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A High Rate (20%–30%) of Parental Consanguinity in Cytochrome-Oxidase Deficiency

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Summary

By studying a large series of 157 patients, we found that complex I (33%), complex IV (28%), and complex I+IV (28%) deficiencies were the most common causes of respiratory chain (RC) defects in childhood. Truncal hypotonia (36%), antenatal (20%) and postnatal (31%) growth retardation, cardiomyopathy (24%), encephalopathy (20%), and liver failure (20%) were the main clinical features in our series. No correlation between the type of RC defect and the clinical presentation was noted, but complex I and complex I+IV deficiencies were significantly more frequent in cases of cardiomyopathy ($P < .01$) and hepatic failure ($P < .05$), respectively. The sex ratio (male/female) in our entire series was mostly balanced but was skewed toward males being affected with complex I deficiency (sex ratio $R = 1.68$). Interestingly, a high rate of parental consanguinity was observed in complex IV (20%) and complex I+IV (28%) deficiencies. When parental consanguinity was related to geographic origin, an even higher rate of inbreeding was observed in North African families (76%, $P < .01$). This study gives strong support to the view that an autosomal recessive mode of inheritance is involved in most cases of mitochondrial disorders in childhood, a feature that is particularly relevant to genetic counseling for this devastating condition.

Introduction

Owing to the twin genetic origins of the mitochondrial respiratory chain (RC), any mode of inheritance can be observed for hereditary defects of oxidative phosphorylation—that is, sporadic, autosomal recessive, autosomal dominant, X-linked, or maternal inheritance. Indeed, among the hundreds of genes encoding the RC components, most are located in the nucleus and undergo classic Mendelian inheritance, whereas a few genes are mitochondrially encoded (13 RC subunits) and therefore follow a maternal inheritance. This genetic heterogeneity hinders gene identification and makes counseling for RC deficiency particularly hazardous, especially since (1) mtDNA mutations/deletions are identified in <7% of cases (Wong and Liang 1997) and (2) nuclear gene mutations are seldom recognized. Indeed, apart from succinate dehydrogenase deficiency (Bourgeron et al. 1995) and Barth syndrome (Bione et al. 1996), systematic sequence analysis hitherto has failed to detect any deleterious base changes in the nuclear genes with influence on the mitochondrial RC.

In an attempt to determine the respective roles of mtDNA and nuclear DNA mutations in the genetic defects of oxidative phosphorylation, we have studied the sex ratio, the rate of parental consanguinity, and the parental age at time of birth of the proband, for a large series of 157 respiratory-enzyme–deficient patients. The observation of a high rate of parental consanguinity in cytochrome oxidase (COX) deficiency (either isolated or associated with complex I deficiency) gives strong support to the view that hitherto unknown nuclear genes account for most cases of COX deficiency, an observation that is highly relevant to both gene cloning and genetic counseling for this devastating condition.

Material and Methods

A total of 157 patients, from 148 families, were included in this study. Inclusion criteria were (1) a defect of oxidative phosphorylation, regardless of the presenting symptom or age at onset, that has been fully documented on at least one tissue sample from the proband (muscle, liver, or endomyocardial biopsy; circulating lymphocytes or cultured skin fibroblasts) and (2) the availability of detailed clinical and laboratory information on the disease.

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In each case, a genetic consultation allowed (1) the identification of the two or three major symptoms; (2) the recognition of minor symptoms in parents and siblings; (3) the drawing of an extensive pedigree, with particular attention to known consanguinity, spontaneous abortions, unexplained deaths, and similar cases in the sibship or in previous generations; and (4) the detection of erroneous diagnoses, improper tissue handling, and possible phenocopies. Relatives were considered to be affected with the same disease if they presented a similar enzyme deficiency and/or experienced the same clinical symptoms.

The mitochondrial RC, which catalyzes the oxidation of fuel molecules by oxygen and the concomitant energy transduction into ATP, is divided into five functional units or complexes: complex I (NADH–coenzyme Q [CoQ] reductase; at least 43 subunits, 7 of which are encoded by mtDNA), complex II (succinate-CoQ reductase; 4 nuclear-encoded subunits), complex III ($CoQH_2$–cytochrome c reductase; 11 subunits, 1 of which is encoded by mtDNA), complex IV (COX; 13 subunits, 3 of which are encoded by mtDNA), and complex V (ATPase; 14 subunits, 2 of which are encoded by mtDNA). All complex activities were measured as described elsewhere (Rustin et al. 1994). On the basis of the enzyme deficiency detected, our 157 patients were split into five groups: isolated complex I, II, III, or IV deficiency and combined complex I+IV deficiency. In each subgroup, we determined the mean sex ratio (male/female), the mean parental age at time of birth of the proband, the rate of spontaneous abortion, and the rate of parental consanguinity. Results were compared to a control population by use of the Student's *t*-test or the χ^2 test.

