Higher SBP in female patients with mitochondrial disease

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**Background:** Previous research suggests that hypertension is more prevalent among patients with mitochondrial diseases. Blood pressure (BP) is linearly related to increased cardiovascular risk, and this relationship is strongest for SBP; nevertheless, studies on SBP and DBP in mitochondrial diseases have not yet been performed.

**Method:** In a retrospective case–control study design, BP in mitochondrial disease patients was compared with BP in a population cohort. Secondly, using multiple linear regression, we examined blood pressure differences in various genetic population cohort. Secondly, using multiple linear regression, we examined blood pressure differences in various genetic mitochondrial diseases. Lastly, we explored additional predictors of BP in a subgroup with the m.3243A > G variant.

**Results:** Two hundred and eighty-six genetically confirmed mitochondrial disease patients were included. One hundred and eighty of these patients carried the m.3243A > G mitochondrial DNA variant. SBP was 9 mmHg higher in female mitochondrial disease patients than in the general female population (95% CI: 4.4–13.3 mmHg, \( P < 0.001 \)), whereas male patients had similar BP compared with controls. BP was not significantly different in patients with m.8344A > G and m.8363G > A, a mtDNA deletion or a nuclear mutation compared with m.3243A > G patients. Higher SBP was a predictor for left ventricular hypertrophy in the m.3243A > G subgroup (\( P = 0.04 \)).

**Conclusion:** Novel aspects of the role of mitochondrial dysfunction in blood pressure regulation are exposed in this study. Compared with the general population, female mitochondrial disease patients have a higher SBP. Left ventricular hypertrophy is more prevalent in patients with higher SBP. Clinicians should be aware of this to prevent hypertensive complications in mitochondrial disease patients.

**Keywords:** blood pressure, m.3243A > G, MELAS, mitochondrial disease, mitochondrial inherited diabetes and deafness, mtDNA deletion, myoclonic epilepsy associated with ragged-red fibers, sex-difference

**Abbreviations:** BP, blood pressure; CI, confidence interval; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy associated with ragged-red fibers; MIDD, mitochondrial inherited diabetes and deafness; mtDNA, mitochondrial DNA; NDNA, nuclear DNA; POLG, mitochondrial DNA polymerase (polymerase γ); RIVM, National Institute for Public Health and the Environment

**INTRODUCTION**

Primary mitochondrial diseases are a heterogeneous group of disorders, both genetically and clinically. Mitochondrial diseases can be caused by pathogenic variants in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) [1]. In all patients affected, the origin of the disease can be localized to the mitochondria, which are present in every human cell except red blood cells and play a central role in energy production and cellular metabolism [2]. Multiple organs can be affected, including skeletal muscles, the brain, heart, liver, kidney, eye, ear, pancreas and more [3]. Several factors influence the age of onset, severity, organ involvement and symptomatology of the disease, including the mutated gene, the base position affected and the heteroplasmy level (for mtDNA variants).

Several studies have identified pathogenic mtDNA variants as likely cause for hypertension in hypertensive family or cohort studies [4–7]. Interestingly, most of these studies found homoplasmic variants in patients with no other disease manifestations. More recent studies have suggested that hypertension might also be an underappreciated symptom in ‘classical’ mitochondrial syndromes, such as mitochondrial-inherited diabetes and deafness (MIDD, OMIM #520000), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS, OMIM #540000) and myoclonic epilepsy associated with ragged-red fibers (MERRF, OMIM #545000) [8–10]. The latter three studies included a heterogeneous group of patients but most had one of four common genetic defects: the heteroplasmic mtDNA variant m.3243A > G (located in MT-TL1, OMIM #590050), the m.8344A > G variant (in MT-TK, OMIM #590060), a mitochondrial DNA deletion or a variant in the mitochondrial DNA polymerase, polymerase g (encoded by the nuclear gene POLG, OMIM *174763).

All three studies described an increased prevalence of
hypertension compared with the general population, when matched by age. Standardized prevalence ratios in these studies ranged between 1.3 and 2.5 (Supplementary Table 1, http://links.lww.com/HJH/B864). On the other hand, an earlier study among patients with MIDD, reported that blood pressure (BP) and hypertension prevalence were actually lower in mitochondrial disease patients than in age-matched and sex-matched controls with other causes of diabetes mellitus [11].

