Venter M, Malan L, van Dyk E, Elson JL, van der Westhuizen FH.
[Using MutPred derived mtDNA load scores to evaluate mtDNA variation in hypertension and diabetes in a two-population cohort: The SABPA study.](#)

Journal of Genetics and Genomics (2016).

DOI: <http://dx.doi.org/10.1016/j.jgg.2016.12.003>

Copyright:

© 2016. This manuscript version is made available under the [CC-BY-NC-ND 4.0 license](#)

DOI link to article:

<http://dx.doi.org/10.1016/j.jgg.2016.12.003>

Date deposited:

17/01/2017

Embargo release date:

26 December 2017

This work is licensed under a
[Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International licence](#)

Using MutPred derived mtDNA load scores to evaluate mtDNA variation in hypertension and diabetes in a two-population cohort: The SABPA study

Marianne Venter^a, Leone Malan^b, Etresia van Dyk^a, Joanna L. Elson^{a, c, 1, *} Francois H. van der Westhuizen^{a, 1}

^a Human Metabolomics, North-West University, Potchefstroom 2531, South Africa

^b Hypertension in Africa Research Team (HART), North-West University, Potchefstroom 2531, South Africa

^c Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne NE1 3BZ, United Kingdom

¹ These authors contributed equally to this work.

* Corresponding author *Email address:* j.l.elson@ncl.ac.uk

Abbreviation

24 h ABPM: 24 hour ambulatory blood pressure monitoring; CVD: cardiovascular disease; HbA1c: glycated haemoglobin; mtDNA: mitochondrial deoxyribonucleic acid; SABPA: Sympathetic Activity and Ambulatory Blood Pressure in Africans

Abstract

Mitochondrial DNA (mtDNA) variation has been implicated in many common complex diseases, but inconsistent and contradicting results are common. Here we introduce a novel mutational load hypothesis, which also considers the collective effect of mainly rare variants, utilising the MutPred Program. We apply this new methodology to investigate the possible role of mtDNA in two cardiovascular disease (CVD) phenotypes (hypertension and hyperglycaemia), within a two-population cohort ($n = 363$; mean age 45 ± 9 yrs.). Very few studies have looked at African mtDNA variation in the context of complex disease, and none using complete sequence data in a well-phenotyped cohort. As such, our study will also extend our knowledge of African mtDNA variation, with complete sequences of Southern Africans being especially under-represented. The cohort showed prevalence rates for hypertension (58.6%) and prediabetes (44.8%). We could not identify a statistically significant role for mtDNA variation in association with hypertension or hyperglycaemia in our cohort. However, we are of the opinion that the method described will find wide application in the field, being especially useful for cohorts from multiple locations or with a variety of mtDNA lineages, where the traditional haplogroup association method has been particularly likely to generate spurious results in the context of association with common complex disease.

Keywords

Mitochondrial DNA; MutPred; Mutational load; Hypertension; Diabetes; African; SABPA

1. Introduction

Cardiovascular disease (CVD) is an umbrella term that encompasses several distinctive disease phenotypes inclusive of myocardial infarction, stroke, congenital heart disease and risk factors such as hypertension, and diabetes type 2 (Mensah, 2013). Discrepancies between different population groups exist in the onset, development and outcome of CVDs. (Okin et al., 2011; Moran et al., 2013; Owolabi et al., 2014). Although environmental and lifestyle factors play a role in the risk of developing CVD, genetic factors are likely to account for some of the observed discrepancies in CVD onset, and particularly progression/outcome of disease (Achilli et al., 2011). Nuclear DNA risk factors have not been able to account for all the observed inconsistencies among different population groups (Kaufman et al., 2015). Thus, other sources of variation, such as epigenetics and Mitochondrial DNA (mtDNA) variation might account for some of the missing heritability in CVDs.

mtDNA mutations are a common cause of inherited disease (Gorman et al., 2015). Both diabetes and cardiomyopathy are frequent symptoms in primary mitochondrial disease (Taylor et al., 2003; Yarham et al., 2010), especially in patients with the mtDNA m.3243A>G mutation (Hollingsworth et al., 2012). While clinically manifesting mtDNA mutations are a recognised cause of human disease, many studies have suggested a role for common mtDNA variants (Hernstadt and Howell, 2004; Wallace, 2010) and the combined effect of rare population variants (Elson et al., 2006) in common complex disease. For CVDs specifically, a more recent Framingham Heart sub-study showed significant associations between several population as well as rare variants, and variation in blood pressure and fasting blood glucose levels (Lui et al., 2012). Cardena et al. (2014, 2016) found the hypertensive phenotype to be more prevalent among heart failure patients with an African mitochondrial haplogroup than among those with European haplogroups, in an admixed Brazilian cohort.

Human mtDNA codes for 13 essential polypeptide components of the mitochondrial oxidative phosphorylation (OXPHOS) system. mtDNA undergoes strict maternal inheritance, resulting in the absence of bi-parental recombination (Elson et al., 2001) and has a high mutation rate (Tuppen et al., 2010). As such, the evolution of mtDNA is characterised by the emergence of distinct lineages (or haplogroups) (Hernstadt et al., 2002). This results in high levels of mtDNA variation at the population level despite its rather small size, which is also illustrated by the large number of sub-haplogroups (van Oven and Kayser, 2009). Africa

(haplogroups L0–L6) has the highest levels of nuclear and mitochondrial genetic diversity (Salas et al., 2002); this diversity was reduced by population bottlenecks in groups migrating from Africa (Manica et al., 2007). However, variation in African populations, especially in relation to disease, is still under studied when compared to variation in super clade N (Cavadas et al., 2015; Gurdasani et al., 2015). Only about 12% of mtDNA sequences on GenBank are of African lineages. In terms of mtDNA ancestry, the African haplogroup L3 incorporates super clades M and N, which encompass all the European and Asian haplogroups (Hernstadt et al., 2002; van Oven and Kayser, 2009; Rosa and Brehem, 2011).

Given the unique inheritance pattern of mtDNA, it is worth considering the hypothesis that might link mtDNA population variation to common complex disease. Firstly, studies showing significant associations of several disease phenotypes with specific mtDNA haplogroups have been published, suggesting that one or more common population variants may modify risk or outcome of disease. Secondly, the high mutation rate of mtDNA frequently results in the same variant being present more than once on the phylogeny (Hernstadt et al., 2002). Showing that such a variant modifies risk or alters the course of disease (Yu et al., 2008) in two different haplogroups or global populations, would be excellent evidence of it's role in disease. The third possibility is that rare mtDNA mutations might have an effect, either at the individual level with there being synergist effects of multiple rare variants in patients, or rare variants might just be seen more frequently in the patient group.

The first hypothesis mentioned above, known as the haplogroup association hypothesis, has to date been the classic approach to use when considering the role of mtDNA variation in common disease. These studies have been controversial due to their low repeatability; often the association is not detected in a second cohort, or an association with a different haplogroup might be uncovered (Salas and Elson, 2015). Some studies have taken a two-cohort approach in an attempt to address these problems (Elson et al., 2006; Chinnery et al., 2010). Even so, this approach has proved unsuitable for many studies with cohorts that do not have the large numbers required for well-powered haplogroup association studies (Samuels et al., 2006).

In this study, we take an alternative approach, using MutPred pathogenicity scores to derive “mutational loads”. This is a new version of the “mutational load” hypothesis proposed by Elson et al. (2006), which looked at the frequency of mildly deleterious (rare) variants in patient and control groups, to test the possibility of a cumulative effect of these variants.

After calculating “MutPred mutational loads” by summing the MutPred scores generated for each of the non-synonymous variants on an individual’s mtDNA, we adjusted these for the position of the sequence in the phylogeny, ultimately calculating “MutPred adjusted loads”. Many different tools for predicting pathogenicity of mtDNA variants exist, but in a comparative study by Thusberg et al (2011), MutPred and SNPs&GO outperformed all other methods, which included PolyPhen2, SIFT and SNAP. The MutPred program has also been widely validated in the context of mtDNA variation (Pereira et al., 2011). The MutPred algorithm incorporates elements of the SIFT algorithm, and assigns a pathogenicity score between 0–1, with zero being a benign substitution. A pathogenic score above 0.5 can be considered an “actionable hypothesis”, while a score above 0.75 can be considered a “confident hypothesis” (Li et al., 2009). As there is selection against mildly deleterious variants at the population level (Elson et al., 2004; Soares et al., 2013), variants with MutPred scores above the “actionable hypothesis” threshold (0.5) are less likely to define major haplogroups; rather, they are more likely to be rare and seen on very recent branches (twigs) of the phylogeny (Pereira et al., 2011). Because the number of low-scoring, low-impact common variant differs greatly among different population groups, their inclusion in the calculation of mutational loads could introduce noise that is unlikely to have phenotypic impact. By excluding variants with a pathogenicity score below 0.5, and thus most common population variants, before calculating MutPred adjusted loads, we aim to highlight the impact of rare variants while reducing the effect of population stratification.

Although mtDNA variation involvement in CVDs have previously been investigated (Chinnery et al., 2010), these studies have been predominantly in Caucasian European populations. Very few such studies have been published on African populations or those of African descent, were mostly on small sized cohorts, and often focused on specific previously reported variants (Khogali et al., 2001; Robinson et al., 2004; Ameh et al., 2011). To assume that findings from studies in European populations can easily be extrapolated to less investigated, genetically diverse African population groups would be short sighted (van der Westhuizen et al., 2015), as even clinically proven disease causing mutations as well as the underlying spectrum of mutations are known to have differing impacts in Africans (van der Walt et al., 2012; van der Westhuizen et al., 2015).

In this study, we used the two-population Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) cohort (Malan et al., 2015) (Table 1). This is a South African cohort which consisted of 409 Black and Caucasian South African participants from the same

geographical area (Rosa and Brehem, 2011; Salas and Elson, 2015). Although the participants were matched for gender, age and socio-economic status, a significantly higher percentage of Black participants, compared to Caucasians participants, with optimal blood pressure at the start of the study, developed hypertension within five years (Schutte et al., 2012; Hamer et al., 2015). A wide range of clinical and phenotypical analysis data are available for this cohort, including the golden standard 24 hour ambulatory blood pressure monitoring (24 h ABPM) measurements and a measurement of hyperglycaemia (HbA1c, glycated haemoglobin), which are routinely used to identify hypertension and diabetes respectively in a clinical setup.

Using this unique cohort, we aimed to determine if mtDNA variation, using the MutPred adjusted load as defining parameter, is different in those with hypertension or hyperglycaemia when compared to those without. As such, we present a new and updated method for attempting to associate mtDNA variation with a complex trait. This method would be applicable to all mtDNA association studies, and be less affected by population stratification.

2. Results

After some samples fall-out due to technicalities such as sample unavailability and insufficient DNA extraction, 194 participants with macro-haplogroup L (haplogroups L0–L4) and 169 participants with macro-haplogroup MN (haplogroups M, N, R, B, H, I, J, K, T, U and W) were used in this study. In Table 1, some of the most important phenotypical measurements (age, body mass index, blood glucose levels and blood pressure) are summarised. Immediately, large differences in both systolic and diastolic 24 h ABPM measurements, as well as differences in blood glucose measurements, can be noted between different mtDNA background and gender groups (Fig. 1). For both blood pressure measurements (systolic and diastolic), haplogroup L males have significantly higher values than all other groups ($P < 0.0001$). Haplogroup L females also had significantly higher blood pressure than haplogroup MN females ($P = 0.001$ for both systolic and diastolic 24 h ABPM). Haplogroup MN males also had significantly higher blood pressure than their female counterparts ($P = 0.003$ for systolic 24 h ABPM; $P < 0.0001$ for diastolic 24 h ABPM). For blood glucose measurements (% of HbA1c) haplogroup L males had significantly higher values than both male and female groups from haplogroup MN ($P < 0.0001$), and only

slightly higher values than L haplogroup females ($P = 0.03$); haplogroup L females had significantly higher blood glucose levels than their haplogroup MN counterparts ($P = 0.0004$), (Fig. 1). These differences have been previously reported in the current cohort (Lammertyn et al., 2011; Hamer et al., 2015), and correlates well with similar discrepancies between population groups reported in other studies (reviewed by Mensah, 2013). Consequently, data were divided into four groups based on gender and mtDNA background and analysed separately for subsequent analysis. These groups were as follows: haplogroup L males ($n = 100$); haplogroup L females ($n = 94$); haplogroup MN males ($n = 75$); and haplogroup MN females ($n = 94$).

2.1 Functional network analysis

We performed network analyses on our data, using only variants with MutPred scores above 0.5, as well as rRNA and tRNA variants. Separate and simplified networks, shown in Fig. 2, were calculated for macro-haplogroups L and MN. Several occurrences of homoplasies were found in both macro-haplogroups (indicated in italics). This is not uncommon within the central regions of networks (Hernstadt et al., 2002). Activating the “frequency > 1” criterion, which then excludes all unique taxa, contributed greatly to simplifying the networks, but also resulted in the only participant from haplogroup L4 being excluded from Fig. 2A. The included nodes formed into clusters that correlated very well with the haplogroups that were assigned independently to each participant using the Haplogrep 2.0 program (Weissensteiner et al., 2016). It is interesting to note that the phenotype classifications do not group within specific parts of the network and seem well dispersed throughout the networks (Fig. 2).

