Identification of one novel mutation of the NCSTN gene in one Chinese acne inversa family

Dear Editor,

Acne inversa (AI; OMIM 142690) is an autosomal dominantly inherited skin disorder. Clinically, AI is characterized by painful deep-seated, inflamed lesions in the apocrine gland-bearing area of the body, especially in the axillary, inguinal, and anogenital regions. To date, three genetics regions (6q25.1–25.2, 19p12–19q12, and 1p21.1–1q25.3) have been identified by linkage analysis to be responsible for AI.1,2 A total of 21 mutations have been identified in the γ-secretase genes including PSENEN (19q13.12, NM_172341), PSEN1 (14q24.3, NM_000021), and NCSTN (lies within the previously reported region, 1q22–q23, NM_015331) genes.3 Here, we performed a DNA direct sequencing in two AI families of Chinese Han and identified one novel mutation of the NCSTN gene.

Two AI autosomal dominant multiplex kindred families (Figure 1A and B) and 100 unrelated healthy controls were recruited in our study. The proband of Family 1 is an 18-year-old boy who presented with a 4-year history of painful nodules, pustules, abscesses, and hypertrophic scar throughout the armpits, buttocks, and groin, especially on the neck (Figure 1C). The proband of Family 2 is a 57-year-old man with a 35-year history of painful nodules, pustules, abscesses, and hypertrophic scar, with these lesions spread over the trunk, limbs, armpits, and buttocks (Figure 1D). Other affected individuals of the two families suffered similar symptoms and all of them met the diagnostic criteria of AI.4 Apart from the asterisk-marked individual in Family 2, where the disease was accompanied by psoriasis, no other disorders were observed.

Written consent was obtained from all the individuals and the study was approved by the ethics committee of Shandong Provincial Institute of Dermatology and Venereology. We collected venous blood from 17 triangle-marked family members (Figure 1A and B), including two affected members and two unaffected members in Family 1 and five affected members as well as eight unaffected members in Family 2. DNA was extracted from venous blood using a blood DNA kit (OMEGA Bio-Tek, Norcross, GA, USA). All coding exons including intron–exon boundaries of NCSTN (17 exons), PSEN1 (10 exons), and PSENEN (3 exons) were amplified by PCR using specific primers. After the purification of PCR products, direct sequencing was performed in all the 17 participants and 100 healthy controls using ABI 3130xl Genetic Analyser (Applied Biosystems, Foster City, CA, USA). Those sequences showing suspicious variation would be validated by reverse sequencing.

A heterozygous nonsense mutation c.497C>A (p. S166X) in exon 5 of the NCSTN gene was identified in Family 1 (Figure 1E), and it was not observed in the unaffected family members or 100 unrelated controls. The mutation was identified by comparing with the reported cDNA reference sequence (GenBank accession number: NM_015331). In Family 2, however, we failed to observe any mutation in the coding regions of the three above genes (NCSTN, PSEN1, and PSENEN). Only one novel SNP (c.837+1G>T) in intron 8 of the PSEN1 gene was detected in the proband and two unaffected individuals of Family 2, as well as the proband of Family 1 and two healthy controls (Figure 1F). This SNP has not been reported in the NCBI Single-Nucleotide Polymorphism Database.

The γ-secretase genes are involved in the regulation of the canonical notch signaling pathway, which is required for hair follicle terminal differentiation and for postnatal hair cycle homeostasis. Inhibition of notch signaling results in inhibition of the hair growth cycle, conversion of hair follicles into cysts, and inhibition of sebaceous gland.5 Each of the γ-secretase component genes has its own work to do. The catalytic domain resides within PSEN1 proteins; PSENEN subsequently facilitates the formation of PSEN1 fragments, conferring γ-secretase activity. NCSTN has been suggested to be critical for substrate recognition: it is the most frequently mutated gene among γ-secretase subunits in AI. Among all the mutations identified in γ-secretase genes, 18 (82%) are located within the NCSTN gene (Figure 1G); it is possible, therefore, that the pathogenesis of AI is related to the substrate recognition.

The newly identified nonsense mutation c.497C>A of NCSTN, changed the codon TGG at position 497 to TAG, leading to a substitution of serine by a termination codon. As a result, the nicastrin precursor, the NCSTN encoding protein, lost 544 amino acids and caused the disease.

We failed to identify any mutation in Family 2, indicating the strong genetic heterogeneity of AI as suggested by previous linkage studies.1,2,5 Since Wang et al4 discovery of mutations in γ-secretase genes, 65 families and 37 individuals of AI (from Asia and Europe) have been recruited, no mutation of γ-secretase genes was detected in 48 families and 33 individuals (majority in Europe, that suggests the racial difference).6–8 For this reason, the idea that γ-secretase mutations underpin only a minority of cases of familial AI is now widely accepted. Further exome sequencing of Family 2 will be carried out to clarify the pathogenesis of this family.

In conclusion, we identified one novel mutation c.497C>A of NCSTN gene in one Chinese AI family, which expanded the gene database of AI and should be useful for understanding of the pathogenesis of AI.

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Figure 1 Pedigree, clinical appearance, and sequencing results of the two families as well as all NCSTN mutations of AL. (A) Pedigree of Family 1 (the proband is noted by an arrow). (B) Pedigree of Family 2 (the proband is noted by an arrow). (C) Clinical manifestation of the proband of Family 1, picture of neck. (D) Clinical manifestation of the proband of Family 2, picture of back and buttocks. (E) The novel mutation c.621C>A in Family 1, sequencing figures from the proband of Family 1. (F) The novel SNP in two families, sequencing figures from the proband of Family 2. (G) Eighteen mutations have been reported previously to be located within the NCSTN gene. The red one is the novel mutation we detected.
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References


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