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# Multiple symmetric lipomatosis: Abnormalities in complex IV and multiple deletions in mitochondrial DNA

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P. Eckert, MD; K. Reiners, MD; K.V. Toyka, MD; and H. Reichmann, MD

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**Article abstract**—Multiple symmetric lipomatosis (MSL) is a rare disorder of middle life characterized by large nonencapsulated lipomas distributed around the neck, shoulders, and other axial regions. Neurologic involvement, particularly peripheral neuropathy, is frequent. The pathogenesis of the syndrome is still unknown, but ragged-red fibers are occasionally present in muscle of affected patients, suggesting a mitochondrial abnormality. We studied 11 unrelated patients with MSL by means of neurophysiology, muscle morphology, muscle biochemistry, Southern blot, and PCR analysis of mitochondrial DNA. All patients were men aged 41 to 63 years. Clinical or electrophysiologic signs of a sensorimotor polyneuropathy were present in nine patients, eight of whom had a history of alcoholism. In muscle biopsy specimens, the most prominent feature was pathologic subsarcolemmal aggregates of mitochondria. Biochemical analysis of respiratory chain enzymes revealed a moderate but significant decrease of cytochrome *c* oxidase activity as compared with age-matched controls. In one patient, Southern blot analysis showed multiple deletions of mitochondrial DNA. We conclude that mitochondrial dysfunction is common in MSL and may be based on identifiable defects in the mitochondrial genome.

NEUROLOGY 1994;44:862-866

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Multiple symmetric lipomatosis (MSL) is an uncommon disorder first described by Brodie in 1846.<sup>1</sup> Subsequently, the condition acquired a variety of names, such as Madelung's disease<sup>2</sup> and Launois-Bensaude syndrome.<sup>3</sup> The large subcutaneous fat masses are distributed mainly around the neck and shoulders but may also involve other parts of the trunk. Neurologic involvement, particularly peripheral neuropathy, has been reported in most patients<sup>4</sup> but was found to be unrelated to the high percentage of alcoholism. Thus, neuropathy has been regarded an integral part of the MSL syndrome.<sup>5,6</sup>

Although abnormalities of lipolysis have been described,<sup>7-9</sup> the basic biochemical defect in MSL is still unknown. Recently, an association was suggested between MSL and mitochondrial dysfunction. Berkovic et al<sup>10</sup> found ragged-red fibers in three of four muscle biopsy specimens and reduced cytochrome *c* oxidase activity in two. We also had noticed ragged-red fibers or subsarcolemmal aggregates of mitochondria in occasional MSL patients. Ciafaloni et al<sup>11</sup> reported multiple deletions of mitochondrial DNA (mtDNA) in a patient with multiple

lipomas. Moreover, some patients with the syndrome of myoclonic epilepsy and ragged-red fibers (MERRF) presented with cervical lipomas resembling those of MSL (references 12 and 13 and personal communication by D.C. Wallace and J.M. Shoffner). Those lipomas contained a high fraction of mutated mtDNA in one MERRF patient.<sup>14</sup> Here we report on morphologic, biochemical, and molecular genetic features of 11 patients to test the hypothesis that MSL is associated with mitochondrial dysfunction.

**Methods.** *Subjects.* Eleven unrelated patients with the typical appearance of MSL (figure 1) were seen at the Departments of Neurology or Plastic Surgery, University of Würzburg, from 1985 to 1993. They were all men aged 41 to 63 years. Lipomatosis was restricted largely to the neck and shoulders in eight and was more widespread in three. Most of the lipomas had developed within a few years. Chronic intake of alcohol (>70 g/d) was reported by 10 patients. Clinical signs of a sensory neuropathy were present in seven patients, and five of these seven had signs of distal motor involvement. There were no clinical signs of myopathy in any patient. Patient 11 had ataxia and dysarthria in addition to MSL and neuropathy.

