Birt-Hogg-Dubé syndrome (BHD, OMIM 135150) is an autosomal dominant cancer syndrome characterised by benign skin tumours, renal tumours, and spontaneous pneumothorax. The gene has been mapped to chromosome 17p11.2 and recently identified, expressing a novel protein called folliculin. We report the clinical and genetic studies of four sporadic BHD cases and four families with a total of 23 affected subjects. Haplotype analysis of these families using BHD linked markers showed they did not share the same affected alleles, excluding common ancestry. Mutation analysis of the BHD gene identified two germline mutations on exon 11 (c.1733insC and c.1733delC) in three of four families as well as two of four sporadic cases. A novel somatic mutation, c.1732delT/CinsAC, was detected in a BHD related chromophobe renal carcinoma. Our results confirmed the (C) tract on exon 11 as a mutational hot spot in BHD and should always be considered for future genetic testing. Our observation also indicated that the second hit (of Knudson’s two hit theory) in some BHD related tumours is in the form of somatic mutation rather than LOH. In a large French family in which eight affected subjects carry the c.1733delC mutation, a phenoctype who has multiple episodes of spontaneous pneumothorax was identified. A total of five mutation carriers (aged between 37 to 66) did not have any evidence of BHD features, suggesting either reduced penetrance or late age of onset of the disease. In addition, six out of eight affected subjects who have positive germline mutation have confirmed neoplastic colonic polyps, indicating that colorectal neoplasia is an associated feature of BHD in some families. Our studies have observed several interesting genetic features in BHD: (1) the poly (C) tract in exon 11 as a mutational hot spot; (2) the existence of phenocopy; (3) reduced penetrance or late age of onset of disease; (4) association with colonic neoplasia in some families; and (5) somatic mutation instead of LOH as the second hit in BHD tumours.

**MATERIAL AND METHODS**

**Subjects**

One three generation BHD kindred with 10 affected subjects (F518) (fig 1), one two generation kindred with five affected subjects (F598), one four generation kindred with 10 affected subjects (S001), 9 and one nuclear kindred with two affected subjects (S002) were studied, along with four sporadic cases (S003, S006, F641, F676). All samples were from either France or Sweden. All studies were approved by the Ethical Committee at Le Kremlin-Bicêtre University Hospital in France, the Karolinska Hospital Ethics Committee in Sweden, and the Internal Review Board of the Van Andel Research Institute in the USA. Informed consent was obtained from all participating patients and family members.

Blood samples were obtained and DNA was extracted from lymphocytes using the Qiagen Maxi kit (Qiagen, California, USA). A chromophobe renal carcinoma from an affected member in family S001 was also included for DNA extraction.

**Clinical studies**

Evaluation was carried out at several hospitals in France as well as at the Department of Dermatology and Venerology, and the Department of Clinical Genetics in Karolinska Hospital. Each patient underwent thorough skin examination and diagnosis was confirmed histologically by biopsy. Abdominal

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**ORIGINAL ARTICLE**

Clinical and genetic studies of Birt-Hogg-Dubé syndrome

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Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant cancer syndrome characterised by benign skin tumours, renal tumours, and spontaneous pneumothorax. The gene has been mapped to chromosome 17p11.2 and recently identified, expressing a novel protein called folliculin but its function remains unknown. The identification of this gene provides an opportunity for genetic testing which will lead to a better understanding of the disease. In this study, we report clinical and genetic studies of four apparently sporadic cases and four families with 23 affected subjects from France and Sweden.
CT scans and/or renal ultrasonography were applied to detect the presence of renal tumours. Thoracic CT scans were performed to scan for abnormalities of the lungs and colonoscopy was used to detect colorectal neoplasia.

**Genotyping, haplotyping, and loss of heterozygosity (LOH) analysis**

Ten microsatellite markers from chromosome 17p12-q11.2, D17S921, D17S1857, D17S740, D17S2196, D17S620, D17S805,

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*Figure 1* (A) Pedigree and haplotype of family F518 with BHD. Blackened bars represent the affected haplotype. + designates subjects with the c.1733delC mutation detected and – subjects without mutation. Note the four clinically unaffected subjects (III.2, III.6, III.7, and IV.1) who are BHD haplotype and mutation carriers. III.5 is a phenocopy. Part of the affected haplotype shown in the striped bar (III.1) with the absence of mutation suggests the coincidence of possible allele sharing originating from an unaffected parent (II.1 or II.2). (B) Families F598, S001, and S002 with BHD.
Form 32 subjects from three familial and four sporadic BHD cases

