A Supplementary Materials

Mitochondrial Diabetes Mellitus: Real World Insights from the GENOMIT Registry
- a multinational, longitudinal cohort study.

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eTable 1. Study population characteristics in the subgroup of patients with the m.3243A>G genotype

Parameter	m.3243A>G mDM	m.3243A>G non mDM	m.3243A>G total cohort	Adjusted p value
Count [n]	177	183	360	
Age [yr]	57.4 (47.4-63.8)	43.1 (29.95-53.25)	50.8 (37.8-60.8)	<0.0001
Height [cm]	165 (158-169)	165 (158-172)	165 (158-170)	1.0
Weight [kg]	55 (48.12-65.88)	54 (48-65)	54 (48-65)	1.0
BMI [kg/m²]	20.68 (18.7-23.37)	19.93 (18.03-23.34)	20.11 (18.23-23.39)	1.0
HbA1c [%]	7.1 (6.5-7.2)	5.3 (5.1-5.5)	6.5 (5.62-7.1)	<0.0001
NMDAS [points]	19 (12-28)	11 (5-18.5)	15 (10-26)	<0.0001
SARA [points]	3 (1-8)	2 (0-5.12)	2 (0-7)	1.0
Heteroplasmy in blood of m.3243A>G diabetes [%]	60.02 (44.86-97.99)	46.19 (22.7-86.91)	57.53 (30.28-90.48)	0.062
Age of PMD onset [years]	27.8 (19.7-41.1)	23.3 (13.4-37.2)	25.3 (16.85-39.73)	0.027
Time of follow-up [years]	3.27 (1.6-6.04)	2.8 (1.52-4.61)	3.01 (1.54-5.6)	1.0
Deaths [n (%)]	15 (8.5)	12 (6.6)	27 (7.5)	1.0
Mortality Rate [Deaths per 1,000 person years]	33.8	39.93	36.27	
Sex [n (%)]				0.44
female	117 (66.1%)	113 (61.7%)	230 (63.9%)	
male	60 (33.9%)	70 (38.3%)	130 (36.1%)	
Race [n (%)]				0.52
White European descent	147 (96.1%)	142 (94.7%)	289 (95.4%)	
other	0 (0%)	1 (0.7%)	1 (0.3%)	
Asian (other)	1 (0.7%)	3 (2.0%)	4 (1.3%)	
Multi-racial	1 (0.7%)	2 (1.3%)	3 (1.0%)	
Hispanic	1 (0.7%)	0 (0%)	1 (0.3%)	
Native American	2 (1.3%)	0 (0%)	2 (0.7%)	
Black (African)	1 (0.7%)	2 (1.3%)	3 (1.0%)	
Education [n (%)]				0.07
ISCED 1 - primary education	0 (0%)	4 (5.4%)	4 (2.8%)	
ICSED 2 - lower seconday education	10 (14.1%)	10 (13.5%)	20 (13.8%)	
ISCED 3 - upper secondary education	23 (32.4%)	24 (32.4%)	47 (32.4%)	
ISCED 4 - post-secondary non-tertiary education	13 (18.3%)	10 (13.5%)	23 (15.9%)	
ISCED 5 - short-cycle tertiary education	5 (7.0%)	6 (8.1%)	11 (7.6%)	
ISCED 6 - Bachelor or equivalent	18 (25.4%)	9 (12.2%)	27 (18.6%)	
ISCED 7 - Master or equivalent	1 (1.4%)	5 (6.8%)	6 (4.1%)	
ISCED 8 - Doctoral or equivalent	1 (1.4%)	2 (2.7%)	3 (2.1%)	
ISCED 9 - not elsewhere classified	0 (0%)	0 (0%)	0 (0%)	
Diet [n (%)]				0.02
no diet (normal nutrition)	63 (72.4%)	70 (89.7%)	133 (80.6%)	
other	5 (5.7%)	1 (1.3%)	6 (3.6%)	
vegetarian	0 (0%)	0 (0%)	0 (0%)	
mediterranean	17 (19.5%)	6 (7.7%)	23 (13.9%)	
low protein	2 (2.3%)	0 (0%)	2 (1.2%)	

low fat	0 (0%)	1 (1.3%)	1 (0.6%)	
Smoking [n (%)]				0.22
no	97 (85.8%)	93 (80.9%)	190 (83.3%)	
current smoker	6 (5.3%)	14 (12.2%)	20 (8.8%)	
former smoker	9 (8.0%)	6 (5.2%)	15 (6.6%)	
occasional smoker	1 (0.9%)	2 (1.7%)	3 (1.3%)	
Alcohol [n (%)]				0.71
no	72 (83.7%)	66 (81.5%)	138 (82.6%)	
yes, daily	1 (1.2%)	0 (0%)	1 (0.6%)	
yes, weekly	2 (2.3%)	4 (4.9%)	6 (3.6%)	
yes, occasionally	11 (12.8%)	11 (13.6%)	22 (13.2%)	

Study population characteristics in the subgroup of patients with the m.3243A>G genotype, stratified by mDM status. We excluded n = 17 patients with impaired glucose tolerance (IGT) and/or transient mDM to avoid misclassification bias in both the mDM and control groups. Continuous variables are presented as median (IQR) and categorical variables as number (%). Differences between groups were assessed using the Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and Fisher's exact test for categorical variables. Patients with the m.3243A>G genotype and mDM were significantly older, had a higher HbA1c, and scored higher on the NMDAS compared to those with the m.3243A>G genotype without mDM. Levels of education and diet also differed significantly between the two groups. Abbreviations: BMI: body mass index, HbA1c: glycated haemoglobin, ISCED: International standard classification of education, mDM: mitochondrial diabetes mellitus, NMDAS: Newcastle Mitochondrial Disease Adult Scale, SARA: Scale for the Assessment and Rating of Ataxia

eTable 2. Differences between Italian and German mDM population

Parameter	Italian	German	Adjusted p value
Count [n]	160	121	
Age [yr]	58.2 (47.83-67.58)	57.7 (45.7-67.2)	1.0
Height [cm]	165 (158-169.5)	168 (161-173.25)	0.034
Weight [kg]	54 (49-65.5)	65 (53.72-79.25)	0.00077
BMI [kg/m²]	21.09 (18.73-23.48)	23.02 (19.25-27.82)	0.042
Underweight (BMI < 18.5 kg/m^2) [n (%)]	20 (20 %)	21 (18%)	
Normal (BMI: 18.5-24.9 kg/m^2)	64 (65%)	53 (44%)	
Overweight (BMI: 25.0-29.9 kg/m^2)	11 (11%)	25 (21%)	
Obesity (BMI ≥ 30 kg/m^2)	4 (4%)	21 (18%)	
HbA1c [%]	NA (NA-NA)	6.95 (6.5-7.35)	NA
NMDAS [points]	19.5 (12-28.25)	18 (12-30)	1.0
SARA [points]	6.5 (4.75-10)	2 (0.12-7)	1.0
Heteroplasmy in blood of m.3243A>G diabetes [%]	55.17 (42.1-80.48)	75.95 (50.2-113.33)	1.0
Age of PMD onset [years]	28.05 (19.4-45.27)	27.8 (16.3-46.95)	1.0
Time of follow-up [years]	3.37 (1.53-4.63)	3.25 (1.89-6.72)	1.0
Deaths [n (%)]	16 (10)	4 (3.3)	0.34
Mortality Rate [Deaths per 1,000 person years]	49.7	11.61	
Sex [n (%)]			0.46
female	101 (63.1%)	71 (58.7%)	
male	59 (36.9%)	50 (41.3%)	
Race [n (%)]			0.032
White European descent	125 (96.2%)	115 (95.8%)	
other	0 (0%)	1 (0.8%)	
Asian (other)	0 (0%)	3 (2.5%)	
Multi-racial	0 (0%)	1 (0.8%)	
Hispanic	1 (0.8%)	0 (0%)	
Native American	3 (2.3%)	0 (0%)	
Black (African)	1 (0.8%)	0 (0%)	
Education [n (%)]			0.0034
ISCED 1 - primary education	2 (2.9%)	1 (2.0%)	
ICSED 2 - lower seconday education	14 (20.6%)	7 (14.3%)	
ISCED 3 - upper secondary education	25 (36.8%)	9 (18.4%)	
ISCED 4 - post-secondary non-tertiary education	5 (7.4%)	15 (30.6%)	
ISCED 5 - short-cycle tertiary education	4 (5.9%)	6 (12.2%)	
ISCED 6 - Bachelor or equivalent	17 (25.0%)	8 (16.3%)	
ISCED 7 - Master or equivalent	1 (1.5%)	0 (0%)	
ISCED 8 - Doctoral or equivalent	0 (0%)	2 (4.1%)	
ISCED 9 - not elsewhere classified	0 (0%)	1 (2.0%)	
Diet [n (%)]			0.0001
no diet (normal nutrition)	51 (63.0%)	50 (86.2%)	

