Familial gonadal tumours

Following the letter from Huddart et al., we would like to report a further family with different gonadal tumours. The index case presented with a diencephalic choroid plexus papilloma in the age of 49. Her mother died at the age of 46 having had a diagnosis of an atypical ovarian carcinoma in the ovary made two years previously and her mother's cousin was also diagnosed as having ovarian carcino-

oma. Her son was also diagnosed as having a germline teratoma at the age of 19, which was successfully treated with an orchiecto-

omy and chemotherapy. She has the sister aged 22 who is under surveillance and has so far not developed any malignancies. There is no history of breast cancer or other cancers in the family. The families reported by Huddart et al. had all germl cell tumours whereas this family has a combination of germ cell and serous gonadal tumours. While this could be a chance association, the pedigree suggests an autosomal recessive pattern of inheritance. The index case has given permission for her DNA to be used by any interested research groups and we would be happy to hear from those involved with molecular studies in this field.

Although it is recognised that a small proportion of testicular teratomas are familial, and there have been a handful of reports of families with both male and female germ cell tumours, we are unaware of any reports of familial predisposition to both germ cell and common epithelial gonadal tumours.

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Cystic fibrosis in a Puerto Rican female homozygous for the R1066C mutation

Patients with cystic fibrosis show a wide vari-

ty of clinical symptoms, but the relationship between genotype and clinical phenotype is incompletely understood. The R1066C mis-

sense mutation is one of the four point muta-

tions found at the Cfp dinucleotide (3328-

3329) mutation “hot-spot”. The underlying dinucleotide change is a C to T transition at dinucleotide 3328 in the second half of exon 17, located in the region corresponding to the second transmembrane domain of the CFTR protein. The arginine residue at 1066 is conserved in humans and mice, suggesting the structural-functional importance of this amino acid. The substitution of the hydro-

phobic amino acid leucine for the positively charged arginine, R1066L, results in a pancreatic insufficient phenotype. The substi-

tution of another positively charged histi-

dine for arginine, R1066H, however, was

found in both pancreatic sufficient and insuf-

ficient patients.1 The R1066C mutation was

found in a CF carrier with bronchiectasis. All these reports, however, subjects who were heterozygous for the R1066 hot spot mutations. Thus, our patient with ho-

moyogous R1066C presents the opportunity to investigate the phenotype of this mutation.

The patient is the product of a consanguin-

eous mating between first cousins. Her parents were from Arecibo in Puerto Rico. She was diagnosed at 1 year of age because of failure to thrive and recurrent pneumonias. Her Sweat chloride was 106 mEq/L. During her childhood, the patient claimed to take enzymes, and maintained low to normal lev-

els of vitamins, cholesterol, and albumin. There was no significant change after with-

drawal of enzyme therapy at the age of 16. Despite her bronchiectasis, she was extremely active in sports and noted little impairment in her lung function. At the age of 20, she gave birth to a healthy daughter, who continues to be in good health. During her late 20s, the patient began to have frequent episodes of bronchitis that required antibiotic treatment. At the age of 25, she developed a culture obtained for Aspergillus fumigatus. At the age of 31, she sustained a serious car accident, was unable to breathe because of the back pain, and developed a severe pneumonia. Her lung function was deteriorated rapidly. At the age of 32, her pulmonary function was extremely poor. The peak flow, FEV1, and FVC were 30%, 26%, and 32% respectively. There was no difference in pulmonary function obtained before and after administration of the meter-

dose inhaler was not significant. The patient was colonised with Pseudomonas aeruginosa that were not sensitive to aminoglycosides. The patient died at the age of 36 from respiratory failure compounded by malnutrition. Before death she weighed 32 kg, was 147 cm tall, and had become diabatic. Since fewer than 5% of cysti-

cally surviving CF patients exceed the age of 36, her clinical course can be characterised as moderate.

Mutations in the CFTR gene of this patient were originally studied by a commer-

cial laboratory. None of the 34 point muta-

tions analysed was detected. This pa-


tient's mutant CF alleles were identified by single strand conformational polymorphism (SSCP) and DNA sequencing. The cystic fibrosis gene product reaction of exon 17b followed by direct DNA sequencing and confirmatory allele specific oligonucleotide (ASO) hybridisation. Neither of her parents was a carrier, not even her grandmother.

