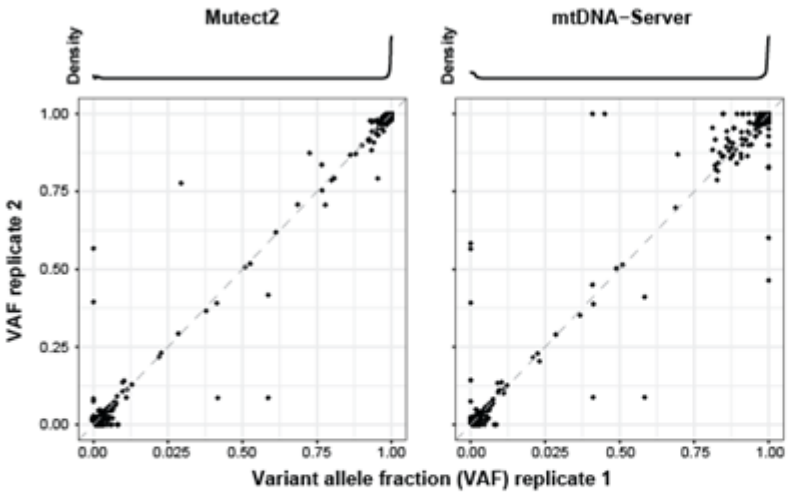
Supplemental Material

Mitochondrial DNA variation across 56,434 individuals in gnomAD

A



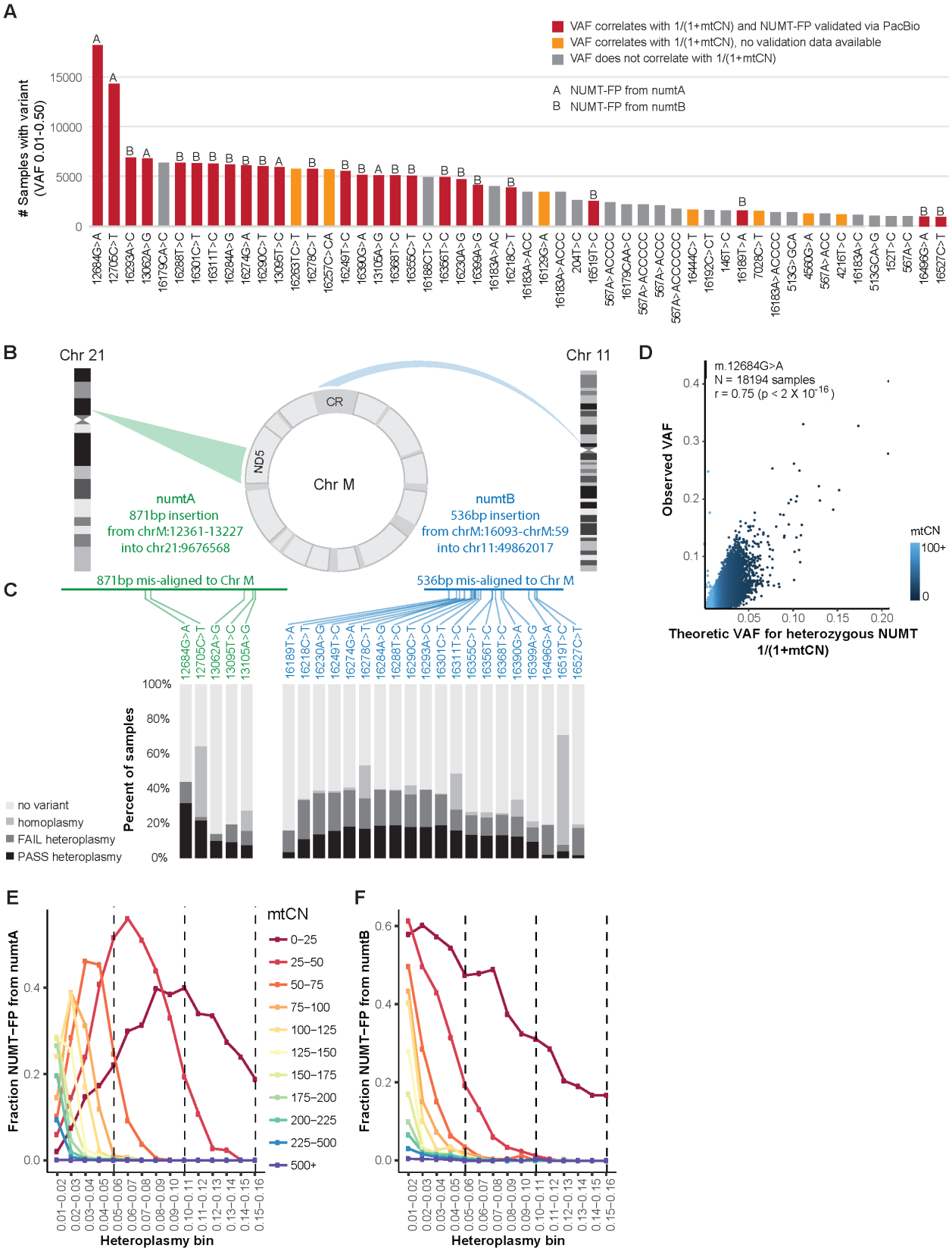
B

Variants	Mutect2 SNVs	Mutect2 Indels	MtDNA-Server SNVs	MtDNA-Server Indels
All	2648/2889 (91.7%)	81/167 (48.5%)	2742/3236 (84.7%)	163/333 (48.9%)
VAF > 0.10	2516/2523 (99.7%)	50/63 (79.4%)	2518/2527 (99.6%)	140/249 (56.2%)
VAF > 0.50	2506/2510 (99.8%)	30/31 (96.8%)	2502/2510 (99.7%)	130/229 (56.8%)
VAF > 0.90	2491/2494 (99.9%)	29/29 (100%)	2462/2485 (99.1%)	129/228 (56.6%)