Results

Complex I (33%), complex IV (28%), and complex I+IV (28%) deficiencies showed similar frequencies in our series, whereas complex II (4%) and complex III (7%) deficiencies were far less frequent (fig. 1*A*). All patients were evaluated for alterations within the mtDNA: we found two deletions and two MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes) A3243G point mutations in patients with complex I+IV deficiency and two MELAS A3243G point mutations and one MERRF (myoclonic epilepsy with ragged red fibers) A8344G point mutation in patients with complex I deficiency (overall rate 4.5%).

Most patients were of western European (43%) or North African (11%) ancestry, but ethnic origin remained questionable or uncertain in 25% of patients (fig. 1*B*). We first looked at the clinical presentation of the disease in our series. Truncal hypotonia, antenatal and postnatal growth retardation, cardiomyopathy, encephalopathy (with or without seizures) and liver failure

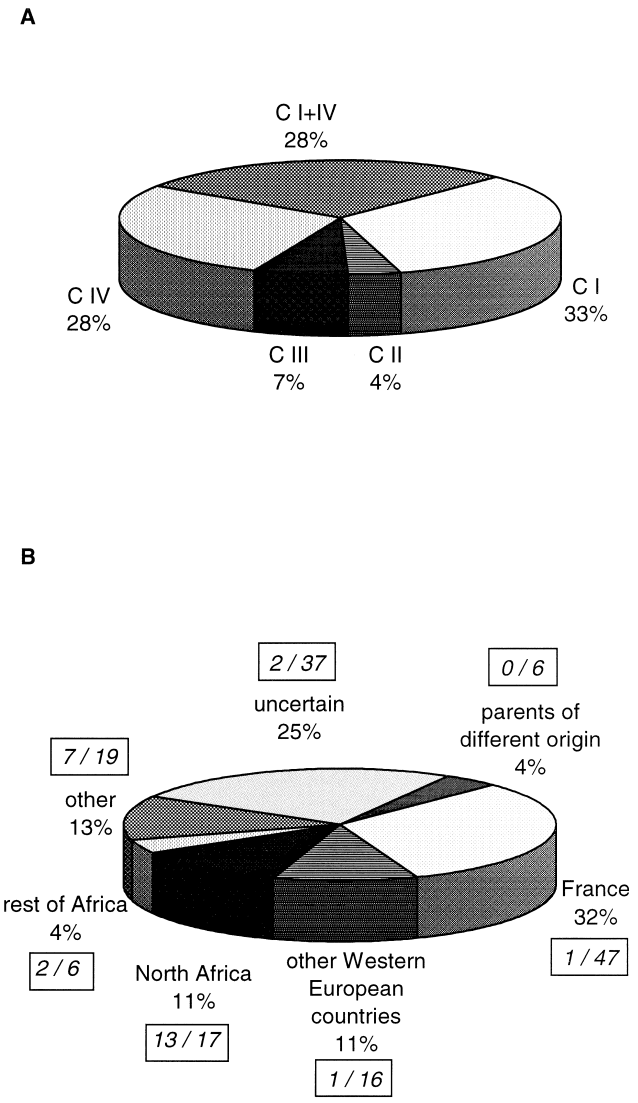

Figure 1 *A*, Distribution of respiratory-enzyme deficiencies. *B*, Geographic origin of affected individuals. Italicized numbers indicate number of consanguineous families/total number of families.

were the main clinical features (table 1). Interestingly, when the patients were split into five groups based on the type of RC deficiency, complex I deficiency appeared to be significantly more frequent in patients with cardiomyopathy ($P < .01$). Similarly, complex I+IV deficiency was significantly more frequent in patients with hepatic failure ($P < .05$), and complex IV deficiency was significantly more frequent in patients with gut involvement ($P < .05$). In addition, complex I+IV deficiency was less frequent in spastic patients ($P < .05$). No significant differences between subtypes were found for the other clinical symptoms (table 1).

