Increased Prevalence of Hypertension in Young Adults with High Heteroplasmy Levels of the MELAS m.3243A>G Mutation

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Abstract Background: The pathophysiology of hypertension in patients with mitochondrial diseases is different from that of the general population. Growing evidence exists linking mtDNA, its mutations, and mitochondrial dysfunction to the pathogenesis of hypertension. No reports on the prevalence of hypertension in late-onset mtDNA diseases have been described.

Methods: We performed a retrospective chart review of adult patients with late-onset mtDNA diseases between January 1999 and January 2012 at our center. We grouped them into age categories to allow comparison with previously reported Canadian Health Measures Survey (CHMS) prevalence data.

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Results: Twenty-three subjects with hypertension were identified for a crude prevalence of 39.7 % (95 % CI 27–53 %) as compared to the CHMS age-predicted prevalence of 30.5 %. When analyzed by individual age group, there were no significant differences between the observed and the CHMS predicted prevalence rates in the 40 years and older cohorts (age category 40–59, $p = 0.63$; age category 60–79, $p = 0.85$). However, hypertension rates were significantly higher than predicted in the under 40 years cohort (55.6 vs. 2.8 %, $p < 0.001$, CI 21–86 %), in which hypertensive patients with the MELAS m.3243A>G mutation were significantly clustered ($p < 0.01$). This younger MELAS cohort ($n = 4$, mean age = 24 years) with hypertension had heteroplasmy levels (mean = 68 %) that were significantly higher than the levels found in the older non-hypertensive MELAS cohort ($n = 8$, mean age = 52 years, mean = 33 %) ($p = 0.04$).

Conclusion: Relative to age, gender, and mtDNA disease subtype, young adults with high heteroplasmy levels of the MELAS m.3243A>G mutation demonstrate an increased prevalence of hypertension. Further prospective data are needed to confirm this initial finding, which has potentially important treatment implications.

Introduction

The mitochondrion is an important cellular structure responsible for energy production. Multiple causes of mitochondrial dysfunction are recognized and can be grouped into primary “inherited” (Schapira 2006; Koopman et al. 2012) or secondary causes (Koopman et al. 2012; Coskun et al. 2011; McCoy and Cookson 2011; Cairns et al. 2011; Hoppel et al. 2009; Sleight et al. 2011; Finsterer and Segal 2010; Cohen 2010). This dysfunction, regardless

of cause, disrupts cellular energy metabolism and produces reactive oxygen species (Nageswara et al. 2007) that lead to accumulation of mitochondrial DNA (mtDNA) mutations, and further impair mitochondrial function (Nageswara et al. 2007).

Despite the heterogeneity of clinical manifestations of late-onset mtDNA diseases (Koopman et al. 2012; Thorburn 2004), certain genetic mutations are associated with a predisposition to select phenotypes (Koopman et al. 2012; Thorburn 2004). The most common clinical syndrome observed in our clinic is the chronic progressive external ophthalmoplegia plus (CPEO+) syndrome, usually associated with multiple mtDNA deletions (Pfeffer et al. 2011). The most common clinical manifestations in this syndrome are bilateral ptosis and ophthalmoparesis due to myopathy affecting the extraocular muscles (Pfeffer et al. 2011). There is also a variable degree of skeletal myopathy with 62 % of patients having one or more of the following findings: objective muscle weakness, exertional myalgia, and polyneuropathy (Pfeffer et al. 2011). The Kearns-Sayre (KSS) syndrome is similar to the CPEO syndrome but includes pigmentary retinopathy and cardiac conduction abnormalities (Pfeffer et al. 2011). This syndrome is usually associated with a sporadic onset major deletion in the mtDNA (Pfeffer et al. 2011). The second most common syndrome is the mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome associated with the m.3243A>G mutation (Yatsuga et al. 2012). The most common clinical manifestations of the late-onset form of this syndrome are stroke-like episodes and seizures (each affecting more than 60 % of patients), diabetes mellitus (40 %), and proximal muscle weakness and general fatigue (each affecting greater than 30 % of patients) (Yatsuga et al. 2012). Another relatively common form is the myoclonic epilepsy with ragged red fiber syndrome (MERRF) associated with the m.8344A>G mutation (Silvestri et al. 1993). The most common clinical manifestations of this syndrome are central nervous system manifestations of myoclonus, seizures, and ataxia in combination with a skeletal myopathy that frequently manifests with proximal weakness and exercise intolerance (Silvestri et al. 1993). Less common forms have a variable combination of multisystemic disease manifestations. Hypertension is now associated with select subtypes of mtDNA mutations (Map of the human mitochondrial DNA 2012) including mtDNA mutations affecting mitochondrial transfer RNA coding sequences, and those affecting coding sequences for electron transport chain complex I subunit proteins.