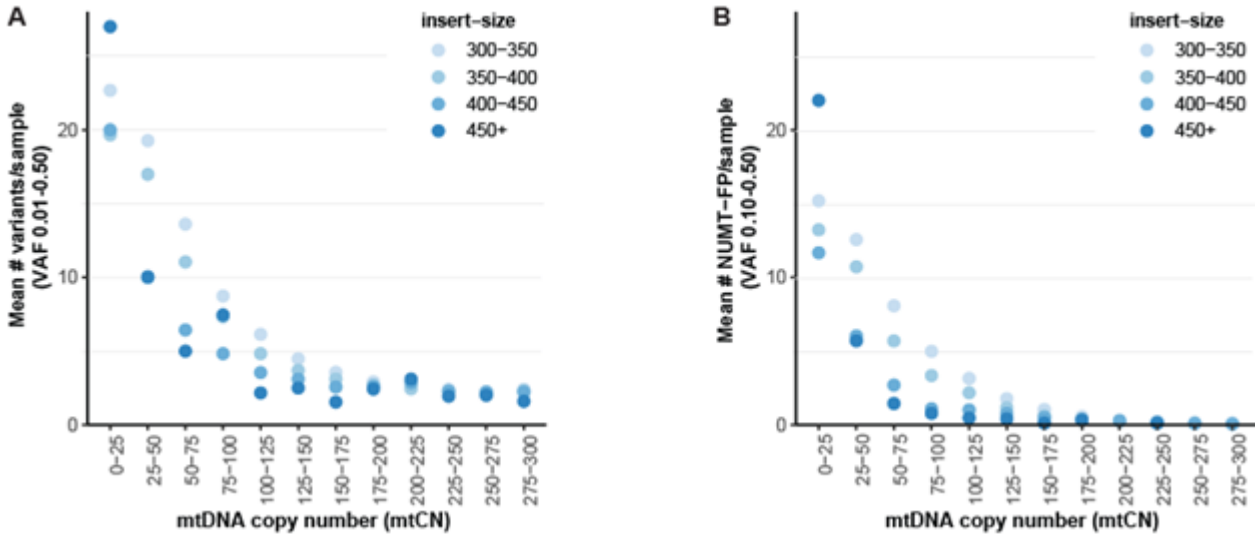
C

Mix fraction	Mutect2 Sensitivity	Mutect2 Precision	Mix fraction	mtDNA-Server Sensitivity	mtDNA-Server Precision
0.01	31.7%	99.7%	0.01	66.2%	89%
0.05	98.8%	99.7%	0.05	98.1%	93%
0.50	99.7%	99.9%	0.50	99.5%	93%
0.90	99.9%	99.5%	0.90	99.7%	89%
0.99	99.9%	98.9%	0.99	100%	89%