A remarkably high rate of parental consanguinity was observed in families of North African ancestry (76%; fig. 1*B*), with the mean rates of parental consanguinity

Table 1

Frequency of Clinical Symptoms and Findings, for Our Entire Series and for Each Type of Respiratory-Enzyme Deficiency

	Frequency (%)				No. of Patients	
Symptom	All Complexes [n = 157; N = 148]	Complex I [n = 52; N = 51]	Complex IV [n = 44; N = 41]	Complex I+IV [n = 44; N = 40]	Complex II [n = 6; N = 6]	Complex III [n = 11; N = 10]
Truncal hypotonia	36	35	39	36	4	2
Growth failure	31	25	36	34	2	3
Cardiomyopathy	24	35*	9*	32*	1	1
IUGR	20	25	23	11	0	3
Encephalopathy	20	23	23	18	1	0
Liver failure	20	12**	20**	34**	0	1
Cranial nerve involvement	18	19	18	16	1	2
Myopathy	13	12	14	14	2	0
Spasticity	11	13**	18**	0**	1	2
Basal-ganglia involvement	8	10	7	9	1	0
Ocular involvement	8	8	11	7	0	1
Gut involvement	8	4**	18**	7**	0	0
Cerebellar syndrome	8	8	9	5	1	1
Mental retardation	8	6	5	11	1	1
Renal involvement	8	0	9	9	1	3
Facial dysmorphism	8	6	9	9	1	0
Pancytopenia	7	6	9	9	0	0
Malformation	3	4	2	5	0	0
Peripheral neuropathy	3	0	7	2	0	0
Ketoacidotic coma	3	4	0	2	0	1
Endocrine involvement	2	4	0	0	0	1
Fetal distress	2	2	0	2	0	1
Hypermethioninemia	1	0	2	2	0	0

Note.—Owing to the small size of the sample, data for clinical symptoms for complex II and complex III deficiencies are given in absolute values. n = total no. of patients; and N = total no. of families.

* $P < .01$.

** $P < .05$.

in the corresponding North African countries within the range 29%–49% ($P < .01$) (Khlat 1997). A similar trend was noted in families of western European origin, 3% of which were consanguineous, as compared with a mean parental consanguinity of <1% in a corresponding control population (Vogel and Motulsky 1997, p. 554). Notably, high rates of parental consanguinity were observed in families of children with complex IV (20%) or complex I+IV (28%) deficiency in our series. The rate was lower among families of patients with complex I (10%), complex II (17%), or complex III (10%) deficiency (fig. 2).

Several pedigrees provided clinical and/or enzymological evidence of recurrence of the disease in the offspring of consanguineous parents (fig. 3). The observation of several pedigrees that show more than one affected individual with apparently unrelated parents and that are not suggestive of maternal transmission gives additional support to the view that autosomal recessive genes are involved (fig. 3).

The mean parental age at birth of the affected child

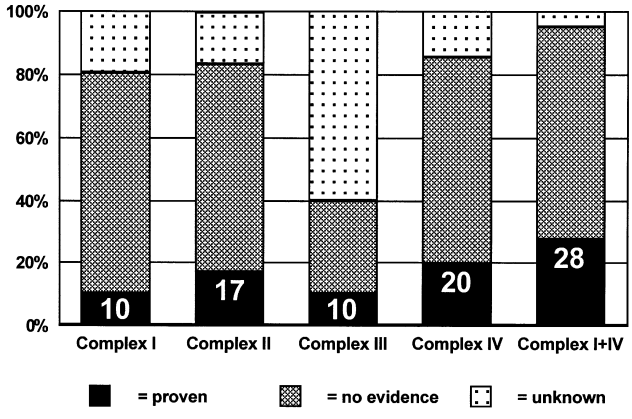

Figure 2 Rate of parental consanguinity in respiratory-enzyme deficiency. The proportion (%) of proven consanguinity is given.