In these pioneering studies, some questions remain unanswered. Are SBP and DBP both elevated in mitochondrial diseases? Is BP elevated to the same degree in genetically different mitochondrial disease, when comparing by type of variant or by heteroplasmy level? Furthermore, studying hypertension rather than BP wastes power [12] and might lead to bias because of spurious identification of hypertension [13], especially in mitochondrial patients who visit a physician more often than the general population [14].

We hypothesized that mitochondrial disease patients have higher SBP and DBP in general, and that this effect would be more pronounced for a genetic subgroup of mitochondrial diseases. Using a retrospective study design, we analyzed BP in 286 patients with genetically proven mitochondrial diseases. BP was compared with a national reference cohort using case–control matching. Secondly, we studied BP differences among distinct mitochondrial diseases grouped by genotype. Finally, we explored the correlation between BP and mitochondrial disease characteristics in the m.3243A>G subgroup, including heteroplasmy levels, presence of diabetes mellitus and presence of left ventricular hypertrophy (LVH).

MATERIALS AND METHODS

Patient inclusion
We used a retrospective design to study two patient cohorts. For the first cohort, we retrospectively identified and included patients of at least 16 years of age with genetically proven mitochondrial disease, who visited the department of Internal Medicine of the Radboudumc between January 2005 and January 2020. Patients who were not capable of making an informed decision about consent for study participation were excluded. BP was measured at the moment of their first referral to the Radboudumc. Data on all other variables was collected from the same date in most cases, and if not possible, the measurement closest to the BP measurement was taken (maximized to 1 year). For the second cohort (acronym Mitostraat), we collected BP data and all other data during an in-patient, 4-day multidisciplinary evaluation program (as part of usual care, usually planned at or shortly after the first presentation). These patients visited the Radboudumc between March 2015 and March 2020. For both cohorts, we collected data on the following variables: sex, age in year of measurement, age at diagnosis, clinical diagnosis, the exact pathogenic mtDNA or nDNA variant, smoking status, heteroplasmy levels in leukocytes and urine epithelial cells, diabetes status, hypertension status, presence of kidney disease, presence of (micro)albuminuria, SBP, DBP, height, weight, BMI, estimated glomerular filtration rate (calculated with CKD-EPI), antihypertensive drug treatment at the time of the BP measurement and presence of LVH on electrocardiogram/echocardiogram.

As a reference cohort, we used anonymized BP data obtained by NLdeMaat, a national public health survey among 3847 men and nonpregnant women aged 30–70 years, executed by the National Institute for Public Health and the Environment (RIVM) [15].

Measurement of variables
In the out-patient cohort, manual sphygmomanometer BP measurements were performed according to standard guidelines [16]. During the visit, three measurements were performed with a manual BP monitor (Maxi Stabil 3, Welch Allyn GmbH & Co. KG, Germany) and the average of the last two was recorded in the patient record. In the in-patient cohort, BP was recorded with an automated BP monitor (Langezeithypertensiometer Mobil-O-Graph NG, Köln, Germany). In the national reference cohort, BP was recorded with an automated monitor, Omron M6 (Omron, Kyoto, Japan).

Data was collected from electronic health records and entered in Castor EDC [17].

Genetic assessment
Mitochondrial DNA was obtained from urine epithelial cells by centrifuging urine sediments for 10 min at 3000 rpm, the pellet was washed with a phosphate-buffered saline. Additionally, DNA was isolated from leukocytes in peripheral venous blood using a salting-out method. A commercially available DNA isolation kit (Gentra Puregene Blood kit, #158389; Qiagen, Venlo, the Netherlands) was used to extract the DNA and the percentage of mutant mtDNA was determined using Pyrosequencing technology (Pyrosequencing, Uppsala, Sweden) [18]. The pyrosequence reaction of the m.3243A>G variant had a precision of 1.5%, and the mutation was detected from a heteroplasmy level of 5%. The detection limit for the m.3243A>G variant was determined by serial dilution of a sample containing this mutation with wild type mtDNA [19]. We evaluated pathogenicity by taking into account segregation information, heteroplasmy levels, variant allele frequency, in-silico pathogenicity predictions and biochemical and histochemical results.