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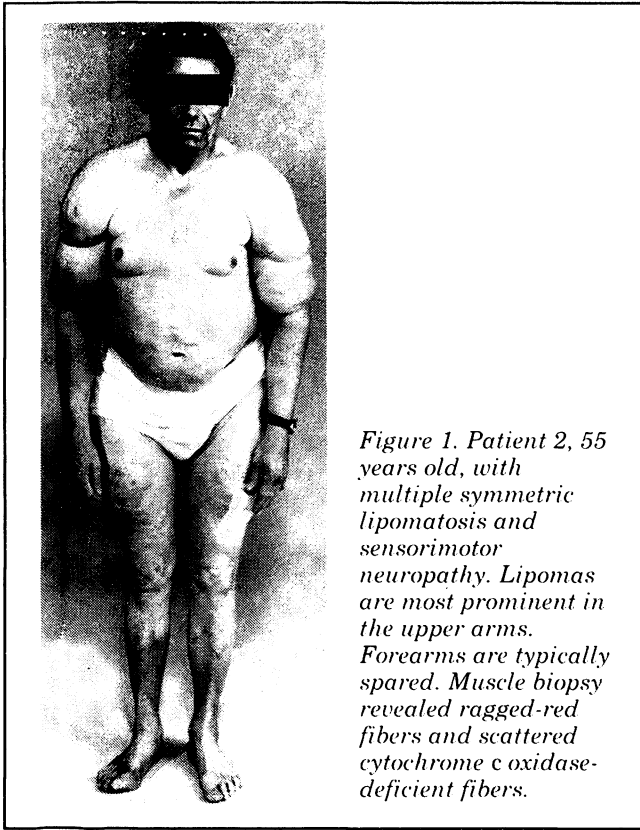
From the Departments of Neurology (Drs. Klopstock, Naumann, Schalke, Seibel, Reiners, Toyka, and Reichmann, and F. Bischof and M. Kottlors) and Plastic Surgery (Dr. Eckert), University of Würzburg, Germany.

Supported by a research grant from the Deutsche Forschungsgemeinschaft (Re 265/8-2). T.K. acknowledges a scholarship by the Deutsche Forschungsgemeinschaft (Kl 795/1-1).

Presented in part at the 45th annual meeting of the American Academy of Neurology, New York, NY, April 1993.

Received August 13, 1993. Accepted for publication in final form October 26, 1993.

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*Figure 1. Patient 2, 55 years old, with multiple symmetric lipomatosis and sensorimotor neuropathy. Lipomas are most prominent in the upper arms. Forearms are typically spared. Muscle biopsy revealed ragged-red fibers and scattered cytochrome c oxidase-deficient fibers.*

**Electrophysiology.** Standard nerve conduction studies were performed in nine patients. Measurements of motor nerve conduction velocity (NCV) were done on the tibial nerve with surface electrodes placed over the abductor hallucis muscle and sensory NCV on the sural nerve by antidromic recording below the lateral ankle and stimulation above the ankle. Needle EMG was done on five subjects, examining proximal and distal muscles. Patients 9 and 10 were seen exclusively at the Department of Plastic Surgery for lipectomy and did not have neurophysiologic examinations.

**Muscle biopsy.** Specimens were taken from one of the following muscles: biceps brachii, triceps brachii, quadriceps femoris, gastrocnemius or, in the context of surgical lipectomy, sternocleidomastoideus, trapezius, or latissimus dorsi.

**Histochemistry.** Ten- $\mu$ m frozen serial sections were stained with hematoxylin-eosin, modified Gomori's trichrome, and oil red O, and by histochemical methods, including NADH tetrazolium reductase, succinate dehydrogenase, cytochrome *c* oxidase, and ATPase.<sup>15</sup>

**Biochemistry.** Muscle samples from 10 patients, which had been stored at  $-70^{\circ}\text{C}$ , were homogenized and assayed for the enzyme activities of respiratory chain complexes as previously described.<sup>16</sup> In patient 3, there was not enough material for biochemical studies.