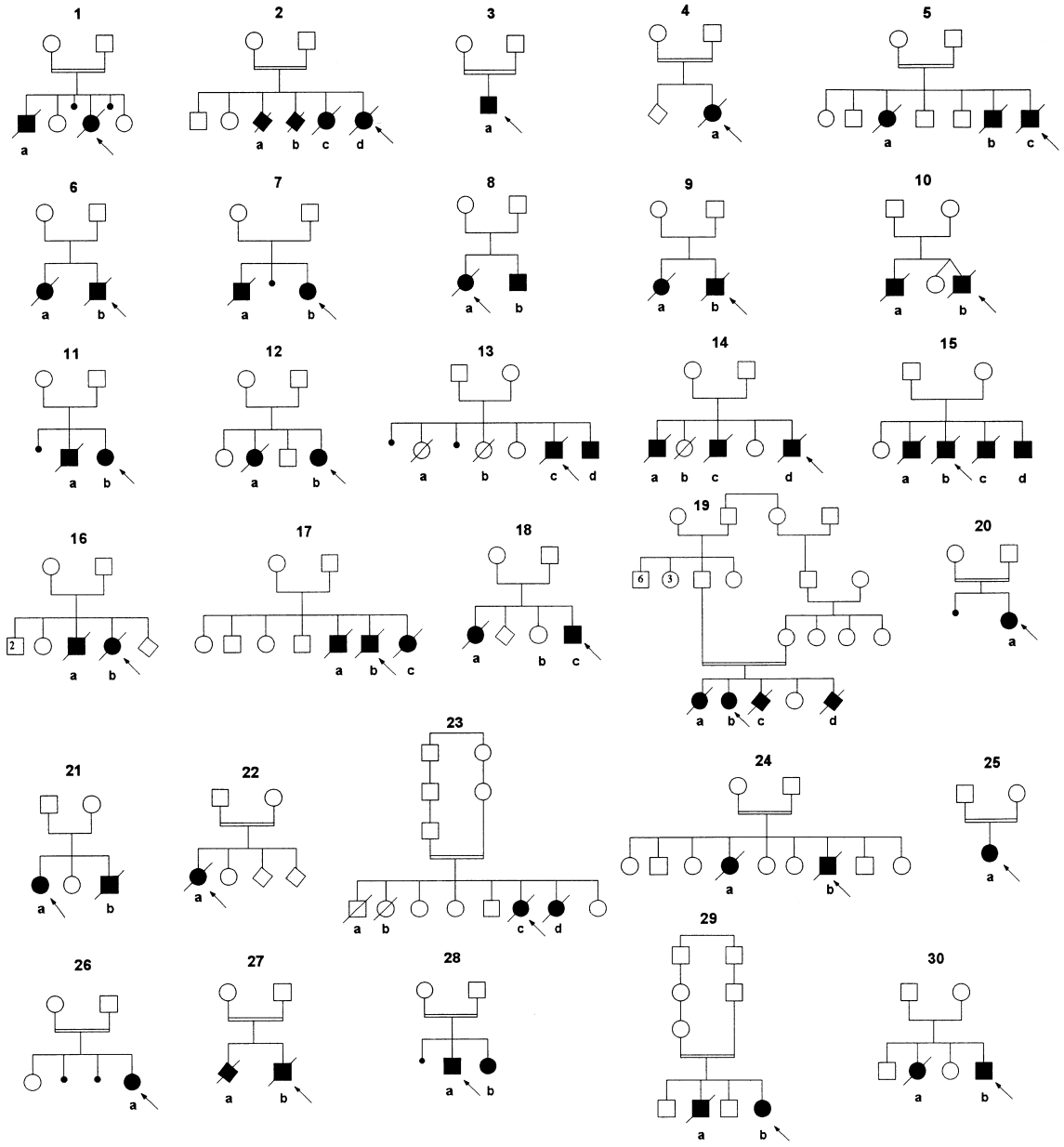

Figure 3 Pedigrees of consanguineous and multiplex families. Arrows indicate index patients. For pedigrees with consanguineous parents, more than two generations are included only if there are contributing events in other generations. *Pedigrees 1–18,* Complex I deficiency. *1,* a: died age 2 years, encephalopathy, truncal hypotonia, neonatal distress. *2,* a and b: died age 3 mo, liver failure; c: died age 4.5 mo, liver cirrhosis, nephrocalcinosis; and d: died age 3 mo, liver failure, nephrocalcinosis. *3,* a: truncal hypotonia, nystagmus, dysmorphism, delayed motor milestones. *4,* a: died age 5 mo, Leigh syndrome. *5,* a: died age 3 d, cardiomyopathy, acidosis; b: died age 2 d, cardiomyopathy, acidosis; and c: died age 2 wk, cardiomyopathy. *6,* a: died age 7 mo, cardiomyopathy; and b: died age 8 mo, truncal hypotonia, cardiomyopathy. *7,* a: died age 1 year; and b: truncal hypotonia, encephalopathy, liver involvement. *8,* a: died age 1 year, growth failure, truncal hypotonia, liver failure, encephalopathy, ketoacidotic coma; and b: growth failure, hepatomegaly. *9,* a: died age 10 mo, Leigh syndrome; and b: died age 7 mo, neurologic involvement. *10,* a: died age 2 mo; and b: died age 3 mo, intrauterine growth retardation (IUGR), neutropenia, cardiomyopathy, Barth syndrome. *11,* a: died age 6 d, cardiomyopathy; and b: truncal hypotonia, cardiomyopathy. *12,* a: died age 45 d, IUGR, diarrhea; and b: IUGR, gut involvement, growth failure, diabetes, facial dysmorphism, liver involvement. *13,* a and b: died age 3 mo; c: died age 10 mo, cardiomyopathy, encephalopathy, truncal hypotonia, growth failure; and d: cardiomyopathy. *14,* a: died age 2 d, IUGR, hydrocephaly; b: died age 1 d, premature, infantile respiratory distress syndrome; c: died age 1 d, cardiomyopathy; and d: died age 3 mo, IUGR, cardiomyopathy, pancytopenia, facial dysmorphism. *15,* a, b, c, and d: Barth syndrome. a: died age 2.5 mo; b: died age 4 mo; and c: died age 2 years. *16,* a and b: Alpers syndrome. b: died age 2 years. *17,* a: died age 6 mo, lactic acidosis; b: died age 5 mo, convulsions, truncal hypotonia, ketoacidotic coma; and c: died age 5 mo, growth failure, truncal hypotonia, multiorgan failure. *18,* a: died age 7 mo, encephalopathy, lactic acidosis; b: mental retardation; and c: truncal hypotonia, mental retardation, spasticity, leukodystrophy, optic atrophy, nystagmus. *Pedigree 19,* Complex II deficiency. a and b: truncal hypotonia, mental retardation; and c and d: discontinued pregnancies (i.e., affected fetuses). *Pedigrees 20 and 21,* Complex III deficiency. *20,* a: growth failure, renal involvement, mild mental retardation. *21,* a: IUGR, neonatal distress, mental retardation; and b: died age 6 d, IUGR, ketoacidotic coma, truncal hypotonia. *Pedigrees 22–36,* Complex IV deficiency. *22,* a: died age 6 mo. *23,* a: stillborn; b: died age 3 mo, vomiting; c: died age 2 mo, truncal hypotonia, retinal dystrophy, renal involvement, spasticity; d: age at death unknown, truncal hypotonia, renal involvement.