Definitions
Hypertension was defined as SBP at least 140 mmHg, DBP at least 90 mmHg [16], or if the medical patient record mentioned a personal history of hypertension. A mitochondrial disease was considered genetically proven when a pathogenic or likely pathogenic mtDNA or nDNA variant was identified. Mean arterial pressure (MAP) was calculated from SBP and DBP by the following formula: MAP = (1/3*SBP) + (2/3*DBP). We defined proteinuria/(micro-)albuminuria as an albumin/creatinine ratio of greater than 3.5 mg/mmol or a urinary albumin excretion of more than 30 mg/l in spot urine. Individuals were counted as smokers if they reported smoking at the time of presentation, regardless of frequency. Past smokers were counted as nonsmokers.

Statistical analyses
We described clinical characteristics with descriptive statistics. Our primary analyses were comparison of BP in a
national reference cohort versus mitochondrial disease patients and among genetically different mitochondrial disease subgroups. As secondary analyses, we explored whether heteroplasmy levels and several mitochondrial disease manifestations (e.g. syndrome classification, presence of diabetes, presence of LVH and presence of (micro-) albuminuria) were correlated with BP in the m.3243A>G subgroup. We imputed missing data under the assumption of data missing at random (Supplementary Material, http://links.lww.com/HJH/B864). We performed sensitivity analyses on the original, unimputed data to check the effect of the imputation.

In our first primary analysis, we control-matched mitochondrial disease patients by age, gender and BMI (Supplemental Material, http://links.lww.com/HJH/B864). We performed a two-tailed, unpaired t-test assuming unequal variances to test for any significant differences in BP, age and BMI between cases and controls. We used a Pearson chi-square test to explore differences in hypertension rates, cardiovascular disease, diabetes and (micro) albuminuria.

For the second primary analysis and secondary analyses, we used multiple linear regression analyses. We included known risk factors for high BP in each model as covariates regardless of significance; we, therefore, included age, age-squared (age²) and BMI as continuous variables, and included sex and smoking status as binary variables. Age² was included as age is known to have a strong but not linear relationship with BP. We also included the cohort as binary variable (automatic measurement cohort or manual measurement cohort). Dummy variables were created for each genotype subgroup (analysis 2), the largest subgroup (m.3243A>G) was chosen as reference group. We assessed significance of the correlation between each subgroup and BP by stepwise selection, and subsequently entered all subgroups together to display an estimate of effect sizes and directions in nonsignificant subgroups.

For each regression analysis, before interpreting results, we examined whether the dataset met basic assumptions for correct interpretation of multiple regression. We, thus assessed normality of the residuals, homoscedasticity, absence of multicollinearity and in case of a continuous independent variable, linearity of the relationship with the outcome.

As part of sensitivity analyses, we examined whether our results were different from the same analysis on the unimputed (original) data. As the observed BP cannot be used for the analysis directly, we performed a transformation on the BP values suggested by Tobin et al. [12]. Thus, we obtained the formula:

\[ Y_i = \begin{cases} Y_i + \text{Constant} & \text{if treat}_i = 1 \\ Y_i & \text{if treat}_i = 0 \end{cases} \]

On the basis of previous research [12,20], we set the constant to 10 mmHg for imputation of the underlying SBP and 5 mmHg for imputation of the underlying DBP. For sensitivity analyses, we varied the constant factor between 6 and 15 mmHg for SBP, and between 3 and 10 mmHg for DBP.

The regression formulas can be found in the Supplementary Material, http://links.lww.com/HJH/B864.

Data analysis was performed with SPSS version 24.0.0.1, 64-bit edition for Windows (IBM, Armonk, New York, USA). Figures were produced with Graphpad Prism 9.0.1 for MacOS (Graphpad Software, San Diego, California, USA). P values below 0.05 were considered statistically significant and 95% confidence intervals (CI) are given wherever applicable.

**RESULTS**

**Cohort description**

Two hundred and eighty-six patients with genetically proven mitochondrial diseases were included, as well as 3847 individuals from a national reference population (Supplementary Table 2, http://links.lww.com/HJH/B864). Missing data were below 5% for variables used in primary analyses, except for smoking status (14% missing) (Supplementary Table 3, http://links.lww.com/HJH/B864). To reduce bias, missing values were imputed for all analyses. Clinical characteristics were similar for imputed and original data (Supplementary Table 4, http://links.lww.com/HJH/B864).