The links between mitochondrial dysfunction, mtDNA mutation, and hypertension have not been widely appreciated prior to the past decade. In this time, mitochondrial haplogroup analysis, case reports of patients with mtDNA

diseases, and genetic studies in hypertensive pedigrees have all uncovered connections between the genetic disorder and the clinical phenotype of hypertension. Specifically, mitochondrial haplogroups represent common population-specific variants that confer relative susceptibility to common diseases such as diabetes mellitus, atherosclerosis, cancer, aging, Alzheimer's, and schizophrenia (Koopman et al. 2012; Coskun et al. 2011; McCoy and Cookson 2011; Cairns et al. 2011; Hoppel et al. 2009; Sleight et al. 2011; Finsterer and Segall 2010; Cohen 2010). These mitochondrial haplogroups are also known to influence the maternal inheritance pattern of hypertension (Schwartz et al. 2004). Moreover, several studies have shown that specific heteroplasmic mtDNA mutations, which may cause clinical symptoms in childhood or in adulthood, specifically predispose to hypertension (Schwartz et al. 2004; Borhani et al. 1969; Gerson and Fodor 1975; Bengtsson et al. 1979; Havlik et al. 1979; Higgins 1980; Hutchinson and Crawford 1981; Longini et al. 1984; Brandao et al. 1992; DeStefano et al. 2001; Sun et al. 2003; Levin et al. 1999). Finally, mtDNA sequencing in multigenerational hypertensive pedigrees reveals a high prevalence of mtDNA mutations (Schwartz et al. 2004).

Given the evolving recognition of the importance of hypertension in select cases of mtDNA diseases, we sought to determine the prevalence of hypertension in a large cohort of patients with confirmed late-onset mtDNA diseases as compared to age-matched national figures. A secondary aim was to determine whether any potential increase in the prevalence of hypertension, relative to age-matched national figures, was attributable to specific subtypes of mtDNA disease.

Methods

Study Design and Population

We undertook a retrospective chart review of 914 adult patients seen at our center between 1999 and 2012 for the investigation of questionable late-onset mtDNA diseases. Patients with definite disease (defined as the identification of either two major criteria or one major plus two minor criteria, as set by Bernier et al. (2002)) were included in the analysis. The charts were reviewed for the following variables: demographic characteristics, age at diagnosis, type of late-onset mtDNA diseases, list of medications, family history of mtDNA diseases, and hypertension. Finally, we recorded the heteroplasmy levels for each patient where available (assessed in muscle, urine epithelial cells, and/or white blood cells, using restriction fragment length polymorphism analysis with estimation of relative band intensities on ethidium bromide-stained gels). For

each group, we tabulated BP and serum TSH, glucose, ALT, and serum creatinine during the last assessment at our clinic (data not shown).

Our cohort with late-onset mtDNA diseases was further subdivided into different age categories and matched for age using the data from the Canadian Health Measures Survey (CHMS) (Wilkins et al. 2010), which is a survey on the 2007–2009 prevalence of hypertension in the 20–79 years of age cohort (total respondents = 3,514, with hypertension = 864), weighted to be representative of 23.7 million Canadian adults in this age range.

