

Pauline Ashfield-Watt, Kate Haralambos, Rhiannon Edwards, Delyth Townsend, Rob Gingell, Kah Wa Li, Steve E Humphries and Ian McDowell

Estimation of the prevalence of Cholesteryl Ester Storage Disorder (CESD) in a cohort of patients with clinical features of Familial Hypercholesterolaemia.

Background. Classical monogenic familial hypercholesterolaemia (FH) is caused by mutations in the LDL metabolic pathway involving *LDLR*, *APOB* and *PCSK9* genes. Genetic testing for variants in these genes as part of the Wales FH Testing Service identifies pathogenic mutations in only 25% index patients. It has recently been reported that patients with Cholesteryl Ester Storage Disease (CESD) may present with a lipid profile resembling that of FH, though the more classical presentation is with a mixed hyperlipidaemia and disturbed liver function tests in childhood. CESD is a recessive disorder with a phenotype that is expressed in homozygous or compound heterozygote individuals. The most common CESD mutation is an exon 8 splice junction mutation in the *LIPA* gene (c.894G>A;E8SJM) which was found to have an allele frequency of 0.0011 (1 in 450 individuals) in a large European population. No population estimate is available for the United Kingdom. We sought to determine the prevalence of this mutation in patients in whom the common FH causing mutations had been ruled out.

Method. 993 patients in whom the standard FH mutations had not been found were invited to participate in the study. Of these, 545 patients provided informed, written consent. Stored DNA samples from these patients were genotyped for the E8SJM mutation.

Results. Three heterozygotes were identified (allele frequency 0.0028). Whole gene sequencing of the *LIPA* gene was undertaken in these 3 individuals, but no other mutations were found. Therefore there were no CESD patients (homozygote or compound heterozygote) in this cohort.

Conclusion The allele frequency 0.0028 (1 in 182 individuals) for the E8SJM mutation was marginally more prevalent in this cohort than in the European population study, but no cases of CESD (homozygotes) were detected.