**Molecular genetic studies.** Total DNA was isolated from 30 to 50 mg muscle tissue<sup>17</sup> by homogenization and digestion overnight at  $55^{\circ}\text{C}$  with 100  $\mu\text{g}/\text{ml}$  proteinase K and 0.5% sodium dodecyl sulfate. DNA was extracted with phenol and chloroform and precipitated with 2 volumes of ethanol and 0.3 M NaAc. The precipitate was dissolved in 50  $\mu\text{l}$  of TRIS-EDTA buffer and stored at  $-20^{\circ}\text{C}$ . For Southern blot analysis,<sup>18</sup> DNA was digested with the restriction endonucleases *Pvu* II and *Bam*HI (Boehringer Mannheim, Germany), and subjected to elec-

trophoresis on 0.5% agarose gels. After blotting onto nylon membranes, mtDNA was visualized by hybridization to a radioactively labeled probe (nucleotide [nt] 4831 to nt 5917 of mtDNA). The proportion of deleted mtDNA was estimated by scanning the autoradiograph of the Southern blot with a laser densitometer.

The polymerase chain reaction (PCR) was used to screen for the most common mitochondrial point mutations of MERRF at nt 8344,<sup>19</sup> of MELAS at nt 3243,<sup>20</sup> and of Leber's hereditary optic neuropathy (LHON) at nt 11778.<sup>21</sup> The 100- $\mu\text{l}$  PCR reactions contained 200  $\mu\text{M}$  each of dNTP, 50  $\mu\text{M}$  KCl, 10 mM TRIS-HCl (pH 8.3), 1.5 mM  $\text{MgCl}_2$ , 0.01% gelatin, 30 pM of each primer, and 2.5 U of Ampli-Taq polymerase (Perkin-Elmer/Cetus). Amplification was performed for 30 cycles at a denaturation temperature of  $93^{\circ}\text{C}$  (1 minute), a hybridization temperature of  $58^{\circ}\text{C}$  (1 minute), and an elongation temperature of  $72^{\circ}\text{C}$  (1 minute). Allele-specific PCR was performed in a single reaction for the MERRF mutation at nt 8344 of mtDNA (primer A: nt 8149-8166; primer B: nt 8363-8344) and the MELAS mutation at nt 3243 (primer A: nt 3007-3023; primer B: nt 3261-3243); the LHON mutation at nt 11778 was also tested by allele-specific PCR (primer A: nt 11141-11158; primer B: nt 11796-11778).

**Results. Neurophysiology (table).** Tibial and sural nerve conduction studies in nine patients showed pathologic findings in all examined cases, mostly a reduction in amplitude of the compound muscle action potentials. Needle EMG demonstrated a chronic neurogenic pattern in five of these patients, including spontaneous activity (fibrillation potentials and positive sharp waves) in three.

