γ -Secretase Genetics of Hidradenitis Suppurativa: A Systematic Literature Review

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Keywords

Hidradenitis suppurativa/acne inversa · Genetics · γ -Secretase

Abstract

Background: Acne inversa/hidradenitis suppurativa (HS) is a chronic, recurrent inflammatory disease of the skin that can significantly affect patients' quality of life. The etiology and pathogenesis of HS are unclear and gene mutations might play a role. **Summary:** The primary focus of the review is on aggregating the gene mutations reported, summarizing the structure of γ -secretase and analyzing and speculating about the mechanism and the underlying relations between gene mutation and functional changes of protein. The systematic literature review was done by searching the PubMed, Embase, and Web of Science databases. γ -Secretase is an intramembrane protease complex responsible for the intramembranous cleavage of more than 30 type-1 transmembrane proteins including amyloid precursor protein and Notch receptors. The protein complex consists of four hydrophobic proteins: presenilin, presenilin enhancer-2 (PSENEN), nicastrin, and anterior pharynx defective 1 (APH1). To date, 57 mutations of γ -secretase genes have been reported in 70 pa-

tients or families worldwide, including 39 in NCSTN, 14 in PSENEN, and 4 in PSEN1, of which 17 are frameshifts, 15 result in nonsense mutations, 13 in missense mutations, and 12 are splice site mutations. Given the structure of γ -secretase and analysis of related mutation loci of NCSTN, PSENEN, and PSEN1, mutations in γ -secretase genes could affect activation of presenilin, prevent substrate binding, and hinder intramembrane cleavage of select proteins.

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Introduction

Acne inversa (OMIM 142690) or triad occlusion, hidradenitis suppurativa (HS) is a chronic, recurrent inflammatory disease of the skin, characterized by painful, inflamed lesions predominantly on flexural areas. The disease usually presents after puberty and mostly in the third and fourth decades. The prevalence of HS ranges among 0.05–8% in different studies, and recently a prevalence of 0.7–1.2% was claimed in the US and European population [1, 2]. Diagnostic criteria include typical lesions (painful nodules, abscesses, sinus tracts, bridged scars, or open comedones), typical sites (axillae, groin,

Fig. 1. Flowchart of Methods.

perineal region, perianal region, infra- and intermammary folds, or buttocks), and chronic and recurrent courses [3].

More than one-third of HS patients have family histories, and two large HS case series revealed the familial ratio to be 35% [4, 5]. These HS kindreds may follow autosomal dominant inheritance with incomplete penetrance [6]. Familial HS cases are supposed to present a more severe phenotype; however, a large case series of 302 patients revealed a negative association between family history and severity of HS [5]. Buttock involvements tend to be more common in familial HS [7].

The physiological and psychological consequences of HS can significantly affect patients' quality of life. However, the specific etiology and pathogenesis of HS are still unclear and therapies including antibiotics, antiandrogens, and surgery applied in clinical courses could only make partial improvements. Mutations of γ -secretase have been found in familial HS of 6 Chinese kindreds 10 years ago [8], and thereafter a great many novel gene mutations have been reported in recent years. The prevalence of γ -secretase was uncommon, as estimated to be 6.4% in a large HS cohort [9]. HS patients with γ -secretase gene mutation might suffer from severe and widespread skin lesions [10]. This review, therefore, focused on studies concentrating on the genetics of γ -secretase in HS in the period 2010–2020. The primary focus of the review is on

aggregating the gene mutations reported, summarizing the structure of γ -secretase and analyzing and speculating about the mechanism and the underlying relations between gene mutation and functional changes of protein.

Methods

We conducted a systematic literature review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [11]. The search was conducted in PubMed, Embase, and Web of Science, last updated September 2020, using the following search terms: “hidradenitis suppurativa” AND “mutation.” Studies were considered for inclusion provided that they reported mutations of γ -secretase in HS patients or family. Additionally, three studies of our research group published in Chinese were included. Papers irrelevant to γ -secretase or reporting insufficient data were excluded. We extracted data on the genetic features from each study independently (Fig. 1 and online suppl. Table at www.karger.com/doi/10.1159/000512455).