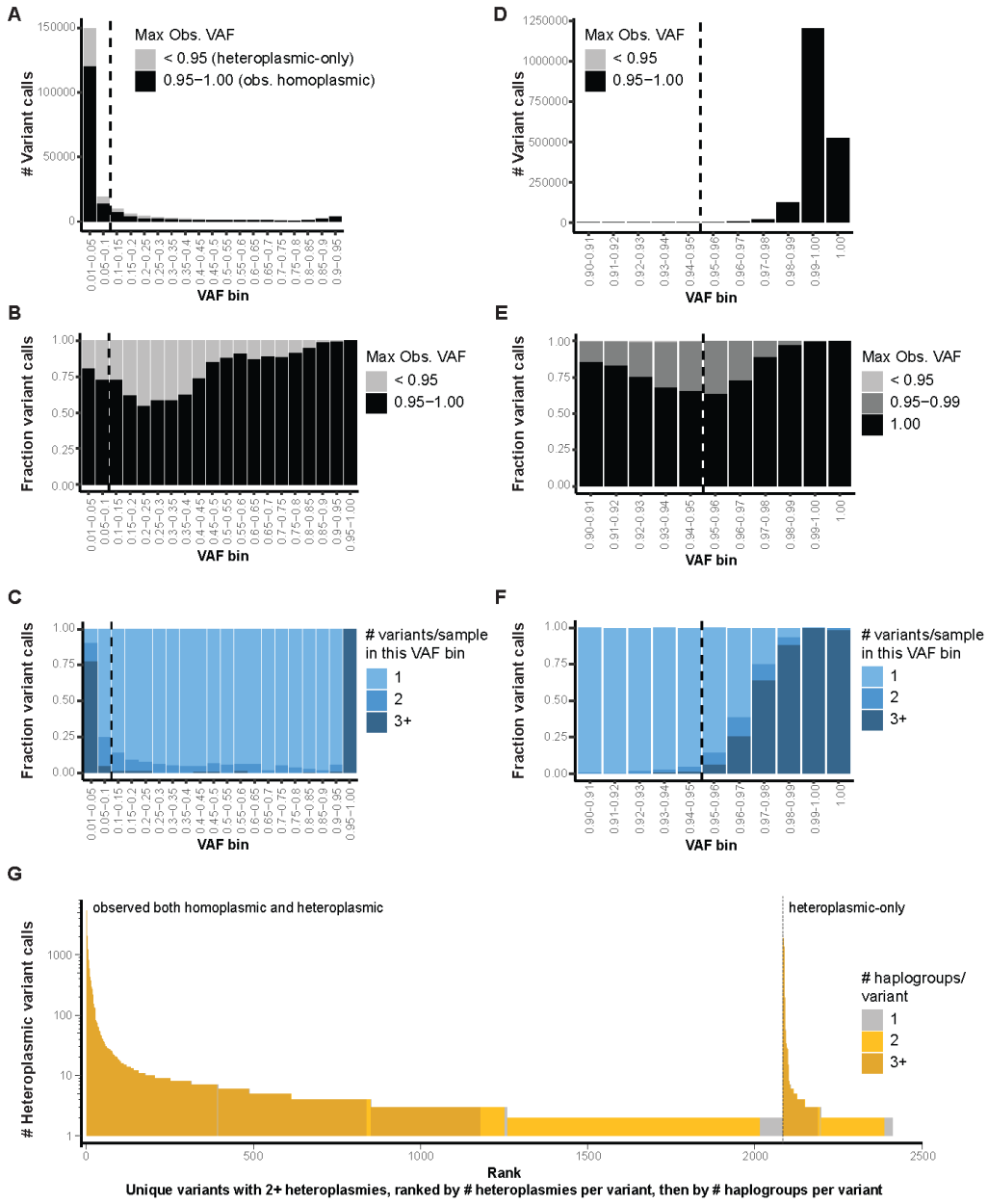
Supplemental Figure S1 - Comparison of mtDNA variant pipelines. (A) Reproducibility of mtDNA SNV calls on 91 WGS replicate samples between GATK Mutect2 pipeline versus mtDNA-Server. Density plot above shows most variants are homoplasmic. (B) Jaccard index (# variants detected in both replicates/# variants detected in either replicate) is shown at different VAF thresholds. (C) Heatmap shows estimated accuracy of single-sample pipelines for SNV detection (Mutect2 and mtDNA-Server) for samples with mtCN > 500 based on “in silico” mixing data. Note indels were not included in this table since mtDNA-Server formatted equivalent indels in a different way from the truth dataset, which caused inaccurate comparisons. Even for SNVs, some of mtDNA-Server’s reduced precision is due to differences in formatting variants compared to the truth data. As described in the text, neither the replicate analysis nor in silico mixing analysis estimates false positives derived from NUMTs.


A
VAF correlates with 1/(1+mtCN) and NUMT-FP validated via PacBio
VAF correlates with 1/(1+mtCN), no validation data available
VAF does not correlate with 1/(1+mtCN)
A NUMT-FP from numtA
B NUMT-FP from numtB
Samples with variant (VAF 0.01-0.50)
B Chr 21
Chr 11
CR
ND5
Chr M
numtA
871bp insertion
from chrM:12361-13227
into chr21:9676568
numtB
536bp insertion
from chrM:16093-chrM:59
into chr11:49862017
C
871bp mis-aligned to Chr M
536bp mis-aligned to Chr M
Percent of samples
no variant
homoplasmy
FAIL heteroplasmy
PASS heteroplasmy
D
m.12684G>A
N = 18194 samples
r = 0.75 (p < 2 X 10^-16)
Observed VAF
Theoretic VAF for heterozygous NUMT
1/(1+mtCN)
mtCN
E
Fraction NUMT-FP from numtA
Heteroplasmy bin
mtCN
0–25
25–50
50–75
75–100
100–125
125–150
150–175
175–200
200–225
225–500
500+
F
Fraction NUMT-FP from numtB
Heteroplasmy bin

Supplemental Figure S2 - Two polymorphic NUMTs cause 25 NUMT false positives (NUMT-FPs). (A) Barplot shows the 52 most common putative heteroplasmies, colored by correlation with 1/(1+mtCN) including all 25 NUMT-FPs. (B) Schematic shows the location of two NUMTs not in the reference genome that were validated by PacBio long-read sequencing, derived from mtDNA regions within the *MT-ND5* gene and the non-coding control region (CR). (C) When misaligned to Chr M, numtA gives rise to 5 NUMT-FPs (green) and numtB gives rise to 20 NUMT-FPs (blue). Schematic at top shows the position of the NUMT-FPs and the bar graph at bottom shows the percent of all samples with variants. (D) For variant m.12684G>A from numtA, scatterplot shows the observed VAF across samples versus the theoretical VAF if the NUMT were heterozygous and all reads misaligned to Chr M. Points represent samples with passing variants (VAF 0.01-0.50) and are colored by mtCN. Variants from numtA typically show significantly higher observed VAF than those from numtB (Fig. 2E), perhaps indicating they are present at more than one copy in the nuclear genome. (E-F) X-axis indicates VAF bin and Y-axis indicates the percent of detected variants that occur at 5 NUMT-FP sites derived from numtA (E) or 20 NUMT-FP sites from numtB (F), where samples are grouped by mtCN. NUMT-FPs are counted only when a sample has at least 2 PASS variants (VAF 0.01-0.50) from the same NUMT. These panels again suggest numtA is present at higher copy number in the nuclear genome compared to numtB.