other	3 (3.7%)	7 (12.1%)	
vegetarian	0 (0%)	1 (1.7%)	
mediterranean	24 (29.6%)	0 (0%)	
low protein	2 (2.5%)	0 (0%)	
low fat	1 (1.2%)	0 (0%)	
Smoking [n (%)]			0.63654
no	71 (85.5%)	94 (84.7%)	
current smoker	3 (3.6%)	8 (7.2%)	
former smoker	7 (8.4%)	8 (7.2%)	
occasional smoker	2 (2.4%)	1 (0.9%)	
Alcohol [n (%)]			0.0002
no	75 (94.9%)	38 (64.4%)	
yes, daily	0 (0%)	2 (3.4%)	
yes, weekly	0 (0%)	3 (5.1%)	
yes, occasionally	4 (5.1%)	16 (27.1%)	

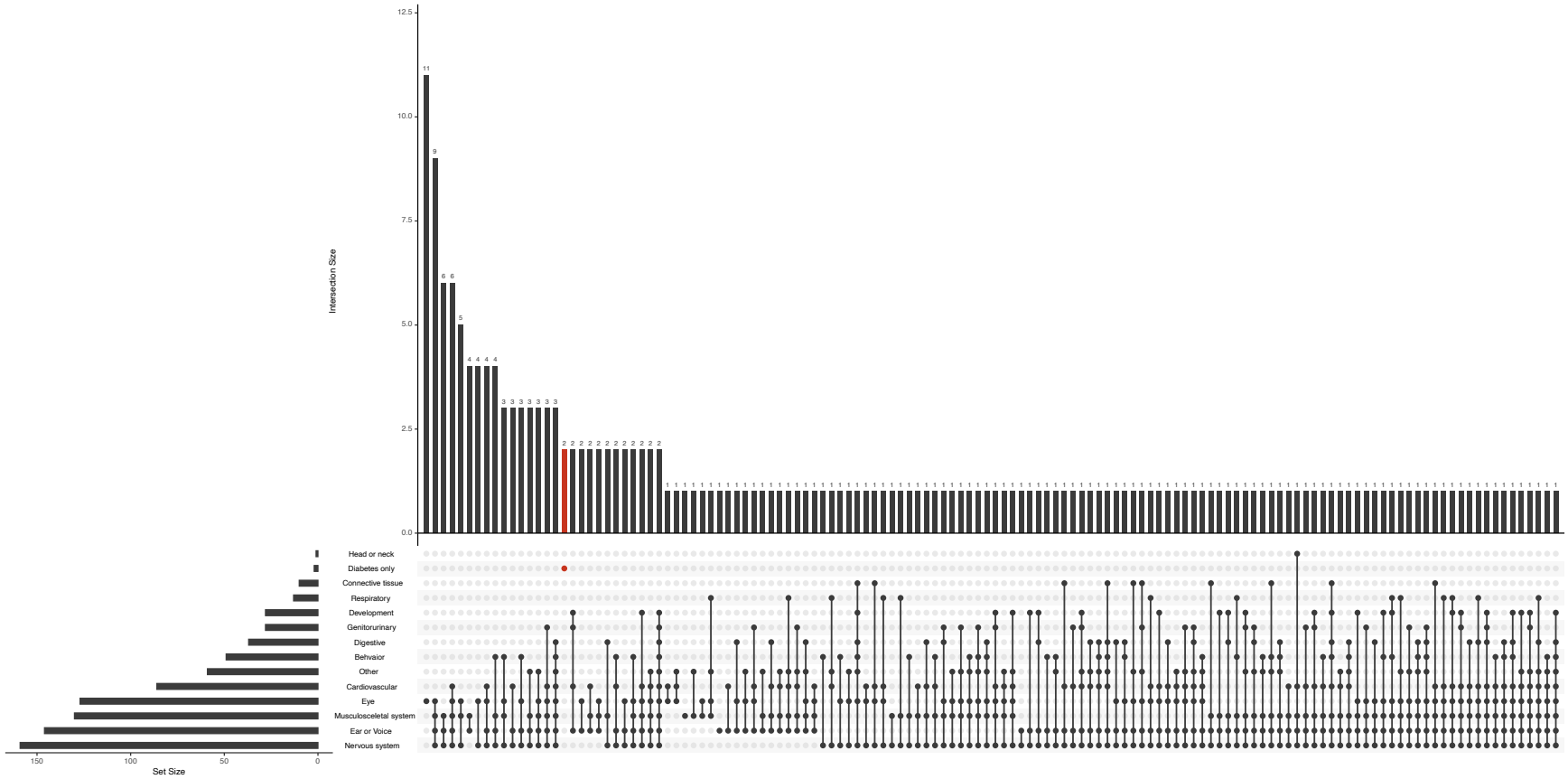
Descriptive analysis for continuous and categorical variables separately for the Italian, and German study populations. Continuous variables are given in median (IQR), categorical variables in number (%). Differences between the groups were assessed using Wilcoxon rank-sum test (Mann-Whitney) for continuous variables and Fisher exact test. German patients with mDM were significantly taller, had a higher body weight, and an increased BMI compared to the Italian mDM population; further differences occurred in race distribution, education level, dietary regimens, and alcohol consumption. Abbreviations: BMI: body mass index, HbA1c: glycated haemoglobin, ISCED: International standard classification of education, mDM: mitochondrial diabetes mellitus, NMDAS: Newcastle Mitochondrial Disease Adult Scale, SARA: Scale for the Assessment and Rating of Ataxia.

eTable 3. Distinct genotypes associated with mDM

Genotype	Frequency, No. (%)
ETFDH	1 (0.4)
m.11778 G>A	8 (2.9)
m.14258G>A; m.14582A>G	1 (0.4)
m.14484 T>C	3 (1.1)
m.14709 T>C	2 (0.7)
m.3243 A>G	177 (63.0)
m.3243 A>T	1 (0.4)
m.3248 G>A	1 (0.4)
m.3255A>G	1 (0.4)
m.3260A>G	1 (0.4)
m.3302 A>G	1 (0.4)
m.3460 G>A	2 (0.7)
m.3697 G>A	1 (0.4)
m.7471insC	1 (0.4)
m.8344 A>G	5 (1.8)
m.8363 G>A	1 (0.4)
m.8364 G>A	1 (0.4)
m.8782 G>A	1 (0.4)
m.8993 T>C	1 (0.4)
m.9049G>A; m.14724G>A	1 (0.4)
m.9176 C>T	1 (0.4)
m.9176T>C	1 (0.4)
m.9334 T>C	1 (0.4)
multiple mtDNA deletions	11 (3.9)
OPA1	5 (1.8)
POLG	6 (2.1)
single mtDNA deletion	40 (14.2)
SLC25A4	1 (0.4)