**Table 1**

<table>
<thead>
<tr>
<th>Family</th>
<th>Subject</th>
<th>Current age</th>
<th>Cutanous lesions</th>
<th>Renal lesions</th>
<th>Colorectal lesions</th>
<th>Pneumothorax</th>
<th>Other lesions</th>
<th>Mutation</th>
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<td>F518</td>
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<td>NA</td>
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<tr>
<td></td>
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<tr>
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<td>NA</td>
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<tr>
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<td>None</td>
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<td>None</td>
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<tr>
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<td>x</td>
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<td>None</td>
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<td>None</td>
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<tr>
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<td>41</td>
<td>xx</td>
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<tr>
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<td>37</td>
<td>x</td>
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<tr>
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<td>7</td>
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<td>None</td>
<td>Lung carcinoma</td>
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<td>xx</td>
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<tr>
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<td>II.3</td>
<td>52</td>
<td>xxx</td>
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<tr>
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<td>II.4</td>
<td>65</td>
<td>xxx</td>
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<tr>
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<td>xxx</td>
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<td>Retinoblastoma</td>
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<tr>
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<td>I.1</td>
<td>66</td>
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<td>NA</td>
<td>Multiple</td>
<td>Three</td>
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<td>39</td>
<td>x</td>
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<td>49</td>
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<tr>
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<td>61</td>
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<tr>
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<td>63</td>
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<td>NA</td>
<td>None</td>
<td>Meningioma; vulvar epitheliomas</td>
<td>None</td>
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</table>

Bold letters = age at death; x = 10–10 lesions; xx = 10–100 lesions; xxx = >100 lesions; NA = not available.

RESULTS

Clinical data

The clinical data of all affected subjects, except those from family S001, are summarised in table 1. Family F518 (fig 1A) is a large three generation family first described by Binet et al in 1986. This family has 10 members with typical cutaneous fibrofolliculomas and was therefore considered as affected with BHD. Multiple recurrent pneumothorax occurred in six of the affected members. III.5 (aged 47) who has many recurrent pneumothorax was initially considered as affected, but was tested negative for the mutation, therefore representing a phenocopy. Regarding the occurrence of kidney tumours, apart from two benign cysts detected in III.9 (aged 71), none of the eight examined affected patients has a renal tumour. In contrast, neoplastic colorectal polyps of different histological types (villous, tubulovillous, or tubular), mainly with a mild to moderate degree of dysplasia, were observed in six of the affected patients: II.5, III.9, IV.2, IV.4, IV.5 and IV.6. II.7 died at...
Figure 2 Representative BHD sequence of normal (A) and affected subjects (B, C), as well as a novel c.1732delTCinsA mutation (D) detected in a chromophobe tumour. These results support the poly C tract as a mutational hot spot in exon 11.
He was then treated with BCG vaccine immunotherapy. In contact with his mother. At the age of 35, he had a right deteced in subject S006.

Fibrofolliculomas were found in both patients, but renal ultrasound showed no sign of cutaneous lesions or other BHD related features. Fibrofolliculomas and breast sarcoma were superficial spreading malignant melanoma in the leg (II.3) and lung carcinoma in a dead obligate carrier (I.1).

Family S001 (fig 1B) has been previously described and has 10 members affected with BHD. One subject (V.4) had a spontaneous pneumothorax and atypical cyst in his kidney, while two other members (IV.4 and V.3) have renal cell carcinoma as well as pneumothorax. Other clinical features included sarcoma dorsi, fibroadenomatosis of the breast, and multiple lipomas.

Family S002 (fig 1B) is a newly ascertained BHD Swedish family. Multiple skin lesions were detected in the father (I.1) and daughter (II.1). Both have pneumothorax but no kidney lesion. Colonoscopy was not performed.

S003 and S006 are sporadic cases of BHD. In both cases, both of their parents have died and their sibs did not show any sign of cutaneous lesions or other BHD related features. Fibrofolliculomas were found in both patients, but renal ultrasound did not show any abnormalities. One episode of pneumothorax, unclassified colon polyps, and breast sarcoma were detected in subject S006.

Sporadic case F641 is a white male with multiple face and neck fibrofolliculomas. His father has died and he has lost contact with his mother. At the age of 35, he had a right nephrectomy where an 8 cm “malignant oncocytooma” infiltrating the capsule and loco-regional nodes was disected. He was then treated with BCG vaccine immunotherapy. In 1999, a thoracic CT scan of this patient showed a 3 cm metastasis of the upper right lobe of the lung and many bilateral emphysematous blebs. Resection of a segment of the lung showed renal tumour metastasis with papillary structures and many infrapleural emphysematous blebs. Reinterpretation of histological slides of the initial tumour gave the diagnosis of an unclassifiable malignant Fuhrman grade 4 renal cell tumour with a preponderant eosinophilic contingent. Colonoscopy was not performed in this patient.

