Hereditary nonpolyposis colorectal cancer families not complying with the Amsterdam criteria show extremely low frequency of mismatch-repair-gene mutations

Wijnen J, Meera Khan P, Casen H, *et al.* *Am J Hum Genet* 1997;61:329-35.

Hereditary non-polyposis colorectal cancer (HNPCC) is a common autosomal dominant cancer susceptibility condition characterised by early onset colorectal cancer. Germline mutations in one of four DNA mismatch repair (MMR) genes are implicated. Families which were used to map the MMR genes satisfied the "Amsterdam criteria", that is, (1) at least three relatives in two generations, one of whom is a first degree relative of the other two, are affected with histologically verified colorectal adenocarcinoma; (2) at least one of these relatives is diagnosed before 50 years; and (3) familial polyposis coli is absent. Use of these strict criteria certainly enabled targeted screening for mutations in the MMR genes (hMSH2, hMLH1, hPMS1, and hPMS2), but the role of these genes in families which did not fit the criteria was not known. In this study 125 kindreds were investigated, of which 86 families fulfilled the criteria and 39 did not (25 families fulfilled two criteria and the remaining 14 families fulfilled only one). Two genes, hMSH2 and hMLH1, were analysed by GC clamped

denaturing gradient gel electrophoresis (DGGE). Of the 86 families which fulfilled the criteria, mutations were found in 49%, while in the remaining 39 families the mutation detection rate was only 8%. A small number of tumours was also examined, and in four of six colorectal tumours from patients from kindreds fulfilling the criteria there was microsatellite instability, whereas this was found in only three of 11 tumours from the other set of families. This suggests that the Amsterdam criteria are effective in separating out families which have a high chance of having a MMR gene mutation, but with a mutation detection rate of 8% in the families which do not fulfil the criteria there may well be considerable demand for testing too.

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Positional cloning of the gene associated with X-linked juvenile retinoschisis

Sauer C, Gehrig A, Warnecke-Wittstock R, *et al.* *Nat Genet* 1997;17.2:164-70.

X linked juvenile retinoschisis is a recessive vitreoretinal degeneration disease exhibiting wide phenotypic variation. Loss of visual acuity begins early in life and ranges from mild to severe with some patients not being severely affected until the fifth or sixth decade of life. Linkage analysis has mapped the gene

locus to approximately 1 Mb, YAC contigs have been constructed spanning this region, and part of the region has been sequenced. Sauer *et al* have searched for transcripts within this region using a number of approaches including exon trapping, cDNA selection, database searches, and Grail exon prediction. Twenty putative exons were identified and 33 distinct expressed sequence tags. One EST represented a 224 amino acid precursor protein with a 23 amino acid leader sequence and northern blot analysis showed expression exclusively in retina. The gene is provisionally designated XLRS1, has six coding exons, and is predicted to mediate protein export. It has sequence homology to discoidin 1, a slime mould protein implicated in phospholipid binding and cell-cell interactions on membrane surfaces. Mutation analysis in nine unrelated XLRS families, seven of which had linkage to Xp22.2, the other two pedigrees being too small for linkage analysis, showed nine distinct mutations, suggesting that no one common mutation is causative of the disease. However, four mutations were in exon 4 and three were in exon 6. The authors do not describe any genotype-phenotype correlations, so it remains to be seen if the wide variation in phenotype characteristic of this disease is related to the nature of the XLRS1 gene mutations.

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