Genotype	Frequency, No. (%)
TK2	1 (0.4)
TWNK	1 (0.4)
TYMP	2 (0.7)

eFigure 1. Affected organ systems in mDM patients and their interactions



UpSet plot visualizing intersections between different organ involvements of mDM patients. Each column in the matrix represents a unique combination of sets (intersection), with black dots indicating membership. The horizontal bar chart on top shows the number of occurrences of the respective organ involvement intersections; the vertical bar chart on the left shows the total size of each set. Most frequently, large intersections with multiple affected organ systems were present. Only in two patients, diabetes was an isolated symptom without other organs being affected.

eFigure 2. Time between MD onset and mDM onset stratified by genotype

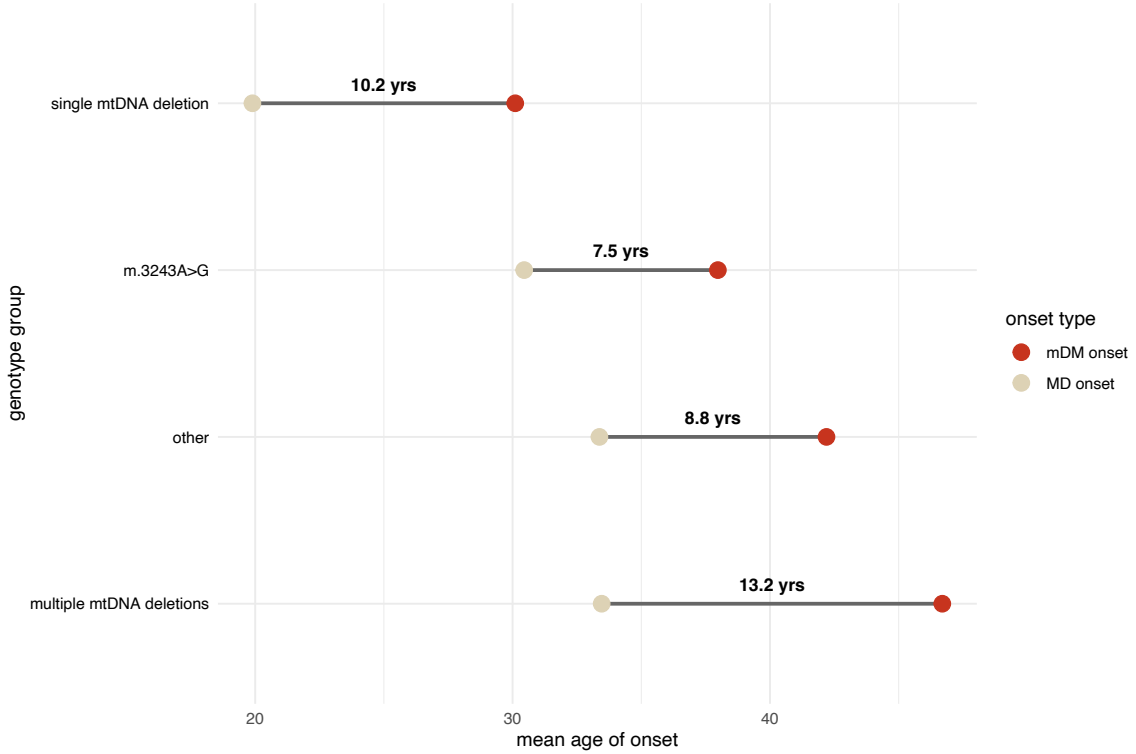
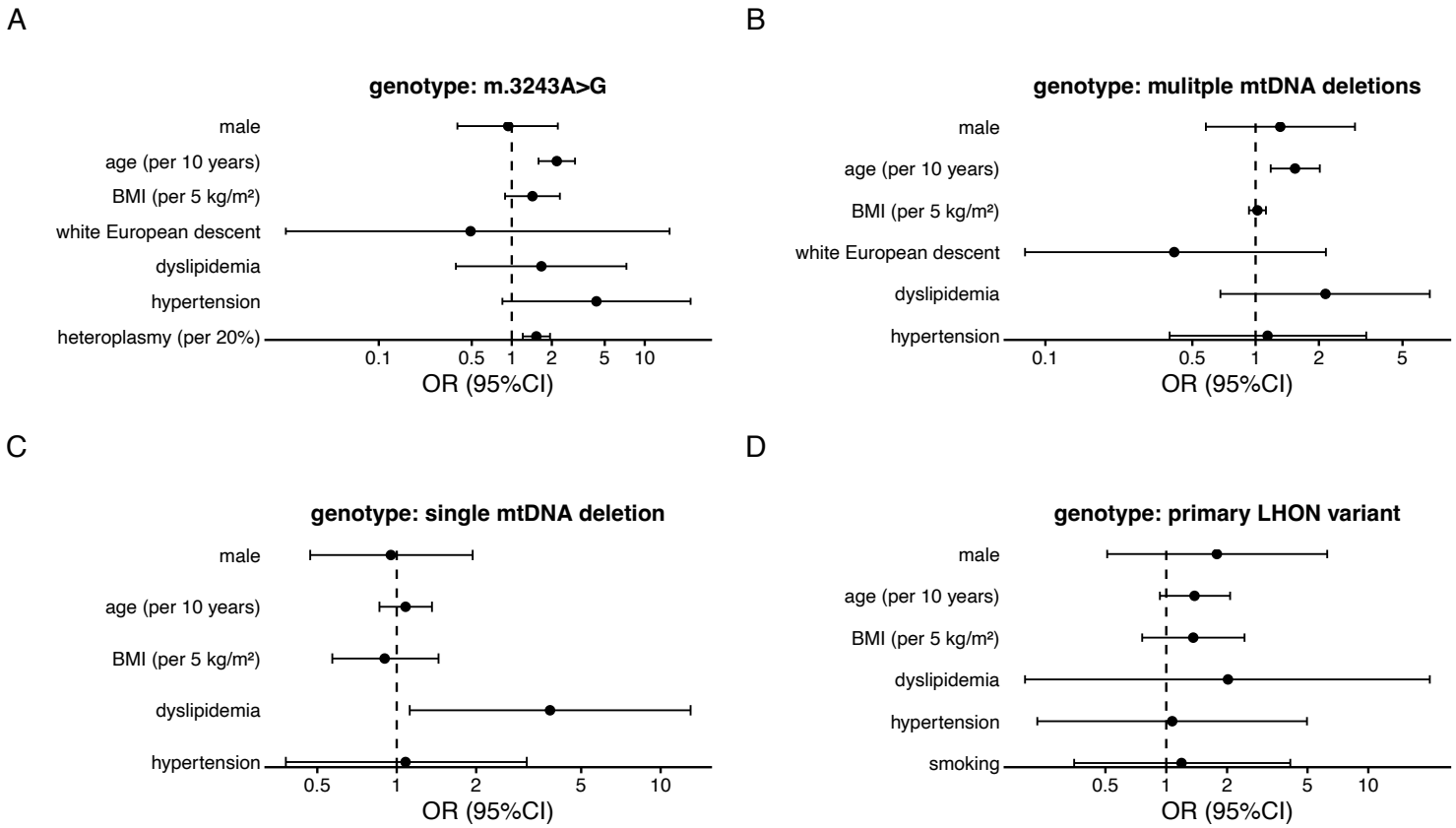