2.2 mtDNA variants

We found very few heteroplasmies over 10% and therefor did not consider the possible contribution of these sites to the phenotypes investigated here. We also found no clinically proven mutations at appreciable heteroplasmies among any of our participants. In our current dataset, we found 17 changes not present in GenBank sequences. Of those, twelve changes were transitions and five changes were transversions. Four of these changes have however been previously reported, according to the MITOMAP database. The properties of these changes are listed in Table 2.

To capture any differences in the population frequency of rare population alleles, we compared the number of rare (<0.1%) and common (>1%) non-synonymous population

alleles unique to each group as defined by haplogroup background (L or MN), gender and phenotype (in this analysis, a two-group classification for blood glucose levels were used instead of three groups, i.e., optimal or pre-diabetic glucose levels, using a cut-off of HbA1c = 5.7%). Although rare population allele counts were higher in both male and female haplogroup L hypertensives groups, as well as in the haplogroup L pre-diabetic group, these differences did not prove to be statistically significant. Possibly, the amount of rare population alleles identified in these groups is influenced by the under-representation of African sequences in the Genbank database, or the disproportionate number of haplogroup L participants that are classified as hypertensive (about 80%). As can be seen in Table 3, no statistically significant differences were found between any of the other groups when looking at either hypertension or hyperglycaemia.

2.3 Mutational load calculations and adjustments using MutPred pathogenicity scores

Next, MutPred adjusted loads, which serve as an estimate of the likely impact of a person's non-synonymous mtDNA substitutions on the functioning of their mtDNA encoded proteins, were calculated as described in the Introduction. Since i) the possible pathogenicity of variants with a MutPred score greater than 0.5 can be considered an “actionable hypothesis” (Li et al., 2009), and ii) these higher scoring variants are thought to be rarer and less likely to be common population variants (Pereira et al., 2011), we applied specific MutPred score criteria while carrying out statistical analyses. Table S1 shows the sum of MutPred scores (MutPred mutational load), the number of MutPred scored variants, and the calculated MutPred adjusted load for each participant, using these different criteria. Table 4 summarises the data by giving the means and standard deviations for the above mentioned genetic parameters, when using either all MutPred scored variants, or only those with MutPred scores above the 0.5 threshold. The impact of the reference sequence location is greatly reduced when only variants with MutPred scores greater than 0.5 are considered. As shown in Fig. 3, doing this resulted in a 37% change in calculated MutPred adjusted loads in haplogroup L groups, but only a 13% change in haplogroup MN groups, underlining the utility of applying this type of correction in studies using diverse populations. As previously mentioned, variants with low MutPred scores are likely to be close to neutral; we do not expect these variants to impact on phenotype. This is supported by the lack of purification selection against these variants (Cavadas et al., 2015). Our own data also reflected this, as haplogroup L participants had an average of 10.2 variants with MutPred scores below 0.5, while haplogroup MN participants only had an average of four low scoring variants. This ratio is greatly reduced

when moving to the other side of the MutPred scale: haplogroup L participants had an average of 1.6 variants with MutPred scores above 0.5, while Haplogroup MN participants had an average of 1.1 variants with scores above this threshold. Excluding these variants (MutPred scores less than 0.5) from further statistical analyses that followed then also allowed us to minimise their impact on our genetic parameter (MutPred adjusted load). The large standard deviations present in Fig. 3, when only variants with MutPred scores above 0.5 are included, can be attributed to the fact that 37% of participants (45 from haplogroup L and 89 from haplogroup MN) do not have any variants above this threshold.

2.4 Correlations between MutPred adjusted loads and measurements of blood pressure and blood glucose levels

To determine if there is any relationship between MutPred adjusted loads and measurements of blood pressure (Table 5) or blood glucose (Table 6), Pearson's correlation analyses were carried out for each of the four gender/mtDNA background groups. From Table 5, it can be seen that several MutPred adjusted loads were significantly correlated with blood pressure measurements. However, none of these significant associations remained after correcting for multiple comparisons. From Table 6, it can be seen that none of the MutPred adjusted loads, for either the entire mtDNA molecule, or those of individual electron transport chain (ETC) complexes, correlated significantly with blood glucose measurements.

2.5 Comparison of MutPred scores between different classifications of blood pressure and blood glucose levels

Next, we classified participants into different groups within the two CVD phenotypes that were investigated (hypertension and hyperglycaemia) as described in Materials and Methods (Table S1). To investigate the role of mtDNA variants in hypertension, we compared the mean values for genetic parameters of normotensive and hypertensive participants using independent *t*-tests. From Table 7, it is apparent that the total MutPred adjusted load differed significantly between normotensives and hypertensives within haplogroup L females, as well as haplogroup MN males. Similar to the above associations, after correction for multiple comparisons, significance was lost. We then compared the mean values for genetic parameters of participants with optimal blood glucose levels, those classified as pre-diabetic and those classified as diabetic within the different gender/mtDNA background groups, using one-way ANOVAS. None of these comparisons differed significantly (results not shown).

2.6 Comparison of high MutPred scoring variant frequency between different classifications of blood pressure and blood glucose levels

To see if having one or more variants with very high MutPred pathogenicity scores can increase the risk of disease, we determined the frequency of these high scoring variants within the different classifications in our CVD phenotypes. The number of participants with one or more variants with MutPred scores above 0.6, 0.7 or 0.8 within each gender/mtDNA background group are listed in Table 8 (hypertension classifications) and Table 9 (hyperglycaemia classifications). Also, in Fig. 4, the average number of variants per person belonging to a specific macro-haplogroup is represented. It can be seen that haplogroup L participants are no more likely than haplogroup MN participants to have one or more variants with a MutPred score above 0.6; haplogroup MN participants are slightly more likely to have at least one variant with a MutPred score above 0.7. For variants with MutPred scores above 0.8, the average number of instances is higher in haplogroup L participants compared to haplogroup MN participants (0.03 vs. 0.005), but these refer to a very low number of counts. This data correlate well with previous reports by Pereira et al. (2011) and Cavadas et al. (2015), who demonstrated that high MutPred scoring variants are more numerous in more recent branches (here haplogroup MN) of the phylogenetic tree, than branches deeper within the phylogenetic tree (here haplogroup L), due to purification selection. However, we found no significant differences in the number of participants carrying high MutPred scoring variants when comparing normotensives with hypertensives in any of the groups. We also found no significant differences between the three hyperglycaemia classifications within any of the groups.

3. Discussion

From the landmark Framingham Heart Studies (Mahmood et al., 2014), several risk factors have been identified as significant predictors of hypertension. In the SABPA cohort also, these factors, which included gender and population group, significantly predicted blood pressure (Hamer et al., 2015; Malan et al., 2015). Disparities in CVD onset and development between different population groups are often linked to gross socio-economic inequality (Kaufman et al., 2015). However, it is important to note that even though participants were matched on several factors, including socio-economic status, this disparity is still present in the SABPA cohort. In this study also, we showed that both gender and background

contributed to significant differences in measurements of blood pressure and blood glucose. Consequently, the cohort was divided into four gender/mtDNA background groups and analysed separately as has been done in other studies using the SABPA participants.

Assuming that rare non-synonymous population alleles (present in <0.1% of GenBank sequences) are more likely to be deleterious than common population alleles (present in >1% of GenBank sequences), one would expect rare population alleles to be present more frequently in the affected members of the cohort if mildly deleterious mtDNA variants were affecting susceptibility to disease. That was however not the case in our cohort, as no significant differences in the numbers of these population alleles were identified when the groups were compared. This is a less sophisticated analysis however, as the likelihood of pathogenicity of each allele is assumed, but not qualified by the use of more robust criteria. Using the MutPred program to qualify the pathogenicity of variants enabled us to carry out more sophisticated analyses. The usefulness of the MutPred scoring system to predict pathogenicity has been thoroughly demonstrated by Pereira et al. (2011) and Cavadas et al. (2015).

Genetic parameters such as the MutPred mutational load per participant, the number of MutPred scored variants per participant, and the MutPred adjusted load per participant, were calculated using specified variant inclusion criteria. Because of the position of the revised Cambridge Reference Sequence (rCRS) in the phylogeny, African lineages are expected to have more variants than European lineages which lie closer on the phylogeny to the reference. Importantly, many of these variants have MutPred scores below 0.5, are common population polymorphisms, and thus have a low likelihood of being mildly deleterious. The exclusion of variants with MutPred scores below 0.5 reduced the differences in the mean number of variants between haplogroup L and MN groups. Interestingly, it also increased the mean MutPred adjusted loads in haplogroup L groups, while it decreased this mean in haplogroup MN groups (Table 4). However, some common haplogroup defining variants do have MutPred scores above 0.5, and are still included (Table S2). It is for this reason that a second step of correction is needed, i.e., adjusting mutational load scores according to sequence position within the phylogeny. By excluding these low-impact variants from analyses, and then calculating MutPred adjusted loads, any bias that is potentially introduced by phylogenetic distance, when utilizing mutational load methods, is largely corrected.

We investigated the role of mtDNA variants in the presentation (or severity) of two major CVD phenotypes (hypertension and hyperglycaemia). MutPred adjusted loads for variants with MutPred pathogenicity scores above 0.5 were used in correlation tests. Although some significant differences were found when comparing MutPred adjusted loads between hypertensives and normotensives, these significances were not robust enough to withstand corrections for multiple testing. No significant differences between any groups were found within the hyperglycaemia classifications.

Although haplogroup L participants were more likely to have at least one high MutPred scoring variant above 0.5 than haplogroup MN participants, they were no more likely to have very high MutPred scoring variants (above 0.7). We found no significant relationship between the prevalence of potentially deleterious variants and any phenotypical classification.

Thus, from our data, we could not identify a relationship between MutPred adjusted loads or high MutPred scoring variants and the presentation of our investigated phenotypes. We however did not investigate the role of these genetic parameters in the outcome of disease. It is also important to note that this study was not sufficiently powered to detect differences in individual ETC complexes, which would provide a much more refined outcome. We did however present a new and updated method for attempting to associate mtDNA variation with a complex trait.

The current study is one of very few mtDNA genetic studies conducted in a cohort that includes African participants with extensively phenotyped CVD. The global burden of CVDs and the rising burden thereof in Africa make this collection of phenotypes especially important to investigate. More rare non-synonymous population alleles (present in <0.1% of GenBank sequences) were identified in haplogroup L participants than haplogroup MN participants, possibly influenced by the low presence of African sequences in the GenBank database. This underscores again the need to sequence more mtDNA from African populations, and especially from under-represented Southern African population groups.

Despite our data not indicating a statistically significant link between mtDNA variation and the two phenotypes investigated here, we are of the opinion that the method proposed here delivered well-powered results for the specific questions we posed, especially considering the modest size of the cohort. With the validity of the MutPred system being well established, we suggest the Mutational adjusted load method proposed here could be useful in similar investigations on other phenotypes and diseases. These investigations should indeed be

plentiful in the near future, with many associations between mtDNA variation and common complex disease being proposed.

4. Materials and methods

4.1 Cohort recruitment and sample collection

We included participants of the SABPA cohort in this study. Details on participant recruitment, and sample and data collection have been published elsewhere (Hamer et al., 2015; Malan et al., 2015). Inclusion criteria for the SABPA study were urban Black and Caucasian male and female teachers from South Africa ($n = 409$), with similar socio-economic status, aged 20–65 years, from the North-West Province (Malan et al., 2015). Participants were enrolled in the project in 2008–2009, having their first follow up in 2011–2012. During recruitment and before consent, study participants were informed about the objectives and procedures of the study, including investigations of genes involved in CVD. The study complied with criteria on human research set by the Helsinki declaration (2004) and was approved by the Ethics Committee of the North-West University (NWU 00036-07-S6).

4.2 Sequencing and data management

The complete mtDNA genome of each participant was sequenced at an average base coverage of about 1800× from two overlapping long range PCR products as previously described (van der Walt et al., 2012), using the Ion PGM and 200-bp templating and sequencing chemistry. This method was validated using two additional sequence chemistries (Illumina and pyrosequencing, QIAGEN, USA). Base calling and alignment were automatically performed by the Ion Torrent Suite 4.4 software. Variants were identified by the VariantCaller plug-in (version 5.0) using the rCRS (Andrews et al., 1999). A list of variants for each participant can be found in the supplementary file “JGG Supplementary variants SABPA”. Only consensus variants were used in this study. We did not investigate the effect of heteroplasmy here. Haplogroups were assigned using the online Haplogrep 2.0 tool (haplogrep.uibk.ac.at). MutPred scores were assigned to all non-synonymous variants (mutpred.mutdb.org/about.html). MutPred adjusted loads were calculated by obtaining the average of N , where N is the set of MutPred score values for variants within a specific target region, i.e., a single gene, a set of genes within an enzyme complex or the entire mtDNA

genome. A functional maximum parsimony (MP) network analysis was performed with the NETWORK (version 5) and NETWORK Publisher (version 2.0.0.1) software packages (<http://www.fluxus-engineering.com/sharenet.htm>), by using only mtDNA variants with MutPred pathogenicity scores above 0.5, rRNA variants and tRNA variants. The processing strategy to produce the networks, were aimed at reducing complexity (introduced by the large amount of sequences). Transversions, being chemically less likely to occur, were weighted three times more than transitions. Reduced median (RM) (Bandelt et al., 1995) processing split loci on the basis of genetic distance (reduction threshold r was 3 and 2 for macro-haplogroup L and MN networks respectively). This step was followed by median joining (MJ) (Bandelt et al., 1999) to calculate all possible shortest trees (ϵ was set to 30 and 0 for macro-haplogroup L and MN networks respectively) and produce a network. The “frequency > 1” criterion was activated to ignore unique sequences/taxa and reduce complexity. Finally, an MP clean-up step (Polzin and Daneschmand, 2003) was performed to remove unnecessary median vectors and links.