Supplemental Figure S3 - Putative heteroplasmies by mtCN and WGS insert size.
Mean number of putative heteroplasmies (VAF 0.01-0.50) (A) or NUMT false positives (NUMT-FP) variants (VAF 0.01-0.50) (B) is shown for samples grouped by mtDNA copy number (X-axis) and sample median insert size (color). These plots show that shorter WGS fragments are more likely to misalign to the mtDNA and cause NUMT-FPs, but this effect is observed more in samples with low mtCN (where misalignment causes FPs with VAF > 0.01).



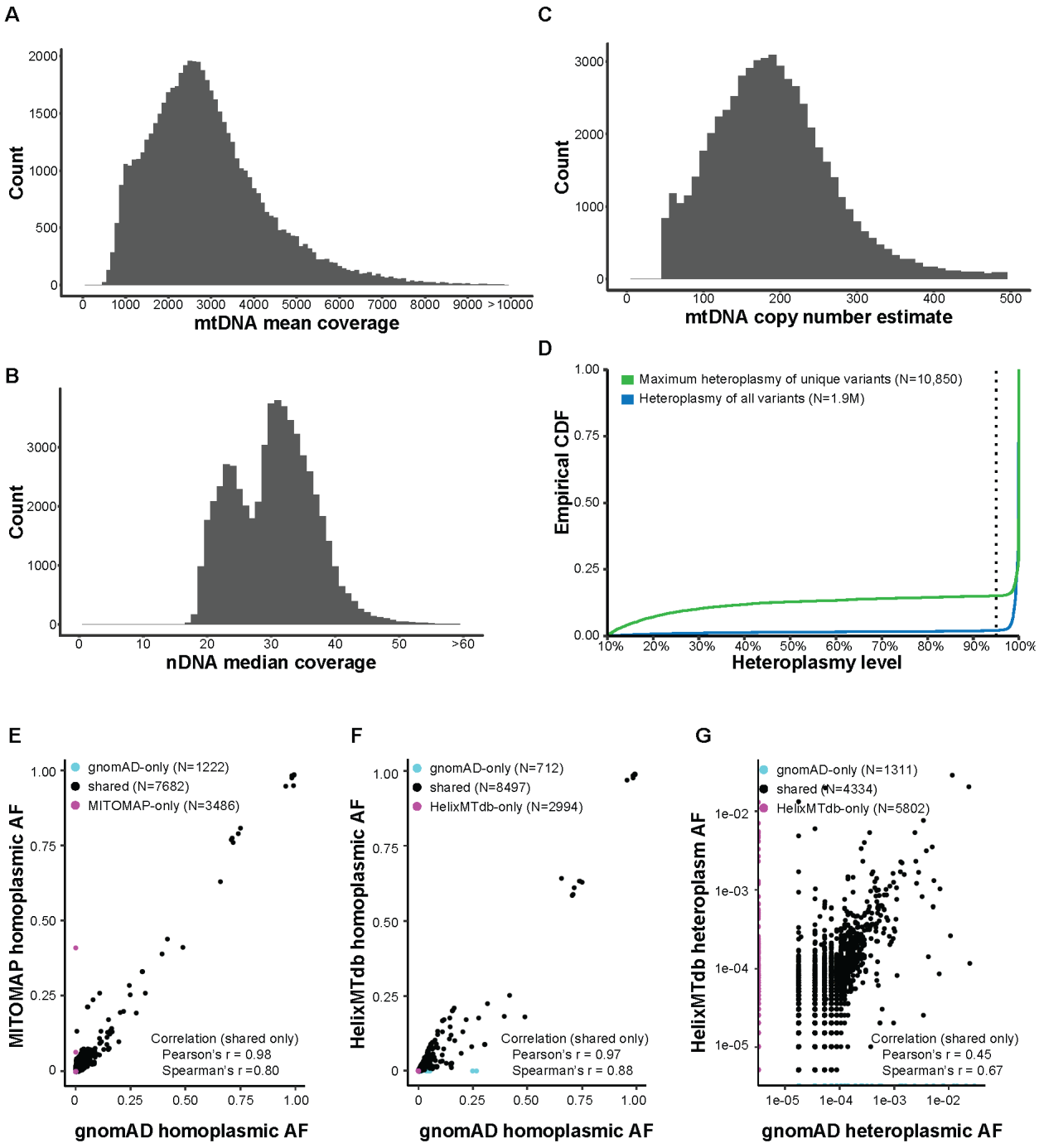
Supplemental Figure S4 - Characteristics of heteroplasmic and homoplasmic (or near-homoplasmic) variants.

(A) Number of heteroplasmic variant calls versus the reference assembly shown by Variant Allele Fraction (VAF), with variants colored by maximum observed VAF for the variant across all 56,434 released samples. Dashed line indicates the selected threshold for PASS variants (VAF >= 0.10). Bin label X-Y indicates X <= VAF < Y.

(B) Fraction of variant calls at each VAF level, colored by maximum observed VAF for the variant.