Chart displaying the time difference between mDM onset (red) and MD (sand) onset per genotype. The line between the points indicates the time difference in years; calculations were performed on an individual level and summarized before plotting. mDM occurred on average 8.5 years after the diagnosis of MD. This time varied depending on the genotype from 7.5 years in the m.3243A>G to 13.2 years in the multiple mtDNA deletion group.
mDM: mitochondrial diabetes mellitus, MD: mitochondrial disease.

eFigure 3. Multiple logistic regression analyses on the risk of developing mDM within each genotype group



Forest plots of the multivariable logistic regressions performed to assess the association between the onset of mDM and the genotypes A m.3243A>G (n = 176), B multiple mtDNA deletions (n = 392), C single mtDNA deletion (n = 272), and D primary LHON variants (n = 420). The models were adjusted for age, sex, BMI, dyslipidemia, and hypertension; as well as model A for the age-corrected blood heteroplasmy level and model D for smoking. OR with 95% CI are shown for each predictor. Reference categories: genotype = other, sex = female; race = non-white, dyslipidemia = no dyslipidemia, hypertension = no hypertension, smoking = no smoking. Analysis was conducted in R using the glm() function with binomial family on imputed datasets. Abbreviations: CI: confidence interval, mDM: mitochondrial diabetes mellitus, OR: Odds ratio.

eTable 4. Multiple logistic regression analyses on the occurrence of mDM within the respective genotype groups

	A **m.3243A>G** Nagelkerle R^2 = 0.43, AUC = 0.83, p <0.0001, Hosmer-Lemeshow p=0.30		**B** **multiple mtDNA deletions** Nagelkerle R^2 = 0.10, AUC = 0.75, p =0.012, Hosmer-Lemeshow p=0.008		**C** **Single mtDNA deletion** Nagelkerle R^2 = 0.037, AUC = 0.59, p =0.33, Hosmer-Lemeshow p=0.59		**D** **Primary LHON variant** Nagelkerle R^2 = 0.073, AUC = 0.73, p =0.28, Hosmer-Lemeshow p=0.35	
Parameter	**Odds ratio (95%CI)**	**P value**	**Odds ratio (95%CI)**	**P value**	**Odds ratio (95%CI)**	**P value**	**Odds ratio (95%CI)**	**P value**
Intercept	0.00 (0.00–0.14)	0.0038	0.01 (0.00–0.07)	<0.0001	0.17 (0.03–1.04)	0.055	0.00 (0.00–0.04)	0.00041
Male	0.94 (0.39–2.22)	0.88	1.31 (0.58–2.97)	0.52	0.95 (0.47–1.94)	0.90	1.78 (0.51–6.26)	0.37
Age (per 10 years)	2.18 (1.59–2.99)	<0.0001	1.54 (1.18–2.02)	0.002	1.08 (0.86–1.36)	0.51	1.38 (0.93–2.07)	0.11
BMI (per 5kg/m2)	1.43 (0.89–2.30)	0.14	1.02 (0.93–1.12)	0.63	0.90 (0.57–1.44)	0.66	1.36 (0.76–2.43)	0.3
White European descent	0.49 (0.02–15.37)	0.67	0.41 (0.08–2.16)	0.29	NA	NA	NA	NA
Dyslipidemia	1.67 (0.38–7.28)	0.49	2.15 (0.68–6.74)	0.19	3.81 (1.12–12.99)	0.033	2.02 (0.20–20.15)	0.55
Hypertension	4.33 (0.85–22.12)	0.078	1.14 (0.39–3.36)	0.81	1.08 (0.38–3.11)	0.88	1.07 (0.23–4.97)	0.94
Heteroplasmy (per 20%)	1.53 (1.21–1.94)	0.0005	NA	NA	NA	NA	NA	NA
Smoking	NA	NA	NA	NA	NA	NA	1.19 (0.35–4.11)	0.78

Numeric values of the multivariable logistic regression (forest plots shown in eFigure3) between the onset of mDM and the genotypes A m.3243A>G (n = 176), B multiple mtDNA deletions (n = 392), C single mtDNA deletion (n = 272), and D primary LHON variants (n = 420). The models were adjusted for age, sex, BMI, dyslipidemia, and hypertension; as well as model A for the age-corrected blood heteroplasmy level and model D for smoking. OR with 95% CI are shown for each predictor. P values indicate statistical significance ($p<0.05$).

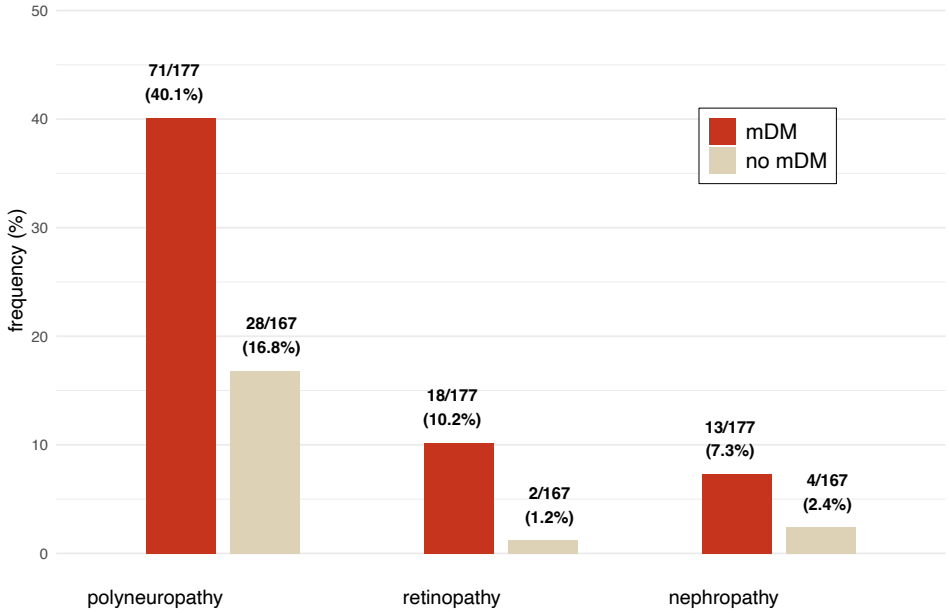
eTable 5. Imputed versus non-imputed data