Case F676 is a white female whose parents did not have BHD syndrome. Both her parents have died. She was diagnosed with BHD at age 51, owing to the presence of multiple fibrofolliculomas on her face and hands. This patient has neither renal tumour nor pneumothorax. Colonoscopy performed at the age of 61 showed absence of lesions.

Mutations

Three familial cases (F518, F598, S002) and two sporadic cases (S003, F641) showed mutations, all in exon 11. A c.1733insC (fig 2B) germline mutation was detected in S002 and S003, while all affected subjects from a family with colonic neoplasia (F518) have a c.1733delC (fig 2C) germline mutation, along with F598 and F641. The C deletion mutation in F518 also cosegregated with four BHD haplotype carriers (III.2, III.6, III.7, and IV.1, fig 1A). The same pattern of cosegregation was also observed in one BHD haplotype carrier (II.2) in family F598. A novel mutation, c.1733delTCinsA (fig 2D), in exon 11 not reported before was detected in the chromophobe tumour from an affected subject (V.3) from family S001, where no germline mutation was present in any affected members. Two isolated cases (S006 and F676) also did not show any germline mutation.

Haplotypes and LOH

All genotype and haplotype results confirmed the BHD region that was previously mapped. A detailed haplotype for family F518 is shown in fig 1. In this family, four unaffected subjects (II.2, III.6, III.7, and IV.1) shared the same haplotype as the rest of the affected subjects and are defined as BHD haplotype carriers. The four families did not share the same affected haplotype (table 2). In family S001, no LOH was found in the chromophobe renal carcinoma of an affected member who has the disease haplotype (V.3) (data not shown).

DISCUSSION

BHD is a classical hereditary cancer syndrome. The identification of the BHD gene facilitates the genetic characterisation of the patients and their tumours, including genotype-phenotype correlation, as well as functional studies of the gene. In the present study, three different frameshift mutations in exon 11, c.1733insC, c.1733delC, and c.1733delTCinsAC, were identified. The c.1733insC and c.1733delC germline mutations were detected in 75% (3/4) of familial cases and 50% (2/4) of sporadic cases. Unfortunately DNA from the parents of the sporadic patients was unavailable for further analysis to determine if they were de novo mutations. The c.1733delTCinsAC mutation is a novel somatic mutation that was detected in a chromophobe renal carcinoma of a BHD patient. All mutations involve a poly C tract (nt 1733-1740) in exon 11, confirming the hypermutable (C), tract recently reported, where 18 c.1733insC mutations and nine c.1733delC mutations were identified in 62 BHD patient samples. This instability appears to be “slippage” during DNA replication, resulting in gains or losses of repeat units, such as in BRCA1, NFI, and APC, causing cancer predisposition. To date, besides exon 11, three other exons (7, 9, 12) were found to harbour BHD mutations. All four exons should be the focus of genetic testing, leading to saving in cost, labour, and time.

Haplotypic analysis of four BHD families (table 2) showed a different disease haplotype within each family, implying that they are unlikely to share a common ancestor and ruling out the possibility of a founder effect in their mutations. All affected members in family S001 shared the same disease haplotype, which was mapped on chromosome 17p11.2, but none of them have germline mutation. This can be explained
by (1) mutation in the promoter region; (2) a small germline deletion between marker D17S540 and D17S2196; or (3) a second BHD gene located in the vicinity of the mapped locus. The difference between family S001, which has no germline mutation, and those cases which have mutations (F518, F598, S002, S003, and F641) is the presence of breast tumours in some BHD members in S001. Interestingly, breast tumour also occurred in S006, who is a sporadic case without any germline mutation.

The majority of hereditary cancer syndrome genes follow the paradigm of a tumour suppressor gene or Knudson’s two hit theory. Tumours usually carry a copy of an inactivating germline mutation and lose the other copy via loss of heterozygosity, hypermethylation, or mutation. The latter is most commonly found in hereditary tumours, but in BHD only 17% of hereditary renal tumours showed LOH. In the only BHD related chromophobe tumour available in this study, LOH could not be detected; instead a somatic inactivating mutation, which is absent in the matched constitutional DNA, was identified. The somatic mutation represents the second hit of Knudson’s theory, and should be screened for in BHD related tumours without LOH. Other mechanisms, such as hypermethylation, may also be involved and merit further investigation.

