

A pilot genetic study of families with a high incidence of Acne Inversa (hidradenitis suppurativa)

Introduction

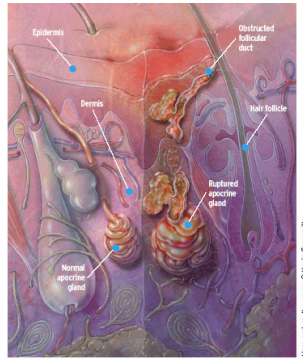
Acne inversa (AI), also known as Hidradenitis Suppurativa, is a chronic inflammatory skin disease of the apocrine gland follicles characterised by draining sinuses, painful skin abscesses and scarring.

The disease can be sporadic, however, several families show a high incidence of AI with an autosomal dominant pattern of inheritance.

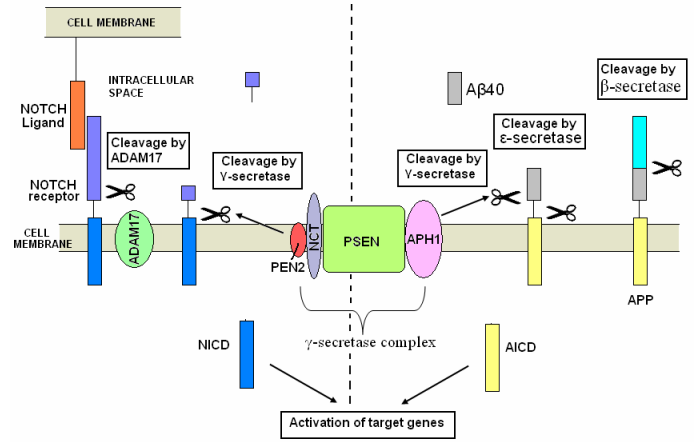
A recent study in China (Wang *et al.* 2010) has identified pathogenic mutations in *PSEN1* (14q24.3), and other components of the Gamma-secretase complex including *NCSTN* (1q22-q23) and *PSENEN* (19q13), in several families with familial Acne Inversa.

Mutations in *PSEN1* have previously been associated with familial early onset Alzheimer's disease suggesting that AI is an allelic disorder with familial Alzheimer's disease.

Aim – the aim of this pilot genetic project was to recruit patients with a family history of Acne Inversa. Screening of the gamma secretase genes would then be initiated in these patients to identify the familial mutations. A number of patients with sporadic disease were also to be screened.



Function of the gamma-secretase complex



SKIN – γ-secretase and NOTCH signalling

NOTCH receptor is first cleaved by ADAM17 then γ-SECRETASE producing the NICD peptide which activates gene transcription.

Mutations in γ-secretase proteins may affect the stability of the complex resulting in reduced NOTCH signalling.

This may affect apocrine gland differentiation resulting in the rupture of the apocrine gland and subsequent blockage and infection leading to **Acne Inversa**.

BRAIN – γ-secretase and APP signalling

APP is cleaved by a succession of secretases.

γ-secretase cleaves the APP protein to produce the Aβ40 polypeptide and AICD which activates gene transcription.

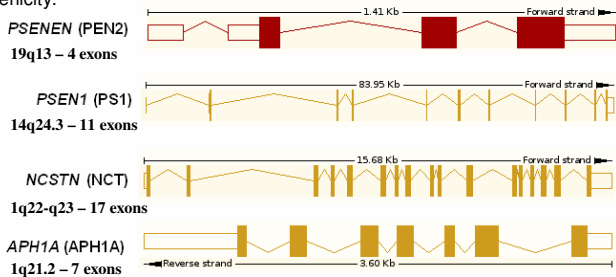
Mutations in PSEN1 affect the kinase activity of the γ-secretase complex producing more Aβ42/43 polypeptides.

Aβ42/43 polypeptides aggregate leading to amyloid fibrillogenesis resulting in **Alzheimer's disease**.

Experimental design

There is a high incidence of Acne Inversa in several families in Gwent, South Wales. Affected patients from these families were recruited, including a number of patients with no family history of the disease. The key clinical criteria was a least five boils at flexural sites.

