The genotype frequencies for mutations in the HFE gene found in the present study are shown in table 1. In the Basque population we have detected a frequency of 2% for the C282Y allele, a value that falls in the "south European range". The H63D allele in this population shows a frequency of 27.4%. This value, which is similar to that reported by Merryweather-Clarke et al., is, together with the 29.5% found in the Dutch, the highest in the world population. Even today little is known of the origin of the Basques, a not very large population located in the west Pyrenees. It has been suggested that many of the mesolithic settlers of western Europe could have mixed with neolithic tribes to give rise to present day Europeans and a few groups of mesolithic people in the Pyrenean region could have remained sheltered from subsequent invasions, thus giving rise to the present day Basques. It has also been stated that the Basques share a people that have successfully resisted absorption by a succession of conquering or neighbouring cultures, and in a more recent study, Aguirre et al. reported that the Basque population has undergone some genetic admixture with other Europeans and that the distribution of their genetic frequencies differentiates them from other populations. The high frequency of the H63D allele in the Basque population can be regarded as an additional genetic marker, which also lends support to the singularity of their genetic characteristics.

The Spanish Gypsy population represents the largest Gypsy community in western Europe with approximately half a million people distributed all over the country. In the group of Spanish Gypsies studied, we found a frequency of the C282Y allele within the range reported in Europe. As for the H63D allele, we found a low frequency (8.62%) compared with that of the European population. The arrival of Gypsies in Europe can be traced back to the 14th century and linguistic evidence suggests that Gypsies originally came from India where a trickle of small nomadic bands moved to the west. On the basis of the available data, the frequency of this allele in the Indian continent is 8.4%, which resembles the value found in Spanish Gypsies. Interestingly, similar frequencies are found in populations in the Middle East, on the route from India to the west.

The results obtained for the group of blood donors show allele frequencies for both substitutions comparable with the frequencies of the European population as a whole.

Mitochondrial DNA mutations and pathogenicity

We read with interest the case described by Dr Albin in the March issue of the Journal. We agree that some features of the clinical presentation of the 48 year old woman are highly suggestive of mitochondrial disease. A mitochondrial aetiology should be considered in any patient with bilateral sensorineural deafness and impaired glucose tolerance. Additional clinical features that affect multiple systems (such as the cerebellum, basal ganglia, and pyramidal tracts), coupled with the high signal in the deep white matter on MRI, would add weight to the clinical diagnosis. It would be interesting to know whether there were oligoclonal bands in the CSF which were not matched in the serum, particularly because of the possible association of mitochondrial DNA (mtDNA) disease with multiple sclerosis. Being highly metabolically active, corneal endothelial cells may be particularly vulnerable to mitochondrial dysfunction, and although corneal dystrophy has been noted in patients harbouring established pathogenic mtDNA mutations, classical Fuch's corneal dystrophy has not been described in this context. Fuch's corneal dystrophy is a relatively common disorder, accounting for 15% of all corneal grafts, and, as Dr Albin suggests, it is possible that the corneal disease was an incidental finding in the case that he described.

Despite the clinical evidence supporting a diagnosis of mtDNA disease, it is unlikely that the T4216C and G15257A transitions on their own are responsible for the symptoms of the patient described by Dr Albin. The T4216C and G15257A mutations are present in between 5 and 20% of the normal population, and phylogenetic analysis indicates that they are both ancient caucasian polymorphisms. There is a heavy phylogenetic clustering of patients who harbour the primary pathogenic G11778A and T14448C mutations (which cause Leber's hereditary optic neuropathy (LHON)) in mtDNA haplotype J. This haplotype also carries the T4216C transition in all branches and the G15257A transition in one branch. However, there is no evidence that non-LHON neurological mtDNA disorders cluster in haplotype J. By contrast, there is an unexplained association of multiple sclerosis with haplotype T, which also carries the T4216C transition. Clearly the relationship between mtDNA haplotype and disease is highly complex, and it would be wise to draw firm conclusions from any one individual case.

