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Is the association of the p.N34S SPINK1 variant explicable by a high risk halpotype rather than the polymorphism?

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Background: The p.N34S polymorphism of the SPINK1 gene (PSTI) is associated with idiopathic chronic pancreatitis however there is no clear functional effect of the sequence variant. It has been suggested that the polymorphism is associated with a high risk haplotype but this is widely disputed.
Aim: To identify whether a haplotype exists that distinguishes pancreatitis cases from controls where both cohorts have the p.N34S variant.
Patients & methods: DNA from patients with chronic pancreatitis of no known aetiology (idiopathic) and controls were analysed by pyrosequencing to test for the p.N34S variant. A 2MB region (146Mb and 148Mb of chromosome 5) surrounding the SPINK1 gene was targeted using a custom designed liquid based capture system (SureSelect, Agilent) and sequenced using next generation sequencing (Illumina GAIIx) in 5 pancreatitis and 5 control patients, heterozygous for the p.N34S variant. Identified sequence variants were then filtered based on their increased frequency within chronic pancreatitis patients, revealing 7 haplotype segments. Seven variants (Single Nucleotide

Polymorphisms), one selected within each haplotype segment, were then screened in 38 pancreatitis patients and 20 controls (both groups heterozygous for p.N34S).
Results: 29 haplotypes were identified; only haplotype 13 was significantly associated with pancreatitis (p=0.0009, hapscore: -3.31).
Conclusion: It is possible that a high-risk haplotype rather than a simple base variant is responsible for SPINK1 associated pancreatitis.