Cox proportional hazard model **Full imputed dataset: n = 1162, Complete cases: n = 788**				
Variable	**HR (95% CI) - Imputed**	**HR (95% CI) - Complete case**	**p - Imputed**	**p - Complete case**
m.3243A>G	10.31 (5.22–20.36)	10.13 (5.17–19.86)	<0.0001	<0.0001
multiple mtDNA deletions	1.25 (0.50–3.17)	1.23 (0.49–3.08)	0.63	0.66
single mtDNA deletion	1.50 (0.65–3.46)	1.48 (0.65–3.37)	0.33	0.35
primary LHON variant	0.67 (0.24–1.90)	0.66 (0.24–1.85)	0.45	0.43
Male sex	0.82 (0.55–1.22)	0.83 (0.56–1.24)	0.32	0.37
BMI (per 5 kg/m²)	1.02 (0.97–1.07)	1.02 (0.97–1.07)	0.52	0.52
White European descent	1.30 (0.40–4.25)	1.31 (0.41–4.23)	0.66	0.65
Dyslipidemia	1.74 (0.91–3.31)	1.72 (0.91–3.25)	0.092	0.095
Hypertension	1.39 (0.88–2.20)	1.39 (0.88–2.19)	0.16	0.15
Smoking	0.86 (0.47–1.57)	0.86 (0.47–1.57)	0.63	0.63
Logistic regression m.3243A>G **Full imputed dataset: n = 176, Complete cases: n = 119**				
Variable	**OR (95% CI) - Imputed**	**OR (95% CI) - Complete case**	**p - Imputed**	**p - Complete case**
Male sex	0.94 (0.39–2.22)	0.56 (0.20–1.55)	0.88	0.27
Age (per 10 years)	2.18 (1.59–2.99)	2.34 (1.60–3.71)	<0.0001	<0.0001
BMI (per 5 kg/m²)	1.43 (0.89–2.30)	1.46 (0.87–2.55)	0.14	0.16
White European descent	0.49 (0.02–15.37)	0.40 (0.02–5.46)	0.67	0.49
Dyslipidemia	1.67 (0.38–7.28)	5.34 (0.97–42.91)	0.49	0.071
Hypertension	4.33 (0.85–22.12)	8.35 (1.25–170.23)	0.078	0.064
Heteroplasmy (per 20%)	1.53 (1.21–1.94)	1.58 (1.23–2.15)	0.00050	0.0012
Logistic regression multiple mtDNA deletions **Full imputed dataset: n = 392, Complete cases: n = 223**				
Variable	**OR (95% CI) - Imputed**	**OR (95% CI) - Complete case**	**p - Imputed**	**p - Complete case**
Male sex	1.31 (0.58–2.97)	0.97 (0.38–2.44)	0.52	0.95
Age (per 10 years)	1.54 (1.18–2.02)	1.43 (1.10–1.91)	0.0017	0.011
BMI (per 5 kg/m²)	1.02 (0.93–1.12)	1.00 (NA–1.08)	0.63	0.96
White European descent	0.41 (0.08–2.16)	0.46 (0.10–3.30)	0.29	0.36
Dyslipidemia	2.15 (0.68–6.74)	3.51 (0.92–12.23)	0.19	0.053
Hypertension	1.14 (0.39–3.36)	0.81 (0.21–2.63)	0.81	0.74
Logistic regression single mtDNA deletion **Full imputed dataset: n = 272, Complete cases: n = 223**				
Variable	**OR (95% CI) - Imputed**	**OR (95% CI) - Complete case**	**p - Imputed**	**p - Complete case**
Male sex	0.95 (0.47–1.94)	1.13 (0.49–2.53)	0.90	0.77
Age (per 10 years)	1.08 (0.86–1.36)	1.27 (0.99–1.65)	0.51	0.068
BMI (per 5 kg/m²)	0.90 (0.57–1.44)	0.94 (0.62–1.36)	0.66	0.75
Dyslipidemia	3.81 (1.12–12.99)	2.76 (0.54–11.71)	0.033	0.18
Hypertension	1.08 (0.38–3.11)	0.50 (0.11–1.71)	0.88	0.32

Logistic regression primary LHON variant **Full imputed dataset: n = 420, Complete cases: n = 268**				
Variable	**OR (95% CI) - Imputed**	**OR (95% CI) - Complete case**	**p - Imputed**	**p - Complete case**
Male sex	1.78 (0.51–6.26)	2.29 (0.56–11.88)	0.37	0.27
Age (per 10 years)	1.38 (0.93–2.07)	1.69 (1.03–2.89)	0.11	0.042
BMI (per 5 kg/m²)	1.36 (0.76–2.44)	1.41 (0.75–2.43)	0.30	0.24
Dyslipidemia	2.02 (0.20–20.15)	0.00 (NA-3809299037083526738766865435312260848605617936185021072690553353666 56.00)	0.55	0.99
Hypertension	1.07 (0.23–4.97)	1.18 (0.20–5.70)	0.94	0.84
Smoking	1.19 (0.35–4.11)	1.57 (0.41–6.02)	0.78	0.50

Presentation of imputed versus non-imputed datasets used for the Cox-proportional hazards model as well as the logistic regressions within the genotype groups m.3243 A>G, multiple mtDNA deletions, single mtDNA deletion, and primary LHON variants. Multiple imputation by chained equations (R package *mice*) was used resulting in 5 imputed datasets; estimates from imputed datasets were pooled using Rubin rules. OR as well as p values (p) are given separately for imputed and non-imputed (complete cases). In the single mtDNA deletion group, dyslipidemia was significantly associated with mDM in the multiply imputed dataset (OR: 3.81; 95% CI, 1.12-12.99; p=0.033) but not in complete-case analysis (p=0.18). Abbreviations: BMI: body mass index, CI: confidence interval, HR: hazard ratio, OR: odds ratio.

eFigure 4. Polyneuro-, retino-, and nephropathy in m.3243A>G patients with mDM compared to those without mDM



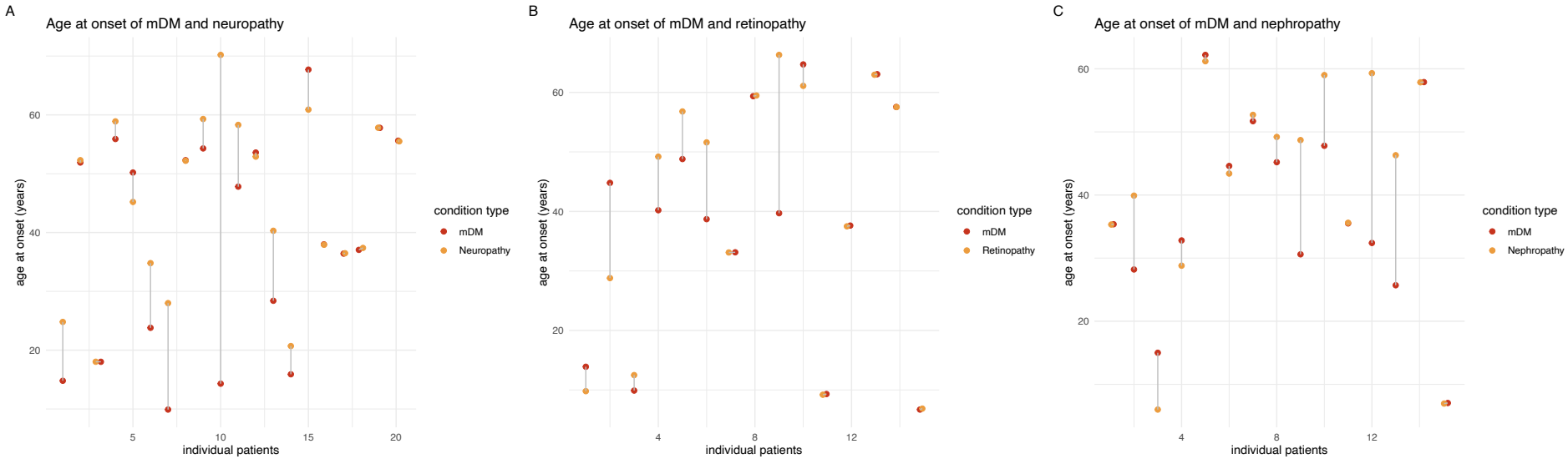
Bar plot indicating the number of mDM patients (red) and non-mDM patients (sand) with the m.3243A>G variant who have polyneuropathy, retinopathy, or nephropathy. The total amount of occurrences within each group is given above the bar along with the respective percentage. Abbreviations: mDM: mitochondrial diabetes mellitus

eTable 6. Logistic regression on the relevance of mDM status for having complications such as polyneuro-, retino-, and nephropathy