In this study, we have analysed by several well known commercial laboratories in the United States, we found that the R1066 mutation has not been included in any of the mutation panels screened. We recommend that the R1066 mutation hot spot be analysed, especially if the patients are of Spanish, Portuguese, or Hispanic origin.

All reported R1066 cases were hetero-

zygous, and most of the clinical cases were not described except one compound hetero-

zygous carrier, with a rare variant from a
decision. While this mutation has not been reported, it is unclear at the present time if these polymorphisms have any clinical significance.

The substitution of a serine residue for arginine could potentially be a severe muta-

tion since these two amino acids are structur-

ally and electrochemically distinct. However, R1066 is located at the cystolytic loop between the fourth and fifth transmembrane segments of the second membrane spanning domain.10 Replacement of the positively charged arginine with a neutral, slightly hydrophilic cysteine at the cystolytic loop may not completely knock out the protein function. This may explain the patient’s overall moderate clinical features and borderline pancreatic insufficiency. Functional studies of the in vitro expressed R1066 mutant CFTR protein will be necessary in order to under-

stand further the potential effect of this mutation on the biochemical and clinical outcome.

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cation of eight novel mutations in a collabora-

tion analysis of a part of the second trans-


7 Dork T, Mukus F, Schmidt K, et al. Detection of mutations in more than 50 different CFTR mutations in a large group of German cystic fibrosis patients. Hum Genet 1994;94:533-42.


Lack of evidence for genetic heterogeneity in Best vitelliform macular dystrophy

We have previously presented data suggesting that the VMD2 disease locus in the pericentromeric region of chromosome 11 may be excluded in a small German kindred (family E) segregating Best’s disease. We ran a multipoint linkage analysis, using markers D11S905-D11S1357, D11S935, D11S986, and D11S1357 that excluded in excess of 10 cM on either side of these markers. Given the estimate that the critical region was between D11S903 and PYGM, and approximated 3.7 cM in distance, we suggested that the data provided evidence for genetic heterogeneity in this disorder. However, it has been suggested that, as the markers used all map to the centromeric side of the VMD2 disease locus, and that estimates of the extent of the VMD2 critical region differ, some doubt would still exist as to whether or not there is substantive evidence for genetic heterogeneity. We used markers known to be on both sides of the disease locus to run a multipoint analysis in the family. Accurate distances between these markers were determined by the construction of a detailed map of the region (fig 1). Multipoint linkage analysis using markers 11p-D11S903-D11S1357-D11S4191-D11S1883-PYGM-D11S1889-D11S191 excluded a region between D11S903 and PYGM. However, haplotype analysis showed that exclusions on the 11q distal side of the disease locus were based on two unaffected subjects who shared the same haplotype as all the affected members of the family. Clinical reassessment resulted in the redetermination of these as affected. It was not possible to see the other patient for re-examination; her status was therefore deemed uncertain as non-penetrance has previously been noted in VMD2. Reanalysis of marker data under these circumstances gives a maximum lod score (Zmax) of 2.709 at 0=0.00 with the marker PYGM. Multipoint analysis using the same markers as listed above also gives maximum lod scores just under 3 at zero recombination with D11S1883 and PYGM (fig 2). This would suggest linkage of the disease locus to the VMD2 region, thus overturning previous evi- dence of locus heterogeneity in Best’s disease based on family E.

Data from the CEPH version 8.0 database is available through ftp://ftp.ceph.fr/pub/


Figure 1. Diagram of a linkage map of microsatellite markers in the region of the VMD2 disease locus. This map was created using CRI-MAP version 2.4. Genotype data used to create this map was downloaded from the CEPH database, converted to CRI-MAP format using MAP+1, and merged with data from markers run through families E and BTM2 (a second, larger family segregating Best’s disease). Uniquely placed markers are indicated by underlining and are given code numbers from 1 to 22. Markers indistinguishable by recombination from just one other locus are placed beside it and are assumed to occupy roughly the same position. Markers indistinguishable by recombination from a number of similarly placed markers are indicated by brackets. The arrows define the interval between which the non-uniquely placed marker or markers beside and to the right hand side of the arrow in question can be found. Numbers at either end of the arrows indicate the closest uniquely placed markers distinguishable by recombination from the indicated markers. (For example, D11S987 is located somewhere between markers 16 and 19 (PYGM and D11S916).) Sex averaged and sex specific centimorgan values for the genetic distances between the uniquely placed markers are given to the extreme left of the diagram.
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