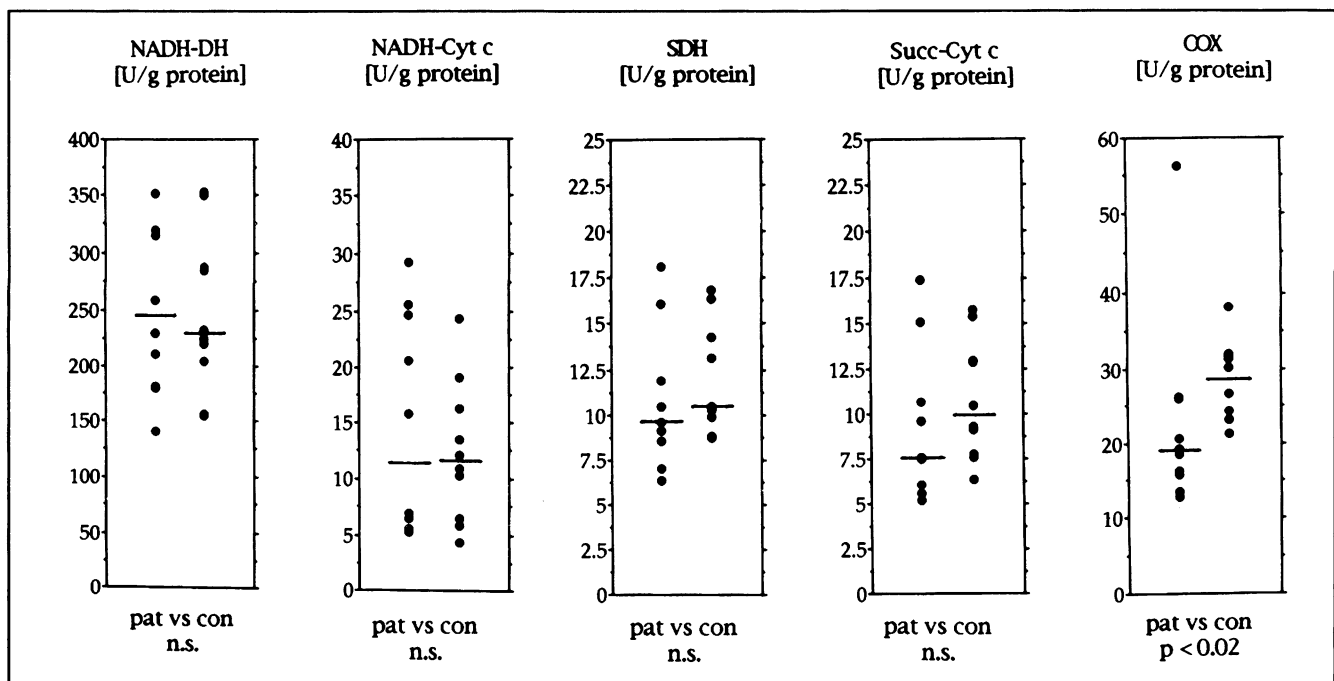
**Muscle morphology (table).** Muscle biopsy was performed on all patients, either from cervical muscles in a context of cervical lipectomy or from proximal limb muscles in an effort to detect mitochondrial abnormalities. Most specimens revealed mild myopathic changes with increased fiber diameter variability, occasional atrophic fibers, and fiber splitting. Neurogenic alterations were seen in only two patients, most likely due to the selection of proximal muscles that were not affected by overt neuropathy. In seven specimens, we found subsarcolemmal aggregates of mitochondria in Gomori's trichrome stain with the typical appearance of ragged-red fibers in two patients. Additionally, three patients showed increased subsarcolemmal staining for NADH tetrazolium salt reductase; another had scattered cytochrome *c* oxidase-deficient fibers; and two of five had subsarcolemmal accumulations of mitochondria on electron microscopy.

**Muscle biochemistry (figure 2).** Analysis of the respiratory chain enzymes in 10 patients revealed a moderately reduced activity of cytochrome *c* oxidase (complex IV) in the MSL patients compared with age-matched controls. This reduction was statistically significant ( $p < 0.02$ , nonparametric Mann-Whitney U test), with seven patients having cytochrome *c* oxidase values below the 10th percentile of controls. There was no significant difference in the activities of NADH dehydrogenase (complex I), NADH cytochrome *c* reductase (complex I + III), succinate dehydrogenase (complex II),

**Table. Clinical, electrophysiologic, and morphologic data of 11 patients with MSL**

Pt no.	Age (yr)	Alcohol (>70 g/d)	Clinical signs of neuropathy	Nerve conduction				EMG	Morphology
				Tibial nerve (motor)		Sural nerve (sensory)			
				CV	Ampl	CV	Ampl		
1	55	+	Sensory	<	n	nd	nd	Ø	
2	55	+	Sensorimotor	<	<	n	<	Neurogenic	
3	41	+	Sensorimotor	n	n	n	<	Neurogenic	
4	58	+	Sensory	<	n	nd	nd	rrf, NADH+	
5	63	+	None	n	n	n	<	nd	
6	59	+	Sensorimotor	n.o.	<	n.o.	nd	rrf, NADH+	
7	44	+	Sensorimotor	<	<	n	<	Neurogenic	
8	54	+	None	n	n	n	<	Neurogenic	
9	60	+	None		nd	nd	nd	rrf	
10	56	+	None		nd	nd	nd	rrf	
11	53	-	Sensorimotor	<	<	n.o.	Neurogenic	RRF	

nd Not done.  
 n.o. Not obtainable.  
 CV Conduction velocity.  
 Ampl Amplitude.  
 n Normal.  
 < Below normal values.  
 EMG Electromyography.  
 Neurogenic Chronic neurogenic pattern.  
 RRF Ragged-red fibers.  
 rrf Increased subsarcolemmal Gomori staining.  
 COX - COX-deficient fibers.  
 NADH+ Increased subsarcolemmal NADH tetrazolium staining.  
 Ø No mitochondrial myopathy.