All figures were produced using Excel (Microsoft Office 365) or NETWORK Publisher (version 2.0.0.1) and were finalised in PowerPoint (Microsoft Office 365) and Adobe Photoshop Elements (Version 10.0).

4.3 Phenotyping

Normotensive and hypertensive classifications are based on 24 h ABPM measurements. A hypertensive classification was assigned to males with 24 h systolic ABPM ≥ 130 mmHg and/or 24 h diastolic ABPM ≥ 80 mmHg, and females with 24 h systolic ABPM ≥ 125 mmHg and/or 24 h diastolic ABPM ≥ 75 mmHg (Hermida et al., 2013; Mancia et al., 2013). Glycated haemoglobin (HbA1c) expressed as a percentage, which is measured to calculate the three month average plasma glucose concentration measurements, were used to classify participants as having either optimal blood glucose levels (HbA1c below 5.7%), falling within pre-diabetic ranges (HbA1c from 5.7% to 6.4%) or diabetic ranges (HbA1c above 6.4%) (American Diabetes Association, 2010). For a two-group classification (optimal or pre-diabetic glucose levels), a cut-off value of HbA1c = 5.7% was used.

4.4 Statistical analysis

All statistical analyses were carried out using IBM SPSS Statistics (version 23) or Prism GraphPad Prism software (version 6.05). A one-way analysis of variance (ANOVA) followed

by a post-hoc Tuckey test, was carried out to assess the relationships between gender and mtDNA background and two CVD clinical measurements (blood pressure and blood glucose levels).

The population frequency of rare population alleles, defined as having a frequency (Genbank frequency) below 0.1% on the global databases of more than 30000 sequences (MITOMAP: A human mitochondrial genome database. <http://www.mitomap.org>), was compared between those with optimal and those with high blood pressure or high blood glucose levels using a Fisher's exact test.

To assess the number of participants in each phenotype classification who possess one or more variants with MutPred pathogenicity scores above 0.6, 0.7 or 0.8, we applied Fisher's exact tests; a Bonferroni correction for multiple testing was applied to both sets of comparisons.

Pearson's correlation analyses were used to assess the correlation between MutPred adjusted loads, blood pressure and blood glucose levels in each of the four gender/mtDNA background groups, using a Bonferroni correction for multiple comparisons.

Mean MutPred adjusted loads of normotensive and hypertensive participants in the four groups were compared using independent *t*-tests, with a Bonferroni correction for multiple comparison. For participants with optimal blood glucose levels, those within pre-diabetic ranges, and those within diabetic ranges, mean MutPred adjusted loads were compared using one-way ANOVA, with a Tukey post-hoc test.

Acknowledgments

We acknowledge the Faculty of Natural Sciences of the North-West University for contributing to funding and Thermo Fisher South Africa for providing additional technical resources to this study. The present study was partially funded by the South African National Research Foundation; Medical Research Council; ROCHE Diagnostics; North-West University, South Africa; as well as the Metabolic Syndrome Institute, France. We would also like to acknowledge funding support from the Royal Society and the National Research Foundation of South Africa, for the academic meeting at which the project was mapped out.

References

- Achilli, A., Olivieri, A., Pala, M., Hooshyar Kashani, B.C., Perego, U.A., Gandini, F., Santoro, A., Battaglia, V., Grugni, V., Lancioni, H., Sirolla, C., Bonfigli, A.R., Cormio, A., Boemi, M., Testa, I., Semino, O., Ceriello, A., Spazzafumo, L., Gadaleta, M.N., Marra, M., Testa, R., Franceschi, C., Torroni, A., 2011. Mitochondrial DNA backgrounds might modulate diabetes complications rather than T2DM as a whole. *PLoS One* 6, e21029.
- Ameh, J., Godwin, I., Obi, I., Puepet, F., Aminu, B., Suleiman, T., 2011. The search for mitochondrial tRNA^{Leu(UUR)} A3243G mutation among type 2 diabetes mellitus patients in the Nigerian population. *Afr. J. Biotechnol.* 10, 13383-13389.
- American Diabetes Association, 2010. Standards of medical care in Diabetes. *Diabetes Care* 33(Suppl 1), S11-S61.
- Andrews, R.M., Kubacka, I., Chinnery, P.F., Lightowlers, R.N., Turnbull, D.M., Howell, N., 1999. Reanalysis and revision of the Cambridge reference sequence for human mitochondrial DNA. *Nat. Genet.* 23, 147.
- Bandelt, H-J., Forster, P., Röhl, A., 1999. Median-joining networks for inferring intraspecific phylogenies. *Mol. Biol. Evol.* 16, 37-48.
- Bandelt, H-J., Forster, P., Sykes, B.C., Richards, M.B., 1995. Mitochondrial portraits of human populations. *Genetics* 141, 743-753.
- Cardena, M.M., Ribeiro-dos-Santos, A., Santos, S., Mansur, A.J., Pereira, A.C., Fridman, C., 2014. Amerindian genetic ancestry is associated with higher survival rates compared to African and European ancestry in Brazilian patients with heart failure. *Int. J. Cardiol.* 176, 527-528.
- Cardena, M.M., Ribeiro-Dos-Santos, A.K., Santos, S.E., Mansur, A.J., Bernardez-Pereira, S., Santos, P.C., Pereira, A.C., Fridman, C., 2016. Mitochondrial and genomic ancestry are associated with etiology of heart failure in Brazilian patients. *J. Hum. Hypertens.* 30, 120-123.
- Cavadas, B., Soares, P., Camacho, R., Brandao, A., Costa, M.D., Fernandes, V., Pereira, J.B., Rito, T., Samuals, D., Periera, L., 2015. Fine time scaling of purifying selection on human nonsynonymous mtDNA mutations based on the worldwide population tree and mother-child pairs. *Hum. Mutat.* 36, 1100-1111.

489 Chinnery, P.F., Elliott, H.R., Syed, A., Rothwell, P.M., Oxford vascular study., 2010.
 490 Mitochondrial DNA haplogroups and risk of transient ischaemic attack and ischaemic stroke:
 491 a genetic association study. *Lancet Neurol.* 9, 498-503.

492 Elson, J.L., Andrews, R.M., Chinnery, P.F., Lightowlers, R.N., Turnbull, D.M., Howell, N.,
 493 2001. Analysis of European mtDNAs for recombination. *Am. J. Hum. Genet.* 68, 145-153.

494 Elson, J.L., Herrnstadt, C., Preston, G., Thal, L., Morris, C.M., Edwardson, J.A., Beal, M.F.,
 495 Turnbull, D.M., Howell, N., 2006. Does the mitochondrial genome play a role in the etiology
 496 of Alzheimer's disease? *Hum. Genet.* 119, 241-254.

497 Elson, J.L., Turnbull, D.M., Howell, N., 2004. Comparative genomics and the evolution of
 498 human mitochondrial DNA: assessing the effects of selection. *Am. J. Hum. Genet.* 74, 229-
 499 238.

500 Gorman, G.S., Schaefer, A.M., Ng, Y., Gomez, N., Blakely, E.L., Alston, C.L., Feeney, C.,
 501 Horvath, R., Yu-Wai-Man, P., Chinnery, P.F., Taylor, R.W., Turnbull, D.M., McFarland, R.,
 502 2015. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial
 503 disease. *Ann. Neurol.* 77, 753-759.

504 Gurdasani, D., Carstensen, T., Tekola-Ayele, F., Pagani, L., Tachmazidou, I., Hatzikotoulas,
 505 K., Karthikeyan, S., Iles, L., Pollard, M.O., Choudhury, A., Ritchie, G.R., Xue, Y., Asimit, J.,
 506 Nsubuga, R.N., Young, E.H., Pomilla, C., Kivinen, K., Rockett, K., Kamali, A., 2015. The
 507 African genome variation project shapes medical genetics in Africa. *Nature* 517, 327-332.

508 Hamer, M., von Känel, R., Reimann, M., Malan, N.T., Schutte, A.E., Huisman, H.W., Malan,
 509 L., 2015. Progression of cardiovascular risk factors in black Africans: 3 year follow up of the
 510 SABPA cohort study. *Atherosclerosis* 238, 52-54.

511 Hermida, R.C., Ayala, D.E., Mojon, A., Fontao, M.J., Chayan, L.F., 2013. Differences
 512 between men and woman in Ambulatory blood pressure thresholds for diagnosis of
 513 hypertension based on cardiovascular outcomes. *Chronobiol. Int.* 30, 221-232.

514 Herrnstadt, C., Elson, J.L., Fahy, E., Preston, G., Turnbull, D.M., Anderson, C., Ghosh, S.S.,
 515 Olefsky, J.M., Beal, M.F., Davis, R.E., Howell, N., 2002. Reduced-median-network analysis
 516 of complete mitochondrial DNA coding-region sequences for the major African Asian, and
 517 European haplogroups. *Am. J. Hum. Genet.* 70, 1152-1171.

518 Hernstadt, C., Howell, N., 2004. An evolutionary perspective on pathogenic mtDNA
519 mutations: haplogroup associations of clinical disorders. *Mitochondrion* 4, 791-798.

520 Hollingsworth, K.G., Gorman, G.S., Trenell, M.I., McFarland, R., Taylor, R.W., Turnbull,
521 D.M., MacGowan, G.A., Blamire, A.M., Chinnery, P.F., 2012. Cardiomyopathy is common
522 in patients with the mitochondrial DNA m3243A>G mutation and correlates with mutation
523 load. *Neuromuscul. Disord.* 22, 592-596.

524 Kaufman, J.S., Dolman, L., Rushani, D., Cooper, R.S., 2015. The contribution of genomic
525 research to explaining racial disparities in cardiovascular disease: A systematic review. *Am. J.*
526 *Epidemiol.* 181, 464-472.

527 Khogali, S.S., Myosi, B.M., Beattie, J.M., McKenna, W.J., Watkins, H., Poulton, J.A., 2001.
528 A common mitochondrial DNA variant associated with susceptibility to dilated
529 cardiomyopathy in two different populations. *Lancet* 357, 1265-1267.

530 Lammertyn, L., Schutte, A., Schutte, R., 2011. Blood glucose and nocturnal blood pressure in
531 African and Caucasian men: The SABPA study. *Diabetes Res. Clin. Pract.* 93, 235-242.

532 Li, B., Krishnan, V.G., Mort, M.E., Xin, F., Kamati, K.K., Cooper, D.N., Mooney, S.D.,
533 Radivojac, P., 2009. Automated inference of molecular mechanisms of disease from amino
534 acid substitutions. *Bioinformatics* 25, 2744-2750.

535 Liu, H., Prugnolle, F., Manica, A., Balloux, F., 2006. A geographically explicit genetic model
536 of worldwide human-settlement history. *Am. J. Hum. Genet.* 79, 230-237.

537 Lui, C., Yang, Q., Hwang, S., Sun, F., Johnson, A.D., Shirihai, O.S., Vasan, R.S., Levy, D.,
538 Schwartz, F., 2012. Association of genetic variation in the mitochondrial genome with blood
539 pressure and metabolic traits. *Hypertension* 60, 949-956.

540 Mahmood, S.S., Levy, D., Vasan, R.S., Wang, T.J., 2014. The Framingham Heart Study and
541 the epidemiology of cardiovascular disease: a historical perspective. *Lancet* 383, 999-1008.

542 Malan, L., Hamer, M., Frasure-Smith, N., Steyn, H.S., Malan, N.T., 2015. Cohort Profile:
543 Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) prospective
544 cohort study. *Int. J. Epidemiol.* 44, 1814-1822.

545 Mancina, G., Fagard, R., Narkiewicz, K., Redón, J., Zanchetti, A., Böhm, M., Christiaens, T.,
546 Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D.E., Ruilope, L.M.,

547 2013. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force
 548 for the management of arterial hypertension of the European Society of Hypertension (ESH)
 549 and of the European Society of Cardiology (ESC). *J. Hypertens.* 31, 1281-1357.

550 Manica, A., Amos, B., Balloux, F., Hanihara, T., 2007. The effect of ancient population
 551 bottlenecks on human phenotypic variation. *Nature* 448, 346-348.

552 Mensah, G.A. (2013). Descriptive epidemiology of cardiovascular risk factors and diabetes in
 553 Africa. *Prog. Cardiovasc. Dis.* 56, 240-250.

554 Pereira, L., Soares, P., Radivoiac, P., Li, B., Samuels, D.C., 2011. Comparing phylogeny and
 555 the predicted pathogenicity of protein variations reveals equal purifying selection across the
 556 global human mtDNA diversity. *Am. J. Hum. Genet.* 88, 433-439.