Logistic regression on the occurrence of complications within the m.3243A>G genotype group.	Odds Ratio (95%CI)	p value
mDM presence	3.72 (1.64 to 8.44)	0.0019

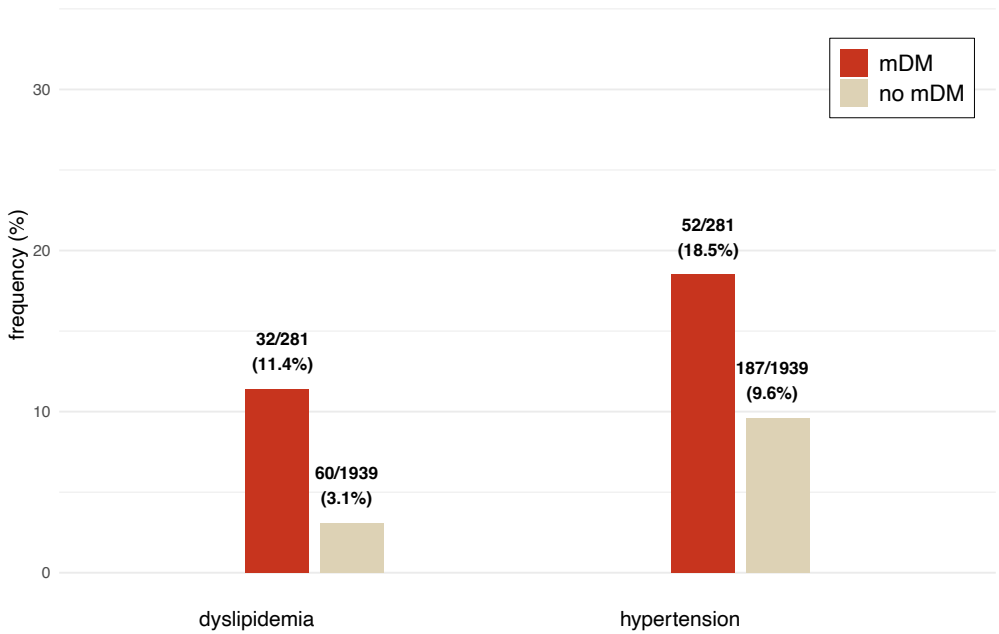
The logistic regression was performed on the imputed m.3243A>G dataset, as indicated in the flowchart eFigure 1. Complication (Polyneuropathy, Nephropathy, and Retinopathy) was used as the dependent variable of interest, whereas the presence of mDM was used as the independent variable; the model was controlled for the covariates sex, age, BMI, dyslipidemia, hypertension, and the age-corrected heteroplasmy level in blood. mDM presence was significantly associated with the occurrence of complications (OR: 3.72 (1.64 to 8.44), p=0.0019) Abbreviations: BMI: body mass index, CI: confidence interval, mDM: mitochondrial diabetes mellitus, OR: odds ratio.

eFigure 5. Occurrence of mDM and complication diagnosis



Presentation of the time between mDM onset and the respective complication A polyneuropathy, B retinopathy, or C nephropathy. The orange dots represent onset of polyneuropathy in A, retinopathy in B, and nephropathy in C, while the red dots represent mDM onset in all charts. The line between the points indicate the time difference in years; calculations were performed on an individual level and results are displayed for all patients with both time points available, irrespective of the underlying genotype. Abbreviations: mDM: mitochondrial diabetes mellitus.

eFigure 6. Prevalence of cardiovascular risk factors dyslipidemia and hypertension in mDM and non-mDM patients



Bar plot indicating the number of mDM patients (red) and non-mDM patients (sand) with the m.3243A>G variant who have dyslipidemia, or hypertension. The total amount of occurrences within each group is given above the bar along with the respective percentage. Abbreviations: mDM: mitochondrial diabetes mellitus.

eTable 7. Logistic regression analysis on the influence of mDM presence on the likelihood of having hypertension in m.3243A>G patients

Logistic regression on the occurrence of hypertension within the m.3243A>G genotype group.	Odds Ratio (95%CI)	p value
mDM presence	5.42 (1.08 to 27.21)	0.040

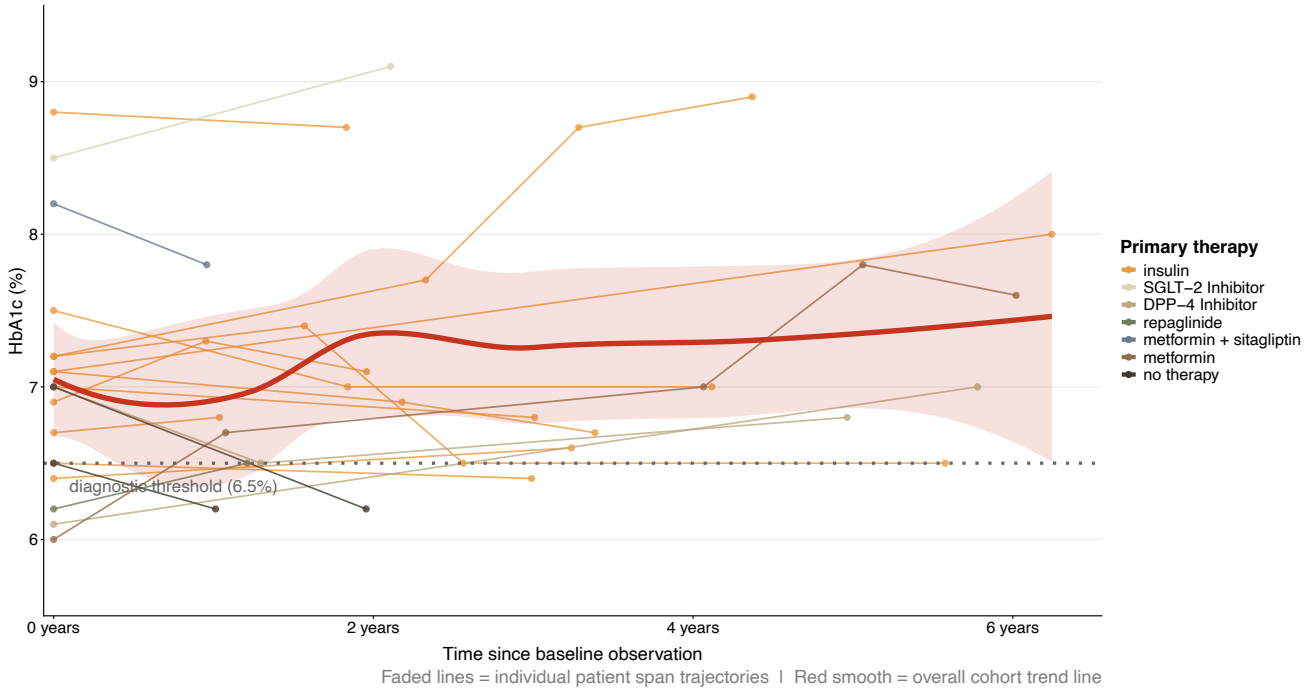
The logistic regression was performed on the imputed m.3243A>G dataset, as indicated in the flowchart eFigure 1. Hypertension was used as the dependent variable of interest, whereas the presence of mDM was used as the independent variable; the model was controlled for the covariates sex, age, BMI, dyslipidemia, and the age-corrected heteroplasmy level in blood. mDM presence was significantly associated with the occurrence of complications (OR: 5.42 (1.08 to 27.21), p=0.040) Abbreviations: BMI: body mass index, CI: confidence interval, mDM: mitochondrial diabetes mellitus, OR: odds ratio.

