GENETIC DISEASES AND MOLECULAR GENETICS

SP010 CLINICAL AND GENETIC ANALYSIS OF A COHORT OF ENGLISH CYSTINURIA PATIENTS

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Introduction and Aims: Cystinuria is a rare inherited renal stone disease. Mutations in the amino acid exchanger, System b0,+, the two subunits of which are encoded by SLC3A1 and SLC7A9, predominantly underlie this disease. This work analysed the epidemiology of cystinuria and the influence of mutations in these two genes on disease severity in a UK cohort.

Methods: Cohorts from the North-East and the South-West of UK were studied. Clinical phenotypes were defined and genetic analysis of SLC3A1 and SLC7A9, combining Sanger sequencing and Multiplex Ligation Probe-dependent Amplification performed.

Results: A total of 76 patients (42 male, 34 female) were studied. Median age of presentation (1st stone episode) was 24 years but 21% of patients presented after 40. Patients had varied clinical courses, with 37% of patients having 10 or more stone episodes. 70% had evidence of chronic kidney disease and 9% had reached end-stage renal disease as a result of cystinuria and its complications. Cystinuria patients received a variety of different therapies, with no apparent treatment consensus. Notably, 20% of patients had staghorn calculi with associated impaired renal function in 80%. Genetic analysis revealed that bi-allelic mutations were present in either SLC3A1 (n=27) or SLC7A9 (n=20). 23 patients had only one mutated allele detected (5 in SLC3A1 and 17 in SLC7A9). A total of 37 different mutant alleles were identified, including 12 novel mutations. 22% of mutations were due to large gene rearrangements.

Conclusions: This UK cystinuria cohort demonstrates significant genotype-phenotype diversity. Patients often present atypically with staghorn calculi, over 40 years of age and go on to have significant renal impairment. Treatments directed towards reducing stone formation in cystinuria needs to be rationalised to optimise patient care.