557 Polzin, T. Daneschmand, S.V., 2003. On Steiner trees and minimum spanning trees in
 558 hypergraphs. *Oper. Res. Lett.* 31, 12-20.

559 Robinson, M.T., Fischel-Ghodsian, N., Fraser, H.S., Nicholson, G.D., Grim, C.M., Wilson,
 560 D.M., Wilson, T.W., Grim, C.E., 2004. Genetic influences on the increase in blood pressure
 561 with age in normotensice subjects in Barbados. *Ethn. Dis.* 14, 57-63.

562 Rosa, A., Brehem, A., 2011. African human mtDNA phylogeography at-a-glance. *J.*
 563 *Anthropol. Sci.* 89, 25-58.

564 Salas, A., Richards, M., De La Fe, T., Lareu, M-V., Sobrino, B., Sánchez-Diz, P., Macaulay,
 565 V., Carracedo, Á., 2002. The making of the African mtDNA landscape. *Am. J. Hum. Genet.*
 566 71, 1082-111.

567 Salas, A., Elson, J.L., 2015. Mitochondrial DNA as a risk factor for false positives in case-
 568 control association studies. *J. Genet. Genomics* 42, 169-172.

569 Samuels, D.C., Carothers, A.D., Horton, R., Chinnery, P.F., 2006. The power to detect
 570 disease associated with mitochondrial DNA haplogroups. *Am. J. Hum. Genet.* 78, 713-720.

571 Schutte, A.E., Schutte, R., Huisman, H.W., van Rooyen, J.M., Fourie, C.M., Malan, N.T.,
 572 Malan, L., Mels, C.M., Smith, W., Moss, S.J., Towers, W.G., Kruger, S.H. Wentzel-Viljoen,
 573 E., Vorster, H.H., Kruger, A., 2012. Are behavioural risk factors to be blamed for the
 574 conversion from optimal blood pressure to hypertensive status in Black South Africans? A 5-
 575 year prospective study. *Int. J. Epidemiol.* 14, 1114-1123.

576 Soares, P., Abrantes, D., Rito, T., Thomson, N., Radivojac, P., Li, B., Macaulay, V., Samuels,
577 D.C., Pereira, L., 2013. Evaluating purifying selection in the mitochondrial DNA of various
578 mammalian species. *PLoS One* 8, e58993.

579 Taylor, R.W., Giordano, C., Davidson, M.M., d'Amati, G., Bain, H., Hayes, C.M., Leonard,
580 H., Barron, M.J., Casali, C., Santorelli, F.M., Hirano, M., Lightowers, R.N., DiMauro, S.,
581 Turnbull, D.M., 2003. A homoplasmic mitochondrial transfer ribonucleic acid mutation as a
582 cause of maternally inherited hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* 41, 1786-
583 1796.

584 Thusberg, J., Olatubosun, A., Vihinen, M., 2011. Performance of mutation pathogenicity
585 prediction methods on missense variants. *Hum. Mutat.* 32, 358-368.

586 Tuppen, H.A., Blakely, E.L., Turnbull, D.M., Taylor, R.W., 2010. Mitochondrial DNA
587 mutations and human disease. *Biochim. Biophys. Acta.* 1797, 113-128.

588 van der Walt, E.M., Smuts, I., Taylor, R.W., Elson, J.L., Turnbull, D.M., Louw, R., van der
589 Westhuizen, F.H., 2012. Characterization of mtDNA variation in a cohort of South African
590 paediatric patients with mitochondrial disease. *J. Hum. Genet.* 20, 650-656.

591 van der Westhuizen, F.H., Sinxadi, P.Z., Dandara, C., Smuts, I., Riordan, G., Meldau, S.,
592 Malik, A.N., Sweeney, M.G., Tsai, Y., Towers, G.W., Louw, R., Gorman, G.S., Payne, B.A.,
593 Soodyall, H., Pepper, M.S., Elson, J.L., 2015. Understanding the implications of
594 mitochondrial DNA variation in the health of Black Southern African populations: The 2014
595 Workshop. *Hum. Mutat.* 36, 569-571.

596 van Oven, M., Kayser, M., 2009. Updated comprehensive phylogenetic tree of global human
597 mitochondrial DNA variation. *Hum. Mutat.* 30, E386-394.

598 Wallace, D., 2010. Bioenergetics and the epigenome: Interface between the environment and
599 genes in common diseases. *Dev. Disabil. Res. Rev.* 16, 114-116.

600 Weissensteiner H., Pacher D., Kloss-Brandstätter A., Forer L., Specht G., Bandelt H.-J.,
601 Kronenberg F., Salas A., Schönherr S., 2016. HaploGrep 2: mitochondrial haplogroup
602 classification in the era of high-throughput sequencing. *Nucleic Acids Res.* 44(W1), W58-63.

603 Yarham, J.W., Elson, J.L., Blakely, E.L., McFarland, R., Taylor, R.W., 2010. Mitochondrial
604 tRNA mutations and disease. *Wiley Interdiscip. Rev. RNA* 1, 304-324.

605 Yu, X., Koczan, D., Sulonen, A-M., Akkad, D.A., Kroner, A., Comabella, M., Costa, G.,
606 Corongiu, D., Goertsches, R., Camina-Tato, M., Thiesen, H-J., Nyl, H.I., 2008. mtDNA
607 nt13708A variant increases the risk of multiple sclerosis. PLoS One 3, e153.

608 | Table 1. Phenotypical data on SABPA cohort

Parameter	Haplogroup L male	Haplogroup L female	Haplogroup MN male	Haplogroup MN female
Number of participants (<i>n</i>)	100	94	75	94
Age (years)	43.2 ± 8.17	45.7 ± 7.86	45.4 ± 10.5	44.5 ± 10.7
Body mass index	27.6 ± 5.77	32.9 ± 7.23	29.0 ± 5.33	26.2 ± 5.74
HbA1c (%)	6.23 ± 1.23	5.90 ± 1.14	5.66 ± 0.49	5.36 ± 0.29
24 h systolic ABPM (mmHg)	137.7 ± 16.0	128.6 ± 15.2	128.1 ± 10.6	120.7 ± 12.7
25 h diastolic ABPM (mmHg)	87.9 ± 10.7	78.8 ± 8.50	79.7 ± 7.72	73.8 ± 7.89

609 For each parameter, the group mean value is given ± standard deviation. Body mass index is a measure of body fat based on height and weight.
610 HbA1c, glycated haemoglobin is measured to calculate the three month average plasma glucose concentration. 24 h ABPM, 24 hour ambulatory
611 blood pressure monitoring.

612 Table 2. A list of novel variants found in the current cohort

rCRS position	rCRS NT	Variant NT	Mutation type	Gene	Mutation effect	MITOMAP report	Conservation (%)	MutPred pathogenicity score
8423	C	T	transition	<i>MT-ATP8</i>	syn: L→L	-	88.9	-
7351	T	C	transition	<i>MT-COI</i>	non-syn: L→P	-	48.9	0.432
7291	C	T	transition	<i>MT-COI</i>	non-syn: T→M	-	86.7	0.353
14945	G	A	transition	<i>MT-CYB</i>	non-syn: A→T	-	40.0	0.523
15577	C	T	transition	<i>MT-CYB</i>	syn: A→A	-	97.8	-
15124	A	G	transition	<i>MT-CYB</i>	syn: T→T	Single published	97.8	-
14718	A	G	transition	<i>MT-TE</i>	tRNA	-	2.2	-
4842	A	G	transition	<i>MT-ND2</i>	non-syn: T→A	Single unpublished	35.6	0.386
5106	A	G	transition	<i>MT-ND2</i>	non-syn: T→A	-	20.0	0.379
4479	C	T	transition	<i>MT-ND2</i>	syn: L→L	-	46.7	-
13552	G	A	transition	<i>MT-ND5</i>	non-syn: A→T	-	84.4	0.513
13538	T	C	transition	<i>MT-ND5</i>	non-syn: M→T	-	20.0	0.341
2603	C	A	transversion	<i>MT-RNR2</i>	rRNA	-	100.0	-
6320	T	G	transversion	<i>MT-COI</i>	syn: P→P	-	22.2	-
5232	C	A	transversion	<i>MT-ND2</i>	non-syn: P→T	Single unpublished	100.0	0.780
4906	C	A	transversion	<i>MT-ND2</i>	non-syn: S→Y	-	53.3	0.535
12969	C	G	transversion	<i>MT-ND5</i>	syn: T→T	Single unpublished	8.9	-

613

614 A list of variants found in this cohort, but not present on GenBank is given. The nucleotide (NT) change for each position is given, followed by
615 descriptive information about the variant. Four variants have been reported according to MITOMAP records, three are from unpublished records.
616 syn, synonymous change; non-syn, non-synonymous change.

617

618

619

620 Table 3. Number of non-synonymous variants unique to each group

GenBank frequency (%)	HT group	NT group	<i>P</i> -value	PD-BG group	O-BG group	<i>P</i> -value
Haplogroup L male						
<0.1	18	3	1	13	4	1
>1	5	1		4	1	
Haplogroup L female						
<0.1	14	2	1	6	10	0.19
>1	9	2		1	9	
Haplogroup MN male						
<0.1	1	4	0.28	2	2	0.52
>1	6	4		2	9	
Haplogroup MN female						
<0.1	8	3	0.38	2	8	1
>1	4	4		2	7	

621 The number of non-synonymous variants were calculated according to set criteria: very rare variants were those that are present in less than 0.1%
622 of GenBank sequences; common variants are those that are present in more than 1% of GenBank sequences. Only non-synonymous variants that
623 are unique for a specific group as defined by haplogroup, gender and disease classification were counted. *P*-values for a two-tailed Fisher's exact
624 test are given next to counts. HT, hypertensive; NT, normotensive; PD-BG, pre-diabetic blood glucose levels; O-BG, optimal blood glucose
625 levels.

626

627 Table 4. Summary of mtDNA variants parameters.

Group	MutPred mut. load per par.		Number of var. per par.		MutPred adj. load per par.	
	All var. included	Var. with MutPred scores > 0.5	All var. included	Var. with MutPred scores > 0.5	All var. included	Var. with MutPred scores > 0.5
Haplogroup L male	3.94 ± 1.50	0.85 ± 0.80	11.5 ± 3.6	1.4 ± 1.3	0.33 ± 0.04	0.44 ± 0.26
Haplogroup L female	4.18 ± 1.58	1.02 ± 0.99	12.1 ± 3.6	1.7 ± 1.7	0.34 ± 0.04	0.48 ± 0.23
Haplogroup MN male	2.04 ± 1.01	0.70 ± 0.72	5.3 ± 2.4	1.1 ± 1.2	0.39 ± 0.05	0.34 ± 0.31
Haplogroup MN female	1.94 ± 0.98	0.64 ± 0.66	4.9 ± 2.5	1 ± 1.1	0.40 ± 0.04	0.35 ± 0.31

628

629 The means ± standard deviation are given for specified genetic parameters per group. MutPred mutational load is the sum of MutPred scores for
630 either all variants per participant, or only for variants with a MutPred score above 0.5. Number of variants refer to those variants with a MutPred
631 score. The MutPred adjusted load is the MutPred mutational load per participant divided by the number of variants per participant. MutPred, a
632 pathogenicity score assigned to a variant using the MutPred program (mutpred.mutdb.org/about.html); mut, mutational; var, variants; par,
633 participant; adj, adjusted.

634

635 Table 5. Pearson's correlation coefficients for genetic parameters compared to mean values of 24 h ABPM measurements

Group	24 h ABPM	Total cohort (<i>n</i> = 363)		Haplogroup L males (<i>n</i> = 100)		Haplogroup L females (<i>n</i> = 94)		Haplogroup MN males (<i>n</i> = 75)		Haplogroup MN females (<i>n</i> = 94)	
		MutPred	Pearson <i>r</i>	MutPred	Pearson <i>r</i>	MutPred	Pearson <i>r</i>	MutPred	Pearson <i>r</i>	MutPred	Pearson <i>r</i>
Total mtDNA	Systolic	0.41 ± 0.28	.096	0.43 ± 0.25	.234*	0.48 ± 0.23	−.063	0.33 ± 0.31	−.110	0.34 ± 0.30	.156
	Diastolic		.075		.233*		−.067		−.241*		.122
CI	Systolic	0.37 ± 0.28	.051	0.41 ± 0.26	.110	0.45 ± 0.24	−.062	0.30 ± 0.30	−.073	0.28 ± 0.30	.011
	Diastolic		.040		.128		−.050		−.198		−.052
CIII	Systolic	0.09 ± 0.22	−.105*	0.05 ± 0.17	−.018	0.07 ± 0.19	−.177	0.10 ± 0.23	−.015	0.12 ± 0.25	.037
	Diastolic		−.129*		−.007		−.113		−.217		.001
CIV	Systolic	0.05 ± 0.17	.117*	0.07 ± 0.19	.217*	0.06 ± 0.19	−.014	0.01 ± 0.09	−.082	0.03 ± 0.13	.271**
	Diastolic		.116*		.154		−.009		−.253*		.358**
CV	Systolic	0.07 ± 0.20	.067	0.05 ± 0.18	.271**	0.04 ± 0.16	.234*	0.05 ± 0.19	−.205	0.07 ± 0.21	.161
	Diastolic		.009		.182		.093		−.164		.099

636 Pearson's correlations were carried out to investigate the relationship between MutPred adjusted loads for mtDNA loci as indicated, and blood
637 pressure measurements. Means ± standard deviations of MutPred adjusted loads are given with Pearson's correlation coefficients (*r*) for systolic
638 and diastolic 24 h ambulatory blood pressure monitoring (24 h ABPM) respectively. Correlations of significance (before correction for multiple
639 testing) are indicated in bold and by * (significant at the 0.05 level) and ** (significant at the 0.01 level). CI, NADH:ubiquinone oxidoreductase;
640 CIII, cytochrome c oxidoreductase; CIV, cytochrome c oxidase; CV, ATP synthase.

