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Insights from γ -secretase: Functional Genetics of Hidradenitis Suppurativa

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Abstract

Hidradenitis Suppurativa (HS) is a chronic, relapsing, and remitting inflammatory disease of the skin with significant heritability and racial disposition. The pathogenesis of HS remains enigmatic, but occlusion of the terminal hair follicle and dysregulation of the local innate immune response may contribute to pathogenesis. Genetic predisposition might also contribute to disease susceptibility and phenotypic heterogeneity since mutations in γ -secretase have been found to underly a minor but characteristic subset HS patients. In this review, we synthesized the current data on γ -secretase in HS, evaluated its importance in the context of disease pathobiology, and discuss avenues of future studies.

Keywords

Hidradenitis Suppurativa; γ -secretase; Genetics

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Introduction

Hidradenitis Suppurativa (HS), also known as acne inversa, is a chronic, relapsing inflammatory disease of the skin characterized by painful acne-like lesions, nodules, abscesses, sinus tracts, and scar formation primarily in intertriginous regions (i.e. axillae, submammary folds, groin). HS is associated with a high comorbidity burden and the lowest quality of life among any dermatologic condition, yet remains under-recognized and poorly understood (Reddy et al., 2019). Global incidences of HS vary by country. In the United States the incidence of HS is rising. HS is reported in individuals of all age groups, races, and genders but shows a predilection toward African Americans and women. Registry studies estimate the prevalence of HS at 0.3%, 0.22% and 0.09% in individuals of African, biracial and Caucasian descent, respectively. Furthermore, among these groups, the prevalence peaks between 20–40 years of age and declines after 50 (Garg et al., 2017a, Garg et al., 2017b, Sabat et al., 2020). Despite this demonstrated need, the pathogenesis of HS remains poorly studied.

Studies report that 30–42% of HS patients report a positive family history of the disease, which points towards a potential genetic etiology. A recent Dutch twin cohort study found a narrow-sense heritability of 77% for HS (van Straalen et al., 2020). Furthermore, a minority of these patients across multiple ethnicities have been found to exhibit a monogenic form of the disease that is associated with heterozygous mutations in the γ -secretase complex (Ingram, 2016). There is an increased incidence of HS in the setting of other genetic inflammatory syndromes, and multiple syndromic forms of HS have been identified such as PASH (pyoderma gangrenosum, acne, and HS) and Dowling-Degos disease (DDD), many of which have been tracked to specific mutations in a handful of candidate genes (Scheinfeld, 2013). The sporadic form of HS, in contrast to the familial form, appears to encompass the majority of disease burden (60–70%) and is thought to be driven by a polygenic architecture (Jfri et al., 2019). Several unique phenotypes have even been identified in both familial and sporadic HS, and in certain endemic populations (such as males of Asian ancestry) with clear evidence of heritability (Pink et al., 2012, Wang et al., 2010, Xu et al., 2016). Studies have found associations between environmental factors and HS, which suggests a multifactorial etiology. Whether specific genetic variations increase susceptibility to developing HS in the presence of specific environmental triggers remains an open question and suggests the existence of previously undescribed genetic risk factors.

The paucity of HS genome-wide association studies (GWASs) have made systematic dissection of HS pathophysiology challenging from a genetic level and due to its inflammatory nature some have turned to immune-profiling for insights (Gudjonsson et al., 2020, Lowe et al., 2020). Furthermore, a more complete understanding of genetic features underlying HS may help to develop a more nuanced classification system with better prognostic value, improve patient management and identify key candidate therapeutics. To date no genotype-phenotype correlation has been established, but combined genetic and immunological studies could bridge the gap (Frew et al., 2019). Although a minority of the total HS patients exhibit family history, clinical, genetic and molecular studies in familial cohorts harboring γ -secretase mutations began to define pathological mechanisms involved in the etiology of HS. Subsequent studies in laboratory animals further identify molecular

mechanisms involved in HS. Together, GWASs and laboratory studies have shown feasibility in dissecting potential mechanisms of HS pathology. In this review, we synthesize the current information on γ -secretase genetics underlying a subpopulation of patients with HS and evaluate its importance in the context of disease pathobiology and future research.

