

# $\gamma$ -Secretase Gene Mutations in Familial Acne Inversa

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Acne inversa (AI), also known as hidradenitis suppurativa, is a chronic inflammatory disease of hair follicles whose characteristic features include draining sinuses, painful skin abscesses, and disfiguring scars (1). The German philosopher Karl Marx is thought to have suffered from this skin condition (2). AI typically occurs after puberty and can be either familial or sporadic. Familial AI [Online Mendelian Inheritance in Man (OMIM) 142690] usually shows an autosomal-dominant inheritance pattern and appears to be genetically heterogeneous (1, 3).

$\gamma$ -Secretase is a transmembrane protease consisting of four essential protein subunits: one catalytic presenilin subunit and three cofactor subunits [presenilin enhancer 2 (PEN2), nicastrin (NCT), and anterior pharynx defective 1 (APH1)] (Fig. 1). It mediates intramembranous cleavage of various type I membrane proteins, including amyloid precursor protein and Notch (4). Genetic inactivation of  $\gamma$ -secretase in mouse skin produces epidermal and follicular abnormalities that are histopathologically similar to those observed in human AI and that arise through alterations in Notch signaling (5).

To investigate the genetic mechanisms underlying AI, we collected samples from six Han Chinese families with features of AI as well as additional skin lesions on back, face, nape, and waist (figs. S1 and S2). By means of a combined genome-wide linkage scan and haplotype analysis in two large four-generation families (families 1 and 2), we mapped an AI locus to an interval on chromosome 19q13 (6). The PEN2-coding *PSENEN* gene maps to this region. Sequence analysis of all *PSENEN* exons and introns in family 1 revealed a guanine deletion (c.66delG), producing a frameshift and premature termination codon (p.F23LfsX46) (Fig. 1 and fig. S3). In family 2, we identified a

cytosine deletion (c.279delC) in *PSENEN*, causing a frameshift and delayed termination codon (p.F94SfsX51) (Fig. 1 and fig. S3). These two deletions were predicted to change the distal three-fourths and the functionally important C-terminal domain of PEN2, respectively (7). In families 3 to 6, we found a cytosine deletion (c.725delC, family 4) in *PSENEN*, the gene encoding presenilin 1, and different mutations in the NCT-coding *NCSTN* gene, including a guanine deletion (c.1752delG, family 3), a guanine-to-adenine transition at the invariant +1 position of the donor site of intron 13 (c.1551+1G>A, family 5), and a cytosine-to-thymine transition (c.349C>T, family 6) (Fig. 1 and fig. S3). The single-base deletion in *PSENEN* would result in a frameshift and premature termination codon (p.P242LfsX11) (Fig. 1). The three distinct *NCSTN* mutations were predicted to cause a frameshift and premature termination codon (p.E584DfsX44), an abnormal splicing event, and a nonsense mutation at codon 117 (p.R117X), respectively (Fig. 1). In each family, the independent heterozygous mutations were detected in all available affected individuals. None of the mutations were detected in chromosomes from 200 ethnically matched control individuals.

To study mRNA expression of the mutant alleles, we conducted reverse transcription polymerase chain reaction (RT-PCR) analysis by using peripheral lymphocytes available from the affected individuals of families 3 to 6. In the individuals carrying a frameshift or nonsense mutation in *PSENEN* or *NCSTN*, we observed a marked reduction in transcript expression from the mutant allele, suggesting that these mutations most likely cause nonsense-mediated mRNA decay and thus result in a complete loss of function (figs. S3 and S4). In the carrier of the splicing mutation in *NCSTN*,

we confirmed the skipping of exon 13, leading to loss of 32 amino acid residues in the NCT protein (p.A486\_T517del) (Fig. 1 and fig. S3).

Overall, our results establish haploinsufficiency of the  $\gamma$ -secretase component genes as the genetic basis for a subset of familial AI and implicate the  $\gamma$ -secretase-Notch pathway in the molecular pathogenesis of AI, making  $\gamma$ -secretase a promising target for anti-AI therapeutic drug development.

Our genetic findings also demonstrate that familial AI can be an allelic disorder of early-onset familial Alzheimer's disease (AD). It is well known that mutations in the two presenilin genes (*PSEN1* and *PSEN2*), but not the other  $\gamma$ -secretase component genes, cause early-onset familial AD and non-Alzheimer dementias (4, 8). Notably, all the AD/dementia-causing *PSEN* mutations identified so far are missense or in-frame deletions or insertions (www.molgen.ua.ac.be/ADMutations), and no AD case has been reported to co-occur with AI. Of the 50 affected individuals we genotyped in our study families, 15 were age 50 or above. Interestingly, none of these individuals had symptoms of AD or dementias, although definitive exclusion of these diagnoses will require careful neurological evaluation of the patients.

If further studies confirm that familial AD and AI are mutually exclusive phenotypes in individuals with *PSEN1* mutations, then our findings suggest that *PSEN1* mutations may cause familial AD and AI through distinct mechanisms and that simple inactivation of a single *PSEN1* allele may not be sufficient to cause familial AD.

## References and Notes

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## Supporting Online Material

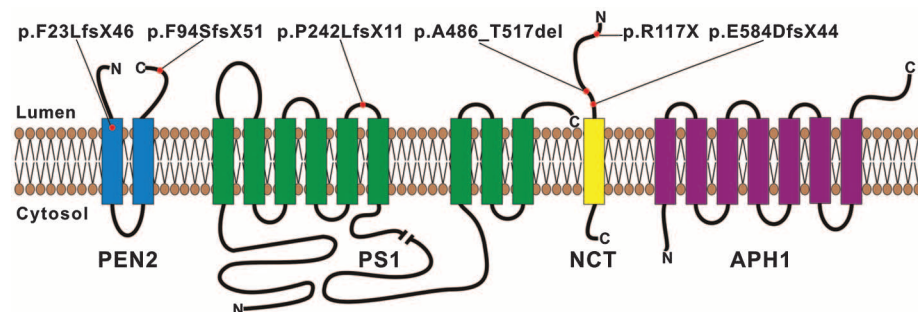
www.sciencemag.org/cgi/content/full/science.1196284/DC1  
Materials and Methods  
SOM Text  
Figs. S1 to S4  
Tables S1 to S4  
References

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**Fig. 1.** Schematic diagram of the  $\gamma$ -secretase complex with a summary of acne inversa-associated mutations. Colored bars represent the transmembrane domains. Mutations are shown as red dots.