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Further evidence for genetic heterogeneity of autosomal dominant disorders with accumulation of multiple deletions of mitochondrial DNA

EDITOR—Disorders of oxidative phosphorylation are highly heterogeneous from both a clinical and a genetic point of view. The nuclear as well as the mitochondrial genomes contain genes that are necessary for respiratory chain function. Consequently, different modes of inheritance are encountered in disorders of oxidative phosphorylation.

Single large scale deletions of mitochondrial DNA (mtDNA) usually occur in sporadic cases.[1] However, multiple deletions of mtDNA also occur in autosomal dominant disorders.[2] These deletions are generated de novo as somatic mutations in each affected subject. The nuclear gene defects predisposing to secondary mtDNA deletions in these patients remain unknown.

The disorder discovered by Zeviani *et al*[2] was later found in several families and was called autosomal dominant progressive external ophthalmoplegia (ADPEO),[3] as ptosis and external ophthalmoplegia are the major clinical findings.[4–7] More generalised weakness of the skeletal muscles and sudden unexpected death are also common clinical features.[4–7] Additional features vary among different families.[4 6–8]

Linkage analysis provided direct evidence for genetic heterogeneity of ADPEO. One locus predisposing to ADPEO in a Finnish family was assigned to chromosome 10q23.3-q24.3.[3] Another locus was assigned to chromosome 3p14.1-p21.2 in three Italian families.[9] In another Italian ADPEO family the disorder is linked to chromosome 4q34-q35.[10]

We previously reported three unrelated Belgian families with progressive external ophthalmoplegia and multiple deletions of mtDNA.[6] Only one of these families was of sufficient size to examine cosegregation of PEO with the known loci on chromosomes 10q, 3p, and 4q.

Fig 1 shows the updated pedigree of the Belgian PEO family. Several male to male transmissions indicate clear autosomal dominant inheritance. The diagnosis of ADPEO was based on the clinical symptoms and the presence of multiple mtDNA deletions on Southern blots of muscle biopsy specimens in two patients. The detailed clinical features and the muscle biopsy findings with mtDNA analysis have been described elsewhere.[6]

Blood samples were obtained after informed consent. The primer sequences for the polymorphic DNA markers on chromosomes 3, 4, and 10 were obtained from the Genome Database (http://gdbwww.gdb.org). The linkage analysis was carried out by MLINK 5.1 using a disease gene frequency of 1/10 000. Since variable penetrance of the disease was shown in the 10q linked Finnish family,[3] only affected subjects were included in our linkage analyses. Subjects were considered affected when clinical examination showed PEO and absent Achilles tendon reflexes (fig 1). Dead, but not clinically examined subjects were considered affected if there was a positive family history obtained from relatives and the appearance of PEO in photographs.

The average expected maximum lod score in computer simulation analysis was 1.5, assuming a 80% informative linked marker at 5% recombination distance from the PEO gene. In 500 simulated replicates, the maximum lod score obtained was 3.60. Linkage analysis excluded all three known loci (table 1). Few markers generated minor positive lod scores (Z) of 0.5 to 1 at large recombination distances (θ), but flanking markers and haplotype analysis clearly excluded the candidate regions.

Our data provide further evidence for the genetic heterogeneity of autosomal dominant PEO, indicating that

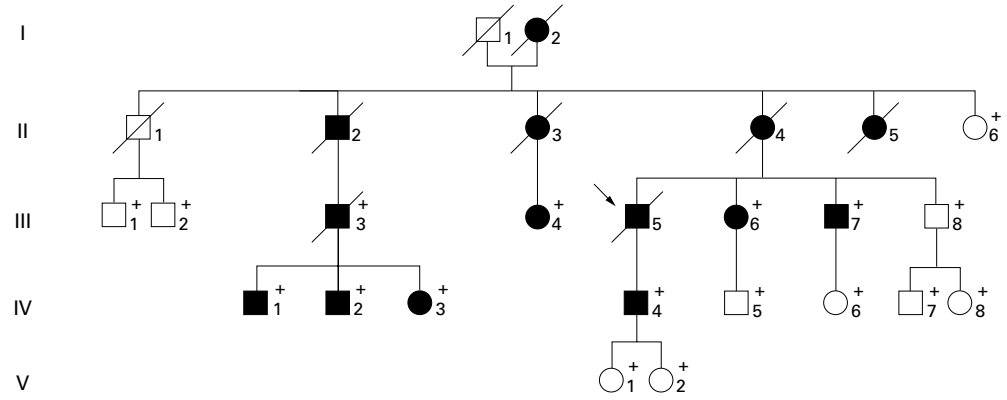

Figure 1 Pedigree of the autosomal dominant Belgian PEO family. Filled symbols indicate affected subjects. Subjects III.5 and III.7 had multiple mtDNA deletions on Southern blots of DNA isolated from skeletal muscle biopsies.[6] Open symbols indicate healthy subjects. A plus sign (+) denotes subjects from whom DNA samples were available for genetic analysis. The proband is indicated by an arrow.