Main Text

Gene Mutations

Heterozygous mutations in γ -secretase genes PSENEN, PSEN1, and NCSTN were first described in 6 Chinese multiplex kindreds, and mutations have since been reported in 64 patients or families worldwide, including 19

Table 1. All the γ -secretase mutations in HS that have been reported

Gene	Mutation	Protein
NCSTN	c.210_211delAG	p.T70fsX18
	c.218delC	p.P73LfsX15
	c.450_459del	p.S151QfsX48
	c.487delC	p.Q163SfsX39
	c.687_688insCC	p.C230PfsX31
	c.978delG	p.M326IfsX30
	c.1325_1326insGTTGTTCTGTAGTGGC	p.D443LfsX6
	c.1752delG	p.E584DfsX44
	c.1912_1915delCAGT	p.S638fsX32
	c.97G>A	p.G33R
	c.182G>T	p.G61V
	c.223G>A	p.V75I
	c.553G>A	p.D185N
	c.632C>G	p.P211R
	c.647A>C	p.Q216P
	c.887A>G	p.E296G
	c.944C>T	p.A315V
	c.1229C>T	p.A410V
	c.1727G>T	p.G576V
	c.1768A>G	p.S590AfsX3
	c.349C>T	p.R117X
	c.477C>A	p.C159X
	c.497C>A	p.S166X
	c.617C>A	p.S206X
	c.1258C>T	p.Q420X
	c.1300C>T	p.R434X
	c.1285C>T	p.R429X
	c.1381delC	p.L461X
	c.1695T>G	p.Y565X
	c.1702C>T	p.Q568X
	c.1747C>T	p.R583X
	c.1876C>T	p.R626X
	c.582+1delG	
	c.996+7G>A	
	c.1101+1G>A	
	c.1101+10A>G	
	c.1180-5C>G	
	c.1352+1G>A	
	c.1551+1G>A	p.A486_T517del
PSENEN	c.43_56del	p.C15fs
	c.66delG	p.F23LfsX46
	c.66_67insG	p.F23VfsX98
	c.229_230insCACC	p.I77HfsX45
	c.279delC	p.F94SfsX51
	c.304T>A	p.X102RextX50
	c.194T>G	p.L65R
	c.35T>A	p.L12X
	c.115C>T	p.R39X
	c.168T>G	p.Y56X
	c.62-1G>C	
	c.166+2T>C	
	c.167-2A>G	
	g.1412T>C	
PSEN1	c.725delC	p.P242LfsX11
	c.1167_1168insGA	p.S390EfsX20
	c.953A>G	p.E318G

Chinese [12–25], 7 Caucasian [9, 26], 5 Japanese [27–31], 4 Jewish Ashkenazi [32], 3 French [33], 2 British [34], 2 Indian [35, 36], 1 African American [37], 1 German [36], 1 Dutch [38], 1 South Welsh [39] kindreds, and 2 kindreds with unknown origin [40, 41], 7 sporadic cases (2 British, 2 Caucasian 1 Afro-Caribbean, 1 Chinese, and 1 unknown origin) [9, 26, 42, 43], and 9 patients (1 German, 1 French, 1 Singaporean, 3 South Welsh, and 3 unknown) [36, 39, 44, 45] with unknown familial history. To date, 57 mutations of γ -secretase genes have been reported including 39 in NCSTN, 14 in PSENEN, and 4 in PSEN1, of which 17 are frameshifts, 15 result in nonsense mutations, 13 in missense mutations, and 12 are splice site mutations (shown in Table 1).