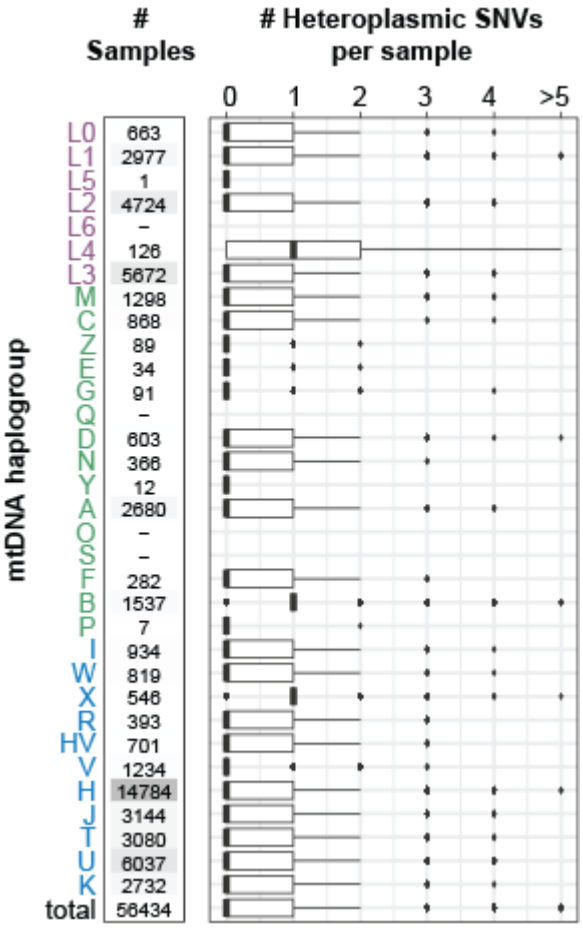
(C) Fraction of variant calls at each VAF level, colored by the number of variants in the same sample at the given VAF bin. Samples with 3 or more heteroplasmic variants at the same VAF may indicate artifacts from contamination or NUMT-misalignment – and are strongly enriched at VAF level 0.01-0.05, and substantially enriched at VAF level 0.05-0.10. Excludes multi-allelic variants.

(D) Number of heteroplasmic variant calls between VAF 0.90-1.00, showing there are very few variant calls with VAF 0.90-0.96. Dashed line indicates selected threshold for “homoplasmic or near homoplasmic” variants (VAF >= 0.95). Bin label X-Y indicates X <= VAF < Y.
(E) Fraction of variant calls at each VAF 0.90-1.00, colored by maximum observed VAF for the variant, showing that nearly all these variants are also observed with VAF >= 0.95 (dark gray or black) in at least one other sample.
(F) Fraction of variant calls at each VAF 0.90-1.00, colored by the number of variants in the same sample at the given VAF level. Samples with 3 or more heteroplasmic variants at the same VAF may indicate true homoplasmic variants that appear at VAF < 1.00 due to artifacts from contamination or NUMT-misalignment – and are enriched at VAF >= 0.95, justifying the selected threshold of 0.95 used to indicate variants “homoplasmic or near homoplasmic”. Multiallelic variants are excluded.
(G) Barplot shows unique heteroplasmic variants (VAF 0.10-0.95) that are detected heteroplasmic (VAF 0.10-0.95) in at least two individuals. Y-axis shows number of heteroplasmies (VAF 0.10-0.95) at each unique variant. X-axis ranks unique variants by (i) presence at homoplasmy-and-heteroplasmy vs heteroplasmic-only, (ii) number of heteroplasmies per variant, and (iii) number of distinct haplogroups observed for that variant (where distinct haplogroups are defined based on the first 2 haplogroup symbols, e.g. L1 or H2). Plot shows that most heteroplasmic variants are found in at least 2 distinct haplogroups (yellow and orange) and not on the same haplogroup (gray).