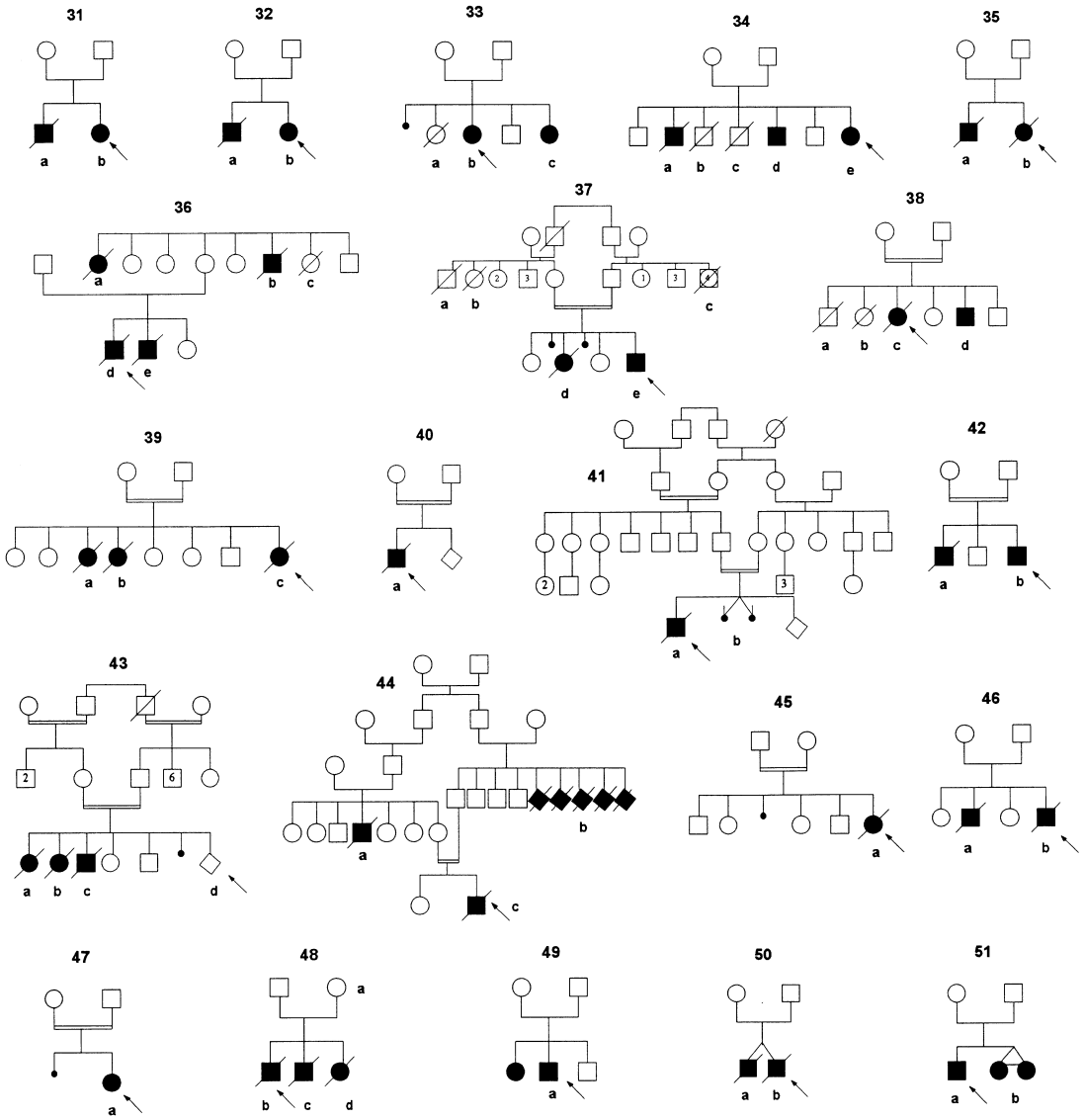

Figure 3 (*continued*) *24,* a and b: leukodystrophy, renal involvement, growth failure; a: age at death unknown, truncal hypotonia, retinal dystrophy; and b: died age 3 years, spasticity. *25,* a: encephalopathy, convulsions. *26,* a: IUGR, gut involvement, growth failure. *27,* a and b: died during neonatal period; and b: truncal hypotonia, convulsions. *28,* a: cerebellar syndrome, growth failure, peripheral neuropathy, retinal dystrophy, strabismus; and b: strabismus, muscular wasting. *29,* a: died age 9 mo, encephalopathy, leukodystrophy; and b: leukodystrophy, peripheral neuropathy. *30,* a: died age 27 mo, IUGR, liver failure; and b: sensorineural deafness, cataract, liver involvement, gut involvement, growth failure, facial dysmorphism, mental retardation. *31,* a: died age 2 years; and b: encephalopathy, deafness, blindness. *32,* a: died age 4 mo, hypoglycemia, liver failure; and b: liver failure, truncal hypotonia. *33,* a: died age 3 mo, IUGR, sudden infant death syndrome; b: IUGR, dysmorphism, mental retardation, spasticity; and c: IUGR, dysmorphism, mental retardation, spasticity, growth retardation. *34,* a: died age 6 mo, truncal hypotonia, muscular wasting; b: died at birth; c: died by accident; d: truncal hypotonia, cystinuria, muscular wasting; and e: truncal hypotonia, vomiting episodes, cystinuria, growth failure. *35,* a: died age 4 wk, IUGR, cardiomyopathy; b: died age 3 mo, IUGR, cardiomyopathy, truncal hypotonia. *36,* a: died age 1 mo, limb paralysis; b: died age 11 mo, vomiting; c: died age 4 years, by accident; d: died age 2 mo, convulsions, truncal hypotonia; and e: died age 5 d, truncal