Statistical Analysis

We calculated the crude prevalence of hypertension in the entire cohort. We further divided the mtDNA diseases patients into three age categories, 20–39, 40–59, and 60–79, to determine the age-specific prevalence with 95 % confidence intervals. The prevalence within each category was compared with CHMS data (Wilkins et al. 2010) using Chi square analysis.

Results

Our chart review encompassed 914 charts of which 63 were deemed to have definite late-onset mtDNA diseases. Of the 63, 5 charts were excluded on the basis of incomplete information regarding the diagnosis of hypertension.

The demographic characteristics, mtDNA disease syndromes, comorbidities and hypertension diagnoses for the 58 patients are summarized in Table 1. The overall prevalence of hypertension in our cohort was 23/58 or 39.7 % (95 % CI 27–53 %). Based on the CHMS data (Wilkins et al. 2010); the expected prevalence based on age was 17.7 or 30.5 %. When analyzed by age groups, there was no significant difference in the prevalence of hypertension within our cohort as compared to the equivalent prevalence figure in the CHMS data (Wilkins et al. 2010) in patients 40 years of age and older. However, the observed prevalence rate was significantly higher than the equivalent CHMS data (Wilkins et al. 2010) in the younger cohort (age category 20–39), with a prevalence of 5/9 (56 %, CI 21–86 %), as compared to a CHMS rate of 2.8 % (Wilkins et al. 2010) ($n = 33/1185$) ($p < 0.001$). The increased prevalence of hypertension in this younger cohort was attributable to the high prevalence rate in the subgroup with the MELAS m.3243A>G mutation Table 2.

As the high prevalence of hypertension in the younger MELAS cohort was not observed in the 40–59 years of age MELAS cohort, we compared mtDNA disease severity between the younger and older age groups. mtDNA heteroplasmy (proportion of mtDNA that is mutated) was

selected as the marker of disease severity. Muscle and urine epithelial cell sources of mtDNA were utilized, where available (14/16 patients), as previous studies in MELAS cohorts have identified heteroplasmy levels in these specific tissue sources as reliable predictors of disease severity (McDonnell et al. 2004). Two of the 16 MELAS patients had heteroplasmy measurements performed only in white blood cells (WBC): one was a normotensive patient in his 6th decade with a WBC heteroplasmy level of 10 %, the other was a hypertensive patient in his 3rd decade who had a WBC heteroplasmy level of 80 %. The WBC heteroplasmy level from the former patient (WBC heteroplasmy level of 10 %) was not used in further calculations as WBC heteroplasmy levels are known to underestimate muscle heteroplasmy levels, with the underestimation increasing with patient age (Mehrazin et al. 2009). Therefore, subsequent analyses utilized information on tissue heteroplasmy levels from the remaining 15 of the 16 MELAS patients.

The mean mitochondrial heteroplasmy level in the 20–39 years of age MELAS patient cohort ($n = 4$, mean = 68 %, range: 45–80 %) was higher than that of the 40–59 years of age MELAS patient cohort ($n = 7$, mean = 39 %, SD = 30 %) although this difference did not reach statistical significance ($p = 0.11$). The mean heteroplasmy level in the 20–39 years of age MELAS patient cohort with hypertension ($n = 4$, mean = 68 %, range: 45–80 %) was significantly higher than the heteroplasmy level in the cohort of MELAS patients over 40 years of age who did not have hypertension ($n = 8$, mean = 33 %, SD = 28 %, $p = 0.04$).

Discussion

In view of the accumulating knowledge that variation in the mtDNA sequence accounts for a significant proportion of the heritability of hypertension, we sought to determine the prevalence of hypertension in a cohort of definite late-onset mtDNA diseases due to a wide variety of mtDNA genotypes. We sought to answer this question by specifically targeting patients with an unambiguous diagnosis of definite disease, as mitochondrial dysfunction may otherwise be associated with overlap clinical syndromes (including aging itself), (Schapira 2006; Koopman et al. 2012; Coskun et al. 2011; McCoy and Cookson 2011; Cairns et al. 2011; Hoppel et al. 2009; Sleight et al. 2011; Finsterer and Segall 2010; Cohen 2010; Nageswara et al. 2007) which could confound any potential associations with hypertension.