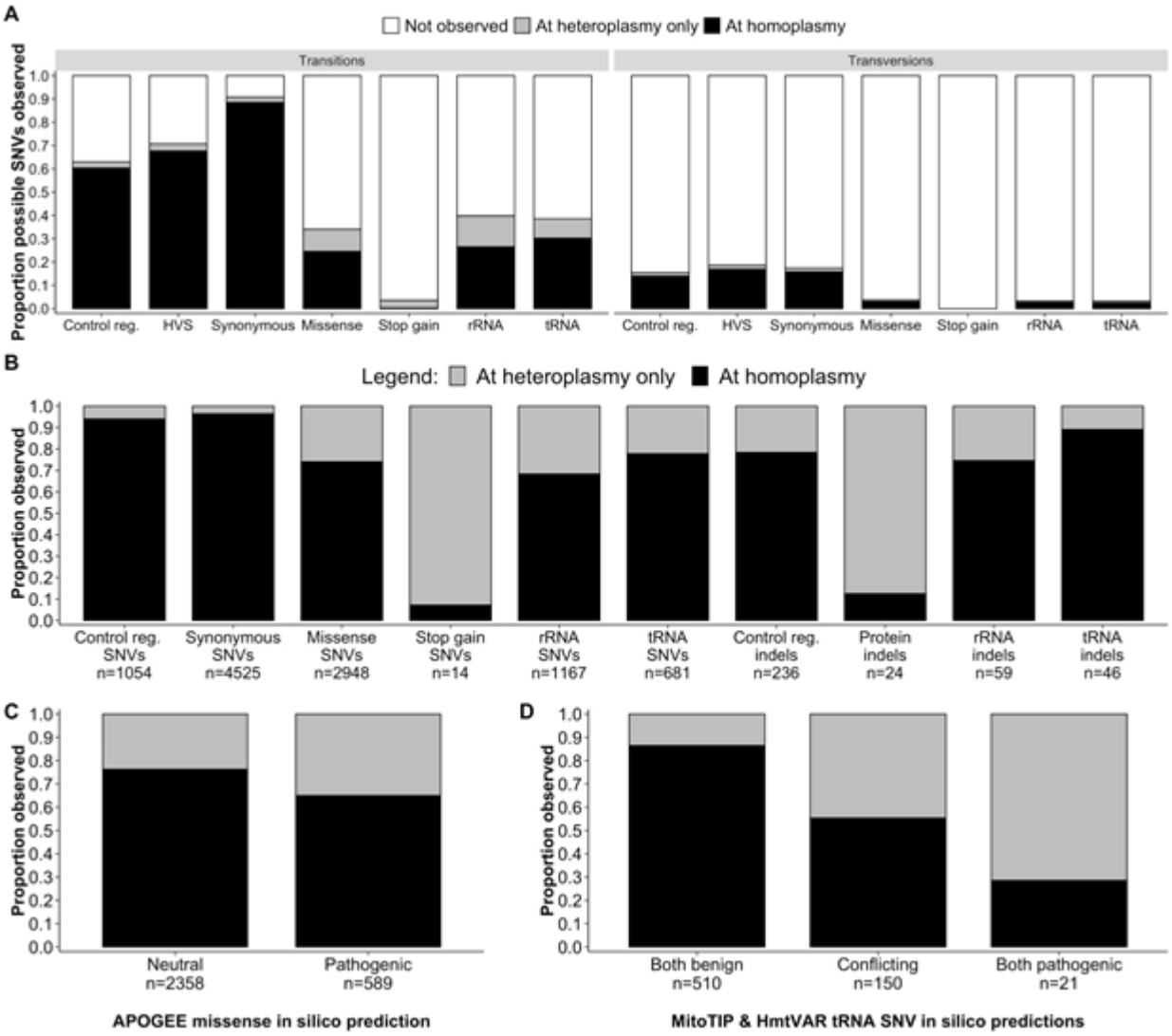


Supplemental Figure S5 - Coverage and variants in 56,434 gnomAD samples in v3.1 (after filtering). (A) Histogram shows mean mtDNA coverage. (B) Histogram shows median nuclear (nDNA) coverage. (C) Histogram shows mtDNA copy number defined as 2 × mDNA mean coverage/nDNA median coverage. (D) Empirical cumulative distribution function shows heteroplasmy levels for all variants and unique variants. Dotted line shows 95% heteroplasmy above which variants are categorized "homoplasmic or near homoplasmic". (E) Comparison of homoplasmic allele frequency (AF) of SNVs in gnomAD v3.1 versus MITOMAP (indels excluded since MITOMAP reports right-aligned indels whereas gnomAD reports left-aligned indels). (F) Comparison of homoplasmic AF of all homoplasmic variants in

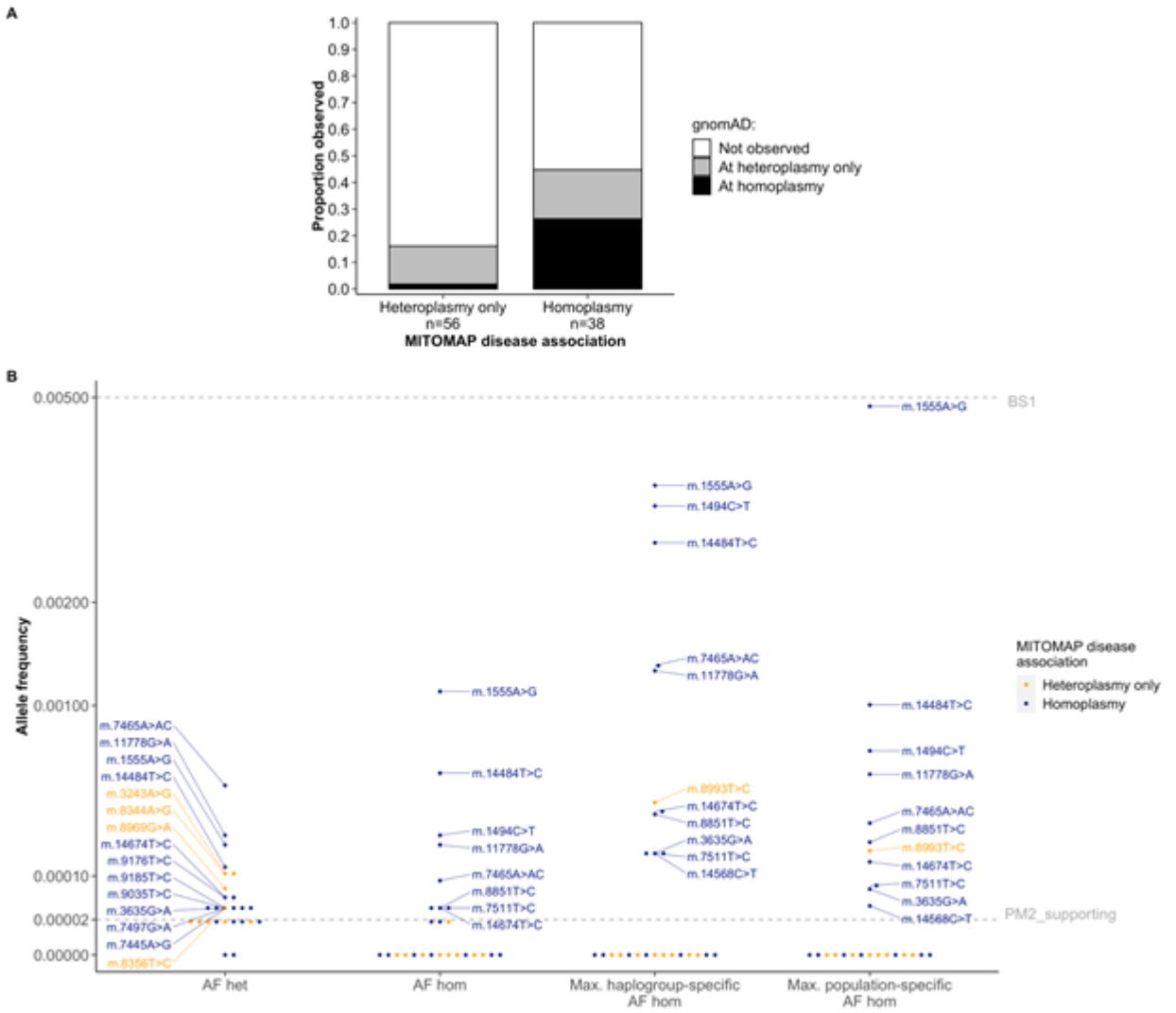
gnomAD v3.1 vs HelixMTdb. (F) Comparison of heteroplasmic AF of all heteroplasmic variants in gnomAD v3.1 vs HelixMTdb (note axes are shown log10 since maximum AF < 0.03 for shared variants).