Several groups have reported cases of colorectal neoplasia in BHD families, but a more recent clinical study7 of the absence of colorectal neoplasia in 152 patients from 49 families. One study5 showed statistical non-significance comparing the presence of colon cancer in 111 BHD affected and 112 BHD unaffected subjects, as well as colon polyps of 45 BHD affected and 38 BHD unaffected subjects, concluding that there is no risk increment for the development of colon polyps or colon carcinoma in BHD patients. In the present study, we identified six family members with true neoplastic colorectal polyps and two with probable colon cancer, indicating that colorectal neoplasia is involved in this particular BHD family. It is not uncommon to find certain unique clinical features associated with certain families in hereditary cancer syndromes. Environmental or additional genetic factors may be the possible cause. The latter would suggest the involvement of a “modifier” gene(s) which is related to BHD, or a distinct colorectal neoplasia related gene which happened to cosegregate with the BHD gene in some of the family members. Additional studies will be necessary fully to understand the role of BHD in colorectal tumorigenesis. In addition, our present study indicates that BHD patients may have a predisposition to other malignancies, such as melanoma, as well as gastrointestinal, lung, head and neck, and breast cancers.

Subject III.5 from family F518 had multiple episodes of spontaneous pneumothorax but without any skin lesions. The absence of germline mutation suggests that she is a phenocopy. However, c.1733delC germline mutations were detected in her two brothers, III.6 and III.7 (aged 53 and 40, respectively), although they have not yet developed any symptoms of BHD. In addition, two other subjects from F518 (III.2, aged 41) were also found to have germline mutations but with no clinical evidence of the disease. The findings can be explained by the late age of onset of BHD syndrome, although it is also quite possible that BHD has reduced penetrance in certain people. Further and long term studies on these families are warranted to address these issues. This study also supports the idea of a modifying gene(s) which affects the expression of a BHD phenotypic trait. The latter is a common phenomenon in other inherited cancer syndromes such as the Cowden syndrome.

ACKNOWLEDGEMENTS

The first two authors contributed equally to this work. We would like to thank all the BHD patients and family members who participated in the studies. We also thank Dr J Amiel, Dr E Beltzer-Garely, Dr H J Bertrand, Dr C Bizollon, Professor G Benoît, Dr J M Corréas, Dr B David, Dr W Godard, Professor J P Grünfeld, Dr J P Jacquot, Professor A Jardin, Dr G Turcat, and Dr G Allègre for their very valuable help. This study was supported by grants from French Ligue Nationale Contre le Cancer (Comité du Cher), the Swedish Cancer Society, and the Van Andel Foundation.

REFERENCES


Molecular Cytogenetics Protocols and Applications

This book is a very up to date manual covering the background, methodologies, and applications of molecular cytogenetics techniques. The emphasis is on the diagnostic applications of FISH in the many areas of medicine on which it impinges, including paediatrics, fetal and reproductive medicine, pathology, haematology, oncology, and, of course, medical genetics. With 27 chapters and over 60 authors, all of whom are experts in their field, this book clearly shows how far molecular cytogenetics techniques have developed over the last two decades.

The book is divided into three parts. Part I covers the basic concepts and techniques. The opening chapter by the editor Yao-Shan Fan provides a very helpful overview of the scope of the book and an extensive set of references for further reading. The following chapters cover probe labelling (DNA and RNA probes) and basic FISH techniques. The second part of the book is devoted to evolving techniques and applications and includes chapters on microdissection, PRINS, SKY FISH, M FISH, CGH, colour banding FISH, fibre FISH, multilamere FISH, fluorescence genotyping for telomeric regions, and microarray CGH. Special applications of molecular cytogenetics techniques in chromosomal disorders are covered in part 3 of the book. These include chapters on the application of FISH to the delineation of marker chromosomes and the diagnosis of microdeletion syndromes. Other chapters cover FISH interphase nuclei screening for prenatal diagnosis including preimplantation diagnosis and fetal cells in the maternal circulation, in addition to the interphase FISH screening of routine amniotic fluid samples. This section concludes with a chapter on the application of FISH and CGH in reproductive pathology. The fourth and final section of the book covers the application of molecular cytogenetic techniques to cancer diagnosis. Chapters include the use of CGH in cancer investigations and the application of interphase FISH for the BCR/ABL rearrangements in CML and for HER2 amplification in breast cancer. Also included in this section are the interesting combined approaches, firstly of chromogenic in situ hybridisation with FISH in pathology and secondly simultaneous fluorescence immunophenotyping and FISH on tumour cells.