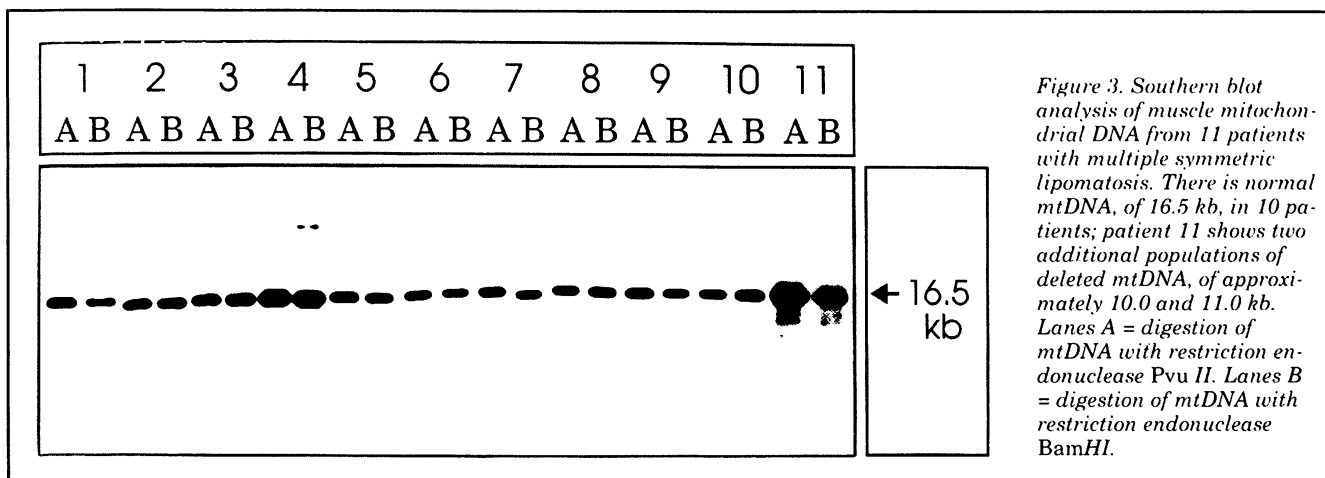


**Figure 2. Enzyme activities of respiratory chain complexes in 10 patients with MSL compared with age-matched controls.** Activities are given in U/g protein. NADH-DH = NADH dehydrogenase (complex I), NADH-Cyt c = NADH cytochrome c reductase (complex I + III), SDH = succinate dehydrogenase (complex II), Succ-Cyt c = succinate cytochrome c reductase (complex II + III), COX = cytochrome c oxidase (complex IV). There were no measurements in patient 3 due to lack of material. Mean age  $\pm$  SD of patients was  $55.6 \pm 5.2$ , and for controls it was  $57.8 \pm 5.8$  years; pat = patients; con = controls; n.s. = not significant.

or succinate cytochrome c reductase (complex II + III).

**Molecular genetics (figure 3).** Total DNA was isolated from the muscle biopsies of all patients. Southern blot analysis showed a single DNA species of approximately 16.5 kb in 10 patients,

representing normal linearized mtDNA. In patient 11, however, there was a hybridization pattern consistent with the presence of multiple populations of mtDNA, one corresponding to wild-type mtDNA and two others to mtDNA molecules with deletions of approximately 5.5 and 6.5 kb. The proportion of



mutant DNA was estimated by laser densitometry and was about 10%. PCR analysis revealed no point mutations at nt 3243 (MELAS), nt 8344 (MERRF), or nt 11778 (LHON) in any patient.

**Discussion.** In this study, we confirm and extend earlier reports on MSL and describe in more detail the morphologic, biochemical, and molecular genetic abnormalities of muscle mitochondria. In seven of 11 patients, we observed morphologic signs of mitochondrial dysfunction, and biochemically assessed cytochrome *c* oxidase activity was significantly lower than in controls. Multiple deletions of mtDNA were identified in one patient. The 10 remaining patients had no major deletions nor known point mutations of mtDNA.