hypotonia, neonatal distress. *Pedigrees 37–51,* Complex I+IV deficiency. *37,* a, b, and c: cause of death unknown; d: died age 3 years, convulsions, blindness; and e: microcephaly, anemia, developmental delay. *38,* a: died age 14 years, leukemia; b: died age 4 mo, encephalitis; c: died age 43 years, cardiomyopathy, convulsions, optic neuropathy; and d: cardiomyopathy, cerebellar syndrome, scoliosis. *39,* a: died age 2 mo; b: died age 7 d; and c: died age 10 d, IUGR, cerebellar hypoplasia, hypoplasia of corpus callosum, cortical atrophy, hypoventilation. *40,* a: died age 5 d, truncal hypotonia, respiratory failure. *41,* a: died age 2 years, IUGR, convulsions, facial dysmorphism; and b: fetuses affected. *42,* a: died age 3 d, hepatomegaly, neurologic distress; and b: liver involvement, growth failure, gut involvement. *43,* a, b, and c: liver and ocular involvement; and d: prenatal diagnosis. *44,* a and b: died during neonatal period; and c: died age 3 mo, truncal hypotonia, liver failure, renal involvement. *45,* a: died age 21 mo, growth failure, encephalopathy, liver failure. *46,* a: died age 4 years, Leigh syndrome, hypoglycemia, liver failure; and b: died age 3.5 years, encephalopathy, hypoglycemia, liver failure, truncal hypotonia. *47,* a: encephalopathy, growth failure, liver failure, facial dysmorphism. *48,* a: facial paralysis, migraine, walking problems; b: died age 5 mo, Leigh syndrome; c: age at death unknown, Leigh syndrome; and d: died age 7 mo, truncal hypotonia. *49,* a: cardiomyopathy, deafness, growth failure. *50,* a: died age 5 mo, cardiomyopathy; and b: dizygote, died age 6 mo, cardiomyopathy. *51,* a and b: cardiomyopathy.