Supplemental Figure S6 - Heteroplasmic variants by mtDNA haplogroup.
For each haplogroup, the number of samples is shown along with a box plot of the number of heteroplasmic SNVs (VAF 0.10-0.95) per sample. Color indicates mtDNA haplogroups phylogenetically associated with African (purple), Asian (green), or European (blue) origin (Lott et al. 2013). Unlike homoplasmic SNVs (Fig. 4B), the number of heteroplasmies does not depend on haplogroup.



Supplemental Figure S7 - Relative proportion of variants observed. (A) The barchart shows the proportion of possible transitions and transversions observed, including those observed at homoplasmy (in at least one individual) (black), those only observed at 10-95% heteroplasmy (gray), or not observed in gnomAD (white). "Control reg." represents the non-coding control region m.16024-576, and "HVS" represents the three hypervariable segments within this region (m.57-372, m.438-574, m.16024-16383). (B-D) Of unique variants observed in gnomAD, barchart shows proportion detected at homoplasmy (in at least one individual) or only at heteroplasmy for different categories of variants (B), and for in silico prediction algorithms recommended for mtDNA missense (C) and tRNA variant interpretation (D) per McCormick et al (2020). Note "protein indels" in (B) includes both frameshift and in-frame indel variants, and (C) excludes variants with N/A annotations. For (D), MitoTIP annotations "likely pathogenic" and "possibly pathogenic" were regarded as pathogenic, and "likely benign" and "possibly benign" were regarded as benign; for HmtVAR, "pathogenic" and "likely pathogenic" were regarded as pathogenic, and "polymorphic" and "likely polymorphic" were regarded as benign. "Conflicting" includes variants with HmtVAR annotation of "null". For all figures, "n" represents the number of variants per category.



Supplemental Figure S8 - Allele frequencies of known pathogenic variants in gnomAD. (A) For variants curated in MITOMAP as causing disease only at heteroplasmy or at homoplasmy (where the latter includes those only associated with disease at homoplasmy, or at both homoplasmy and heteroplasmy), we show the proportion detected in gnomAD at homoplasmy (in at least one individual) (black) or only at heteroplasmy (gray). Note that the variant in the 'Heteroplasmy only' group seen at homoplasmy is m.8993T>C, which was recently described in adult-onset cases at homoplasmy (Stendel et al. 2020). (B) The allele frequencies of the 26 pathogenic variants observed in gnomAD are shown, colored by their association with disease curated by MITOMAP. The allele frequencies in gnomAD at heteroplasmy (AF het) and homoplasmy (AF hom), as well as for each mtDNA haplogroup and inferred nuclear ancestry population (see Fig. 4), are displayed. The dashed lines represent the threshold at which benign criteria BS1 (AF > 0.005) or pathogenic criteria PM2 supporting (AF < 0.00002) can be applied. Variants with allele frequency > 0.00002 per category are labelled.

SUPPLEMENTAL TABLES

Supplemental Table S1 - NUMT-Derived False Positives. Details on the 25 NUMT-FP sites validated by PacBio (tab 1), all 124 common heteroplasmic variants (tab 2), and co-occurrence of 67 common heteroplasmies that correlated with 1/(1+mtCN) (tab 3). Available as Excel file downloaded separately.