Mutations in γ -secretase demonstrate clinical significance in a subset of HS patients

The γ -secretase complex is a heterogenous transmembrane protease complex composed of the catalytic presenilin-1/2 (PSEN1/PSEN2) and co-factor subunits presenilin-enhancer-2 (PSENEN), Nicastrin (NCSTN), and anterior pharynx defective 1 (APH1A/APH1B). It functions to cleave over 70 type I membrane proteins such as cadherins, notch, and amyloid precursor protein (APP) (Merilahti et al., 2017). Dysfunctional γ -secretase-APP axis is well-known in the development of Alzheimer's disease; however, epidemiological studies to-date have not identified an increased risk of Alzheimer's among HS patients with γ -secretase complex mutations or overlapping pathogenic variants between the two disease populations (Garg and Strunk, 2017, Theut Riis et al., 2017). Alzheimer's and HS associated γ -secretase mutations may have distinct functional outcomes with regards to downstream signaling and efficacy in cleaving different substrates. More specifically, one could hypothesize that HS-associated γ -secretase mutations have no effect on the ability of γ -secretase to cleave APP or that these mutations are found in isoforms not expressed in the brain.

In 2006, Gao et al. identified a putative risk locus within 1p21.1–1q25.3, a >900 gene region, in a four-generation Chinese family using genome-wide linkage scan (GWLS) (Gao et al., 2006). This was further narrowed to a >200 gene region within 1q21.3–1q23.2 in a follow-up Chinese case report. In a 2010 GWLS, Wang et al. identified γ -secretase mutations in a cohort of 6 Han Chinese families with an autosomal dominant transmission pattern that harbored separate heterogenous rare variants in *NCSTN*, *PSEN1*, or *PSENEN* which localized to the 1q23.2 locus (Wang et al., 2010). Gao et al. and Wang et al. represented two of four genetic studies employing a genome-wide approach in HS kindreds to date. The final two identified putative risk loci at 1q23.2 (*NCSTN*) in an Iranian family, and both chromosome 19 and 6q25.1–25.2 in a number of European families, respectively (Faraji Zonooz et al., 2016, Irwin McLean et al., 2006). In addition, a handful of other studies probing African American, Indian, Japanese, British, and French families identified γ -secretase mutations that co-segregated with a disease phenotype (Ratnamala et al., 2016, Takeichi et al., 2019). The remainder of mutations were identified via targeted sequencing; overall, 50 single-nucleotide polymorphisms (SNPs) associated with HS have been identified in Chinese (23), French (3), British (3), Thai (3), African American (1) encompassing the *NCSTN*, *PSEN1*, and *PSENEN* genes (Table 1), 23 of which were determined to be “likely pathogenic” by American College of Medical Genetics (ACMG) criteria (Frew et al., 2017). The locations of these mutations in γ -secretase protein domains are shown in Figure 1. Current population data indicate that such heterozygous, nonsynonymous γ -secretase mutations are rarely found in healthy controls and demonstrate high penetrance in affected pedigrees (Wang et al., 2010). Interestingly, linkage disequilibrium was identified in 12 pairs of variants, and two specific mutations, *NCSTN*-

R117X and *-Q568X*, were each found in families from different races (Frew et al., 2019, Li A. et al., 2018).

Most of these γ -secretase-mutation-positive patients, are identified in families, often with multiple affected family members. Of note, classification terms such as ‘familial’, ‘typical’, ‘atypical’, ‘syndromic’, ‘sporadic’, are unreconciled and require further validation (Frew et al., 2019). The majority of these patients are found in particular demographics (e.g. male, Asian) and observed to have severe, widespread, treatment-resistant, anatomically atypical, or syndromic disease with superimposed comorbidities such as acne conglobata, pyoderma gangrenosum, and hyperpigmentation, among others (Pink et al., 2013). Comparisons against existing HS classification systems demonstrate that γ -secretase mutation positive patients, compared with sporadic HS patients, fit best with the categories of LC2 or “follicle-centered”, atypical, nodular, and scarring folliculitis using the Canoui, Naasan, Martorell-Calatayud, and van der Zee classification systems, respectively (Canoui-Poitrine et al., 2013, Ingram and Piguet, 2013, Martorell et al., 2020, Naasan and Affleck, 2015, van der Zee and Jemec, 2015, Xu et al., 2016). However, poor interrater reliability and the lack of validation limit the utility of these classification systems (van Straalen et al., 2018).

In the Alzheimer’s IDENTITY trial, semagacestat, a γ -secretase inhibitor, was administered but resulted in unspecified skin toxicity in a large portion of patients (Henley et al., 2014). More striking is that in a subsequent study of patients with desmoid tumor niragacestat, another γ -secretase inhibitor, 12/17 exhibited adverse skin toxicities. 6/7 evaluated by dermatology exhibited new-onset, recurring follicular and cystic lesions with surrounding inflammation in intertriginous areas, strongly resembling the HS phenotype (O’Sullivan Coyne et al., 2018). Biopsies of two patients showed inflamed follicular cysts, confirming pathology localized to the hair follicle. These lesions then resolved upon halting of treatment. These patients had no personal or family history of HS or its commonly cited comorbidities, suggesting that targeted γ -secretase inhibition can induce HS-like lesions, which supports the findings from genetic studies identifying loss-of-function mutations in components of the γ -secretase complex.