We estimate the prevalence of hypertension in this cohort of mtDNA diseases to be 39.7 % ($n = 23/58$). This prevalence rate is not unexpected given the average age of our cohort, which was in the 6th decade of life. When

Table 1 Comparison of demographic, comorbid, and disease characteristics between the hypertensive and non-hypertensive mtDNA diseases cohort

Patient variable	All patients	mtDNA diseases without hypertension	mtDNA diseases with hypertension	p-value
Age group, n, years				
20–39	9	4	5	
40–59	26	20	6	
60–79	23	11	12	
Total	58	35	23	
Age, mean (SD), years				
20–39	28.7 (6)	32.5 (5)	24.8 (6)	0.07
40–59	49 (6)	58 (6)	52.5 (5)	0.11
60–79	68 (8)	65.7 (6)	71 (9)	0.16
Total	58 (15.7)	52 (12)	56 (20)	
Gender (female/age subtotal), n (%), years				
20–39	4/9 (44)	3/4 (75)	1/5 (20)	0.099
40–59	16/26 (62)	12/20 (60)	4/6 (67)	0.77
60–79	16/23 (70)	7/11 (64)	9/12 (75)	0.55
Total female, n (% of cohort)	36/58 (40)	22/35 (44)	14/23 (39)	
Ethnicity (white/age subtotal), n (%), years				
20–39	5/9 (56)	2/4 (50)	3/5 (60)	0.76
40–59	20/26 (77)	15/20 (75)	5/6 (83)	0.67
60–79	20/23 (87)	9/11 (82)	11/12 (92)	0.48
Total white, n (% of cohort)	45/58 (78)	26/35 (74)	19/23 (83)	
Inactivity (inactive/age subtotal), n (%), years				
20–39	7/9 (78)	3/4 (75)	4/5 (80)	0.86
40–59	17/26 (65)	13/20 (65)	4/6 (67)	0.94
60–79	16/23 (70)	4/11 (36)	12/12 (100)	0.0009
Total inactive, n (% of cohort)	40/58 (69)	20/35 (57)	20/23 (87)	
Diabetes (total with diabetes/age subgroup), n (%), years				
20–39	0/9 (0)	0/4 (0)	0/5 (0)	N/A
40–59	2/26 (8)	2/20 (10)	0/6 (0)	0.42
60–79	8/23 (35)	5/11 (45)	3/12 (25)	0.30
Total with diabetes, n (% of cohort)	10/58 (17)	7/35 (20)	3/23 (13)	
Smoking (total smokers/age subgroup), n (%)				
20–39 years	1/9 (11)	1/4 (25)	0/5 (0)	0.23
40–59 years	7/26 (27)	5/20 (25)	2/6 (33)	0.68
60–79 years	5/23 (22)	1/11 (9)	4/12 (33)	0.15
Total smokers, n (% of cohort)	13/58 (22)	7/35 (20)	6/23 (26)	
Heart disease (HD) (total with HD/age subgroup), n (%)				
20–39 years	1/9 (11)	0/4 (0)	1/5 (20)	0.34
40–59 years	9/26 (35)	4/20 (20)	5/6 (83)	0.004
60–79 years	11/23 (48)	6/11 (54)	5/12 (42)	0.66
Total HD, n (% of cohort)	21/58 (36)	10/35 (28)	11/23 (48)	

Table 2 Ratio of hypertensive to non-hypertensive patients in our mtDNA cohort organized by patient age and clinical syndrome subcategories

	<i>Age category, years</i>		
	20–39	40–59	60–79
<i>Clinical syndrome subcategories</i>			
CPEO+ ^a	1:2	4:9	9:8
MELAS ^a	4:0 ^b	1:7	2:2
MERRF ^a	0:0	0:3	0:1
KSS ^a	0:0	0:1	0:0
Complex I deficiency ^a	0:2	1:0	1:0