was similar among the biochemical subtypes and did not significantly differ from the mean parental age in western Europe (fig. 4) (Bouvet et al. 1974). Similar results were observed when parental age in the subgroup of sporadic cases was compared (data not given). Yet, a nonsignificant increase of mean paternal age was noted in the subgroup of complex III–deficient children (fig. 4).

Finally, we determined the sex ratios in our entire series and in each biochemical subtype. The sex ratio was mostly balanced among patients with complex I+IV deficiency (sex ratio $R = 1$ and 1.27, for all families and for noninbred families, respectively) and was not significantly reduced among patients with complex IV deficiency ($R = 0.77$ and 0.75, for all families and noninbred families, respectively). Interestingly, the sex ratio was markedly skewed toward males being affected with complex I deficiency ($R = 1.68$ and 1.45, for all families and for noninbred families, respectively; $P < .1$; see table 2). This observation strongly suggests that one (or several) X-linked recessive gene(s) accounts for complex I deficiency in our series. Finally, the number of miscarriages was examined in our series (29 miscarriages, for 23 [15.6%] of 148 couples) and in each biochemical subtype. No significant difference in the rate of miscarriages was noted when the different types of deficiencies were compared.

Table 2

Sex Ratios for Respiratory-Enzyme Deficiencies

Deficiency	Ratio for All Families		Ratio for Nonconsanguineous Families	
	Patients Only	+ Affected Sibship	Patients Only	+ Affected Sibship
Complex I	1.36	1.68	1.12	1.45
Complex IV	.57	.77	.47	.75
Complex I+IV	1.15	1.00	1.33	1.27

Discussion

By studying a cohort of 157 patients with RC-enzyme deficiency, we have observed that complex I, complex IV, and complex I+IV deficiencies show comparable frequencies in our series. A variety of neuromuscular and nonneuromuscular symptoms could have been observed, but truncal hypotonia, growth retardation, cardiomyopathy, encephalopathy, and liver failure were the most frequent symptoms. No obvious correlation between the type of RC deficiency and the clinical presentation was noted, but cardiomyopathy and liver failure were significantly more frequent in complex I and complex I+IV deficiencies, respectively. Interestingly, the sex ratio of the probands and affected sibs was skewed toward males being affected with complex I deficiency, suggesting that a significant proportion of patients may suffer from an X-linked recessive disease, in this subgroup. Since cardiomyopathy was significantly associated with complex I deficiency in our series, it is tempting to hypothesize that the excess of affected males with complex I deficiency is accounted for (at least in part) by mutations either in the NDUFA1 gene on chromosome Xq24, which codes for a subunit of complex I (Zhuchenko et al. 1996), or in the G4.5 gene on chromosome Xq28 (Bione et al. 1996), mutations of which are believed to cause Barth syndrome (cardiomyopathy, cyclic neutropenia, and complex I deficiency) (Bolhuis et al. 1991). In keeping with this hypothesis, Barth syndrome has