γ -secretase dysfunction leads to defective terminal hair follicle homeostasis

Occlusion of the follicular infundibulum, due to mechanisms including hyperkeratosis and disrupted epithelial differentiation, is considered the initiating event in HS pathogenesis (Prens and Deckers, 2015), though some believe subclinical inflammation may precede or even contribute to the occlusion (Frew et al., 2018). Several studies suggest that γ -secretase may play a key role in occlusion.

Developmentally, the absence of γ secretase in mice is known to convert hair follicles into epidermal cysts by altering the differential fate of outer root sheath cells (Pan et al., 2004). Several studies have linked impaired functionality of γ secretase to the formation of HS-like lesions in mice. Conditional knock-out of γ secretase components results in many histopathologic features of HS (He et al., 2018, Kamp et al., 2011, Pan et al., 2004).

In vitro, haploinsufficiency of NCSTN in keratinocyte cell lines upregulated the expression of type I interferon genes (Cao et al., 2019). In molecular studies of familial HS, NCSTN deficiency has been found to impact keratinocyte differentiation and proliferation through several candidate pathways (He et al., 2019, He et al., 2018, Xiao et al., 2016). Six patients with HS and DDD, a hair follicle-centered pigmentary disorder, were found to possess *PSENFEN* mutations co-segregating with the unique phenotype and were histopathologically distinguished from *PSENFEN*-mutation positive DDD-only patients by the presence of follicular hyperkeratosis (Ralser et al., 2017), suggesting a potential link between gene dysfunction and keratinocyte proliferation. Interestingly, a study of hair follicle keratinocytes from 18 HS patients (7 with family history, 11 without) found that they released greater pro-inflammatory cytokines IL-1 β , IP-10, and CCL5 when stimulated *in vitro*, leading the authors to implicate an intrinsic pro-inflammatory keratinocyte phenotype in HS (Hotz et al., 2016). In addition, a systematic review encompassing immunohistochemical data from ~500 HS patients demonstrated the localization of IL-1 β , IL-22, IL-36, IL-37 with keratinocytes and highlighted the intimate relationship between the pro-inflammatory milieu and dysregulated hyperkeratosis (Frew et al., 2018). The abovementioned data on *NCSTN* and *PSENFEN* suggest γ -secretase dysfunction may be linked to HS-associated follicular disruption by mechanisms localized to the keratinocyte. Importantly, the γ -secretase inhibitor-induced, pathologically-confirmed folliculo-cystic lesions in healthy individuals regressed after cessation, which supports a role for γ -secretase as a potential target for treatment in at least a subset of patients.

The predominance of loss-of-function mutations implicate haploinsufficiency as a likely mechanism of γ -secretase-induced disease in familial HS (Wang et al., 2010, Yang et al., 2015). However, the presence of missense mutations in both sporadic (4) and familial (6) cases, as well as conflicting results from translational biology may implicate altered functional enzymatic activity. Loss of a single *PSENF1* allele in mice does not produce skin disorders, and only occurs with more severe reduction in presenilin expression. WT mice treated with a γ -secretase inhibitor, which maintained levels of γ -secretase but specifically inhibited its enzymatic activity, produced similar epidermal abnormalities to *Ncstn* +/- mice, including follicular hyperkeratosis and inclusion cyst formation (Li et al., 2007). Another study of *Ncstn* -/- mice and *Ncstn* -/-; *Psen1* -/- mice found that both developed follicular inclusion cysts compared with wild-type, but the double-knockout mice developed these lesions earlier, and this was dependent on the level of γ -secretase (O'Brien and Wong, 2011). *In vitro* study of human tissue from HS patients harboring γ -secretase mutations found that membrane expression of γ -secretase was unchanged despite reduction in cellular protein expression (Table 1) (Pink et al., 2016), which may be due to physiologic post-transcriptional selection of <5% of fully assembled complexes that are then localized to the membrane (Yang et al., 2018). It seems likely that patients with only a partial loss of function may still produce enough amounts of functional protein to support normal physiology above a certain threshold. Any reduction in the level of functional protein, γ -secretase activity or increasing the threshold may subsequently elicit a clinical phenotype (Melnik and Plewig, 2013). A recent study identified a new NCSTN mutation causing HS in a Dutch family. The associated immunobiological functions of NCSTN and its co-expressed genes Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) and Peroxisome

Proliferator Activated Receptor Delta (PPARD) link genetics to the most common environmental and metabolic HS risk factors, smoking and obesity (Vossen et al., 2020). This begs the question, how do environmental factors increase the risk of developing HS in those that harbor γ -secretase mutations?