**Female patients have higher blood pressure than female controls**

To correct for the marked differences in age, gender and BMI between the two cohorts, case–control matching was performed. No significant differences were detectable between the two cohorts after matching for age, gender, and smoking status, with a Pearson \(x^2\) test assuming unequal variances. Significance for dichotomous variables was determined with a Fisher’s exact test. Missing values were imputed, numbers represent pooled imputed data. LVH, left ventricular hypertrophy; MAP, mean arterial pressure.

**TABLE 1. Matched comparison for mitochondrial disease patients and controls**

| Variable                  | Mitochondrial disease patients \(n = 231\) | Reference population \(n = 231\) | Significance |
|---------------------------|-------------------------------------------|---------------------------------|--------------|
| Age [mean (SD)]           | 46.0 (10.8)                               | 46.3 (10.6)                     | 0.800        |
| BMI [mean (SD)]           | 23.8 (4.1)                                | 24.2 (3.8)                      | 0.276        |
| SBP [mean (SD)]           | 132 (19)                                  | 127 (19)                        | 0.002        |
| DBP [mean (SD)]           | 80 (12)                                   | 78 (12)                         | 0.074        |
| MAP [mean (SD)]           | 97 (13)                                   | 94 (14)                         | 0.019        |
| Female sex [no. (%)]      | 151 (65)                                  | 151 (65)                        | 1.000        |
| Smoker [no. (%)]          | 45 (19)                                   | 57 (25)                         | 0.140        |
| Hypertension [no. (%)]    | 104 (45)                                  | 86 (37)                         | 0.072        |
| Antihypertensive use [no. (%)] | 73 (32)                              | 20 (9)                          | <0.001       |
| Cardiovascular disease [no. (%)] | 28 (12)                              | 14 (6)                          | 0.014        |
| Diabetes [no. (%)]        | 95 (41)                                   | 9 (4)                           | <0.001       |
| (Micro-)albuminuria [no. (%)] | 64 (28)                               | 23 (10)                         | <0.001       |
| Automatic measurement [no. (%)] | 135 (58)                             | 231 (100)                       | <0.001       |

Mitochondrial disease patients matched on age, sex and BMI with individuals from a national population survey. Blood pressure was corrected for use of antihypertensives [11]. Significance for continuous variables was determined with an unpaired, two-tailed \(t\) test assuming unequal variances. Significance for dichotomous variables was determined with a Pearson \(x^2\) test. Missing values were imputed, numbers represent pooled imputed data. LVH, left ventricular hypertrophy; MAP, mean arterial pressure.
SBP was 5 mmHg higher in mitochondrial disease patients than in individuals from the national population cohort (95% CI 2–8.9 mmHg; Table 1). MAP was significantly higher too in mitochondrial disease patients (3 mmHg, 95% CI 0.7–5.7 mmHg) and DBP showed a similar trend (2 mmHg, 95% CI –0.2 to 4.2 mmHg). When exploring sex-differences, we found that this was solely attributable to higher BP in female patients (Fig. 1, Supplementary Table 5, http://links.lww.com/HJH/B864). Female mitochondrial disease patients had on average 8.8 mmHg higher SBP than female controls (95% CI 4.4–13.3) and plotting mean SBP against age showed SBP elevation across all ages. Male mitochondrial disease patient SBP was on average similar to that of male controls (–0.9 mmHg, 95% CI –5.95 to 4.16).

We also explored differences in hypertension prevalence, antihypertensive use and several hypertension-related comorbidities (Table 1). The hypertension prevalence was 44% in mitochondrial disease patients versus 37% in control individuals (prevalence ratio 1.2, $\chi^2$ test $P = 0.09$). Use of at least one antihypertensive, presence of diabetes and presence of (micro-)albuminuria were all significantly higher in mitochondrial disease patients (respective odds ratios: 5.2, 19 and 6.3, for all $P < 0.001$; Table 1). Mitochondrial disease patients also had a higher incidence of cardiovascular disease (odds ratio 2.3; 95% CI 1.2–4.6), specifically female patients (Supplementary Table 6, http://links.lww.com/HJH/B864).

