Medical genetics: advances in brief

Specificity, sensitivity, and predictive value of apolipoprotein-E genotyping for sporadic Alzheimer's disease. Saunders AM, Hulette C, Welsh-Bohmer KA, *et al.* *Lancet* 1996;348:90-3.

Polymorphisms in the apolipoprotein E locus are known to be associated with a variable degree of risk of Alzheimer's disease. Saunders *et al* examined the sensitivity, specificity, and positive predictive value of apolipoprotein E genotype in testing for the pathological diagnosis of Alzheimer's disease. Sixty seven patients with a clinical diagnosis of Alzheimer's disease, but without a family history, were followed up until death, and had postmortem examinations. Relatives of all patients who died from Alzheimer's disease were approached for permission for necropsy and there were no exclusions from the study, other than those where consent was not obtained. The diagnosis of Alzheimer's disease was confirmed in 57 (85%) of the patients at necropsy. A single $\epsilon 4$ allele had a sensitivity of 75% (percentage of postmortem confirmed diagnoses positive for the test), specificity of 100% (percentage of postmortem cases without the diagnosis negative for the test), positive predictive value of 100% (chance that a positive result is truly affected), and negative predictive value of 42% (chance that a negative result is truly unaffected). For people with a $\epsilon 4/\epsilon 4$ genotype the sensitivity was 19%, specificity 100%, positive predictive

value 100%, and negative predictive value 18%. The authors suggest that apolipoprotein E genotype can be usefully determined in the clinical evaluation of patients with dementing illnesses, but not for general population screening for Alzheimer's disease. They also comment on possible variation in response to therapy in Alzheimer's disease being dependent on apolipoprotein E genotype. This is still a small study, but important because of the pathological confirmation of the diagnosis in each case. The authors point out the need for further research of the relationship between apolipoprotein E genotype and pathological evidence of Alzheimer's disease so that accurate data on the value of this information can be obtained.

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Type of mutation in the neurofibromatosis type 2 gene (NF2) frequently determines severity of disease

Ruttledge MH, Andermann AA, Phelan CM, *et al.* *Am J Hum Genet* 1996;59:331-42.

Genotype/phenotype correlation studies are under way with many single gene disorders for which the gene has been cloned, and some interesting results are emerging which may be useful clinically when giving newly diagnosed patients some indication of their likely prognosis. The gene for NF2 is on chromosome 22, and a wide variety of different mutations

has been described. In this study 111 affected people from 73 unrelated families were studied. Sixty seven people from 41 kindreds (56%) were found to have 36 different mutations, including 26 protein truncating mutations (frameshift deletions/insertions and nonsense mutations), six splice site mutations, two missense mutations, one base substitution in the 3' ITR of the NF2 cDNA, and a single 3 bp in frame insertion. Seventeen of these mutations were novel, and the rest have been described previously. Sufficient clinical data were available in 59 cases for the phenotype to be classified as mild, moderate, or severe. Patients with a protein truncating mutation were found to have a more severe clinical course in most cases (only two out of 28 in this category had mild NF2, and two more were moderately affected), whereas all 16 patients with single codon changes were mildly affected. Of the 14 cases with splice site mutations, nine were mildly affected and five severely affected, and the patient with a mutation in the 3' UTR had a severe phenotype. The phenotypes of the remaining eight patients were unknown. The results did not help to clarify whether or not presenile lens opacities are associated with a particular genotype, however. Overall, it appears that there is considerable genotype/phenotype correlation in NF2, but other factors must also be involved.

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