^a CPEO+, MELAS, MERRF, KSS, Complex I deficiency: mitochondrial genetic/clinical syndromes as described in the introduction

^b The ratio of total MELAS to total non-MELAS patients in the 20–39 years of age hypertensive group is significantly higher than expected ($p < 0.01$) by Chi squared analysis

analyzed by age group, in comparison to the CHMS cohorts (Wilkins et al. 2010), the 40–59 and 60–79 years of age cohorts had respective prevalence values that did not deviate significantly from the expected values. In contrast, the 20–39 years of age cohort had a surprisingly high prevalence at 56 % (CI 21–86 %). This prevalence was higher than expected based on the CHMS data (Wilkins et al. 2010) ($p < 0.001$).

There are several lines of data which suggest that the observed high prevalence rate of hypertension in the young late-onset mtDNA diseases cohort is a causal association. First, the increased prevalence rate observed in mtDNA diseases-related hypertension was primarily attributable to young patients who carry relatively high heteroplasmy levels of the common MELAS (m.3243A>G) mutation. This finding suggests that the risk of hypertension in mtDNA diseases is dependent on both the type and heteroplasmy level of the disease-causing mutation. The increased prevalence of hypertension in the younger cohort could not be solely explained by other monitored risk factors including physical inactivity (4/5), diabetes mellitus (0/5), or smoking status (0/5) as these prevalence rates did not differ significantly when compared to the older age groups (Table 1).

Second, our findings replicated data from previous studies that have shown links between mitochondrial dysfunction due to mtDNA mutations and hypertension. For instance, several studies showed evidence that novel mtDNA mutations (e.g., tRNA^{Ala} 4263A>G (Schwartz et al. 2004)) are directly associated with hypertension. One study of a hypertensive pedigree carrying a mitochondrial tRNA mutation demonstrated that the fraction of hypertension potentially due to mitochondrial dysfunction was 55 % (95 % CI 45–65 %) (DeStefano et al. 2001). Another case study identified a MELAS associated syndrome characterized by pulmonary hypertension (Sproule et al. 2008). These case studies are corroborated by studies of familial

hypertensive pedigrees, which identify high rates of mitochondrial sequence changes. In all cases, the associations between mtDNA diseases and hypertension match our findings of a link mediated by particular types of mtDNA diseases – those that involve mutations of mitochondrial tRNA (such as the common MELAS mutation) or complex I subunit coding sequences. In contrast, in our study, CPEO + status was not associated with an increased prevalence rate of hypertension. These findings reinforce the specificity of the association between mitochondrial tRNA coding region mutations and the increased prevalence of hypertension. In our findings, we also considered the possibility that the high prevalence of hypertension in the young MELAS cohort was related to particular familial nuclear genetic or environmental factors. However, the four young hypertensive MELAS patients are unrelated.

Cumulatively, these reports support the contention that the high prevalence of hypertension observed in the young late-onset mtDNA diseases cohort is in part due to a causal association. The mechanism for the putative causal association between mtDNA diseases and hypertension is that of overproduction of reactive oxygen species from dysfunctional mitochondria within endothelial cells leading to the development of vascular disease, including hypertension (Nageswara et al. 2007). However, an alternate hypothesis is that deficient endothelial cell nitric oxide production may play a role (Romero and Reckelhoff 1999).

Specific forms of mtDNA disease have been recognized as having pathology related specifically to impaired endothelial function. The MELAS syndrome, in particular, is associated with stroke-like episodes that predominate in the parieto-occipital region of the brain (Yatsuga et al. 2012). Stroke-like episodes in MELAS are atypical strokes in which the affected brain region is noted to cross regions supplied by more than one major artery (Finsterer 2009). The precise cause of the stroke-like episodes is unknown but is thought to be a combination of endothelial cell

