 ANs and 18 patients with normal skin (10 SKs, 8 ANs) as matched controls were recruited into this study. All of the patients had no other system disease. Each case was diagnosed, based on clinical manifestations and histopathological examination.

Genomic DNA was extracted from the peripheral paraffin-embedded tissues using the QIAamp DNA FFPE Tissue Kit (QIAGEN, Hilden, Germany). We screened for 11 activating mutations in exon 7,10,15 of FGFR3 by the SnaPshots multiplex assay: c.742C>T(R248C), c.746C>G(S249C), c.1114G>T(G372C), c.1117A>G(S373C), c.1124A>G(Y375C), c.1144G>A(G382R), c.1178C>A(A393E), c.1850A>G(D617G), c.1888G>A(V630M), c.1954A>G(K652E), c.1955A>T(K652M). The assay covered all yet identified FGFR3 mutations in benign acanthotic skin tumors (seborrheic keratoses, epidermal nevi) and urothelial carcinoma.

FGFR3 mutations were found in 20 of 48 SKs (42%), while 28 of 48 (58%) revealed a wild-type status at the investigated loci. However, two ANs revealed G382R mutation of FGFR3. This is the first report of FGFR3 mutations in AN. These mutations were not found in 18 matched controls (Figure 1). Five mutations

Figure 1 (A) The R248C mutation was the most frequent FGFR3 mutation detected in seborrheic keratosis (SK) (no. 31), while normal controls showed a wild-type FGFR3 status; (B) the SK of patient no. 32 revealed a Y375C mutation; (C) the SK of patient no. 14 revealed a S373C mutation; (D) the SK of patient no. 7 showed a G372C mutation; (E) the SK of patient no. 38 revealed a K652M mutation; and (F) multiplex SnapShot reaction showed the G382R mutation in patient no. 22 of acanthosis nigricans (AN), which has not been described in ANs so far.
(S249C, A393E, D617G, V630M, K652E) included in the assay were not found.

The FGFR3 gene contains 19 exons and encodes an extracellular region for ligand binding composed of three immunoglobulin (Ig)-like domains, a hydrophobic transmembrane domain and two cytoplasmic tyrosine kinase domains. In SKs, R248C mutations were the most frequent type of FGFR3 mutation (19%). It is a C→T transition at a tripyrimidine site linked to UV light. R248C mutations create an unpaired cysteine residue in the mutated protein.3 K652M mutations are localized in the tyrosine kinase domain.4 In ANs, G382R is a novel mutation affecting the transmembrane domain.5 G382R mutations also induce a shift in the FGFR3 segment that is embedded in the membrane. Although AN is a benign skin disorder which histologically closely resembles SK, we did not find the same mutations in FGFR3.

In summary, we identified five reported mutations in SK and one novel mutation in AN. Our findings provided an addition to the FGFR3 mutation database, and will contribute further to the understanding to the pathogenesis of benign skin tumors. As specific inhibitors of FGFR3 are already available, topical treatment with inhibitors of FGFR3 may represent a promising new non-invasive therapy option in the treatment.

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References


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