Emerging studies have provided import data supporting this stance. A systematic review and *in silico* analysis of 34 HS γ -secretase-mutations predicted structural alterations in substrate recruitment sites, catalytic domains, and post-translational modifications, consistent with altered enzymatic activity and substrate processing (Li A. et al., 2018). A second, more extensive *in silico* analysis bolstered these results by showing that 39 pathogenic familial HS associated γ -secretase mutations underwent significant structural changes in known sites of substrate binding and cleavage, either through nonsense mediated decay (23) or altered binding affinity (16) (Frew and Navrazhina, 2019). Such changes were found to be distinct from those found in Alzheimer's associated γ -secretase mutations HS-associated γ -secretase (Frew and Navrazhina, 2019, Li A. et al., 2018). One studied HS *PSEN1* mutation was found to affect the opposite side of the transmembrane-5 domain from the affected sites of reported Alzheimer's mutations (Frew and Navrazhina, 2019). Such mechanistic differences, as well as the myriad of γ -secretase substrates, may shed light on the lack of co-occurrence between the familial forms Alzheimer's and HS despite overlapping loci.

γ -secretase may act through multiple secondary pathways such as Notch, PI3K, and EGFR

Isolation of γ -secretase-dependent pathways specific to HS genesis is complicated by the large number of known γ -secretase substrates, the pleiotropy of its components, and the lack of a reliable animal model for *in vivo* study. Thus, while the following pathways are the most well-described, many likely remain undiscovered.

The Notch pathway has gained attention in HS due to its role in maintaining the hair follicle stem cell pool, functional regulatory T cells (T_{reg}) in the hair follicle and promoting antimicrobial defenses at the epidermis (Sabat et al., 2020). In the skin, notch normally maintains stemness in the hair follicle stem cells and disruption of signaling leads to aberrant differentiation and proliferation of keratinocytes and their precursors. T_{reg} cells are required for development and maintenance of the hair follicle (Ali et al., 2017), as well as immunological balance in the skin, both of which notch signaling supports. Lastly, studies have shown an essential role for notch in supporting T cell derived IL-22, which maintains the skin microbiome (Sabat et al., 2020). These roles might explain why, γ -secretase mutations that influence notch signaling can elicit the diverse aberrations seen in HS skin lesions (e.g. follicular cystic formation, inflammatory immune cell infiltration, and altered skin microbiota).

Notch 1–4 are well-characterized targets of γ -secretase, and controlled disruption of Notch pathway components in mice results in epidermal and follicular aberrations that resemble histopathological findings in HS (Pink et al., 2012). While some Notch molecules are abnormally expressed in HS tissue and HaCaT cells with γ -secretase mutations (Li A. et al., 2018, Xiao et al., 2016), minimal evidence exists that indicates Notch aberrations are

specific to HS or of sufficient statistical significance to be considered risk-associated loci for disease development (Frew et al., 2019). Functional assessment of four *NCSTN* missense mutations found that three maintained downstream Notch signaling while the fourth did not, casting doubt on the assumption that Notch-dependent pathways drive monogenic HS (Zhang and Sisodia, 2015). *In silico* and gene expression analyses of identified pathogenic mutations have failed to identify Notch as a specific marker of HS (Blok et al., 2016, Frew and Navrazhina, 2019), and genotype-phenotype correlation revealed no significance between impact on notch signaling and the HS phenotype (Frew et al., 2019). A recent study demonstrated that mRNA levels of *NCSTN*, Notch, and *PI3K/AKT* are overexpressed in lesional HS skin versus controls and there is no association between positive family history and mRNA levels (Hessam et al., 2020). The lack of direct evidence from animal models or human studies makes the role of Notch in HS controversial, suggesting that other pathways play a role in the molecular pathogenesis of HS.