641

642 Table 6. Pearson’s correlation coefficients for genetic parameters compared to blood glucose measurements

Group	Total cohort (<i>n</i> = 363)		Haplogroup L male (<i>n</i> = 100)		Haplogroup L female (<i>n</i> = 94)		Haplogroup MN male (<i>n</i> = 75)		Haplogroup MN female (<i>n</i> = 94)	
	MutPred	Pearson <i>r</i>	MutPred	Pearson <i>r</i>	MutPred	Pearson <i>r</i>	MutPred	Pearson <i>r</i>	MutPred	Pearson <i>r</i>
Total mtDNA	0.41 ± 0.28	.039	0.43 ± 0.25	.062	0.48 ± 0.23	−.003	0.33 ± 0.31	−.076	0.34 ± 0.30	−.147
CI	0.37 ± 0.28	.048	0.41 ± 0.26	.013	0.45 ± 0.24	.019	0.30 ± 0.30	−.045	0.28 ± 0.30	−.164
CIII	0.09 ± 0.22	−.064	0.05 ± 0.17	−.002	0.07 ± 0.19	.035	0.10 ± 0.23	−.099	0.12 ± 0.25	.006
CIV	0.05 ± 0.17	.035	0.07 ± 0.19	.115	0.06 ± 0.19	−.040	0.01 ± 0.09	−.078	0.03 ± 0.13	−.069
CV	0.07 ± 0.20	−.005	0.05 ± 0.18	−.040	0.04 ± 0.16	.181	0.05 ± 0.19	−.041	0.07 ± 0.21	.088

643 Pearson’s correlations were carried out to investigate the relationship between MutPred adjusted loads for mtDNA loci as indicated, and blood
644 glucose (HbA1c%) measurements. Means ± standard deviations of MutPred adjusted loads are given with Pearson’s correlation coefficients (*r*).
645 CI, NADH:ubiquinone oxidoreductase; CIII, cytochrome c oxidoreductase; CIV, cytochrome c oxidase; CV, ATP synthase.

646

647 Table 7. Mean MutPred adjusted loads of normotensive participants compared to that of hypertensive participants

Group	Blood pressure status	Total cohort (NT = 115, HT = 248)		Haplogroup L male (NT = 22, HT = 78)		Haplogroup L female (NT = 18, HT = 76)		Haplogroup MN male (NT = 33, HT = 42)		Haplogroup MN female (NT = 42, HT = 52)	
		MutPred	<i>t</i> (df)	MutPred	<i>t</i> (df)	MutPred	<i>t</i> (df)	MutPred	<i>t</i> (df)	MutPred	<i>t</i> (df)
Total mtDNA	Normal	0.41 ± 0.29	-0.06 (384)	0.32 ± 0.30	1.97 (28)	0.59 ± 0.04	-4.67 (89)**	0.41 ± 0.30	-2.01 (73)*	0.33 ± 0.31	0.24 (92)
	Hyper	0.4 ± 0.27		0.47 ± 0.23		0.45 ± 0.24		0.27 ± 0.30		0.35 ± 0.30	
CI	Normal	0.36 ± 0.29	0.21 (384)	0.32 ± 0.30	1.62 (29)	0.56 ± 0.14	-2.84 (46)**	0.36 ± 0.30	-1.5 (-73)	0.28 ± 0.30	0.03 (92)
	Hyper	0.37 ± 0.28		0.43 ± 0.25		0.43 ± 0.26		0.26 ± 0.30		0.28 ± 0.30	
CIII	Normal	0.12 ± 0.25	-1.59 (209)	0.05 ± 0.18	0.10 (98)	0.13 ± 0.25	-1.15 (-20)	0.14 ± 0.27	-1.2 (-57)	0.11 ± 0.25	0.45 (92)
	Hyper	0.08 ± 0.20		0.05 ± 0.17		0.05 ± 0.17		0.07 ± 0.20		0.13 ± 0.26	
CIV	Normal	0.05 ± 0.18	-0.27 (384)	0.06 ± 0.19	0.30 (98)	0.15 ± 0.29	-1.48 (-19)	0.03 ± 0.14	-1.4 (-32)	0.01 ± 0.09	1.15 (85)
	Hyper	0.05 ± 0.16		0.07 ± 0.19		0.04 ± 0.15		0 ± 0		0.04 ± 0.16	
CV	Normal	0.07 ± 0.21	-0.30 (384)	0.02 ± 0.13	0.83 (98)	0 ± 0	2.75 (75)**	0.09 ± 0.24	-1 (-45)	0.07 ± 0.21	-0.03 (92)
	Hyper	0.06 ± 0.19		0.06 ± 0.19		0.05 ± 0.17		0.02 ± 0.13		0.07 ± 0.21	

648 Independent *t*-tests were carried out to compare means of MutPred adjusted loads for mtDNA loci as indicated, between normotensive (NT) and
649 hypertensive (HT) participants. Means ± standard deviations of MutPred adjusted loads are given with the test statistic (*t*) and degrees of
650 freedom (df). Differences of significance (before correction for multiple testing) are indicated in bold and by * (significant at the 0.05 level) and
651 ** (significant at the 0.01 level). CI, NADH:ubiquinone oxidoreductase; CIII, cytochrome c oxidoreductase; CIV, cytochrome c oxidase; CV,
652 ATP synthase.

653

Table 8. Number of participants within each gender, mtDNA background and blood pressure phenotype group having one or more variants with a MutPred score above 0.6, 0.7 or 0.8.

Number of variants	Number of haplogroup L male		Number of haplogroup L female		Number of haplogroup MN male		Number of haplogroup MN female	
	NT (<i>n</i> = 22)	HT (<i>n</i> = 78)	NT (<i>n</i> = 18)	HT (<i>n</i> = 76)	NT (<i>n</i> = 33)	HT (<i>n</i> = 42)	NT (<i>n</i> = 42)	HT (<i>n</i> = 52)
MutPred score > 0.6								
1	8	32	11	36	4	5	8	9
2	4	10	2	6	15	11	10	18
3	0	5	2	4	2	1	2	0
4	0	0	1	1	0	0	0	0
MutPred score > 0.7								
1	2	6	2	3	7	3	4	5
2	0	0	1	0	0	0	0	0
MutPred score > 0.8								
1	1	2	0	1	1	0	0	0
2	0	0	1	0	0	0	0	0

The number of participants in a specified group (e.g., hypertensive haplogroup L males) that have one or more variants (as indicated in the left first column) with a MutPred pathogenicity score above 0.6, 0.7 or 0.8 is given. Normotensive (NT) and hypertensive (HT) classifications are based on 24 hour systolic and diastolic ambulatory blood pressure measurements (24 h ABPM).

Table 9. Number of participants within each gender, mtDNA background and blood glucose phenotype group having one or more variants with a MutPred score above 0.6, 0.7 or 0.8

Number of variants	Number of haplogroup L male			Number of haplogroup L female			Number of haplogroup MN male			Number of haplogroup MN female		
	O-BG (n = 30)	PD-BG (n = 51)	D-BG (n = 19)	O-BG (n = 45)	PD-BG (n = 41)	D-BG (n = 8)	O-BG (n = 45)	PD-BG (n = 27)	D-BG (n = 3)	O-BG (n = 77)	PD-BG (n = 16)	D-BG (n = 6)
MutPred score > 0.6												
1	9	23	8	18	21	7	6	3	0	15	1	0
2	3	9	2	5	3	0	14	11	1	24	4	0
3	2	2	1	3	3	0	2	1	0	2	0	0
4	0	0	0	1	1	0	0	0	0	0	0	0
MutPred score > 0.7												
1	2	4	2	3	2	0	5	5	0	8	1	0
2	0	0	0	0	1	0	0	0	0	0	0	0
MutPred score > 0.8												
1	1	2	0	1	0	0	0	1	0	0	0	0
2	0	0	0	0	1	0	0	0	0	0	0	0

The number of participants in a specified group (e.g., African males with optimal blood glucose levels) that have one or more variants with a MutPred pathogenicity score above 0.6, 0.7 or 0.8 is given. HbA1c measurements were used to classify participants as having either optimal blood glucose levels (O-BG, optimal blood glucose levels, HbA1c < 5.7%), being prediabetic (PD-BG, prediabetic blood glucose levels, HbA1c from 5.7% to 6.4%) or diabetic (D-BG, diabetic blood glucose levels, HbA1c > 6.4%).

List of figures

Fig. 1. Comparison of differences in systolic and diastolic 24 hour ambulatory blood pressure monitoring measurements (ABPM), and glycated haemoglobin (HbA1c) as representation of blood glucose level, between gender and mtDNA background groups. ** P -value < 0.0001 ; * P -value < 0.001 ; ‡ P -value < 0.01 ; † P -value < 0.05

Fig. 2. Networks of haplogroup L (**A**) and haplogroup MN (**B**) participants. Ellipses indicate clusters of branches forming sub-haplogroups. Red nodes indicate potential median vectors. Coloured pie-chart nodes indicate the proportion of individuals per phenotype classification, as well as the number of participants per node. mtDNA variants responsible for links are listed in boxes; homoplasic variants are shown in italics, while transversions are shown in bold and marked with an *

Fig. 3. Representation of the effect on MutPred adjusted load when a correction is applied to address population stratification.

Fig. 4. The average number of variants with MutPred scores above different thresholds, per person within a specific haplogroup (L or MN).

Revised Figure 1
[Click here to download high resolution image](#)

Revised Figure 2
[Click here to download high resolution image](#)

Figure 3
[Click here to download high resolution image](#)

Figure 4
[Click here to download high resolution image](#)

Table S1. Important phenotypical and genetic data for each participant

Gender	24 h systolic / diastolic ABPM (mmHg)	HbA1c (%)	Blood pressure and blood glucose classifications	Complete cohort			Variants with a MutPred pathogenicity score above 0.3			Variants with a MutPred pathogenicity score above 0.5			Variants with a MutPred pathogenicity score above 0.6		
				Mut. load	Num of var	Adj load	Mut. load	Num of var	Adj load	Mut. load	Num of var	Adj load	Mut. load	Num of var	Adj load
Haplogroup L participants															
Male	136 / 82	5.5	Hyper and optimal	4.97	13	0.38	4.24	9	0.47	1.92	3	0.64	1.92	3	0.64
Male	148 / 83	5.7	Hyper and pre-diabetic	7.63	19	0.40	6.93	15	0.46	3.38	6	0.56	1.82	3	0.61
Male	152 / 97	6.4	Hyper and pre-diabetic	4.65	14	0.33	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	124 / 74	5.7	Hyper and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	145 / 89	6.1	Hyper and pre-diabetic	2.67	8	0.33	2.19	5	0.44	0.56	1	0.56	0.00	0	0.00
Female	143 / 75	5.8	Hyper and pre-diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	181 / 112	6.1	Hyper and pre-diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Female	136 / 82	5.3	Hyper and optimal	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	124 / 70	6.4	Hyper and pre-diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Female	121 / 78	6	Hyper and pre-diabetic	4.87	14	0.35	4.21	10	0.42	0.61	1	0.61	0.61	1	0.61
Female	117 / 77	5	Hyper and optimal	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	145 / 93	6.1	Hyper and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	158 / 101	12.3	Hyper and diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	143 / 90	5.9	Hyper and pre-diabetic	3.21	10	0.32	2.29	5	0.46	1.12	2	0.56	0.61	1	0.61
Male	147 / 97	5.6	Hyper and optimal	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Male	146 / 95	10.4	Hyper and diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Male	137 / 78	5	Hyper and optimal	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	157 / 105	6.2	Hyper and pre-diabetic	4.65	14	0.33	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	124 / 81	6.3	Hyper and pre-diabetic	4.89	14	0.35	4.23	10	0.42	1.12	2	0.56	0.61	1	0.61
Male	144 / 91	6.5	Hyper and diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61