γ -Secretase

γ -Secretase is an intramembrane protease complex with 20 transmembrane domains (TMs), responsible for the intramembraneous cleavage of more than 30 type-1 transmembrane proteins including amyloid precursor protein and Notch receptors [10, 46]. The protein complex is assembled from four hydrophobic proteins, presenilin, presenilin enhancer-2 (PSENEN), nicastrin, and anterior pharynx defective 1 (APH1), which are encoded by PSEN1/PSEN2, PSENEN, NCSTN, and APH1A/APH1B, respectively. Importantly, presenilin can be encoded by PSEN1 or PSEN2 and APH1 can be encoded by APH-1a or APH-1b, but PSEN1 and PSEN2 (or APH-1a and APH-1b) never coexist in any one γ -secretase complex. In addition, APH-1a and APH-1b are alternatively spliced; thus, at least six different combinations might exist in human beings [47, 48].

Presenilin

Among the four protein subunits, presenilin provides the catalytic core to γ -secretase complexes. Presenilin participates in multiple fundamental cellular events, including cell differentiation, intracellular signaling, and membrane trafficking and various biological functions especially the generation of amyloid- β peptides, given that Psen1 knockout mice displayed a Notch phenotype and a tough block in amyloid- β peptide production [47, 49]. Presenilin is best known for its role in early-onset genetic Alzheimer's disease and non-Alzheimer's dementias; notably over 170 mutations have been identified in PSEN1 for Alzheimer's disease [48]. Differently, four mutations of PSEN1 have been reported in HS patients so far, including one mutation considered to be a novel SNP. Presenilin comprises 9 TMs with N-terminus and C-terminus facing the cytosol and extracellular sides, including

a highly flexible and mobile TM2. The mutations of presenilin reported in HS located at the ectodomain (ECD) between TM5 and TM6 (loop5), cytoplasmic loop domain (loop6), and TM7, respectively. Within presenilin, the site of autocatalytic cleavage locates in the sequences between TM6 and TM7, and on TM9, the two catalytic residues, Asp257 and Asp385, might play a role in substrate recognition [46]. Thus, the missense mutation c.953A>G locating between TM6 and TM7 might probably affect the catalytic function of presenilin.

PSENEN

PSENEN is a small membrane protein required for the endoproteolysis and activation of proteolytic subunit presenilin [10]. It has three TMs with N-terminus and C-terminus facing the cytosol and extracellular sides, respectively. PSENEN interacts with both nicastrin and presenilin through van der Waals contacts. All three TMs bind to TM4 of presenilin, including the hydrophobic residues (Leu71, Ile75, and Phe78) from TM3. In addition, Phe94, in the extracellular side of presenilin enhancer-2, also interacts with TM4 of presenilin [46]. Of all the 14 mutations (including 4 splice site mutations) reported in PSENEN, 4 frameshift, 3 nonsense mutations, and 1 missense mutation are likely located within the TMs and 2 frameshift mutations in ECD. Most of the frameshift mutations (p.C15fs, p.F23LfsX46, p.F23VfsX98, p.I77HfsX45, and notably p.F94SfsX51), nonsense mutations (p.Leu12X, p.Arg39X, and p.Y56X), and missense mutation (p.L65R) are involved in the interactions with presenilin, which may affect activation of presenilin.

Interestingly, 85.7% (12/14) of PSENEN gene mutations mentioned below were reported to present with a "clinical subphenotype," Dowling-Degos disease (DDD), a rare autosomal dominant disorder characterized by reticulate hyperpigmentation at the flexural areas [50, 51]. The co-manifestation of HS and DDD was first reported in 1990 [52], with more HS-DDD cases reported; however, the co-occurrence phenomena appear to be more than coincidental. In vivo evidence revealed PSENEN played a role in melanocyte migration and differentiation, given pigmentation abnormalities, especially altered distribution of pigmentation found in zebrafish with PSENEN gene knock-down [36]. Therefore, PSENEN mutations give rise to HS and increase the susceptibility to comorbid DDD simultaneously [51].

