The Association for
Clinical Biochemistry &
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Better Science, Better Testing, Better Care

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Scientific Affairs Committee

Scientific Scholarship Update Report

Name of Scholar: Gemma CLARK **Date of Report:** 7/10/14

Title of Project: The effect of genetic variability within the hepatitis B surface antigen on quantification: an evaluation of diagnostic and clinical impact.

Summary of work completed to date (400 words max):

The hepatitis B surface antigen (HBsAg) is considered to be the serologic hallmark of Hepatitis B virus (HBV) infection, and its eradication is widely regarded as tantamount to a cure. It has been suggested that HBsAg quantitation may have a role in the individualisation and monitoring of patient therapy, but this is dependent upon the availability of sensitive and specific diagnostic assays. HBsAg sequence variation and epitope conformational changes can inhibit HBsAg detection, which in turn can have a profound effect on patient management. Unfortunately, little is known about the mutations that may elicit this effect. Therefore a collection of hepatitis B virus (HBV) strains from patients with chronic hepatitis B (CHB) were selected for sequence analysis of the surface antigen.
Surface gene sequences for 73 HBV strains from CHB patients were obtained using Sanger sequencing. Mutations within these sequences were annotated using multiple sequence alignments to genotype-specific reference genomes, and Single Nucleotide Polymorphisms (SNPs) which resulted in non-synonymous mutations were manually annotated. The results of this investigation demonstrated that an increase in mutation frequency was significantly associated with a lower level of HBsAg serum concentration as determined by immunoassay. However, this association was only significant when the presence of SNP mutations, not detected in the main sequence by base calling software, were included in the analysis.
In addition to mutation frequency, the specific site of mutations may elicit an effect on HBsAg quantitation. Several previously reported mutations were detected in this investigation, including 9 that have been shown to result in an underestimation of HBsAg quantification. In particular, the M198I substitution was significantly associated with samples demonstrating lower HBsAg serum concentrations. Two further non-synonymous mutations postulated to elicit an effect on protein function were annotated within the 'a' determinant epitope cluster to which most HBsAg immunoassays are targeted. If HBsAg quantitation is to become a valuable biomarker for monitoring response to CHB therapy further work is required to characterise the significance of these specific mutations, and monitor their prevalence in the patient population.

Briefly describe any positive impact for patients:

This investigation has added to an expanding area of knowledge concerning the effect of surface gene mutations on the detection and quantitation of HBV. A comprehensive understanding of the phenotypic effects of these mutations will serve to improve diagnostic services for CHB management.

List any citations for Publications arising out of the work:

This work has formed the basis for an MSc thesis and is currently being written up for publication in a peer-reviewed journal.

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