The biochemical defect and the pathophysiology of MSL are still unknown. Because of the frequent distribution of the lipomas in the cervical region, some have suggested that MSL adipocytes may originate from brown fat.<sup>9</sup> Although the light microscopic appearance of MSL adipose tissue is basically that of white fat,<sup>22</sup> ultrastructural investigations resemble brown fat.<sup>23</sup> Most remarkably, cultured MSL preadipocytes transiently develop large mitochondria with parallel cristae and maintain a multivacuolar lipid deposit; these are typical features of brown preadipocytes.<sup>23</sup> From the metabolic point of view, there is a specific insensitivity of MSL adipose tissue to the lipolytic effect of norepinephrine *in vitro*.<sup>7</sup> This observation led to the assumption that adrenergic denervation of brown fat causes the accumulation of triglycerides. Indeed, autonomic neuropathy is frequent in MSL.<sup>24</sup>

How can the abnormalities in complex IV and the mtDNA deletion in one patient be related to MSL? Lipolysis in all tissues requires a continuous supply of energy in the form of ATP as well as a processing of fatty acids by  $\beta$ -oxidation and the respiratory chain. If there was a defect in the respiratory chain, one might suppose that lipolysis would be hindered for lack of energy and because of product inhibition. Brown adipose tissue con-

ferred to mammals functions to dissipate energy in the form of heat. This is accomplished by the action of a specific uncoupling protein that transports protons back through the inner mitochondrial membrane, bypassing the ATP synthesis pathway.<sup>25</sup> There is particularly high activity of respiratory chain enzymes in brown fat to maintain this short-circuit.<sup>26</sup> A defect in one of the respiratory chain complexes I to IV would therefore interfere particularly with the high fat turnover in brown adipose tissue, thus explaining the association of mitochondrial dysfunction and development of lipomas in MSL.

The fact that we found morphologic and biochemical signs of mitochondrial malfunction in almost all patients but a defect of mtDNA in only one might indicate that there are yet-unknown point mutations of mtDNA or defects of nuclear-encoded subunits of the respiratory chain enzymes in our other cases. Moreover, as there are four patients without mitochondrial abnormalities in muscle morphology, a subgroup of MSL might be unassociated with mitochondrial dysfunction. The possibility that cytochrome *c* oxidase deficiency is caused by alcoholism in our MSL patients is unlikely in view of a recent study<sup>27</sup> that shows no defect of respiratory chain complexes in 30 alcoholic patients. The assumption of heterogeneity in MSL is supported by the observation that our patients differ in certain clinical characteristics. The patient with the deletions, for example, the only nonalcoholic one, has ataxia and dysarthria in addition to MSL and neuropathy. The proportion of deleted mtDNA in muscle of this patient is only about 10%, concurrent with the fact that there is no clinical myopathy and only a small number of ragged-red fibers. Considering the segregation of mutant and wild-type mitochondria in different tissues, it is conceivable that there is a higher percentage of mutant mtDNA in clinically affected organs like peripheral nerve or lipomatous tissue. Further studies are in progress to directly address changes in the respiratory chain of these tissues.

## Acknowledgments

We thank Mrs. S. Seufert for technical assistance and Dr. D. Köhnke for helpful discussion.