Male	147 / 75	5.4	Hyper and optimal	5.12	13	0.39	4.40	9	0.49	2.07	3	0.69	2.07	3	0.69
Male	138 / 90	5.5	Hyper and optimal	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	131 / 86	8.8	Hyper and diabetic	8.38	20	0.42	7.68	16	0.48	4.00	7	0.57	2.44	4	0.61
Male	142 / 100	5.8	Hyper and pre-diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	113 / 71	5.3	Normal and optimal	5.54	14	0.40	5.06	11	0.46	1.87	3	0.62	1.87	3	0.62
Male	154 / 103	6.8	Hyper and diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	121 / 79	5.6	Normal and optimal	7.11	18	0.40	6.39	14	0.46	2.97	5	0.59	1.91	3	0.64
Female	151 / 78	5.7	Hyper and pre-diabetic	1.85	7	0.26	1.16	3	0.39	0.00	0	0.00	0.00	0	0.00
Female	110 / 64	5	Normal and optimal	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Female	123 / 73	5.8	Hyper and pre-diabetic	5.58	16	0.35	4.61	11	0.42	0.61	1	0.61	0.61	1	0.61
Female	123 / 74	7.3	Hyper and diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Female	136 / 85	6.9	Hyper and diabetic	8.41	20	0.42	7.70	16	0.48	4.28	7	0.61	3.21	5	0.64
Female	137 / 75	5.7	Hyper and pre-diabetic	2.64	8	0.33	2.16	5	0.43	0.00	0	0.00	0.00	0	0.00
Female	125 / 82	11.2	Hyper and diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	133 / 82	5.1	Hyper and optimal	7.68	19	0.40	6.96	15	0.46	3.54	6	0.59	2.47	4	0.62
Female	124 / 79	5.7	Hyper and pre-diabetic	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	111 / 65	5.5	Normal and optimal	5.55	14	0.40	4.83	10	0.48	2.07	3	0.69	2.07	3	0.69
Female	132 / 84	6.3	Hyper and pre-diabetic	4.94	13	0.38	4.21	9	0.47	1.46	2	0.73	1.46	2	0.73
Male	136 / 83	6.3	Hyper and pre-diabetic	5.38	15	0.36	4.48	10	0.45	1.85	3	0.62	1.34	2	0.67
Male	112 / 73	5.7	Normal and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	139 / 90	5.7	Hyper and pre-diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	152 / 108	6.8	Hyper and diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	145 / 87	6.5	Hyper and diabetic	3.28	9	0.36	2.80	6	0.47	1.15	2	0.57	1.15	2	0.57
Male	131 / 84	5.7	Hyper and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Female	154 / 95	8.7	Hyper and diabetic	7.68	19	0.40	6.96	15	0.46	3.54	6	0.59	2.47	4	0.62
Female	132 / 86	5.1	Hyper and optimal	3.92	10	0.39	3.44	7	0.49	1.79	3	0.60	1.79	3	0.60
Male	147 / 102	10.1	Hyper and diabetic	4.36	13	0.34	3.63	9	0.40	0.61	1	0.61	0.61	1	0.61
Female	133 / 84	5.7	Hyper and pre-diabetic	6.41	15	0.43	5.69	11	0.52	2.91	4	0.73	2.91	4	0.73
Male	151 / 94	6.6	Hyper and diabetic	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	150 / 82	6.8	Hyper and diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00

Female	114 / 67	5.6	Normal and optimal	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	154 / 100	7.5	Hyper and diabetic	4.15	12	0.35	3.42	8	0.43	0.61	1	0.61	0.61	1	0.61
Male	130 / 84	5.5	Hyper and optimal	5.20	13	0.40	4.72	10	0.47	2.38	4	0.60	1.29	2	0.64
Male	135 / 87	5.6	Hyper and optimal	5.35	15	0.36	4.67	11	0.42	1.29	2	0.65	1.29	2	0.65
Male	157 / 91	6.3	Hyper and pre-diabetic	5.20	13	0.40	4.72	10	0.47	2.38	4	0.60	1.29	2	0.64
Male	161 / 111	5.5	Hyper and optimal	5.08	14	0.36	4.42	10	0.44	1.31	2	0.66	1.31	2	0.66
Male	138 / 87	6.4	Hyper and pre-diabetic	2.65	8	0.33	2.17	5	0.43	0.00	0	0.00	0.00	0	0.00
Male	111 / 73	5.6	Normal and optimal	3.25	10	0.32	2.50	6	0.42	0.62	1	0.62	0.62	1	0.62
Male	142 / 96	5.4	Hyper and optimal	4.60	14	0.33	3.44	8	0.43	1.12	2	0.56	0.62	1	0.62
Female	126 / 83	5.7	Hyper and pre-diabetic	4.11	11	0.37	3.64	8	0.45	1.20	2	0.60	0.67	1	0.67
Female	144 / 84	5.7	Hyper and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	133 / 72	6.2	Hyper and pre-diabetic	1.55	6	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	107 / 62	7.6	Normal and diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	123 / 75	5.9	Normal and pre-diabetic	4.40	13	0.34	3.43	8	0.43	1.64	3	0.55	0.58	1	0.58
Male	118 / 79	5.7	Normal and pre-diabetic	5.38	15	0.36	4.48	10	0.45	1.85	3	0.62	1.34	2	0.67
Male	140 / 84	6.1	Hyper and pre-diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Female	137 / 78	6.2	Hyper and pre-diabetic	6.98	18	0.39	6.26	14	0.45	3.28	6	0.55	1.15	2	0.58
Female	115 / 73	5.3	Normal and optimal	5.00	14	0.36	4.35	10	0.43	1.24	2	0.62	1.24	2	0.62
Male	134 / 96	5.9	Hyper and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	129 / 83	5.7	Hyper and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	119 / 79	5.4	Hyper and optimal	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Female	107 / 71	6.2	Normal and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	126 / 90	5.5	Hyper and optimal	7.26	18	0.40	6.56	14	0.47	3.38	6	0.56	1.82	3	0.61
Male	122 / 75	6	Normal and pre-diabetic	5.00	15	0.33	4.11	10	0.41	1.14	2	0.57	0.63	1	0.63
Male	135 / 86	5.9	Hyper and pre-diabetic	3.94	12	0.33	3.28	8	0.41	0.61	1	0.61	0.61	1	0.61
Female	140 / 87	6	Hyper and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	119 / 78	5.7	Hyper and pre-diabetic	3.23	9	0.36	2.75	6	0.46	1.21	2	0.61	1.21	2	0.61
Female	116 / 73	5.6	Normal and optimal	2.60	8	0.33	2.13	5	0.43	0.00	0	0.00	0.00	0	0.00
Male	132 / 82	5.8	Hyper and pre-diabetic	5.20	14	0.37	4.72	11	0.43	1.67	3	0.56	1.15	2	0.58
Male	124 / 79	6.3	Normal and pre-diabetic	4.90	13	0.38	4.42	10	0.44	1.31	2	0.66	1.31	2	0.66

Female	117 / 75	5.7	Hyper and pre-diabetic	1.55	6	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	121 / 73	5.4	Hyper and optimal	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Female	144 / 90	5.5	Hyper and optimal	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Female	131 / 71	5.7	Hyper and pre-diabetic	2.11	7	0.30	1.64	4	0.41	0.00	0	0.00	0.00	0	0.00
Female	120 / 70	6.3	Hyper and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Female	113 / 73	5.4	Normal and optimal	5.34	15	0.36	4.61	11	0.42	0.61	1	0.61	0.61	1	0.61
Female	127 / 79	5.8	Hyper and pre-diabetic	4.39	14	0.31	3.24	8	0.41	0.51	1	0.51	0.00	0	0.00
Female	130 / 81	5	Hyper and optimal	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Female	123 / 80	5.2	Hyper and optimal	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Female	119 / 74	5.8	Normal and pre-diabetic	2.26	7	0.32	1.79	4	0.45	0.56	1	0.56	0.00	0	0.00
Female	105 / 68	6.1	Normal and pre-diabetic	1.82	6	0.30	1.34	3	0.45	0.52	1	0.52	0.00	0	0.00
Female	116 / 77	5.4	Hyper and optimal	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Female	113 / 74	6.4	Normal and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Female	139 / 91	5.7	Hyper and pre-diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Female	163 / 100	6	Hyper and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	132 / 85	5.4	Hyper and optimal	1.13	4	0.28	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	162 / 96	6.3	Hyper and pre-diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	148 / 94	9.5	Hyper and diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Male	128 / 88	6	Hyper and pre-diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	135 / 94	6.3	Hyper and pre-diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Male	152 / 96	6.1	Hyper and pre-diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	133 / 88	6.4	Hyper and pre-diabetic	4.52	14	0.32	3.36	8	0.42	1.04	2	0.52	0.00	0	0.00
Male	118 / 78	5.1	Normal and optimal	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	130 / 82	6.4	Hyper and pre-diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Male	140 / 88	5.6	Hyper and optimal	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	148 / 92	6.2	Hyper and pre-diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	125 / 85	7.4	Hyper and diabetic	4.90	13	0.38	4.42	10	0.44	1.31	2	0.66	1.31	2	0.66
Female	133 / 83	5	Hyper and optimal	5.12	13	0.39	4.40	9	0.49	2.07	3	0.69	2.07	3	0.69
Female	130 / 84	6.3	Hyper and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	132 / 90	6.3	Hyper and pre-diabetic	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61

Male	132 / 85	5.3	Hyper and optimal	3.92	10	0.39	3.44	7	0.49	1.79	3	0.60	1.79	3	0.60
Female	115 / 67	5.2	Normal and optimal	2.84	8	0.35	2.36	5	0.47	0.66	1	0.66	0.66	1	0.66
Male	144 / 92	5.9	Hyper and pre-diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	145 / 85	6.2	Hyper and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	179 / 88	5.6	Hyper and optimal	2.97	10	0.30	2.05	5	0.41	0.51	1	0.51	0.00	0	0.00
Male	199 / 126	5.9	Hyper and pre-diabetic	3.94	12	0.33	3.28	8	0.41	0.61	1	0.61	0.61	1	0.61
Female	130 / 77	5.5	Hyper and optimal	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Female	129 / 78	5.3	Hyper and optimal	1.55	6	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	127 / 81	5.9	Hyper and pre-diabetic	4.32	13	0.33	3.17	7	0.45	1.29	2	0.64	0.78	1	0.78
Female	115 / 64	6	Normal and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Female	129 / 82	6.1	Hyper and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	140 / 84	5.5	Hyper and optimal	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	131 / 82	5.7	Hyper and pre-diabetic	6.83	17	0.40	6.13	13	0.47	3.38	6	0.56	1.82	3	0.61
Female	117 / 78	5.3	Hyper and optimal	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	110 / 72	5.3	Normal and optimal	4.03	10	0.40	3.72	8	0.46	1.84	3	0.61	1.34	2	0.67
Female	111 / 72	5.2	Normal and optimal	2.65	8	0.33	2.17	5	0.43	0.00	0	0.00	0.00	0	0.00
Female	111 / 73	5.5	Normal and optimal	5.75	15	0.38	5.28	12	0.44	1.79	3	0.60	1.29	2	0.64
Female	130 / 84	6.2	Hyper and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	122 / 72	6.1	Normal and pre-diabetic	3.23	9	0.36	2.75	6	0.46	1.21	2	0.61	1.21	2	0.61
Male	172 / 111	5.4	Hyper and optimal	3.23	9	0.36	2.75	6	0.46	1.21	2	0.61	1.21	2	0.61
Male	112 / 72	5.8	Normal and pre-diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	168 / 90	5.2	Hyper and optimal	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	139 / 92	5.2	Hyper and optimal	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	145 / 91	5.1	Hyper and optimal	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Female	116 / 78	5.3	Hyper and optimal	4.71	13	0.36	4.24	10	0.42	1.12	2	0.56	0.61	1	0.61
Female	115 / 75		Hyper and	7.11	18	0.40	6.39	14	0.46	2.97	5	0.59	1.91	3	0.64
Male	114 / 77	5.7	Normal and pre-diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Male	154 / 94	6.6	Hyper and diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	140 / 94	5.4	Hyper and optimal	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	117 / 72	5.4	Normal and optimal	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63

Female	148 / 93	7.4	Hyper and diabetic	6.04	17	0.36	4.98	11	0.45	1.78	3	0.59	1.26	2	0.63
Female	130 / 82	6.4	Hyper and pre-diabetic	4.85	14	0.35	3.97	9	0.44	1.64	3	0.55	0.61	1	0.61
Female	130 / 85	5.6	Hyper and optimal	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	117 / 80	5.3	Hyper and optimal	6.79	16	0.42	6.48	14	0.46	2.86	5	0.57	1.82	3	0.61
Female	129 / 86	5.5	Hyper and optimal	3.60	11	0.33	2.90	7	0.41	0.55	1	0.55	0.00	0	0.00
Female	135 / 85	5.7	Hyper and pre-diabetic	3.73	10	0.37	3.25	7	0.46	1.71	3	0.57	1.21	2	0.61
Female	145 / 88	6.1	Hyper and pre-diabetic	7.11	18	0.40	6.39	14	0.46	2.97	5	0.59	1.91	3	0.64
Female	129 / 70	5.7	Hyper and pre-diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	137 / 76	5.5	Hyper and optimal	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	141 / 94	5.4	Hyper and optimal	4.81	13	0.37	4.34	10	0.43	1.23	2	0.61	1.23	2	0.61
Male	140 / 89	5.9	Hyper and pre-diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	117 / 77	6.2	Normal and pre-diabetic	1.98	6	0.33	1.50	3	0.50	0.68	1	0.68	0.68	1	0.68
Male	128 / 76	6.1	Normal and pre-diabetic	3.97	12	0.33	3.25	8	0.41	0.61	1	0.61	0.61	1	0.61
Male	122 / 82	5.1	Hyper and optimal	3.21	10	0.32	2.29	5	0.46	1.12	2	0.56	0.61	1	0.61
Male	146 / 100	6.1	Hyper and pre-diabetic	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	124 / 80	5.2	Hyper and optimal	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Male	135 / 87	5.5	Hyper and optimal	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	123 / 79	5.9	Normal and pre-diabetic	5.38	15	0.36	4.48	10	0.45	1.85	3	0.62	1.34	2	0.67
Male	158 / 101	9.6	Hyper and diabetic	3.92	10	0.39	3.44	7	0.49	1.79	3	0.60	1.79	3	0.60
Male	125 / 82	9.4	Hyper and diabetic	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	114 / 68	5.6	Normal and optimal	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	124 / 79	6	Normal and pre-diabetic	5.86	16	0.37	4.97	11	0.45	2.33	4	0.58	1.83	3	0.61
Female	160 / 98	5.7	Hyper and pre-diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	181 / 112	9.6	Hyper and diabetic	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	121 / 66	5.3	Hyper and optimal	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	111 / 65	6.2	Normal and pre-diabetic	5.16	14	0.37	4.68	11	0.43	1.11	2	0.56	0.61	1	0.61
Female	113 / 77	5.3	Hyper and optimal	4.40	13	0.34	3.43	8	0.43	1.64	3	0.55	0.58	1	0.58
Male	161 / 97	5.9	Hyper and pre-diabetic	4.21	12	0.35	3.48	8	0.44	1.16	2	0.58	0.61	1	0.61
Female	122 / 77	5.9	Hyper and pre-diabetic	4.93	14	0.35	4.20	10	0.42	0.61	1	0.61	0.61	1	0.61
Male	124 / 79	6	Normal and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00

