γ-Secretase Mutation in an African American Family With Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) (acne inversa; OMIM 142690) is a chronic skin condition associated with the formation of painful, suppurative, and scarring nodules that primarily affect the axillary, inguinal, and perineal areas. Heterozygous mutations in the γ-secretase genes have been identified in the pathogenesis of autosomal dominant forms of HS in 2 British, 11 Chinese, 1 Japanese, and 3 French families.¹ Hidradenitis suppurativa affects all races, and the disease often affects African Americans. To our knowledge, there are no genetic studies of HS in the African American population. Using whole-exome sequencing, we sought to identify the etiologic gene causing HS in an African American family.

Methods | The Johns Hopkins University School of Medicine Institutional Review Board approved this study under the auspices of the Baylor-Hopkins Center for Mendelian Genomics. All participants provided written informed consent to be included in this study and for the study publication. Five individuals from 1 multigenerational family of African American origin (Figure), where HS was inherited as an autosomal dominant trait, were recruited for this study and whole venous blood specimens were collected. Four individuals were affected by HS and one was not affected. The proband, II-2, is an African American woman in her 40s with the highest Sartorius score (score of 98) in the family. The Table depicts the clinical features of the 5 individuals described here.

To capture the target regions, we used the Agilent SureSelect Human All Exon 50Mb Kit (Agilent Technologies) following vendor-provided protocols. We performed whole-exome sequencing (paired-end 100 base-pair reads) on the proband using the Illumina HiSeq2000 platform (Illumina, Inc). We aligned each read to the reference genome (NCBI human genome assembly build 36; Ensembl core database release 50_361; Ensembl is a joint project between the European Molecular Biology Laboratory-European Bioinformatics Institute and the Sanger Institute; http://www.ensembl.org/index .html) using the Burrows-Wheeler Alignment tool and identified single-nucleotide variants and small insertion and deletion.
deletions using Sequence Alignment/Map tools.\textsuperscript{2-4} Polymerase chain reaction duplicates were removed using Picard software (Broad Institute; http://broadinstitute.github.io/picard). We also performed local realignment and base call quality recalibration using the Genome Analysis Toolkit (Broad Institute; https://www.broadinstitute.org/gatk).\textsuperscript{5} Using the phenoDB analysis tool, we applied a filter designed to prioritize conserved, rare functional variants (missense, nonsense, splice site variants, and insertion and deletions) that were heterozygous or homozygous in the proband.

**Results** We identified a heterozygous nonsense mutation in exon 4 of NCSTN (c.C349T; p.R117X) on chromosome 1. By Sanger sequencing, we validated the variant in the proband and genotyped the other 4 family members and identified the p.R117X mutation in 3 other individuals who were affected. The 1 family member who was unaffected had a negative result for the mutation.

**Discussion** To our knowledge, this is the first description of an NCSTN nonsense mutation causing autosomal dominant HS in an African American family and further highlights the pathogenic role of γ-secretase mutations in inherited forms of HS. γ-Secretase is an intramembranous protein complex involved in cleaving a multitude of transmembrane proteins. To date, 17 mutations have been reported in NCSTN, 3 in PSENEN, and 1 in PSEN1, which are components of the γ-secretase complex, in inherited and sporadic forms of HS. Nicastrin, the protein product of NCSTN, is thought to be involved in γ-secretase assembly, maturation, and stabilization. The exact signaling defect caused by these mutations remains unclear. However, work in murine models suggests that aberrant Notch signaling may play a role. Notch is a transmembrane protein thought to be involved in hair follicle and sebaceous gland maintenance. The hair follicles of mice deficient in γ-secretase are phenotypically identical to those of mice deficient in Notch 1 and 2 and both types of follicles are histopathologically similar to those in humans with HS.\textsuperscript{1}

We suggest that this is the first description of an NCSTN nonsense mutation causing autosomal dominant HS in an African American family. Further work characterizing these mutations and their effect in protein signaling in the skin is needed.

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Identification of Bacterial DNA in the Peripheral Blood of Patients With Active Psoriasis

Psoriasis is a systemic autoimmune inflammatory disease that shares some immunological aspects with other inflammatory-based diseases, such as Crohn disease. Bacterial DNA (bactDNA) fragments have been shown to induce a systemic immunological response in Crohn disease and other settings. Although the results of most blood bacterial cultures are negative in patients with psoriasis, we hypothesized that the presence of bactDNA in the blood might act as a molecular trigger in disease outbreaks and induce a systemic inflammatory response in these patients.

Methods | This study included a consecutive series of patients whose psoriasis had previously cleared or was being controlled exclusively with topical medications who had a new flare of psoriasis and a group of sex- and age-matched control participants without psoriasis. The study protocol was approved by the Research Ethics Committee of the Hospital General Universitario de Alicante and all patients gave written informed consent. Exclusion criteria were the use of systemic corticosteroids, methotrexate sodium, cyclosporine, or anti-tumor necrosis factor drugs in the previous 3 months, antibiotic use in the previous 2 weeks, and the concomitant diagnosis of cirrhosis, intestinal bowel disease, and signs of bacterial infection. At the time of inclusion, patients were classified into severe, severe to moderate, moderate, or slight psoriasis, according to the international Psoriasis Area Severity Index.

A peripheral blood sample was collected from all participants and analyzed for routine biochemical laboratory values as well as interleukin (IL) 1β, IL-6, IL-12, tumor necrosis factor, and interferon γ levels. An aliquot of blood was inoculated under aseptic conditions in sterile, rubber-sealed Vacutainer SST II tubes (BD Diagnostics) to detect and identify bactDNA in the blood, as described previously. Statistical analyses were performed using SPSS, version 22 (IBM). The odds ratio and 95% CIs were determined as a measure of effect size. P < .05 was considered significant.

Results | Fifty-four patients with psoriasis and 27 controls were included in the study. The baseline characteristics of these participants are shown in Table 1. Blood bactDNA was present in 16 patients with psoriasis, all of whom showed the phenotype of plaque psoriasis (16 of 45 [35.5%]), whereas 6 patients with guttate psoriasis, 3 with inverse psoriasis, and all 27 controls did not have bactDNA in the blood. Species identification corresponded to Escherichia coli (n = 9), Klebsiella pneumoniae (n = 2), Enterococcus faecalis (n = 2), Proteus mirabilis (n = 1), Streptococcus pyogenes (n = 1), and Shigella fresneli (n = 1).

A higher proportion of findings of bactDNA in the blood was observed in patients with plaque psoriasis compared with patients with other psoriasis phenotypes (35.5% vs 0%; P = .05). The patient’s age at diagnosis of psoriasis and years since the first episode of psoriasis showed statistically significant differences in patients with and without bactDNA in the blood. The systemic inflammatory response was significantly higher in patients with bactDNA compared with other patients and controls (Table 2).

Discussion | In the patients with psoriasis in this study, bactDNA was associated with increased levels of IL-1β, IL-6, IL-12, tumor necrosis factor, and interferon γ. BactDNA induces a po-