dysfunction and neuronal susceptibility to hypoxia. The endothelial dysfunction is in turn attributed to low availability of citrulline, a product of mitochondrial metabolism that is specifically deficient in MELAS patients (Naini 2005). Citrulline is further metabolized via the urea cycle to L-arginine, a precursor of nitric oxide. (Koga et al. 2005; 2006) have shown that supplementation of L-arginine levels improves endothelial function and decreases the rate of stroke-like episodes in MELAS. The relationship of hypertension to stroke-like episodes in the MELAS syndrome is unknown. The observed endothelial dysfunction in this syndrome may represent a secondary phenomenon due to MELAS-associated hypertension. Similarly, the effect of citrulline/arginine/nitric oxide supplementation on modulation of mtDNA disease-related hypertension is unknown. However, the benefits of L-arginine on blood pressure control have been documented in other patient groups (Dong et al. 2011) and this mechanism may explain part of the benefit of this therapy in stroke-like episode prevention in MELAS patients.

Study Limitations

Our study is the first to document the prevalence of hypertension in adult patients with a wide variety of different mtDNA mutations. However, several limitations to our study exist. First, our identification of patients with hypertension was limited by the retrospective nature of the study. Moreover, the age of hypertension diagnosis in the cohort, and the age relative to the onset of mtDNA disease symptoms were difficult to determine. Second, our sample size is small with no controls drawn from the same clinic population. Given the nature of the clinic population, small cohorts of rare and distinct genetic syndromes with known or uncertain associations with hypertension, a reliable control group was not available. Possible and Probable mtDNA disease patients have an unknown prevalence of mtDNA disease and, as such, could not be used as a reliable control group. We also considered the largest group of related disorders, adult-onset carnitine palmitoyltransferase II deficiency, but there were only a total of 12 patients in the clinic. Third, multivariable logistic regression to determine if the MELAS syndrome (with high heteroplasmy levels) was an independent risk factor for hypertension, after accounting for gender, age, and other risk factors for hypertension, was not performed due to the small population size of the MELAS cohort. However, it is clear that the rate of hypertension in the young MELAS cohort is exceptionally high, and is significantly associated with MELAS patients with higher heteroplasmy levels. Therefore, our preliminary findings require confirmation by means of similar studies in other mtDNA disease centers. Specifically, the rate of hypertension in pediatric and adult patients with the MELAS m.3243A>G

mutation should be compared to age-corrected population rates as well as to that present in mtDNA disease patients without the A3243G mutation and to other metabolic disorders affecting mitochondrial metabolism such as fatty acid oxidation disorders. Should such studies specifically confirm the association of the MELAS m.3243A>G mutation with hypertension, interventional studies, such as L-arginine or L-citrulline versus standard blood pressure control, should be pursued.

Conclusion

In conclusion, the prevalence of hypertension in late-onset mtDNA diseases is high in younger adult patients with high heteroplasmy levels of the MELAS m.3243A>G mutation. This finding requires replication in a larger cohort of young MELAS patients. If verified, this relationship has potentially important therapeutic implications for the prevention of cardiovascular and cerebrovascular disease in MELAS patients.

Contribution

Each author has contributed to the conception, design, analysis, data collection, interpretation, writing, critical revision, and final approval of the article. Andre Mattman guarantees the scientific integrity of the work as a whole.

Disclosures

No financial disclosures and potential conflict of interests declared by Fady Hannah-Shmouni, Paula Waters, and Andre Mattman. Sandra Sirrs has received payment for lectures from Shire Human Genetics Therapies, Genzyme Canada, and Actelion Pharmaceuticals but these do not present any conflict with the current manuscript. Michelle Mezei has received payment for lectures from Genzyme Canada that do not present any conflict with the current manuscript.