The investigation of possible mtDNA disease is difficult, particularly when the phenotype is not instantly recognisable. We advocate an integrated approach to the
investigation of these patients, incorporating both clinical and laboratory evidence. It would be of great value to carry out a skeletal muscle biopsy on the patient described by Dr Albini to search for histochemical and biochemical evidence of mitochondrial respiratory chain dysfunction. These investigations are often abnormal in patients with neurological abnormalities resulting from mtDNA mutations, and the characteristic mosaic pattern of cytochrome c oxidase activity in muscle or a biochemical complex deficiency may provide clues as to the nature of the underlying genetic defect. It is often difficult to ascribe pathogenicity to a mtDNA mutation, particularly if the disease has an unusual phenotype.1 Therefore, although the clinical evidence presented by Dr Albini is compatible with a mitochondrial disorder, the inference that the T4216C and G15257A nucleotide transitions are the primary aetiological factor responsible for Fuch’s corneal dystrophy is unfounded.

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"Cataplexy" in Coffin-Lowry syndrome

Crow et al reported an unusual, non-epileptic, cataplexy-like phenomenon in three males with Coffin-Lowry syndrome (CLS). The authors also provided evidence of neuromuscular dysfunction as part of the phenotype by showing abnormalities on muscle ultrasound in four gene carriers, and they commented on our observation of the red dye muscle wasting in two affected brothers, aged 15 and 14 years at the time of our report. In that report, we described the frequent occurrence of generalised epileptic seizures without pathognomonic epileptic elements. However, on examination of the patients we had occasion to follow theseCLS brothers up to their sudden death at the age of 32 and 34 years, respectively. During this follow up it became evident that the "epileptic episodes" were episodic and dystrophic or cataplexy-like with atonia; as in case 1 reported by Crow et al, these episodes were precipitated by a loud noise or excitement. The frequency and severity of these "epileptic attacks" worsened with age and was correlated with a further progression of the peripheral muscle wasting and of a severe thoracolumbar scoliosis, which finally resulted in acute cardiorespiratory failure.

Over the last 25 years we have had the opportunity to examine 20 other CLS males. In one of these patients the same type of sudden, non-epileptic attacks were noted from the age of 4 years. When this boy suddenly dropped, always in a forward position, hurting himself. No epileptic discharge have ever been noted on repeated 24 hour EEG monitoring. Also, a progressive thoracolumbar scoliosis with a large lumbar lordosis became evident. The scoliosis worsened with age and was correlated with a further progression of the peripheral muscle wasting and of a severe thoracolumbar scoliosis, which finally resulted in acute cardio-respiratory failure.

In conclusion, our experience in CLS males confirms that "cataplexy" is not rare in this XLMR syndrome, as we observed it in three of 22 male patients. The aetiology and pathogenesis of this sudden, severe collapse phenomenon remains unclear. In this perspective, it is of interest to note that these cataplexy-like symptoms increased in frequency and severity in the two brothers, together with the progressive thoracolumbar scoliosis and muscle wasting. In contrast, the collapse symptoms disappeared completely in the third male after surgical correction of the scoliosis.

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Autoclaving Guthrie cards does not prevent their use in PCR reactions!

Doctors Rahman, Emery, and Poulton (J Med Genet 1998;35:263) point out their problems in obtaining neonatal screening dried blood spots or Guthrie cards from patients with the MELAS 3243 mutation. They comment that of the four cards they were able to obtain, one had been autoclaved. This, they claim, destroys the DNA.

"Dried blood spot cards are commonly autoclaved or steamed before performing the bacterial inhibition assay for phenylalanine screening for phenylketonuria (PKU)." They have used such blood spots for analysis of the common mutations for medium chain acyl-CoA dehydrogenase deficiency (MCADD), respiratory enzyme intolerance, and the NARP 8993 mutation. One has also been successfully used for identification purposes by DNA fingerprinting. In a study of mitochondrial DNA haplogroups in the West Midlands Region for the common MCADD mutation, a failure rate of PCR of only 0.3% was obtained.

Hence there is no reason to believe autoclaving of Guthrie cards would contribute to a poor PCR. In fact it may be that denaturing contaminating protein by autoclaving may help to reduce the amount of protein carried over during extraction and hence reduce the risk of PCR failure. However, we fully support the authors’ suggestions for central funding for the storage of this important medical resource.

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Genetic Disorders and Pregnancy Outcome


Many clinicians who deal with high risk obstetrics or have specialised in maternal-fetal medicine, obstetric physicians, and geneticists will welcome this guide to pregnancy management of people with genetic disorders who intend to have