As sensitivity analyses, the t tests and $\chi^2$ test were repeated on the unimputed data, yielding very similar results (data not shown). Also, we studied the effect of choosing different constant factors as treatment correction (between 6 and 15 mmHg for SBP and between 3 and 10 mmHg for DBP). Higher constant factors increased the difference between the two cohorts (Supplementary Table 7, http://links.lww.com/HJH/B864).

Genotype is not correlated with blood pressure

Linear regression analyses were performed to study the effect of the genetic mitochondrial disease classification; potentially confounding variables were included. Higher age was significantly associated with higher SBP, DBP and MAP (Fig. 1, Table 2 and Supplementary Table 8, http://links.lww.com/HJH/B864). Higher BMI was also significantly associated with higher BP (0.36–1.17 mmHg per 1-point increment in BMI), with the strongest relationship for SBP (Fig. 1). Male sex was associated with higher BP but this was only significant for DBP ($P = 0.034$). A difference was observable between the manual measurement cohort and automatic measurement cohort, with the manual measurement cohort having a higher BP (7 mmHg difference for SBP) (Fig. 1). Male sex was associated with higher BP but this was only significant for DBP ($P = 0.034$). A difference was observable between the manual measurement cohort and automatic measurement cohort, with the manual measurement cohort having a higher BP (7 mmHg difference for SBP). Stepwise selection of the genetic diagnosis as additional covariate left only the ‘mtDNA mutation, remainder’ subgroup as a significant variable for BP. Analysis of BP residuals per individual could not pinpoint, which DNA mutations were most associated with higher SBP or lower
Higher blood pressure is associated with left ventricular hypertrophy in the m.3243A>G subcohort

To exclude any possible genotype – phenotype interaction effects, we further studied the subcohort of patients with the m.3243A>G variant for predictors of higher blood pressure. Positive correlations of BP with age, BMI and male sex were observed (Table 3 and Supplementary Table 10, http://links.lww.com/HJH/B864). These were similar in size and direction as the associations observed in the total group of mitochondrial disease patients. None of the subgroups with one of three predefined clinical diagnoses (MELAS, myopathic or dormant carrier) had a significantly different blood pressure from the MIDD subgroup. The comorbidities diabetes, (micro)albuminuria, heteroplasmy and cardiovascular disease were not significantly associated with blood pressure either, nor were urinary or blood heteroplasmy levels. Following a stepwise approach that would include significant predictors, only LVH – as assessed by electrocardiogram or cardiac ultrasound – was retained in the model. Entering LVH as separate variable in the model showed 6.6 mmHg higher SBP in patients with LVH (95% CI 0.24–12.9). A logistic regression to investigate factors that determine LVH in our cohort indeed classified higher SBP as significant predictor, as well as lower BMI (Supplementary Table 11, http://links.lww.com/HJH/B864). The odds ratio of having LVH was 1.32 for a 10 mmHg rise in SBP (95% CI 1.01–1.72).

As part of sensitivity analyses, we performed the same analyses on the unimputed data. Results were very similar (data not shown). Also, we investigated whether changing the constant factor added in case of antihypertensive treatment influenced the results. Higher estimations of the treatment effect (up to 15 mmHg) yielded slightly larger confidence intervals that did not include 0 are printed in bold. Confidence intervals that did not include 0 are printed in bold.

Multivariable linear regression on imputed data (n = 180) to study differences between mitochondrial disease genetic subgroups. Missing values were imputed 20 times as reference group and shows results after forced entry of dummies for all genetic subgroups. The automatic measurement cohort was encoded as 1 in the ‘measurement method’ variable. b, unstandardized beta; CI, confidence interval; CI, confidence interval. Confidence intervals that did not include 0 are printed in bold.