References

- Bengtsson B, Thulin T, Schersten B (1979) Familial resemblance in casual blood pressure - A maternal effect. *Clin Sci (Lond)* 57(Suppl 5): 279S–281S
- Bernier F, Boneh A, Dennett X, Chow CW, Cleary MA, Thorburn DR (2002) Diagnostic criteria for respiratory chain disorders in adults and children. *Neurology* 59(9):1406–1411
- Borhani NO, Slansky D, Gaffey W, Borkman T (1969) Familial aggregation of blood pressure. *Am J Epidemiol* 89(5):537–546

- Brandao AP, Brandao AA, Araujo EM, Oliveira RC (1992) Familial aggregation of arterial blood pressure and possible genetic influence. *Hypertension* 19(2 Suppl):II214–II217
- Cairns RA, Harris IS, Mak TW (2011) Regulation of cancer cell metabolism. *Nat Rev Cancer* 11(2):85–95
- Cohen BH (2010) Pharmacologic effects on mitochondrial function. *Dev Disabil Res Rev* 16(2):189–199
- Coskun P, Wyrembak J, Schriener S, Chen HW, Marciniack C, Laferia F, Wallace DC (2011) A mitochondrial etiology of Alzheimer and Parkinson disease. *Biochim Biophys Acta* 1820(5):553–564
- DeStefano AL, Gavras H, Heard-Costa N, Bursztyrn M, Manolis A, Farrer LA, Baldwin CT, Gavras I, Schwartz F (2001) Maternal component in the familial aggregation of hypertension. *Clin Genet* 60(1):13–21
- Dong JY, Qin LQ, Zhang Z, Zhao Y, Wang J, Arigoni F, Zhang W (2011) Effect of oral L-arginine supplementation on blood pressure: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Am Heart J* 162(6):959–965. doi: [10.1016/j.ahj.2011.09.012](https://doi.org/10.1016/j.ahj.2011.09.012)
- Finsterer J (2009) MELAS syndrome as a differential diagnosis of ischemic stroke. *Fortschr Neurol Psychiatr* 77(1):25–31. doi: [10.1055/s-2008-1100821](https://doi.org/10.1055/s-2008-1100821)
- Finsterer J, Segall L (2010) Drugs interfering with mitochondrial disorders. *Drug Chem Toxicol* 33(2):138–151
- Gerson LW, Fodor JG (1975) Family aggregation of high blood-pressure groups in two Newfoundland communities. *Can J Public Health* 66(4):294–298
- Havlik RJ, Garrison RJ, Feinleib M, Kannel WB, Castelli WP, McNamara PM (1979) Blood pressure aggregation in families. *Am J Epidemiol* 110(3):304–312
- Higgins M, Keller J, Moore F, Ostrander L, Metzner H, Stock L (1980) Studies of blood pressure in Tecumseh, Michigan. I. Blood pressure in young people and its relationship to personal and familial characteristics and complications of pregnancy in mothers. *Am J Epidemiol* 111(2):142–155
- Hoppel CL, Tandler B, Fujioka H, Riva A (2009) Dynamic organization of mitochondria in human heart and in myocardial disease. *Int J Biochem Cell Biol* 41(10):1949–1956
- Hutchinson J, Crawford MH (1981) Genetic determinants of blood pressure level among the Black Caribs of St. Vincent. *Hum Biol* 53(3):453–466
- Koga Y, Akita Y, Nishioka J, Yatsuga S, Povalko N, Tanabe Y, Fujimoto S, Matsuishi T (2005) L-Arginine improves the symptoms of stroke like episodes in MELAS. *Neurology* 64(4):710–712
- Koga Y, Akita Y, Junko N, Yatsuga S, Povalko N, Fukuyama R, Ishii M, Matsuishi T (2006) Endothelial dysfunction in MELAS improved by L-arginine supplementation. *Neurology* 66(11):1766–1769
- Koopman W, Willems P, Smeitink J (2012) Mechanisms of disease: monogenic mitochondrial disorders. *N Engl J Med* 366(12):1132–1141
- Levin BC, Cheng H, Reeder DJ (1999) A human mitochondrial DNA standard reference material for quality control in forensic identification, medical diagnosis, and mutation detection. *Genomics* 55(2):135–146