Abnormalities in the phosphoinositide-3-kinases (*PI3K*) and endothelial growth-factor receptor (*EGFR*) pathways have previously been linked to epidermal and follicular dysfunction (Zhang et al., 2007), and emerging studies suggest that these pathways interact with microRNAs to play a role in familial HS pathogenesis. *NCSTN* knockdown in HaCaT cells led to decreased keratinocyte miRNA-100-5p, a microRNA that was previously found to be downregulated in familial HS patients, which then resulted in increased *PI3K* and keratinocyte hyperproliferation (He et al., 2019, Xiao et al., 2016). He et al. found that *NCSTN* mutations lead to reduced miR-30a-3p levels, which increases *RAB31* expression due to diminished negative regulation, and this increase in *RAB31* accelerates the degradation of activated *EGFR* on keratinocytes, leading to abnormal differentiation (He et al., 2018). *In silico* assessment of pathogenic γ -secretase mutations found that HS-associated *ERBB4*, *SCN1B*, and *TIE1* were differentially expressed and that this was specific to HS when compared with other inflammatory dermatoses to account for background cutaneous inflammation (Frew and Navrazhina, 2019).

Questioning the role of γ -secretase: Future Work

Many HS experts cite the poor understanding of disease pathobiology as a significant bottleneck for HS management and a critical area for future work (Hoffman et al., 2017). Despite the myriad of discovered variants, only a minority (<5%) of HS patients have been found to harbor the monogenic γ -secretase-mutation-associated familial HS phenotype, far fewer than even the 30–40% reporting family history. A recent key study of predominantly Caucasian cohort of 188 HS patients found that just 6.4% had mutations in γ -secretase (Duchatelet et al., 2020). Overall, the majority of HS patients studied to date are found negative for γ -secretase-mutations when assessed by targeted sequencing (Frew et al., 2017, Ingram et al., 2013, Pink et al., 2012). While many pathogenic variants co-segregate with the HS phenotype in familial kindreds, others do not and indicate a benign nature (Al-Ali et al., 2010, Jarvik and Browning, 2016, Nomura et al., 2014). The sole whole-genome expression profiling study done on HS patients found no difference in whole-blood mRNA expression in *NCSTN*, *PSEN1*, or *PSENEN* between HS and healthy controls, though a small sample size was studied and no validation was performed (Blok et al., 2016). Most of the disease burden is in sporadic HS (60–70%), yet few studies have been performed in this population

robust enough to probe its polygenic architecture and identify low to moderate impact variants and their attributable risks.

The view that HS has a polygenic foundation has subsequently gained traction, supported by strong, well-documented associations with other chronic inflammatory disorders including inflammatory bowel disease, spondyloarthritis, lupus, and pyoderma (Deckers et al., 2017, van der Zee et al., 2016, Vekic et al., 2016). Numerous genes besides γ -secretase components have also been identified to associate with HS including connexin-26, fibroblast growth factor receptor, and inositol polyphosphate-5-phosphate (Tricarico et al., 2019), albeit with variable phenotypes. The racial predisposition toward African Americans is also important; given that disparate risks in immune-mediated disease development and variable responses to treatment of such conditions can, at least in part, be traced to ancestral heterogeneity (Nedelec et al., 2016), similar assessments in HS, particularly large-scale, hypothesis-free approaches such as GWAS, may be worthwhile.

A handful of studies have employed this approach with promising results. A pharmacogenomics GWAS study of the Pioneer I and II trials found a single variant in *BCL2* that associated with response to adalimumab in HS patients in a TNF-dependent manner localized to the follicular unit (Liu et al., 2019). Sequence investigation of the *IL12RB1* receptor subunit gene identified two haplotype groups associated with significant differences in age at disease presentation, stage of disease, and number of skin areas (Giatrakos et al., 2013). Similar analysis of the TNF gene found significant association between SNPs of the promoter region and susceptibility to HS, disease course, and response to TNF antagonists (Savva et al., 2013). Study of two independent cohorts (total n = 261) showcased that high copy number (>6) of the defensin (*DEFB*) cluster was associated with a markedly increased odds ratio (6.72 after meta-analysis, P < 0.0001) for HS development and fewer than 6 copies was linked with earlier onset, fewer skin localizations, and less frequent purulence (Giamarellos-Bourboulis et al., 2016).

Nonetheless, the several identified HS mutations in *NCSTN*, *PSENEN*, and *PSEN1*, many of which were determined to be causative in familial HS, and their demonstrated relevance at the clinical and pathobiological levels advocate for continued investigation into γ -secretase. The establishment of guidelines for conducting the necessary multi-institutional studies, particularly genotype-phenotype analysis and exome sequencing of affected kindreds, representative of the broader HS population has already been undertaken and are steps in the right direction (Byrd et al., 2019). Conducting larger, prospective studies of familial HS patients that include clinical data collection for rigorous phenotyping will provide more data to establish a reliable, unbiased classification system. HS remains a clinical diagnosis with only anecdotal evidence for the use of biomarkers, histopathologic findings, and objective diagnostics. Yet when approached clinically, the lack of awareness, embarrassment in discussion, low socioeconomic status among patients, lack of follow-up due to increased use of emergency and inpatient care, and dearth of HS specialists in the US all serve as barriers to obtaining accurate clinical information from HS patients (Hoffman et al., 2017). At the experimental level, establishing relevant animal disease models, designing translational studies aimed at distinguishing among the many contributing mechanisms to HS, and performing functional validation of identified variants are key tasks in this process.

