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Single nucleotide polymorphisms around the human IL28B gene and treatment response in HCV infection

Interest in the interleukin 28B (*IL28B*) gene locus and its association with HCV treatment success was triggered in 2009 by several genome-wide association studies designed to identify host determinants of response to HCV therapy[1-3]. This is unsurprising since, in the absence of a vaccine, HCV now affects about 3% of the world's population. The treatments available in 2009 included PEGylated interferonalpha and ribavirin, whereas now many more effective direct acting antiviral drugs exist. Interferon and ribavirin were poorly tolerated treatments for many patients who experienced significant side effects during prolonged periods of therapy. In addition, these treatments appeared ineffective in a sizeable proportion of patients. If those patients that responded poorly to treatment could be identified in advance, they could at least be spared these side effects. Furthermore, financial savings would be made by not prescribing expensive treatments unnecessarily.

Hepatitis C virus genotype and basal viral load have been used for many years to help determine the best therapeutic regime for a given patient. It is clear however that these factors alone did not fully account for the observed variations in response to interferon/ribavirin therapy. Ethnicity is also a known indicator, with patients of AfricanAmerican origin responding poorly compared to those of European origin. The reasons for this are not understood but it does suggest that human genetic variation might be involved. In the first reported genome-wide study[1] the authors described a highly significant association between treatment-induced viral clearance and homozygosity for the 'C' allele at a single nucleotide repeat SNP rs12979860 in well over 1,000 patients infected with genotype 1 HCV. Furthermore, the lower frequency of the 'C' allele in African-Americans accounted for about half of the difference in response rates compared with those of European origin. This particular SNP, which lies about 3kb upstream of the *IL28B* gene, has no known direct functional consequence. The authors sequenced the whole of *IL28B* in a pool of individuals and found additional SNP's, in particular rs8103142, which causes a Lys70Arg substitution, but were unable to show if any of these sites were uniquely responsible for the association with treatment response.

Subsequent independent genome-wide and direct association studies confirmed the role of *IL28B* in HCV SVR following interferon /ribavirin therapy, both with the SNP's mentioned above and several others, most notably rs8099917 and rs12980275. The

functional mechanism responsible for this remains unknown, although there is evidence to suggest that *IL28B* gene expression is significantly lower in individuals possessing the less common alleles at these loci[2,3]. Consequently, positive association results with numerous different SNP's appear to be simply a reflection of their being in strong linkage disequilibrium* either with each other and/or the 'true' causative locus within the particular population under investigation.

Whilst the importance of *IL28B* in HCV interferon/ribavirin treatment response is beyond doubt, until the actual genetic locus or loci responsible for the effect and the mechanism of their action is understood, all current *IL28B* SNP genotyping assays remain proxies for predicting therapeutic response. Which single assay is the best proxy is hard to say. Micropathology Ltd uses rs12979860 because it has been the most studied to date with repeated significant association reported across the widest range of ethnic groups and infecting HCV genotypes. Nevertheless, it should be remembered that whilst the observed associations are highly significant and reproducible, *IL28B* genotype status is still only a 'risk modifier'. Even when combined with information about HCV genotype and basal viral load levels, we may still be some way from defining a comprehensive set of host/virus factors that predict outcome with near absolute accuracy.

This host determinant is relevant to treatment with interferon/ribavirin and its relevance to the more recently developed direct acting antiviral regimes is not defined.

References:

1) Ge D. et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009 Sep 17;461(7262):399-401.

2) Suppiah V. et al. IL28B is associated with response to chronic hepatitis C interferonalpha and ribavirin therapy. Nat Genet. 2009 Oct;41(10):1100-4.

3) Tanaka Y. et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet. 2009 Oct;41(10):1105-9.

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* A non-random association of linked genes. This is the tendency of the alleles of two separate but already linked loci to be found together more frequently than would be expected by chance alone.