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 young ovarian carcinoma at the age of 54. Histology showed a borderline serous tumour and there was no evidence of dissemination. She did not require chemotherapy and has remained well since surgery. Her mother died at the age of 78 having had a diagnosis of well differentiated papillary serous adenocarcinoma of the ovary made two years previously and her mother’s cousin was also diagnosed as having ovarian carcinoma. Her son was diagnosed as having a malignant teratoma at the age of 19, which was successfully treated with an orchidectomy and chemotherapy. She has another sister aged 52 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. all had germ 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 dominant pattern of inheritance. The index case has given permission for her DNA to be used by any interested research groups and we should 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.

MARC TISCHKOWITZ, DANNY MEYER, PETER S HARPER
Institute of Medical Genetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW UK

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

Patients with cystic fibrosis show a wide variety of clinical symptoms, but the relationship between genotype and clinical phenotype is incompletely understood. The R1066C missense mutation is one of the four point mutations found at the Cpf dinucleotide (3328-3329) mutation “hot spot”. The underlying dinucleotide change is a C to T transition at nucleotide 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 hydrophobic amino acid leucine for the positively charged arginine, R1066L, results in a pancreatic insufficient phenotype. The substitution of another positively charged histidine for arginine, R1066H, however, was found in both pancreatic sufficient and insufficient patients.1 The R1066C mutation was found in a CF carrier with bronchiectasis. All these point mutations are heterozygous for the R1066 hot spot mutations. Thus, our patient with homozygous R1066C presents the opportunity to investigate the phenotype of this mutation.

The patient is the product of a consanguineous 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 pneumonia. Sweat chloride was 106 mEq/L. During her childhood, the patient claimed to take enzymes, and maintained low to normal levels of vitamins, cholesterol, and albumin. There was no significant change after withdrawal 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 30 her lung function was extremely poor. The peak flow, FEV1, and FVC were 30%, 26%, and 32% of predicted, respectively. The 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 resistant. The patient had a second membrane spanning domain.11 The pulmonary function at the age of 32, her pulmonary function was extremely poor. The peak flow, FEV1, and FVC were 30%, 26%, and 32% of predicted, respectively. The 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 resistant. The patient had a second membrane spanning domain.11 The patient had a second membrane spanning domain.11 The patient had a second membrane spanning domain.11

Mutations in the CFTR gene of this patient were originally studied by a commercial laboratory. None of the 34 point mutations analysed was detected. This patient’s mutant CF alleles were identified by single strand conformational polymorphism (SSCP) and by direct DNA sequencing of exon 17b followed by direct DNA sequencing and conformational analysis of oligonucleotide (ASO) hybridisation. Neither of her parents was available for DNA testing. In order to eliminate the possibility that the apparent homozygosity is the result of amplifying only one allele, additional primers were used to show that the absence of the normal allele is not the result of mutations at the primer binding sites. No other mutations were detected by SSCP screening of 16 exons (exons 3, 4, 5, 6a, 7, 9, 10, 11, 12, 13a, 13b, 15, 17b, 19, 20, 21) in the CFTR gene. Since the R1066C is a rare mutation and the patient is the product of a consanguineous mating, we conclude that the patient is homozygous for the R1066C mutation. The R1066C missense mutation is relatively uncommon in white populations, occurring with a frequency of 0.3% in the German population, but is more common, at 0.8% in the Chinese population, and 4.8% in the Spanish population. The patient is of Spanish, Portuguese, or Hispanic origin.

All reported R1066C cases were heterozygous, and most of the clinical courses were not described except one compound heterozygous carrier, with a respiratory disorder, whose clinical manifestations were disseminated bronchiectasis.1 In this latter report, the results indicated that disseminated bronchiectasis of unknown origin is frequently associated with CFTR gene mutations or rare DNA polymorphisms. Our patient, homozygous for mutation R1066C, had a classical presentation of CF. During the course of screening 16 exons, including part of the flanking intron sequences, we discovered three polymorphisms. Two of them, 875+40 A→G in intron 6a and 3601-65 C→A in intron 18, have been previously reported.10 The other one (875+40 A→G in intron 4) has not been reported, is 622-58 T→G in intron 4. It is unclear at the present time if these polymorphisms have any clinical significance.

The substitution of a cysteine residue for arginine could potentially be a severe mutation since these two amino acids are structurally and electrochemically distinct. However, R1066C is located at the cytoplasmic loop between the fourth and fifth transmembrane segments of the second membrane spanning domain.11 Replacement of the positively charged arginine with a neutral, slightly hydrophilic cysteine at the cytoplasmic loop may not completely knock out the protein function. This may explain the patient’s overall mild clinical features and borderline pancreatic insufficiency. Functional studies of the in vitro expressed R1066C mutant CFTR protein will be necessary in order to understand further the potential effect of this mutation on the biochemical and clinical outcome.

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MIN-HUI LIANG
LEE-JUN C WONG
Molecular Genetics Laboratory, Department of Pathological Physiology, Hospital Angeles, 4650 Sunset Boulevard, Mail Stop 103, Los Angeles, CA 90027, USA

DEBORAH KLEIN
BERTRAND SHAPIRO
Department of Medicine, USC University Hospital, Ambulatory Health Centre, 1st Floor, 1355 San Pablo Street, Los Angeles, CA 90033, USA

C MICHAEL BOWMAN
LEE-JUN C WONG
Institute for Molecular and Human Genetics, Georgetown University Medical Center, 3800 Reservoir Road NW, Rm M4000, Washington DC 20007, USA

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, D11S1355, D11S903, 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 will 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 D11S903-D11S1357-D11S4191-D11S883-PYGM-D11S1889-11q 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 reclassification of one 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 0.0-0.00 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 evidence 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+ and merged with data from markers run through Timess E and BTM1D (a second, larger family segregating Best’s disease). Unique placed markers are indicated by underlining and are green code numbers from 1 to 22. Markers indistinguishable by recombination from just one other locus are placed beside and are assumed to occupy roughly the same position. Markers indistinguishable by recombination from a number of units placed beside each are indicated by arrows. 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 flanking each side of the arrows. (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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