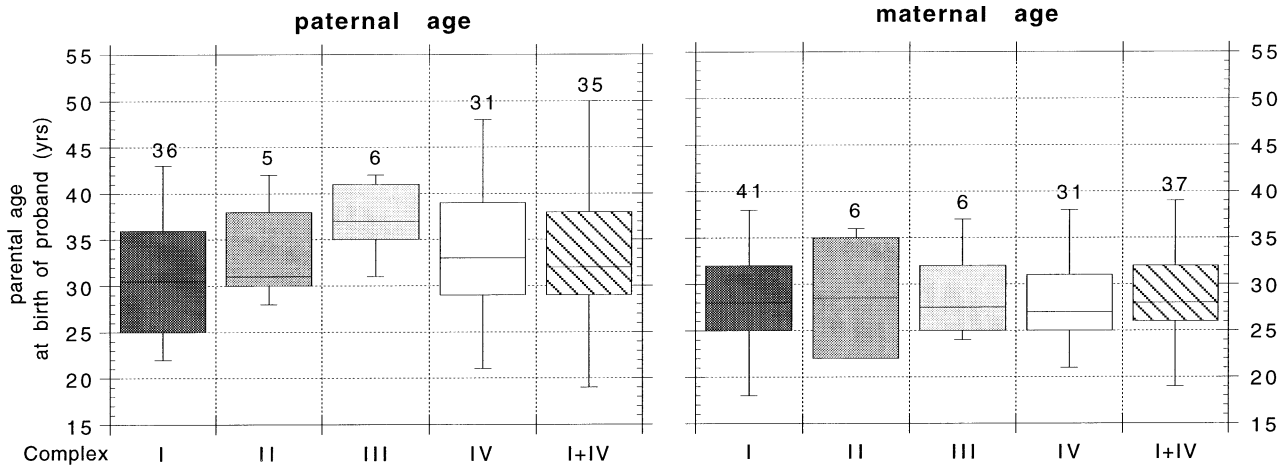

Figure 4 Parental age, in respiratory-enzyme deficiency. The mean value is shown by a horizontal line; the range of absolute values is indicated by a vertical line; and the box represents the 25th–75th percentile of obtained data. For each group, the number of patients (*n*) from which data were available is shown above each box.

been diagnosed in 2 of our 18 families with cardiomyopathy and complex I deficiency. The sex ratio as well as the frequency of cardiomyopathy remain significantly elevated among families with complex I deficiency, even after exclusion of these 2 families.

The wide clinical heterogeneity associated with RC deficiency has been reported often, particularly among children (Robinson et al. 1987; Rowland et al. 1991; Robinson 1993; Jackson et al. 1995; Pitkänen et al. 1996; Rahman et al. 1996). However, the relatively small size of the patient cohorts studied has made it difficult to consider consanguinity, parental age, and sex ratio in order to trace the genetic origin of these diseases.

No significant increase in the mean parental age at time of birth of the probands was noted, suggesting that dominant de novo mutations in RC deficiency are relatively unlikely. However, the remarkably high rate of parental consanguinity both in our entire series and in the subgroup of North African patients strongly supports the view that an autosomal recessive mode of inheritance is involved in complex IV and complex I+IV deficiencies. Additional evidence of nuclear-gene involvement is provided by (1) results from complementation studies of RC-deficient fibroblasts, with control fibroblast strains lacking mtDNA (rho° cells) (Tiranti et al. 1995); (2) the low overall rate (6.85%) of mtDNA mutations/deletions in RC deficiency (Wong and Liang 1997); and (3) the formal exclusion of mitochondrial genes in large series of patients with complex I (Buddiger et al. 1997), complex III (Valnot et al. 1997), or complex IV (Parfait et al. 1997) deficiency.

Yet, although most cases of RC deficiency are likely to follow nuclear inheritance, in humans, very little is known regarding the disease-causing nuclear genes. Indeed, to our knowledge, systematic sequence analysis of nuclear genes encoding subunits of complexes I, III, and IV has failed to detect any deleterious mutations in patients with RC defects. Apart from a flavoprotein gene mutation in succinate dehydrogenase deficiency (Bourgeron et al. 1995), no nuclear-gene mutations have been identified thus far in genes encoding the catalytic subunits of the RC.

On the other hand, the nuclear genes controlling the structure, assembly, and function of the RC complexes are attractive candidate genes for RC deficiencies, especially since mutations of their yeast homologues are known to cause the respiration-deficient *petite* phenotypes. Although little is known regarding these genes in humans, an increasing amount of information on mitochondrial biogenesis in lower eukaryotes (e.g., *Saccharomyces cerevisiae*) has been made available. In particular, the import, assembly, and metabolism of the protein components of the RC complexes in yeast are known to be under the control of numerous nuclear genes, mutations of which result in *petite* phenotypes (Tzagoloff and Dieckmann 1990). We expect that ongoing studies aimed at identifying and mapping the human orthologues of the yeast genes involved in biogenesis of the RC complexes will provide attractive candidate nuclear genes to be tested by homozygosity mapping in the inbred families reported in our series. In conclusion, this study provides what we believe to be the first population-genetics evidence of autosomal recessive gene involvement in most mitochondrial disorders, an observation that is highly relevant to genetic counseling for these devastating conditions.

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