## References

1. Brodie BC. Lectures illustrative of various subjects in pathology and surgery. London: Longman, 1846:275-276.
2. Madelung OW. Über den Fetthals (diffuses Lipom des Halses). *Langenbecks Arch Klin Chir* 1888;37:106-130.
3. Launois P, Bensaude R. De l'adénolipomatose symétrique. *Bull Mem Soc Med Hôp Paris* 1898;1:298-318.
4. Enzi G. Multiple symmetrical lipomatosis: an updated clinical report. *Medicine* 1984;63:56-64.
5. Pollock M, Nicholson GI, Nukada H, Cameron S, Frankish P. Neuropathy in multiple symmetric lipomatosis. *Brain* 1988;111:1157-1171.
6. Chalk CH, Mills KR, Jacobs JM, Donaghy M. Familial multiple symmetric lipomatosis with peripheral neuropathy. *Neurology* 1990;40:1246-1250.
7. Enzi G, Inelmen EM, Baritussio A, Dorigo P, Prosdocimi M, Mazzoleni F. Multiple symmetric lipomatosis: a defect in adrenergic-stimulated lipolysis. *J Clin Invest* 1977;60:1221-1229.
8. Banerjee SP, Sharma VK, Khanna JM. Alterations in  $\beta$ -adrenergic receptor binding during ethanol withdrawal. *Nature* 1978;276:407-409.
9. Kodish ME, Alsever RN, Block MB. Benign symmetric lipomatosis: functional sympathetic denervation of adipose tissue and possible hypertrophy of brown fat. *Metabolism* 1974;23:937-945.
10. Berkovic SF, Andermann F, Shoubridge EA, et al. Mitochondrial dysfunction in multiple symmetrical lipomatosis. *Ann Neurol* 1991;29:566-569.
11. Ciafaloni E, Shanske S, Apostolski S, et al. Multiple deletions of mitochondrial DNA [abstract]. *Neurology* 1991;41(suppl 1):207.
12. Berkovic SF, Carpenter S, Evans A, et al. Myoclonus epilepsy and ragged-red fibres (MERRF): 1. A clinical, pathological, biochemical, magnetic resonance spectrographic and positron emission tomographic study. *Brain* 1989;112:1231-1260.
13. Silvestri G, Ciafaloni E, Santorelli FM, et al. Clinical features associated with the A $\rightarrow$ G transition at nucleotide 8344 of mtDNA ("MERRF mutation"). *Neurology* 1993;43:1200-1206.
14. Holme E, Larsson N-G, Oldfors A, Tulinius M, Sahlin P, Stenman G. Multiple symmetric lipomas with high levels of mtDNA with the tRNA<sup>Lys</sup> A $\rightarrow$ G<sup>(8344)</sup> mutation as the only manifestation of disease in a carrier of myoclonus epilepsy and ragged-red fibers (MERRF) syndrome. *Am J Hum Genet* 1993;52:551-556.
15. Dubowitz V. *Muscle biopsy: a practical approach*. London: Bailliere Tindall, 1985.
16. Reichmann H, Rohkamm R, Zeviani M, Servidei S, Ricker K, DiMauro S. Mitochondrial myopathy due to complex III deficiency with normal reducible cytochrome *b* concentration. *Arch Neurol* 1986;43:957-961.
17. Seibel P, Mell O, Hannemann A, Müller-Höcker J, Kadenbach B. A method for quantitative analysis of deleted mitochondrial DNA by PCR in small tissue samples. *Methods Mol Cell Biol* 1991;2:147-153.
18. Southern EM. Detection of specific sequences among DNA fragments separated by gel electrophoresis. *J Mol Biol* 1975;98:503-517.
19. Shoffner JM, Lott MT, Lezza AMS, Seibel P, Ballinger SW, Wallace DC. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA<sup>Lys</sup> mutation. *Cell* 1990;61:931-937.
20. Goto Y, Nonaka I, Horai S. A mutation in the tRNA<sup>Leu(UUR)</sup> gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 1990;348:651-653.
21. Wallace DC, Singh G, Lott MT, et al. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science* 1988;242:1427-1430.
22. Ruzicka T, Vieluf D, Landthaler M, Braun-Falco O. Benign symmetric lipomatosis Launois-Bensaude. *J Am Acad Dermatol* 1987;17:663-674.
23. Zancanaro C, Sbarbati A, Morrioni M, et al. Multiple symmetric lipomatosis: ultrastructural investigation of the tissue and preadipocytes in primary culture. *Lab Invest* 1990;63:253-258.
24. Enzi G, Angelini C, Negrin P, Armani M, Pierobon S, Fedele D. Sensory, motor and autonomic neuropathy in patients with multiple symmetrical lipomatosis. *Medicine* 1986;64:388-393.
25. Klingenberg M. Mechanism and evolution of the uncoupling protein of brown adipose tissue. *Trends Biochem Sci* 1990;15:108-112.
26. Nèchad M. Structure and development of brown adipose tissue. In: Trayhurn P, Nicholls DG, ed. *Brown adipose tissue*. Baltimore: Edward Arnold, 1986:1-30.
27. Cardellach F, Galofré J, Grau JM, et al. Oxidative metabolism in muscle mitochondria from patients with chronic alcoholism. *Ann Neurol* 1992;31:515-518.