Type	Name	Description	# Unique Variants: 0.01-1.00 VAF	# Total Variants: 0.01-1.00 VAF	# Total Variants: 0.10-1.00 VAF
Genotype filter	strand_bias	(FilterMutectCalls) Evidence for alternate allele comes predominantly from one read direction	2,801	185,452	30,036
Genotype filter	base_qual	(FilterMutectCalls min-median-base-quality=20) Median base quality of alternate allele was below minimum	1,044	82,543	1,344
Genotype filter	weak_evidence	(FilterMutectCalls) Mutation does not meet likelihood threshold	1,296	72,590	312
Genotype filter	contamination	(FilterMutectCalls) Fails contamination filter based on estimate from Haplocheck	707	2,791	1
Genotype filter	position	(FilterMutectCalls min-median-read-position=1) Median distance of variant allele from end of reads was below minimum	302	558	9
Genotype filter	union of above 5 categories	Union of all FilterMutectCalls	4,194	225,193	30,848
Genotype filter	heteroplasmy_ below_min_ het_threshold	VAF < 0.10	14,183	442,973	-
Site filter	artifact_ prone_site	Variant overlaps any of 6 specific mtDNA positions (301, 302, 310, 316, 3107, 16182) where sequence context makes it difficult to distinguish true variants from technical artifacts	446	332,946	121,644
Variant filter	indel_stack	Heteroplasmic indel variant only detected with multi-allelic calls (e.g., 102/182 unique indel variants detected at chrM:5892 are only detected with at least one other heteroplasmic indel at chrM:5892 in the same person)	383	9,385	3,685
Variant filter	npg	No sample had a pass genotype for the variant	7,078	47,944	408
Variant flag	common_low_ heteroplasmy	Allele frequency (AF) > 0.001 (considering PASS variants VAF 0-0.50)	374	1,513,015	1,164,672

Supplemental Table S2 - Pipeline filters and flags.
Filters indicate variants that fail quality control, whereas flags indicate variants that pass quality control but should be interpreted with caution. The single-sample GATK pipeline assigns genotype filters (per sample, per variant) via FilterMutectCalls. The single-sample VCFs are combined, processed, and filtered using Hail scripts that assign additional genotype filters (per sample, per variant), site filters (per mtDNA position), variant filters (per variant), and variant flags (per variant). Statistics are reported on the 56,434 samples that pass quality control filters. Note filters are not mutually exclusive.

Variant	Gene	VEP protein consequence	Type	Max het	AC hom	AC het	Note	Updated protein consequence
m.5185 G>A	MT-ND2	p.Trp239Ter	Stop gained	99.7 %	1	0	On same allele as m.5186A>T, resulting in a missense variant	p.Trp239Tyr
m.8496 TA>T	MT-ATP8	p.Asn46Ilefs Ter?	Frame-shift variant	99.3 %	1	0	Possible translation of a protein the same length as MT-ATP8, as inclusion of the first 3'UTR base produces the 'non-standard' mitochondrial stop codon AGG, with a T immediately preceding as has been suggested for AGG terminator functionality	p.Asn46Ilefs Ter23

Supplemental Table S3 - Homoplasmic stop gain and frameshift variants. Abbreviations het: heteroplasmy; hom: homoplasmy; AC allele count.

Variant	Gene/s	Consequence/s	HGVSc	HGVSp	gnomAD max het	HelixMTdb max het	MITOMAP allele count
m.3315G>A	*MT-ND1*	synonymous	c.9G>A	p.Met3	0	0	1
m.5906G>A	*MT-CO1*	synonymous	c.3G>A	p.Met1	0	0	0
m.7588G>A	*MT-CO2*	synonymous	c.3G>A	p.Met1	63.6%	15.2%	0
m.8368G>A	*MT-ATP8*	synonymous	c.3G>A	p.Met1	0	12.7%	0
m.8529G>A	*MT-ATP6, MT-ATP8*	synonymous, stop gained	c.3G>A, c.164G>A	p.Met1, p.Trp55Ter	0	0	0
m.9209G>A	*MT-CO3*	synonymous	c.3G>A	p.Met1	18.7%	32.9%	1
m.10472G>A	*MT-ND4L*	synonymous	c.3G>A	p.Met1	0	0	0
m.10762G>A	*MT-ND4, MT-ND4L*	synonymous, missense	c.3G>A, c.293G>A	p.Met1, p.Cys98Tyr	0	0	0
m.12345G>A	*MT-ND5*	synonymous	c.9G>A	p.Met3	10.8%	81.1%	0
m.14655G>A	*MT-ND6*	synonymous	c.19C>T	p.Leu7	0	100%	0
m.14749G>A	*MT-CYB*	synonymous	c.3G>A	p.Met1	0	0	0

Supplemental Table S4 - Possible synonymous G>A variants not seen at homoplasmy. The maximum heteroplasmy of these variants in HelixMTdb and their allele count in MITOMAP databases are also shown (heteroplasmy information not available in MITOMAP). The c.3G>A variant in *MT-ND6*, the only protein encoded on the non-reference strand and also with an AUG start codon, was also not observed (equivalent to m.14671C>T). Note maximum heteroplasmy in HelixMTdb was inferred to be 100% if the variant was observed at homoplasmy. Two of these variants lie in two genes and thus have multiple consequences. Max het = maximum heteroplasmy.

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