eTable 8. Logistic regression analysis on the influence of mDM presence on the likelihood of having dyslipidemia in m.3243A>G patients

Logistic regression on the occurrence of dyslipidemia within the m.3243A>G genotype group.	Odds Ratio (95%CI)	p value
mDM presence	1.65 (0.47 to 6.56)	0.47

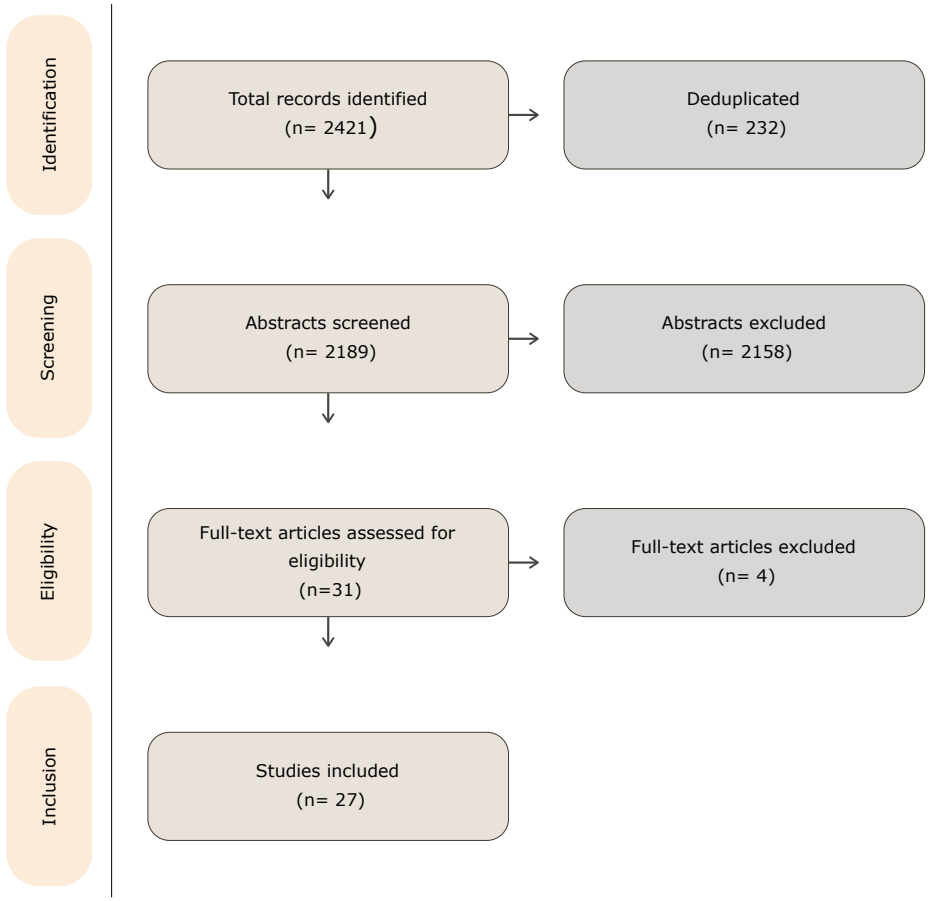
The logistic regression was performed on the imputed m.3243A>G dataset, as indicated in the flowchart eFigure 1. Dyslipidemia was used as the dependent variable of interest, whereas the presence of mDM was used as the independent variable; the model was controlled for the covariates sex, age, BMI, hypertension, and the age-corrected heteroplasmy level in blood. The presence of mDM was not significantly associated with the occurrence of dyslipidemia. Abbreviations: BMI: body mass index, CI: confidence interval, mDM: mitochondrial diabetes mellitus, OR: odds ratio.

eFigure 7. Longitudinal HbA1c Trajectories Relative to Baseline Measurement to display long-term glycemic control



HbA1c measurements over time for individual patients for whom at least two timepoints of measurement were available. The y-axis is showing HbA1c in percent, and the x-axis showing date (individually anchored to initial evaluation as year 0). Points represent HbA1c measurements, colored by primary therapy type. Data include n = 19 patients with n = 45 total HbA1c measurements. Longitudinal data span up to 6.2 years. A LOESS smoothing curve is overlaid to visualize the overall trend in HbA1c over time ranging from 6.9% to 7.5%.

eFigure 8. PRISMA flow chart summarizing the results of the literature search on antidiabetic drug usage in MD patients



PRISMA flow chart indicating the number of identified total records, deduplicated and excluded abstracts as well as full-text articles. As a result, the total number (n = 27) of included studies is given.

eTable 9. Results of the literature review on antidiabetic drug usage in MD patients

Publication (Author, Year)	Study population	Treatment	Key points of clinical presentation/outcome
Shin 2024[2]	• 32-year-old Korean patient with m.3243A>G and MELAS	• Sulfonylurea • Metformin • DPP4-inhibitor	• poor glycemic control under gliclazide → switch to metformin • after metformin start → Lactic acidosis, progression of focal seizures into refractory status epilepticus, occurrence of dysphagia and progressive multifocal lesions on MRI • switch from metformin to gemigliptin → symptoms subsided
Seo 2024[3]	• Patient 1: 48-year-old woman with m.3243A>G and MIDD • Patient 2: 21-year-old man with m.3243A>G and MIDD	• Insulin • DPP-4-inhibitor • Sulfonylurea • Metformin	• patient 1: poor glycemic control with insulin and oral hypoglycemic agents due to incompliance • patient 2: initially good glycemic control on DPP4-inhibitor, sulfonylurea and metformin, 6 years later insufficient glycemic control → additional insulin usage necessary
Tran 2023[4]	• 36-year-old woman with m.3243A>G and MELAS	• Insulin • DPP-4-inhibitor	• good glycemic control on insulin and DPP-4 inhibitor • ongoing SLEs, increased seizure activity and rapid decline in consciousness, hearing capacity, and visual acuity after mDM diagnosis
Murakami 2023[5]	• 40-year-old man with m.3243A>G and MELAS	• DPP-4-inhibitor • Metformin • SGLT2-inhibitor	• 4 months after metformin start presumably first stroke-like lesion • switch from metformin to DPP4-inhibitor and SGLT2-inhibitor
Simoes de Carvalho 2023[6]	• Patient 1: 50-year-old male m.3243A>G and MIDD • Patient 2: 56-year-old male with m.9325T>C and MIDD	• Insulin • DPP-4-inhibitor	• patient 1: 17 years insulin and DPP-4-inhibitor therapy → insufficient glycemic control → additional ultra-rapid insulin → good glycemic control • patient 2: 16 years basal-bolus regimens of insulin → insufficient glycemic control → switch to fast-acting insulin and adaptation of bolus insulin → glucose profile improved
Tong 2022[7]	• 16 patients with m.3243A>G and mDM • One 53-year-old woman with m.3243A>G and mDM	• Metformin • Insulin • DPP-4-inhibitor	• 10/16 patients got metformin (60%) • 7 of those 10 patients developed newly neurologic manifestations • The OR was 3.50 [CI 0.37–33.0; p = 0.3287] and not significant • 53-year-old patient: drowsiness, involuntary twitching and abnormal movement occurred 1 month after starting of metformin → stopped after metformin cessation • 12 years satisfactory glycemic control on insulin and DPP-4-inhibitor
Lin 2022[8]	• 43-year-old man with m.3243A>G and MELAS	• DPP-4-inhibitor • Metformin	• 2 months after metformin and vildagliptin usage first stroke-like episode • switch from metformin and vildagliptin to linagliptin
Zhao 2022[9]	• 12 patients with various mtDNA variants and mitochondrial diabetes (11-50 years of age)	• Metformin • Insulin • GLP-1-agonist • SGLT-2-inhibitor • DPP4-inhibitor	• First visit (before diagnosis of PMD): Metformin was used in 3 patients, 7 needed insulin, in 1 case combined with a DPP4-inhibitor, and in 1 with sulfonylurea • Follow up (longest period was 16 years): 11 patients used insulin, in 6 cases combined with GLP1-agonist, SGLT2-inhibitors, or DPP4-inhibitors; metformin was not used anymore • No adverse events reported
Yeung 2021[10]	• Patient 1: 51-year-old man with m.3243A>G and MELAS • Patient 2: 32-year-old woman with m.3243A>G and MIDD • Patient 3: 72-year-old woman with m.3243A>G and MELAS	• Metformin • Sulfonylurea • SGLT2-inhibitor • DPP-4-inhibitor • GLP-1-agonist	• Patient 1: after development of SLE transition of metformin to SGLT2-inhibitor, sulfonylurea and DPP-4-inhibitor → suboptimal glycemic control → switch to GLP-1-agonist → HbA1c improved, no side effects • Patient 2: Metformin and sulfonylurea therapy → suboptimal glycemic control → switch to SGLT2-inhibitor→ HbA1c improved, no side effects • Patient 3: treated with metformin for 5 years without lactic acidosis → after development of SLE MD diagnosis and thus transition to sulfonylurea and DPP-4-inhibitor → insufficient glycemic control → switch to SGLT2-inhibitor and increase of DPP-4-Inhibitor dose → HbA1c improved, no side effects
Shin 2021[11]	• 48-year-old woman with m.3243A>G and MIDD	• Metformin • Insulin	• 9 years after mDM diagnosis insufficient glycemic control under oral hypoglycemic agents including metformin → transition to insulin