In conclusion, here we review the available literature on γ -secretase in HS and evaluate its evidence in the context of clinical, epidemiologic, pathobiological, and molecular studies. The release of ENCODE 3 and its associated tools poise future studies in HS to uncover important genetic and epigenetic features that may further clarify the etiologies of HS (Moore et al., 2020). Studying the γ -secretase complex as well as the greater genetic architecture of HS will allow for markedly improved and individualized treatment for individuals with this debilitating disease.

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The remaining authors declare that they have no relevant conflicts of interest.

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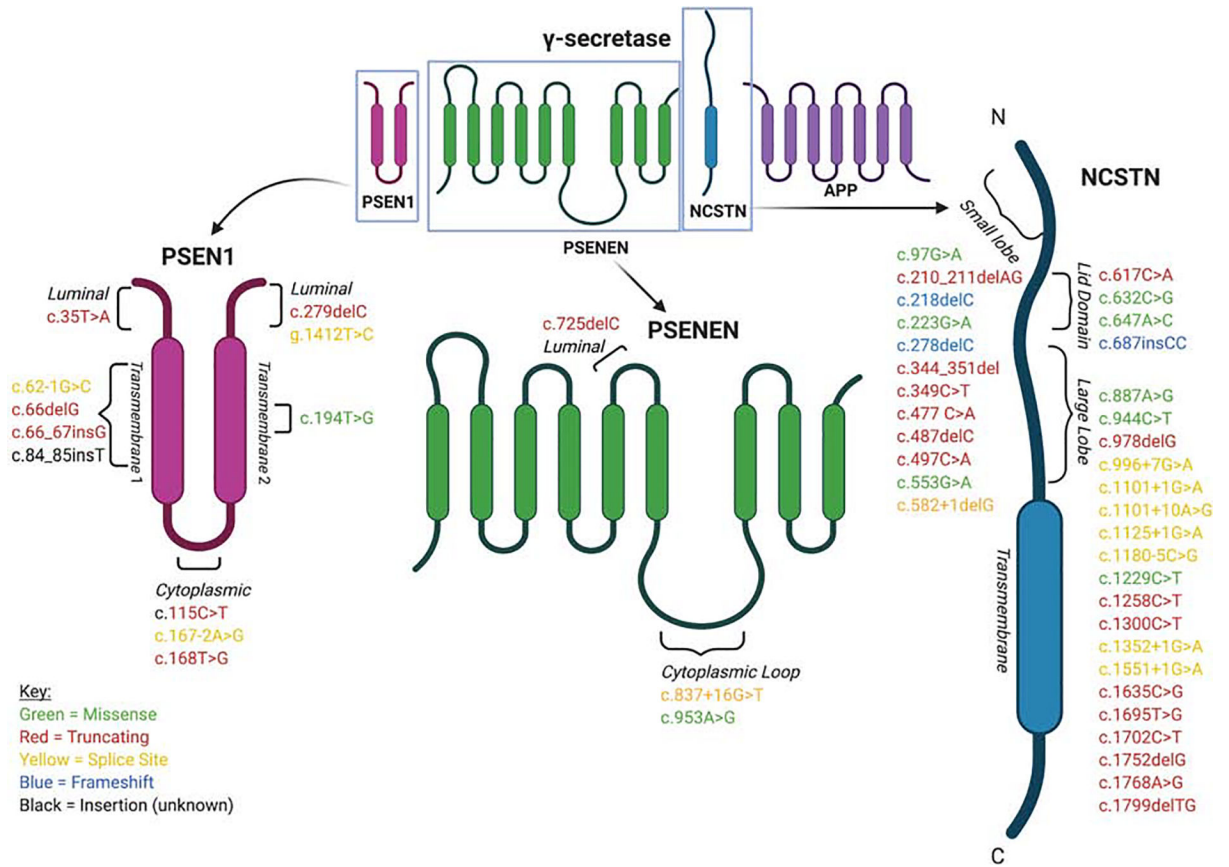


Figure 1,
 The locations of confirmed mutations in γ -secretase protein domains

Table 1:

Identified mutations in HS patients in NCSTN, PSENE1, and PSEN1.