With any multiauthor book, there are bound to be differences in approach to the writing of individual contributions. This book has taken a surprisingly consistent approach, perhaps an illustration of good editorial control. All of the chapters have good introductory sections and are well referenced, as well as containing the authors’ preferred methodologies. Each chapter also includes a comprehensive notes section (effectively tips and troubleshooting advice from the experts). However, a major problem with the book is the lack of comparison between different molecular techniques. In the preface, it is suggested that the book should help the cytogeneticist determine which procedure to perform for an informative result. I am not sure that the book provides this, as most if not all of the contributors are bound to select their own preferred methodology. For example, in the chapter on FISH screening for telomere abnormalities, an otherwise excellent chapter by Samantha Knight and Jonathan Flint, the practical application of only one of the two commercially available probe sets for this test is covered. More importantly, elsewhere in the book there is a first class chapter on interphase FISH for prenatal diagnosis of common aneuploidies by Baruch Feldman et al. This covers the topic extremely comprehensively and provides 89 literature citations. However, there is no mention, as far as I could see, throughout the book of the other alternative molecular approach of quantitative fluorescence PCR for prenatal aneuploidy detection. While it may be reasonable to excuse the editor by saying that the book is not designed to cover purely molecular genetic techniques, in the same section as the prenatal FISH, there is a chapter on the molecular detection of uniparental disomy. This chapter sits rather incongruously among the others, but is in itself a useful and important topic. Another chapter which seems to have lost its place describes the BAC resource for molecular cytogenetics. This is the final chapter in the book, which appears to have been added as an afterthought. Surely this should have been in evolving techniques and applications rather than “special applications in oncology”. The oncology applications would also have benefited from more chapters, for example, haematological disorders other than CML, solid tumour FISH (other than HER2), and perhaps a chapter on the screening of urine samples for bladder cancer.

Perhaps these topics are covered in the companion volume (Methods in molecular biology; volume 220. Cancer cytogenetics: methods and protocols). Another criticism is that the provision of colour plates is very variable. Some chapters are well illustrated, others less so. For example, the chapter on SKY FISH relies on black and white illustrations, whereas the MFIISH chapter has glorious full colour images. Furthermore, the overall size of the book is relatively small (16 cm by 24 cm) and the size of typesetting and tight layout does not make for easy reading when compared with, for example, Rooney’s “Human cytogenetics: a practical approach”.

On the plus side, there is an incredibly large amount of information packed into this volume, none of it superfluous. Although other textbooks that cover FISH techniques are available, this book provides a more comprehensive, up to date, and thorough coverage of diagnostic molecular cytogenetics than any of the other books currently available.

In summary, I would recommend it as a reference source for everyone working in and interested in the exciting field of diagnostic and research molecular cytogenetics.

Lionel Willatt
European Human Genetics Conference 3 – 6 May 2003 ICC, Birmingham, England

Plenary sessions
• Low Penetrance Genes and Cancer Susceptibility
• Public Issues - Population DNA Banks
• Recent Developments in Neurogenetics

Symposia
• Bioinformatics
• Stem cells
• Sensory genetics
• Alternative splicing
• Cancer genetics
• Alzheimer disease
• SNPs and haplotypes
• Chromosomes in genetic disease
• Genetics and endocrine problems

Workshops
• Syndrome identification
• Cytogenetics
• Problems in counselling/ethics
• Genotyping and mutation detection arrays—practical problems
• Quality control
• Prenatal cytogenetics
• Community genetics

Abstract deadline
Will be via world wide web.
Closing date 13 January 2003.
Further information available from: The Vienna Medical Academy of Postgraduate Medical Education and Research, Alserstrasse 4, A-1090 Vienna, Austria. Tel +43 1 405 13 83
Email: eshg@medacad.org

CORRECTIONS
In the October 2002 issue of the journal, in the paper by Van Maldergem et al (J Med Genet 2002;39:722-33), we regret that some of the authors’ names and affiliations were inadvertently omitted. They were:
- N Tubiana-Rufi
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- J Maassen
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- M Polak
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In the July 2002 issue of the journal, in the Online mutation report by Olivieri et al (pe39), there was a missprint in table 2. For No 12 the mutation should have been 1031G>T instead of 1006G>T.

In the December 2002 issue of the journal, in the paper by Khoo et al (pp 906–912), all c.1732delTCinsAC mutations should read C.1732delTCinsA. This error occurs on page 906 (Abstract) and page 910 (Discussion).

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