Female	104 / 63	5.2	Normal and optimal	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	160 / 84	12.8	Hyper and diabetic	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Female	131 / 82	6.5	Hyper and diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	112 / 74	5.6	Normal and optimal	4.66	13	0.36	4.18	10	0.42	0.61	1	0.61	0.61	1	0.61
Male	161 / 108	5.8	Hyper and pre-diabetic	5.23	14	0.37	4.24	9	0.47	1.92	3	0.64	1.92	3	0.64
Female	126 / 82	5	Hyper and optimal	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Female	120 / 74	5.2	Hyper and optimal	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	158 / 94	5.8	Hyper and pre-diabetic	4.42	13	0.34	3.69	9	0.41	0.61	1	0.61	0.61	1	0.61
Male	138 / 93	6.7	Hyper and diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	129 / 82	5.6	Hyper and optimal	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	124 / 83	6.1	Hyper and pre-diabetic	5.34	15	0.36	4.61	11	0.42	0.61	1	0.61	0.61	1	0.61
Female	126 / 81	6.2	Hyper and pre-diabetic	3.46	10	0.35	2.89	7	0.41	0.51	1	0.51	0.00	0	0.00
Female	122 / 68	5.5	Hyper and optimal	7.26	18	0.40	6.56	14	0.47	3.38	6	0.56	1.82	3	0.61
Female	131 / 86	4.8	Hyper and optimal	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Female	145 / 78	5.8	Hyper and pre-diabetic	5.34	15	0.36	4.61	11	0.42	0.61	1	0.61	0.61	1	0.61
Male	131 / 87	5.7	Hyper and pre-diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Male	111 / 72	5.5	Normal and optimal	4.93	14	0.35	4.20	10	0.42	0.61	1	0.61	0.61	1	0.61
Male	122 / 74	5.2	Normal and optimal	4.66	14	0.33	3.77	9	0.42	1.14	2	0.57	0.63	1	0.63
Male	132 / 78	9.2	Hyper and diabetic	4.38	13	0.34	3.72	9	0.41	0.61	1	0.61	0.61	1	0.61
Female	121 / 74	5.5	Hyper and optimal	1.55	6	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	127 / 73	5.2	Hyper and optimal	4.93	14	0.35	4.20	10	0.42	0.61	1	0.61	0.61	1	0.61
Male	153 / 90	5.6	Hyper and optimal	4.56	13	0.35	4.09	10	0.41	0.61	1	0.61	0.61	1	0.61
Male	135 / 98	5.6	Hyper and optimal	5.54	14	0.40	5.06	11	0.46	1.87	3	0.62	1.87	3	0.62
Male	163 / 97	6.3	Hyper and pre-diabetic	2.18	7	0.31	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
<i>Haplogroup MN participants</i>															
Male	133 / 93	5.5	Hyper and optimal	1.35	5	0.27	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	123 / 68	5.6	Hyper and optimal	3.43	8	0.43	3.02	6	0.50	1.81	3	0.60	1.26	2	0.63
Female	190 / 119	5.2	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	128 / 85	5.6	Hyper and optimal	2.09	5	0.42	1.93	4	0.48	1.11	2	0.55	0.00	0	0.00
Female	131 / 72	5.3	Hyper and optimal	4.11	11	0.37	3.33	7	0.48	1.71	3	0.57	1.20	2	0.60

Female	123 / 83	5.7	Hyper and pre-diabetic	0.99	3	0.33	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	120 / 70	5	Hyper and optimal	2.06	6	0.34	1.65	4	0.41	0.00	0	0.00	0.00	0	0.00
Female	111 / 67	5.5	Normal and optimal	3.13	8	0.39	2.86	6	0.48	1.22	2	0.61	1.22	2	0.61
Female	110 / 70	5.4	Normal and optimal	3.88	9	0.43	3.61	7	0.52	1.97	3	0.66	1.97	3	0.66
Male	124 / 82	6.1	Hyper and pre-diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	132 / 83	5.6	Hyper and optimal	1.13	3	0.38	1.13	3	0.38	0.00	0	0.00	0.00	0	0.00
Male	126 / 81	5.7	Hyper and pre-diabetic	2.53	7	0.36	2.11	5	0.42	0.00	0	0.00	0.00	0	0.00
Female	113 / 69	6.3	Normal and pre-diabetic	4.11	11	0.37	3.33	7	0.48	1.71	3	0.57	1.20	2	0.60
Female	113 / 70	5.7	Normal and pre-diabetic	2.26	6	0.38	1.92	4	0.48	0.61	1	0.61	0.61	1	0.61
Female	111 / 69	5.3	Normal and optimal	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	118 / 72	5.4	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	112 / 69	5.7	Normal and pre-diabetic	0.99	3	0.33	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	113 / 72	5.6	Normal and optimal	0.99	3	0.33	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	116 / 76	5.3	Hyper and optimal	4.94	12	0.41	4.31	9	0.48	1.27	2	0.64	0.77	1	0.77
Female	117 / 71	5.1	Normal and optimal	2.78	8	0.35	2.16	5	0.43	0.51	1	0.51	0.00	0	0.00
Female	120 / 73	5.1	Hyper and optimal	0.99	3	0.33	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	130 / 79	5.4	Hyper and optimal	1.44	4	0.36	1.17	3	0.39	0.00	0	0.00	0.00	0	0.00
Female	120 / 74	5.5	Hyper and optimal	1.14	4	0.28	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	133 / 81	5.3	Hyper and optimal	3.25	9	0.36	2.82	6	0.47	1.22	2	0.61	1.22	2	0.61
Male	135 / 89	5.2	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	129 / 82	5.3	Hyper and optimal	2.84	7	0.41	2.51	5	0.50	1.19	2	0.60	1.19	2	0.60
Male	158 / 94	6.3	Hyper and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	133 / 79	7.8	Hyper and diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	120 / 79	5.2	Hyper and optimal	2.57	7	0.37	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Female	110 / 61	5.2	Normal and optimal	1.50	3	0.50	1.50	3	0.50	0.68	1	0.68	0.68	1	0.68
Male	128 / 69	5.1	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	168 / 84	5.7	Hyper and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	126 / 82	5.7	Hyper and pre-diabetic	2.82	7	0.40	2.56	5	0.51	1.74	3	0.58	1.24	2	0.62
Female	124 / 70	5.3	Hyper and optimal	1.22	4	0.30	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	124 / 79	5.2	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00

Female	117 / 71	5.4	Normal and optimal	1.85	6	0.31	1.22	3	0.41	0.00	0	0.00	0.00	0	0.00
Female	120 / 78	5.2	Hyper and optimal	2.80	7	0.40	2.09	4	0.52	1.27	2	0.64	1.27	2	0.64
Female	133 / 80	5.6	Hyper and optimal	3.99	10	0.40	3.55	7	0.51	1.91	3	0.64	1.40	2	0.70
Male	125 / 78	5.7	Normal and pre-diabetic	1.76	5	0.35	1.43	3	0.48	0.61	1	0.61	0.61	1	0.61
Male	123 / 80	5.8	Hyper and pre-diabetic	2.96	9	0.33	2.24	5	0.45	1.09	2	0.55	0.57	1	0.57
Female	129 / 81	5.4	Hyper and optimal	4.11	11	0.37	3.33	7	0.48	1.71	3	0.57	1.20	2	0.60
Female	112 / 72	5.1	Normal and optimal	5.59	15	0.37	4.87	11	0.44	1.29	2	0.64	1.29	2	0.64
Female	124 / 77	5.6	Hyper and optimal	2.57	7	0.37	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Female	125 / 83	5.1	Hyper and optimal	7.12	17	0.42	6.10	12	0.51	2.86	4	0.72	2.86	4	0.72
Female	126 / 74	5.4	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	109 / 70	5	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	122 / 74	5	Hyper and optimal	2.88	8	0.36	2.45	5	0.49	1.22	2	0.61	1.22	2	0.61
Female	122 / 79	5.6	Hyper and optimal	4.11	11	0.37	3.33	7	0.48	1.71	3	0.57	1.20	2	0.60
Male	118 / 74	5.2	Normal and optimal	2.28	5	0.46	2.12	4	0.53	1.29	2	0.65	1.29	2	0.65
Male	114 / 66	5.1	Normal and optimal	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	124 / 72	5.8	Normal and pre-diabetic	3.88	9	0.43	3.61	7	0.52	1.97	3	0.66	1.97	3	0.66
Male	150 / 91	5.6	Hyper and optimal	1.76	5	0.35	1.43	3	0.48	0.61	1	0.61	0.61	1	0.61
Male	136 / 78	5.2	Hyper and optimal	6.40	15	0.43	5.63	11	0.51	2.86	4	0.72	2.86	4	0.72
Female	123 / 74	6.3	Hyper and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	104 / 66	5.6	Normal and optimal	3.52	8	0.44	3.26	6	0.54	2.43	4	0.61	1.88	3	0.63
Female	107 / 61	5.1	Normal and optimal	2.57	7	0.37	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Female	137 / 76	5.1	Hyper and optimal	1.36	3	0.45	1.36	3	0.45	0.54	1	0.54	0.00	0	0.00
Male	124 / 81	5.3	Hyper and optimal	2.32	6	0.39	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Male	124 / 86	5	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	139 / 87	6.4	Hyper and pre-diabetic	1.76	5	0.35	1.43	3	0.48	0.61	1	0.61	0.61	1	0.61
Female	110 / 66	5.4	Normal and optimal	2.28	5	0.46	2.12	4	0.53	1.29	2	0.65	1.29	2	0.65
Female	102 / 61	5.1	Normal and optimal	1.71	4	0.43	1.71	4	0.43	0.00	0	0.00	0.00	0	0.00
Female	106 / 70	5.8	Normal and pre-diabetic	2.26	6	0.38	1.92	4	0.48	0.61	1	0.61	0.61	1	0.61
Female	122 / 70	5.5	Hyper and optimal	2.06	4	0.51	2.06	4	0.51	1.24	2	0.62	1.24	2	0.62
Female	126 / 73	5.3	Hyper and optimal	2.32	6	0.39	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62

Male	140 / 82	5.2	Hyper and optimal	1.79	5	0.36	1.52	4	0.38	0.00	0	0.00	0.00	0	0.00
Female	121 / 72	5.6	Hyper and optimal	1.80	4	0.45	1.80	4	0.45	0.62	1	0.62	0.62	1	0.62
Female	111 / 66	4.8	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	135 / 80	5.3	Hyper and optimal	2.62	6	0.44	2.46	5	0.49	1.29	2	0.65	1.29	2	0.65
Female	115 / 77	5	Hyper and optimal	1.59	4	0.40	1.59	4	0.40	0.00	0	0.00	0.00	0	0.00
Female	119 / 71	5.3	Normal and optimal	2.93	7	0.42	2.59	5	0.52	1.28	2	0.64	1.28	2	0.64
Male	127 / 71	5.6	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	147 / 93	6.1	Hyper and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	113 / 75	5.5	Normal and optimal	3.99	10	0.40	3.55	7	0.51	1.91	3	0.64	1.40	2	0.70
Male	122 / 82	5.5	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	126 / 67	5.7	Normal and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	115 / 63	5.2	Normal and optimal	1.68	3	0.56	1.68	3	0.56	0.86	1	0.86	0.86	1	0.86
Female	112 / 59	5.2	Normal and optimal	3.58	9	0.40	3.14	6	0.52	1.91	3	0.64	1.40	2	0.70
Female	137 / 86	6.4	Hyper and pre-diabetic	1.24	4	0.31	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	125 / 74	5.3	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	115 / 78	5.6	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	125 / 76	5.8	Normal and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	148 / 75	5.7	Hyper and pre-diabetic	2.28	5	0.46	2.12	4	0.53	1.29	2	0.65	1.29	2	0.65
Female	124 / 86	5.2	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	120 / 69	5.2	Normal and optimal	1.13	3	0.38	1.13	3	0.38	0.00	0	0.00	0.00	0	0.00
Female	117 / 70	4.8	Normal and optimal	4.54	14	0.32	3.38	8	0.42	1.06	2	0.53	0.00	0	0.00
Female	127 / 81	5.3	Hyper and optimal	1.60	4	0.40	1.43	3	0.48	0.61	1	0.61	0.61	1	0.61
Female	108 / 66	5	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	120 / 72	5.4	Normal and optimal	1.67	4	0.42	1.67	4	0.42	0.51	1	0.51	0.00	0	0.00
Female	123 / 81	5.6	Hyper and optimal	3.58	9	0.40	3.14	6	0.52	1.91	3	0.64	1.40	2	0.70
Female	140 / 81	5.8	Hyper and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	117 / 74	5.1	Normal and optimal	2.93	7	0.42	2.59	5	0.52	1.28	2	0.64	1.28	2	0.64
Female	115 / 71	5.4	Normal and optimal	0.99	3	0.33	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	117 / 66	6.1	Normal and pre-diabetic	0.99	3	0.33	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	113 / 70	5.4	Normal and optimal	1.37	4	0.34	1.21	3	0.40	0.00	0	0.00	0.00	0	0.00