APH1

In the protease complex, APH1 is the most stable component, serving as the initial scaffold, and it might play a

structural role in the assembly and maturation of γ -secretase [53]. The APH1 proteins contain 7 TMs, with the N-terminus facing the lumen and C-terminus the cytosol [47]. No mutation of APH1 in HS has been reported.

Nicastrin

Nicastrin is the largest and essential component of γ -secretase, and 39 of 57 mutations reported in HS are located in NCSTN [54]. It is a type I transmembrane glycoprotein consisting of a large lobe, a small lobe, and a lone TM, which closely stacks against TM1/TM5/TM7 of Aph-1 [46]. Nicastrin ECD contains at least 11 glycans; the presenilin-dependent nicastrin hyperglycosylation is essential for nicastrin maturation/localization to cell surface and recognizing the N-terminus of substrate protein but is not required for γ -secretase activity [46, 55]. The large ECD of nicastrin forms the bulk of the extracellular portion of γ -secretase, and the ECD undergoes a remarkable conformational change during assembly into γ -secretase complex [46, 47].

Nicastrin TM is involved in γ -secretase assembly, while ECD is crucial for substrate binding. Nicastrin ECD could specifically and directly recognize and bind substrates. Within the DAP domain of nicastrin ECD, Glu333 and Tyr337 are two essential residues required for substrate recruitment, and γ -secretase activity was “abolished” when 28 amino acids (residues 312–340) of DAP domain were deleted by researchers [46, 53].

The structure of nicastrin reported by Bai et al. in 2015 [46] revealed a hydrophilic pocket covered by a Lid. This pocket contributes to substrate recruitment and recognition precedes opening of the Lid for substrates binding. The Lid contains five aromatic residues (Phe145, Tyr148, Tyr152, Phe156, Trp164), and the two important residues Glu333 and Tyr337 and many charged and polar amino acids including four arginine residues (Arg281, Arg285, Arg429, and Arg432) nestle in the pocket. Outside, two glycans on Asn55 and Asn435 “sandwiched” the pocket. Conformation of Lid changes from closed to open during substrate binding, requiring disruptions of interactions between related residues (for instance, van der Waals contacts between Trp164 and Pro424, Phe448, and Gln420) and rotation of the large lobe with Phe287 as the central pivot in a greasy pocket (formed by Phe103, Leu171, Phe176, and Ile180) from the small lobe.

It is noteworthy that all the missense, nonsense, and frameshift mutations and one splice site mutation reported in the γ -secretase gene NCSTN are located within the ECD of nicastrin, with 9 mutations in the DAP domain and 9 affecting the DAP domain. Given the conclusion

that nicastrin ECD is involved in substrate recruitment, recognition, and binding, we speculate that mutations of NCSTN in HS change the structure of nicastrin ECD, causing damage of the “pocket” or hindering the opening of the Lid, consequently preventing substrate binding and intramembrane cleavage of select proteins by γ -secretase, thus affecting regulation of intracellular signaling pathways [49]. Among the frameshift and nonsense mutations, 13 mutations (p.T70fsX18, p.R73LfsX15, p.R117X, p.S151QfsX48, p.C159X, p.Q163SfsX39, p.S166X, p.S206X, p.C230PfsX31, p.M326IfsX30, p.Q420X, p.R429X, and R434X) are supposed to abolish or have an impact on the structure of the Lid and/or pocket and obstruct the conformation change of nicastrin.

Conclusion

Mutations in γ -secretase might play a key role in the etiology of HS, especially familial HS. Till now, 57 mutations of γ -secretase genes, including 39 mutations in NCSTN, have been reported in 70 patients or families worldwide. Given the structure of γ -secretase, mutations in γ -secretase genes could affect activation of presenilin, prevent substrate binding, and hinder intramembrane cleavage of select proteins.

Key Message

To date, 57 mutations of γ -secretase genes have been reported in hidradenitis suppurativa.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Zhongshuai Wang was responsible for drafting the manuscript as well as the acquisition and analysis of the literature; Yan Yan and Baoxi Wang revised the manuscript and approved the final version.

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