Table 1 Pairwise lod scores of chromosomes 3p, 4q, and 10q DNA markers in a Belgian ADPEO family. The 3p DNA markers are ordered from telomere to centromere and the 10q and 4q markers from centromere to telomere conform with their position on the genetic map (Whitehead Institute, http://www-genome.wi.mit.edu/cgi-bin/contig/physmap). For each marker the genetic distance excluded (exclusion limit) was calculated from the recombination distance at Z=−2

	Lod score at θ=							
Marker	*0.00*	*0.01*	*0.05*	*0.10*	*0.20*	*0.30*	*0.40*	*Exclusion limit*
D3S3666	−3.59	−1.31	−0.48	−0.14	0.10	0.11	0.04	0.01
D3S3553	−7.76	−3.02	−1.49	−0.84	−0.28	−0.08	−0.01	0.03
D3S1300	−3.60	−1.02	−0.39	−0.18	−0.05	−0.02	−0.01	0.00
D3S1312	−7.96	−2.87	−1.54	−1.03	−0.59	−0.36	−0.17	0.04
D3S1600	−3.39	−1.22	−0.60	−0.38	−0.20	−0.12	−0.05	0.00
D3S3571	−12.31	−4.63	−2.60	−1.78	−0.98	−0.51	−0.20	0.09
D10S1750	−7.12	−2.05	−0.79	−0.35	−0.06	0.00	0.01	0.01
D10S1773	−11.36	−4.23	−2.21	−1.40	−0.68	−0.33	−0.12	0.04
D10S1731	−15.89	−5.79	−3.06	−1.95	−0.92	−0.42	−0.14	0.10
D10S187	−11.48	−4.13	−2.10	−1.28	−0.56	−0.24	0.08	0.06
D10S190	1.11	1.09	0.97	0.82	0.52	0.26	0.08	
D10S1757	−6.82	−2.00	−0.73	−0.30	0.02	0.03	0.02	0.01
D10S1483	−3.66	−0.98	−0.35	−0.13	0.01	0.04	0.03	0.01
D10S587	−7.34	−2.56	−1.19	−0.65	−0.19	−0.02	−0.02	0.04
D10S1723	−11.36	−4.50	−2.41	−1.53	−0.72	−0.33	0.11	0.08
D10S1656	−7.82	−3.10	−1.70	−1.09	−0.52	−0.23	−0.07	0.04
D10S186	−2.62	0.04	0.58	0.68	0.58	0.35	0.12	0.00
D10S1782	−7.22	−2.40	−1.09	−0.58	−0.18	−0.03	0.01	0.03
D4S1554	−11.57	−3.96	−1.96	−1.18	−0.53	−0.24	−0.09	0.05
D4S2924	−7.39	−2.49	−1.18	−0.68	−0.28	−0.12	−0.05	0.03
D4S2299	−11.48	−4.36	−2.34	−1.52	−0.76	−0.37	−0.13	0.07

at least four loci in the nuclear genome predispose to somatic mutations of mtDNA with accumulation of multiple mtDNA deletions. To localise the fourth disease locus, we will perform a random genome search in this Belgian family.

The different genes involved in autosomal dominant PEO may encode different functional polypeptide subunits of a single multienzyme complex or may be independently functioning molecules. The gene products may play a role in one single or even in several pathogenetic mechanisms resulting in this complex human disease. Indeed, there are several hypotheses of different pathogenetic mechanisms such as defects in mtDNA replication, defects in repair of damaged mtDNA, or in effective elimination of free oxygen radicals and secondary mtDNA damage. Cloning of one of the ADPEO genes may improve our understanding of how the nuclear and the mitochondrial genome interact. In mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), an autosomal recessive disease, also associated with multiple deletions of skeletal muscle mtDNA deletions, functional mutations in the thymidine phosphorylase gene were recently reported.[11] A similar demonstration of molecular defects in autosomal dominant PEO genes might provide a rational basis for treatment or prevention of these disorders.

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Liebenberg syndrome: brachydactyly with joint dysplasia (MIM 186550): a second family

EDITOR—In 1973, Liebenberg[1] described a five generation pedigree with unusual anomalies of the elbows, wrists, and hands and autosomal dominant inheritance (MIM 186550). The same family was re-examined in 1985 by Beighton with corroboration of the distinctive phenotype.[2 3] The most prominent features were dysplasia of all the bony components of the elbow joint, abnormally shaped carpal bones, and brachydactyly. Since then, no other families have been described.

We report on a mother and two sons whose clinical and radiological features closely resemble those of Liebenberg syndrome.

The pedigree of our patients is showed in fig 1. When last examined, the two affected children, III.4 and III.5, were 3 years and 1 year old, respectively. Their older sister, III.3, was aged 6 and was thought to be unaffected. The affected mother, II.2, was 33 and her husband, II.3, 36 years old and were healthy and non-consanguineous. The mother's parents, I.1 and I.2, were said to be unaffected.

Patient III.5 was born at term. Pregnancy and delivery were uneventful. Birth weight was 3800 g, length 50 cm, and head circumference 35 cm. His development mile-