Lebbar 2021[12]	• 50-year-old female with m.3243A>G and MIDD	• Insulin • Metformin • GLP-1-agonist	• Insulin treatment → insufficient glycemic control → Metformin evoked gastrointestinal side effects → GLP-1-agonist in addition to insulin → HbA1c improved, no side effects
Kim 2020[13]	• 27-year-old man with m.3243A>G and MELAS	• Metformin • Sulfonylurea	• After 4 months usage of metformin → first SLE and seizure • Discharged with sulfonylurea
Chen 2019[14]	• 52-year-old woman with m.3243A>G and MELAS	• DPP-4-inhibitor • Sulfonylurea • Metformin	• 1 month after adding metformin to the pre-existing oral antidiabetic therapy with sitagliptin and glimepiride occurrence of first SLE and generalized tonic-clonic seizure
Keidai 2019[15]	• 72-year-old woman with m.3243A>G and mDM	• Insulin	• Insulin treatment for 30 years • Occurrence of diabetic ketoacidosis due to missed insulin injections during gastroenteritis • As diabetic ketoacidosis improved lactic acidosis developed → resolved after few days
Fukuda 2019[16]	• 55-year-old with m.3243A>G and MELAS	• Insulin • Sulfonylurea • DPP-4-inhibitor	• 1 year after mDM diagnosis (age 41) diabetic ketoacidosis occurred → treatment with insulin and sulfonylurea • 12 years later another episode of diabetic ketoacidosis combined with SLE → treatment complemented with DPP-4-inhibitor • 3 months later cessation of sulfonylurea → HbA1c worsened → increasing insulin dose → HbA1c improved
Gragera-Martinez 2017[17]	• 55-year-old woman with m.3243A>G and MIDD	• Metformin	• Metformin intake for 30 years • no neurological manifestation or acidotic decompensation reported
Murakami 2016[18]	• 24-year-old-woman with m.3243A>G and mDM	• Insulin • GLP-1-agonist	• Initial therapy with insulin → desire of patient to reduce daily injections → adding GLP-1-agonist and reducing daily insulin injections → good glycemic control, no adverse events
Ninomiya 2016[19]	• 45-year-old woman with m.3243A>G and MIDD	• Miglitol • Pioglitazone	• Initial diagnosis of gestational diabetes at 41 years of age → well controlled with diet • 4 years later progressive worsening of glycemic control → miglitol start → improved glycemic control, but side effect: diarrhea → pioglitazone, good glycemic control
Inoue 2016[20]	• 32-year-old Japanese male with m.14709T>C mutation, mDM and myopathy	• Insulin • Pyruvate	• Insulin-dependent mDM • Additional therapy with sodium-pyruvate → improved insulin secretion, lower insulin dosage per day was necessary • No side effects, however, therapy was terminated after 10 months (severe phenotype, could not self-administer therapy) • Insulin secretion decreased, HbA1c level increased after cessation
Naing 2014[21]	• 6 patients with m.3243A>G and MIDD (52-77 years of age)	• Sulfonylurea • Insulin • Metformin	• Index case: 77-year-old woman required insulin within 5 years of initial diagnosis of mDM • 5/6 patients were insulin-dependent • All patients have been treated with metformin at some stage of their disease, side effects were not reported
Donovan 2006[22]	• 44-yr-old woman with m.3243A>G and MIDD	• Sulfonylurea • Insulin	• Sulfonylurea poorly tolerated (no details given) → switch to insulin → insufficient glycemic control → start of continuous s.c. insulin infusion device → initially marked improvement, but deterioration again 1 year later
Laloi-Michelin 2006[23]	• 43-year-old woman with large mtDNA deletion and KSS	• Metformin • Sulfonylurea • Insulin	• mDM since the age of 19 years → therapy with metformin and sulfonylurea → insufficient glycemic control → switch to Insulin
Iwase 2001[24]	• 30-year-old female with m.3243A>G and MELAS	• Insulin	• Occurrence of post-treatment retinopathy due to strict glycemic control
Nakamura 1999[25]	• 24-year-old male with m.3243A>G and MIDD	• Insulin	• 1 year after mDM onset: non-ketotic hyperosmolar coma → start insulin → incompliant administration → nephrotic syndrome and insufficient glycemic control
Suzuki 1997[26]	• 15 subjects with m.3243A>G	• Insulin • Sulfonylurea	• 11/15 subjects were treated with coenzyme Q10 • 8 of them additionally received insulin, 2 were on diet therapy and 1 on sulfonylurea

		• Coenzym Q10	• No difference of plasma glucose or HbA1c before and after coenzyme Q10 treatment
Suzuki 1995[27]	• 3 patients with m.3243A>G and mDM (51-71 years of age)	• Insulin • Sulfonylurea	• 3 patients have developed leg edema after start of insulin therapy (acute and chronic, starting 1 month up to 2 years after insulin start) • In 2 patients, leg edema has resolved spontaneously, in one under additional coenzyme Q10 therapy • One patient developed hepatic dysfunction 20 days after start of sulfonylurea therapy
Katagiri 1994 / Oka 1995[28,29]	• Four pedigrees with m.3243A>G and mDM	• Insulin • Sulfonylurea	• 11/18 patients were treated with sulfonylurea → secondary failure with progression into insulin-dependence after 8 years at the latest

Abbreviations: BMI: body mass index, DPP-4: dipeptidyl peptidase 4, GLP-1: glucagon-like peptide 1, KSS: Kearns-Sayre syndrome, mDM mitochondrial diabetes mellitus, MELAS: mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, MIDD: maternally inherited diabetes and deafness, MD: mitochondrial disease, NMDAS: Newcastle Mitochondrial Disease Adult Scale, OR: odds ratio, SLE: stroke-like episode, SGLT-2: sodium-glucose cotransporter 2.

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