- Longini IM Jr, Higgins MW, Hinton PC, Moll PP, Keller JB (1984) Environmental and genetic sources of familial aggregation of blood pressure in Tecumseh, Michigan. *Am J Epidemiol* 120(1):131–144
- Map of the human mitochondrial DNA. Mitomap. Available: <http://www.mitomap.org/MITOMAP> (accessed 2012 June 15)
- McCoy MK, Cookson MR (2011) Mitochondrial quality control and dynamics in Parkinson's disease. *Antioxid Redox Signal* 16(9):869–882
- McDonnell MT, Schaefer AM, Blakely EL, McFarland R, Chinnery PF, Turnbull DM, Taylor RW (2004) Noninvasive diagnosis of the 3243A>G mitochondrial DNA mutation using urinary epithelial cells. *Eur J Hum Genet* 12(9):778–781
- Mehrazin M, Shanske S, Kaufmann P, Wei Y, Coku J, Engelstad K, Naini A, De Vivo DC, DiMauro S (2009) Longitudinal changes of mtDNA A3243G mutation load and level of functioning in MELAS. *Am J Med Genet A* 149A(4):584–587
- Nageswara R, Madamanchi S, Marschall S (2007) Mitochondrial dysfunction in atherosclerosis. *Circ Res* 100(4):460–473
- Naini A, Kaufmann P, Shanske S, Engelstad K, De Vivo DC, Schon EA (2005) Hypocitrullinemia in patients with MELAS: an insight into the “MELAS paradox”. *J Neurol Sci* 229–230:187–193
- Pfeffer G, Sirrs S, Wade NK, Mezei MM (2011) Multisystem disorder in late-onset chronic progressive external ophthalmoplegia. *Can J Neurol Sci* 38(1):119–123
- Romero JC, Reckelhoff JF (1999) State-of-the-Art lecture. Role of angiotensin and oxidative stress in essential hypertension. *Hypertension* 34(4 Pt 2):943–949
- Schapira AHV (2006) Mitochondrial disease. *Lancet* 368(9529):70–82
- Schwartz F, Duka A, Sun F, Cui J, Manolis A, Gavras H (2004) Mitochondrial genome. Mutations in hypertensive individuals. *Am J Hypertens* 17(7):629–635
- Silvestri G, Ciafaloni E, Santorelli FM, Shanske S, Servidei S, Graf WD, Sumi M, DiMauro S (1993) Clinical features associated with the A->G transition at nucleotide 8344 of mtDNA (“MERRF mutation”). *Neurology* 43(6):1200–1206
- Sleigh A, Raymond-Barker P, Thackray K, Porter D, Hatunic M, Vottero A, Burren C, Mitchell C, McIntyre M, Brage S, Carpenter TA, Murgatroyd PR, Brindle KM, Kemp GJ, O’Rahilly S, Semple RK, Savage DB (2011) Mitochondrial dysfunction in patients with primary congenital insulin resistance. *J Clin Invest* 121(6):2457–2461
- Sproule DM, Dyme J, Coku J, de Vinck D, Rosenzweig E, Chung WK, De Vivo DC (2008) Pulmonary artery hypertension in a child with MELAS due to a point mutation of the mitochondrial tRNA (Leu) gene (m.3243A>G). *J Inherit Metab Dis* (Epub ahead of print)
- Sun F, Cui J, Gavras H, Schwartz F (2003) A novel class of tests for the detection of mitochondrial DNA mutation involvement in diseases. *Am J Hum Genet* 72(6):1515–1526
- Thorburn DR (2004) Mitochondrial disorders: prevalence, myths and advances. *J Inherit Metab Dis* 27(3):349–362
- Wilkins K, Campbell N, Joffres M, McAlister F, Nichol M, Quach S, Johansen H, Tremblay M (2010) Blood pressure in Canadian adults. Statistics Canada, Catalogue no. 82-003-XPE • Health Reports. March 2010: Vol. 21, no. 1
- Yatsuga S, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T, Kakuma T, Koga Y (2012) MELAS: A nationwide prospective cohort study of 96 patients in Japan. *Biochim Biophys Acta* 1820(5):619–624