### TABLE 2. Comparison of SBP in different genetic subgroups

| Variable | b (95% CI)       | Model 1 |                |                |
|----------|------------------|---------|----------------|----------------|
| Constant | 74.45 (53.59–95.31) | Model 1 |                |                |
| Age      | –0.01 (–0.02 to 0) | Model 2 |                |                |
| Age      | 1.05 (0.11–1.98)  | Model 2 |                |                |
| Male sex | 2.91 (–1.32 to 7.13) | Model 2 |                |                |
| BMI      | 1.12 (0.63–1.61)  | Model 2 |                |                |
| Smoker   | –0.1 (–7.89 to 3.09) | Model 2 |                |                |
| Measurement method | –6.45 (–10.56 to –2.34) | Model 2 |                |                |
| m.8333A>G and m.8363G>A | –4.19 (–12.22 to 3.83) | Model 2 |                |                |
| mtDNA deletion | 2.16 (–6.71 to 11.03) | Model 2 |                |                |
| Nuclear mutation | –1.95 (–9.7 to 5.8) | Model 2 |                |                |
| Other mtDNA mutations | 5.35 (–0.11 to 10.8) | Model 2 |                |                |

DISCUSSION

Using a retrospective case-control design, this study provides evidence that female patients with a mitochondrial disease have a higher SBP, compared with the general female population. Multiple linear regression analyses show that BP differences between different mitochondrial diseases are small, and in our study, nonsignificant. Lastly, SBP was associated with LVH in patients with the m.3243A>G variant.
attributed to high blood pressure [22]. Female mitochondrial patients in our study had a higher incidence of cardiovascular disease in comparison to the general female population. Careful blood pressure monitoring and treatment of elevated blood pressure would thus be expected to prevent morbidity and mortality, particularly in women.

Novel hypotheses on the pathophysiology of hypertension in mitochondrial disease can be drawn from this study. The more pronounced effect on SBP suggests an increased stiffness of the large conduit arteries or narrowing of smaller, muscular arteries and arterioles [23]. Studies on vascular function in mitochondrial disease are limited but some provide data to support such a hypothesis. For instance, POLO-deficient mice exhibited an increased arterial stiffness [24], whereas hypertensive mitochondrial disease patients showed an increased total peripheral resistance when values were normalized to body surface area [10]. Furthermore, pulse wave contour analysis in a patient with the m.3243A>G variant demonstrated decreased capacitive and oscillatory compliance [25], suggesting both stiffness of the large conduit arteries and narrowing of small arteries and arterioles [26]. Lastly, MELAS patients appear to have a deficiency of nitric oxide [27], which would be expected to lead to increased resistance at muscular arteries.

Why only female patients would suffer from increased stiffness or impaired vascular relaxation is unclear. Sex differences in the pathophysiology of hypertension has been a subject of extensive study and debate in the normal population [28], but whether this would translate to the mitochondrial disease population remains to be determined. For a link between sex differences and altered mitochondrial function specifically, only two rodent studies are to our knowledge available [24,29]. Studies that investigate the pathophysiology of high BP in mitochondrial disease patients are, therefore, needed.

A recent study has suggested that the type of genetic defect plays a significant role in conferring the risk of hypertension in mitochondrial disease patients [9]. We wanted to reinvestigate this after careful correction for confounders, such as age, sex, BMI and smoking, to prevent identification of spurious correlations. Multiple linear regression with correction for such confounders, the investigation of BP instead of DBP as a predictor for blood pressure, and the detailed characterization of the patients and the large sample size of the m.3243A>G-sub-cohort. The retrospective nature of the study also limits expectation bias.

The most important limitation is that the type of BP device could not be standardized because of the retrospective nature of the study. As manual BP measurements generally yield higher BP values in our center, we might have overestimated the BP in the mitochondrial disease patient group. Furthermore, antihypertensive use by a subset of patients necessitated us to estimate the underlying blood pressure in these patients [12]. Additionally, we cannot exclude a modest temporal bias as it was not possible to collect the patient cohort at exactly the same time as the population survey. A last limitation is the relatively small sample size of some subgroups in our study. An example is the small number of patients with nuclear POLO variants compared with the study by Pauls et al. [10].

In conclusion, our study reveals novel aspects of the role of mitochondrial dysfunction in blood pressure regulation. It brings nuance to the observations in earlier studies by showing that specifically female mitochondrial disease patients have a higher SBP compared with the general female population. Furthermore, our data suggest a possible role for elevated BP in the higher incidence of left ventricular hypertrophy often observed in mitochondrial disease patients. Clinicians should be aware of this and consider routine screening of BP in mitochondrial disease patients.
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Conflicts of interest

There are no conflicts of interest.

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