NCSTN - 1q23.2							
	DNA change	Amino Acid Change	Mutation Type	Ethnic Origin (# of families)	Familial (F) or Case (C),	Isolated HS or Syndrome/Associated Conditions	Method of Sequencing (*indicates the use of controls)
1	c.97G>A	p.Gly33Arg	Missense	Japanese (1)(Takeichi et al., 2020)	F	Isolated HS	Whole Exome Sequencing
2	c.223G>A	p.Val75Ile	Missense	Chinese (1) (Zhang et al., 2013)	F	Isolated HS	Targeted Sequencing*
3	c.210_211delAG	p.Thr70fsX 18	Truncating	Chinese (1) (Liu et al., 2011)	F	Isolated HS	Whole Exome Sequencing*
4	c.218delC Exon 4	p.P73Lfs*15	Frameshift	Chinese (1) (Wu et al., 2018)	F	Isolated HS	Targeted Sequencing*
5	c.278del C	p.P93LFSX15	Frameshift	Chinese (1) (Li C. et al., 2018)	C	SAPHO	Whole Exome Sequencing*
6	c.344_351del	p.Thr115As n*20	Truncating	N/A (3) (Duchatelet et al., 2015)	C	PASH	Targeted Sequencing
7	c.349C>T	p.Arg117X	Truncating	Chinese (1) (Wang et al., 2010), Caucasian (1),(Liu M. et al., 2016) African American (1)(Chen et al., 2015), Japanese(1)	F (all)	Isolated HS (all)	GWLS* Targeted Sequencing Targeted Sequencing Targeted Sequencing
8	c.477 C>A	p.C159X	Truncating	Chinese(Savva et al., 2013) (1)	F	Isolated HS	Targeted Sequencing*
9	c.487delC	p.Gln163Ser fsX39	Truncating	French (3)(Miskinyte et al., 2012)	F	Isolated HS	Targeted Sequencing*
10	c.497C>A	p.Ser166X	Truncating	Chinese(Ma et al., 2014)	F	Isolated HS	Targeted Sequencing
11	c.553G>A	p.Asp185Asn	Missense	British (1) (Pink et al., 2013)	C	Isolated HS	N/A
12	c.582+1d e1G	Splice site	Splice site	Japanese (1) (Nomura et al., 2013)	F	Isolated HS	Targeted Sequencing*
13	c.617C>A	p.Ser206X	Truncating	Chinese(Shi et al., 2018)	F	Isolated HS	Targeted Sequencing*
14	c.632C>G	p.Pro211Arg	Missense	Chinese (1) (Li et al., 2011)	F	Isolated HS	Targeted Sequencing*
15	c.647A>C	p.Gln216Pro	Missense	Chinese (1)(Zhang et al., 2013)	F	Isolated HS	Targeted Sequencing*
16	c.687insC C	p.Cys230ProfsX31	Frameshift	Indian (1)(Li et al., 2011)	F	HS + Acne Conglobata (AC)	Targeted Sequencing*
17	c.887A>G	p.Pro296Arg	Missense	Chinese (1)(Xu et al., 2016)	F	Isolated HS	Targeted Sequencing
18	c.944C>T	p.Ala315Val	Missense	Chinese (1)(Zhang et al., 2016)	F	Isolated HS	Targeted Sequencing
19	c.978delG	p.M326IfsX30	Truncating	Singaporean (Haines et al., 2012)	F	Isolated HS	Targeted Sequencing*
20	c.996+7G >A	Splice site	Splice site	Mixed - European (1) (Pink et al., 2012)	F	Isolated HS	Targeted Sequencing*