Genomic DNA from these patients was screened for germ line mutations in the four gamma secretase complex genes. Each variant was evaluated for potential pathogenicity.



Results

21 patients with Acne Inversa were recruited for this research study. 11 patients had a family history of the disease (F) and ten were sporadic (S). Only two patients were from the same family.

A summary of all the variants found is shown. Variants were analysed using Alamut v2.0 software. Nearly all variants identified were known benign SNPs listed in dbSNP. Only one sample identified a variant of unknown clinical significance which may have the potential to affect splicing.

Gene	Variant	Patient samples	Classification
NCSTN NM_015331.2	c.344+28A>G	13 samples	Known SNP rs6669689
	c.237G>A (p.E79E)	16.12F	Known SNP rs34445546
	c.636A>G (p.L212L)	10.6F	Known SNP rs12239747
	c.733+18C>G	7.3F, 21.17S, 22.18S	Known SNP rs2274185
	c.747C>T (p.D249D)	10.6F	Known SNP rs6664627
	c.1180-5C>T	10.6F	VUS
PSEN1 NM_000021.3	c.770-21T>C	4.2F, 5.2F (same family)	Known SNP rs3025786
	c.868+16G>T	20 samples	Known SNP rs165932
	c.953G>A (p.E318G)	15.11F, 20.16S, 23.19F	Known SNP rs17125721
APH1A NM_001077628.1	c.-20C>A	11.7F, 14.10S, 15.11F, 16.12F	Known SNP rs2275780
PSENEN NM_172341.1	c.61+17G>C	9.5 (unknown Fhx), 15.11F	Known SNP rs10402601

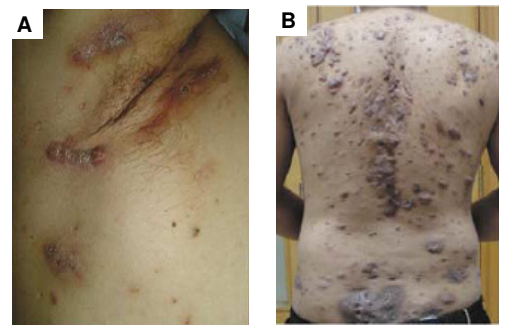
Discussion

The mutations identified in the AI families study by Wang *et al.* 2010 were nearly all small deletions producing a frameshift and premature termination codon.

In our study we found no evidence of mutations of this type, or any other type, in any of the patients screened. This suggests that mutations in the γ-secretase complex genes are not the cause of Acne Inversa in these patients. It is possible that we have missed mutations as this analysis is not able to detect large deletions (although large deletions have not been reported by other groups).

A more defined clinical criteria may be required to identify those patients with gamma secretase mutations. The clinical criteria for our patients was a minimum of five boils at flexural sites. However, the patients recruited for the chinese study (Wang *et al.* 2010) had *features of AI as well as additional skin lesions on back, face, nape and waist* yet AI affects the apocrine gland follicles that are only found in certain areas of the body such as the axillae, groin, chest and underarms suggesting that the chinese patients may have a different and more severe inherited skin condition.

A typical features of AI showing skin abscesses in underarm region (image from Gao *et al.* 2006). **B** Additional skin lesions on the back found in chinese study not characteristic of AI (image from Wang *et al.* 2010).



Alternatively, mutations in other gamma secretase genes (such as PSEN2) or Notch signalling components may contribute to the phenotype in our patients. Other groups have identified pathogenic mutations in families with AI, however, in a number of families the genetic cause is still unknown suggesting that there are additional genes responsible for the AI phenotype. Further linkage studies could be performed to identify the genetic cause of AI in these and our patients.

The high incidence of AI in the Gwent area of South Wales could suggest that there is a founder mutation common to our Welsh families.

References

- Wang *et al.* (2010) γ-secretase Gene Mutations in Familial Acne Inversa. *Science*. **330**: 1065
- Gao *et al.* (2006) Inversa Acne (Hidradenitis Suppurativa): A Case Report and Identification of the Locus at Chromosome 1p21.1–1q25.3. *J. Invest. Derma.* **126**: 1302-1306

Acknowledgements

All lab work was carried out by Bethan John as part of an intercalated medical genetics BSc project.