On disease modifiers

HD is a monogenic disorder, meaning that if you have the mutation you will develop the disease. But within that certainty there is uncertainty. Genome-wide association studies (GWAS) suggest that only about 56 per cent of variation in the onset of HD, as defined by the emergence of motor signs, is determined by CAG repeat length. The remaining 44 per cent must be contributed by so-called genetic and environmental “modifiers”, though there may be many of these and the influence of individual modifiers may be small.

Jong-Min Lee [Boston] presented the findings of two large GWAS conducted in 4,000 HD mutation carriers with the goal of finding common genetic variants (single nucleotide polymorphisms, or SNPs) that correlate significantly with age at onset of the motor symptoms of HD corrected for CAG repeat length. This international effort (the GeM consortium, using DNA collected in HD

MAPS, PREDICT-HD, COHORT and REGISTRY studies) has pinpointed many potential sources of genetic influence, with the most significant lying on chromosomes 8 and 15. Chromosome 15 is home to both good and bad modifiers, SNPs that can significantly delay or bring forward disease onset respectively.

Lesley Jones [Cardiff] and her team, also members of GeM, have used a mathematical tool called pathway analysis to find out which known biological pathways are over-represented among those genetic regions of interest. Pathways involved in DNA repair turn out to be heavily implicated, as do mitochondrial fission and oxidoreductase pathways.

José Florez [Boston], a diabetes researcher, told the conference that clinical trials can be a useful tool for identifying genetic modifiers, because although an individual modifier’s effect may be modest, it can be exacerbated through interaction with a drug or other intervention. He gave examples of trials in which this had happened, and said that in order to maximise their chances of seeing such effects, researchers should work with as large and homogeneous samples as possible, and refine the phenotype of interest as much as possible. He added that there was no correlation between effect size and clinical relevance, with some therapies targeted at genetic modifiers with very small effect sizes having proved highly effective in the clinic.

Jan Frich [Oslo] gave an example of an environmental modifier in the form of physical exercise. He described a one-year programme of intensive, multidisciplinary rehabilitation that his group put in place for early- to mid-stage HD patients, at the end of which they were showing significant improvements in gait, balance, physical quality of life, anxiety and depression. The patients also reported increased self-confidence and a positive impact on their social relations. The intervention now needs to be tested in an RCT and subjected to cost-benefit analyses.