NCSTN - 1q23.2							
	DNA change	Amino Acid Change	Mutation Type	Ethnic Origin (# of families)	Familial (F) or Case (C),	Isolated HS or Syndrome/Associated Conditions	Method of Sequencing (*indicates the use of controls)
21	c.1101+1 G>A	Splice site	Splice site	Mixed- European (2) (Pink et al., 2011)	F	Isolated HS	Targeted Sequencing*
22	c.1101+1 0A>G	Splice site	Splice site	British (1)(Pink et al., 2012)	F	Isolated HS	Targeted Sequencing*
23	c.1125+1 G>A	Splice site	Splice site	British (1)(Pink et al., 2011)	F	Isolated HS	Targeted Sequencing*
24	c.1180- 5C>G	Splice site	Splice site	British (1)(Ingram et al., 2013)	F (1) S (2)	Isolated HS	Targeted Sequencing
25	c.1229C> T	p.A410V	Missense	Caucasian(Liu M. et al., 2016)	F	Isolated HS	Targeted Sequencing
26	c.1258C> T	p.Gln420X	Truncating	Singaporean (Haines et al., 2012) Chinese(Jiao et al., 2013, Yang et al., 2015)	F	Isolated HS	Targeted Sequencing*
27	c.1258C> T	p.Arg429X	Truncating	Japanese(Nishimori et al., 2017)	S	Isolated HS	Targeted Sequencing
28	c.1300C> T	p.Arg434X	Truncating	French (1)(Miskinyte et al., 2012)	F	Isolated HS	Targeted Sequencing
29	c.1352+1 G>A	Splice site	Splice site	Chinese (1)(Liu et al., 2011)	F	Isolated HS	Targeted Sequencing*
30	c.1551+1 G>A	Splice site	Splice site	Chinese (1)(Wang et al., 2010)	F	Isolated HS	GWLS*
31	c.1635C>G	p.Ala486 Thr517del	Truncating	Iranian (1)(Faraji Zonooz et al., 2016)	F	PASH	GWLS*
32	c.1695T>G	p.Tyr565X	Truncating	Chinese (1)(Li et al., 2011)	F	Isolated HS	Targeted Sequencing*
33	c.1702C>T	p.Gln568X	Truncating	Caucasian (1), Japanese (1)(Nomura et al., 2014)	F	Isolated HS	Targeted Sequencing*
34	c.1752delG	p.Glu584As pfxX44	Truncating	Chinese (1)(Wang et al., 2010)	F	Isolated HS	GWLS*
35	c.1768A>G	p.Ser590Al afsX3	Truncating	French(Miskinyte et al., 2012)	F	Isolated HS	Targeted Sequencing*
36	c.1799delTG	p.Leu600X	Truncating	Indian (1)(Li et al., 2011)	F	HS + Acne Conglobata	Targeted Sequencing
37	c.1912_1 915delCA GT	p.S500fs p.S638fs	Frameshift	Dutch (Vossen et al., 2020)	F	Isolated HS	Whole Genome & Targeted Sequencing
PSENE1 - 19q13.12							
1	c.168T>G	p.Tyr56X	Truncating	Ashkenazi Jewish (4) (Pavlovsky et al., 2018)	F	DDD	Targeted Sequencing*
2	c.167- 2A>G	Splice Site	Splice Site	Chinese(Zhou et al., 2016)	F	DDD	Targeted Sequencing*
3	c.194T>G	p.Leu65Arg	Missense	Chinese(Zhou et al., 2016)	F	DDD	Targeted Sequencing*
4	c.66delG	p.Phe23LeufsX46	Truncating	Chinese(Liu Y. et al., 2016, Wang et al., 2010)	F	Isolated HS	Targeted Sequencing

NCSTN - 1q23.2							
	DNA change	Amino Acid Change	Mutation Type	Ethnic Origin (# of families)	Familial (F) or Case (C),	Isolated HS or Syndrome/Associated Conditions	Method of Sequencing (*indicates the use of controls)
5	c.66_67insG	p.Phe23Val fsX98	Truncating	British (1) (Pink et al., 2011)	F	Isolated HS	Targeted Sequencing
6	c.279delC	p.Phe94Ser fsX51	Truncating	Chinese(Pink et al., 2012)	F	Isolated HS	Targeted Sequencing
7	c.84_85insT	p.L28FfsX93	Insertion	Thai (2)(Wenrui et al., 2018)	F	DDD	Targeted Sequencing*
8	c.62-1G>C(Ralser et al., 2017)	Exon 2	Splice Site	Indian (2)(Ralser et al., 2017)	F	DDD	Targeted Sequencing*
9	g.1412T>C	Splice Site	Splice Site	French(Ralser et al., 2017)	F	DDD	Targeted Sequencing*
10	c.35T>A	p.Leu12X	Truncating	German (2)(Ralser et al., 2017)	F	DDD	Targeted Sequencing*
11	c.115C>T	p.Arg39X	Truncating	German (1)(Ralser et al., 2017)	F	DDD	Targeted Sequencing*
PSEN1 – 14q 24.2							
1	c.725delC	p.Phe242L eufsX11	Truncating	Chinese (3)(Wang et al., 2010)	F	Isolated HS	GWLS*
2	c.837+16 G>T	Splice site	Splice site	Chinese(Lazic et al., 2012)	Case	Isolated HS	Targeted Sequencing
3	c.953A>G	p.Glu318Gly	Missense	British (3)(Ingram et al., 2013)	F	Isolated HS	Targeted Sequencing*