Male	132 / 82	5.6	Hyper and optimal	3.43	8	0.43	3.01	6	0.50	1.36	2	0.68	1.36	2	0.68
Female	105 / 73	5.2	Normal and optimal	0.99	3	0.33	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	138 / 85	5.1	Hyper and optimal	4.11	11	0.37	3.33	7	0.48	1.71	3	0.57	1.20	2	0.60
Female	106 / 72	5.1	Normal and optimal	1.49	3	0.50	1.49	3	0.50	0.67	1	0.67	0.67	1	0.67
Male	135 / 90	5.5	Hyper and optimal	1.76	5	0.35	1.43	3	0.48	0.61	1	0.61	0.61	1	0.61
Male	125 / 80	5.5	Hyper and optimal	1.16	3	0.39	1.16	3	0.39	0.00	0	0.00	0.00	0	0.00
Male	134 / 82	5.6	Hyper and optimal	1.34	3	0.45	1.34	3	0.45	0.52	1	0.52	0.00	0	0.00
Female	115 / 77	5.5	Hyper and optimal	2.70	6	0.45	2.48	5	0.50	1.31	2	0.66	1.31	2	0.66
Female	127 / 73	5.7	Hyper and pre-diabetic	1.64	4	0.41	1.64	4	0.41	0.51	1	0.51	0.00	0	0.00
Female	112 / 71	5.2	Normal and optimal	2.57	7	0.37	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Female	126 / 75	5.7	Hyper and pre-diabetic	1.13	3	0.38	1.13	3	0.38	0.00	0	0.00	0.00	0	0.00
Female	118 / 73		Normal and	1.13	3	0.38	1.13	3	0.38	0.00	0	0.00	0.00	0	0.00
Female	119 / 72	4.7	Normal and optimal	1.13	3	0.38	1.13	3	0.38	0.00	0	0.00	0.00	0	0.00
Female	143 / 93	5.4	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	120 / 69	5.1	Hyper and optimal	3.25	9	0.36	2.82	6	0.47	1.22	2	0.61	1.22	2	0.61
Female	112 / 76	5.9	Hyper and pre-diabetic	2.28	5	0.46	2.12	4	0.53	1.29	2	0.65	1.29	2	0.65
Male	123 / 78	5.7	Normal and pre-diabetic	1.47	4	0.37	1.47	4	0.37	0.00	0	0.00	0.00	0	0.00
Male	123 / 73	5.5	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	118 / 75	5.4	Normal and optimal	2.82	7	0.40	2.56	5	0.51	1.74	3	0.58	1.24	2	0.62
Male	151 / 95	6.1	Hyper and pre-diabetic	4.11	11	0.37	3.45	7	0.49	1.80	3	0.60	1.29	2	0.65
Male	123 / 74	5.9	Normal and pre-diabetic	2.09	5	0.42	1.93	4	0.48	1.11	2	0.55	0.00	0	0.00
Female	108 / 69	5.2	Normal and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	121 / 65	5.9	Normal and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	127 / 81	5.4	Hyper and optimal	1.96	7	0.28	1.26	3	0.42	0.00	0	0.00	0.00	0	0.00
Female	123 / 78	5	Hyper and optimal	2.89	7	0.41	2.55	5	0.51	1.24	2	0.62	1.24	2	0.62
Female	110 / 67	5.1	Normal and optimal	2.93	7	0.42	2.59	5	0.52	1.28	2	0.64	1.28	2	0.64
Female	112 / 74	5.2	Normal and optimal	1.78	5	0.36	1.44	3	0.48	0.62	1	0.62	0.62	1	0.62
Male	129 / 82	5.7	Hyper and pre-diabetic	2.73	7	0.39	2.47	5	0.49	1.24	2	0.62	1.24	2	0.62
Male	130 / 83	5	Hyper and optimal	3.21	8	0.40	2.94	6	0.49	1.24	2	0.62	1.24	2	0.62
Male	153 / 99	5.1	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00

Female	107 / 70	5	Normal and optimal	2.53	7	0.36	2.11	5	0.42	0.00	0	0.00	0.00	0	0.00
Female	146 / 85	5.4	Hyper and optimal	2.32	6	0.39	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Male	144 / 85	7.4	Hyper and diabetic	2.57	7	0.37	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Male	117 / 77	5.8	Normal and pre-diabetic	2.28	5	0.46	2.12	4	0.53	1.29	2	0.65	1.29	2	0.65
Male	125 / 76	5.5	Normal and optimal	2.14	6	0.36	1.43	3	0.48	0.61	1	0.61	0.61	1	0.61
Male	120 / 83	5.6	Hyper and optimal	4.11	11	0.37	3.33	7	0.48	1.71	3	0.57	1.20	2	0.60
Female	111 / 72	5.3	Normal and optimal	3.99	10	0.40	3.55	7	0.51	1.91	3	0.64	1.40	2	0.70
Female	122 / 63	5.4	Hyper and optimal	2.06	6	0.34	1.65	4	0.41	0.00	0	0.00	0.00	0	0.00
Female	121 / 69	5.3	Hyper and optimal	2.28	5	0.46	2.12	4	0.53	1.29	2	0.65	1.29	2	0.65
Female	139 / 82	5.7	Hyper and pre-diabetic	2.99	7	0.43	2.62	5	0.52	1.30	2	0.65	1.30	2	0.65
Female	116 / 70	5.6	Normal and optimal	1.56	5	0.31	1.26	3	0.42	0.00	0	0.00	0.00	0	0.00
Male	109 / 65	5.4	Normal and optimal	3.94	12	0.33	3.28	8	0.41	0.61	1	0.61	0.61	1	0.61
Male	127 / 81	5.9	Hyper and pre-diabetic	2.57	7	0.37	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Male	125 / 77	5.4	Normal and optimal	1.28	3	0.43	1.28	3	0.43	0.00	0	0.00	0.00	0	0.00
Female	118 / 75	5.2	Hyper and optimal	2.66	7	0.38	2.25	5	0.45	0.60	1	0.60	0.60	1	0.60
Male	124 / 77	5.1	Normal and optimal	2.66	7	0.38	2.25	5	0.45	0.60	1	0.60	0.60	1	0.60
Male	121 / 74	5.2	Normal and optimal	2.28	5	0.46	2.12	4	0.53	1.29	2	0.65	1.29	2	0.65
Male	147 / 94	5.6	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	118 / 78	5.9	Normal and pre-diabetic	2.36	5	0.47	2.14	4	0.53	1.31	2	0.66	1.31	2	0.66
Male	125 / 82	5.7	Hyper and pre-diabetic	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	127 / 77	5.4	Normal and optimal	3.96	12	0.33	3.24	8	0.40	0.61	1	0.61	0.61	1	0.61
Male	135 / 88	5.4	Hyper and optimal	2.82	7	0.40	2.56	5	0.51	1.74	3	0.58	1.24	2	0.62
Male	121 / 85	6.6	Hyper and diabetic	1.30	5	0.26	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	124 / 73	5.3	Normal and optimal	2.24	5	0.45	1.99	4	0.50	1.17	2	0.59	0.66	1	0.66
Male	130 / 74	5.5	Hyper and optimal	2.66	8	0.33	2.18	5	0.44	0.53	1	0.53	0.00	0	0.00
Female	116 / 68	6.9	Normal and diabetic	3.62	9	0.40	3.19	6	0.53	1.96	3	0.65	1.96	3	0.65
Male	124 / 80	6.1	Hyper and pre-diabetic	2.53	7	0.36	2.11	5	0.42	0.00	0	0.00	0.00	0	0.00
Male	156 / 95	5.8	Hyper and pre-diabetic	1.81	6	0.30	1.22	3	0.41	0.00	0	0.00	0.00	0	0.00
Male	129 / 86	6	Hyper and pre-diabetic	4.54	14	0.32	3.38	8	0.42	1.06	2	0.53	0.00	0	0.00
Female	125 / 79	5.7	Hyper and pre-diabetic	2.89	7	0.41	2.55	5	0.51	1.24	2	0.62	1.24	2	0.62

Female	123 / 78	6	Hyper and pre-diabetic	3.67	9	0.41	3.24	6	0.54	2.01	3	0.67	2.01	3	0.67
Male	112 / 71	5.1	Normal and optimal	1.24	4	0.31	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Male	141 / 93	5.9	Hyper and pre-diabetic	3.99	10	0.40	3.55	7	0.51	1.91	3	0.64	1.40	2	0.70
Female	130 / 84	5.5	Hyper and optimal	5.20	13	0.40	4.72	10	0.47	2.38	4	0.60	1.29	2	0.64
Male	113 / 72	5.5	Normal and optimal	1.85	6	0.31	1.22	3	0.41	0.00	0	0.00	0.00	0	0.00
Male	128 / 77	6.3	Normal and pre-diabetic	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	125 / 77	5.6	Normal and optimal	2.82	7	0.40	2.56	5	0.51	1.74	3	0.58	1.24	2	0.62
Female	119 / 74	5.3	Normal and optimal	1.76	5	0.35	1.43	3	0.48	0.61	1	0.61	0.61	1	0.61
Female	135 / 74	5.3	Hyper and optimal	0.82	2	0.41	0.82	2	0.41	0.00	0	0.00	0.00	0	0.00
Female	104 / 66	5.3	Normal and optimal	1.76	5	0.35	1.43	3	0.48	0.61	1	0.61	0.61	1	0.61
Male	113 / 75	6.2	Normal and pre-diabetic	2.32	6	0.39	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62
Female	114 / 67	5.1	Normal and optimal	3.98	13	0.31	2.83	7	0.40	0.51	1	0.51	0.00	0	0.00
Male	117 / 69	5.4	Normal and optimal	2.32	6	0.39	2.06	4	0.52	1.24	2	0.62	1.24	2	0.62

In this table, several identified and calculated phenotypical and genetic parameters for each participant are listed. The MutPred mutational load (Mut. load) and MutPred adjusted load (Adj. load) as well as the number of variants (Num of var) for each participant is given, when all variants are considered or when only variants with MutPred pathogenicity scores above a specified threshold (0.3, 0.5 or 0.6) are considered. 24 h ABPM, 24 hour ambulatory blood pressure monitoring. Normotensive and hypertensive classifications are based on 24 hour systolic and diastolic ambulatory blood pressure measurements with hypertensive participants being those with 24 h systolic ABPM above 130 mmHg for males, 125 mmHg for females, and/or 24 h diastolic ABPM above 80 mmHg for males, 75 mmHg for females. HbA1c, Glycated haemoglobin is measured to calculate the three month average plasma glucose concentration. HbA1c measurements were used to classify participants as having either optimal blood glucose levels (HbA1c < 5.7%), being pre-diabetic (HbA1c from 5.7% to 6.4%) or diabetic (HbA1c > 6.4%). MutPred, a pathogenicity score assigned to a variant using the MutPred program (mutpred.mutdb.org/about.html).

Table S2. Top twenty-five variants with the highest number of instances in the SABPA cohort data set

Variant	MutPred score	Number of instances in cohort total	Number of instances in haplogroup L participants	Number of instances in haplogroup MN participants	Number of instances on Phylotree	Present in macro-haplogroup L on Phylotree	Present in macro-haplogroup MN on Phylotree
4232C	0.609	87	78	8	6	Yes	Yes
5460A	0.505	58	52	6	43	Yes	Yes
4216C	0.611	39	0	39	13	Yes	Yes
4917G	0.628	25	1	24	6	No	Yes
11172G	0.630	21	21	0	3	Yes	Yes
14798C	0.609	14	0	14	5	No	Yes
14000A	0.552	11	9	2	4	Yes	Yes
14178C	0.516	11	11	0	5	Yes	Yes
13789C	0.576	10	10	0	2	Yes	Yes
13886C	0.571	8	8	0	1	Yes	No
15257A	0.785	8	0	8	3	No	Yes
9098C	0.685	8	0	8	5	Yes	Yes
13780G	0.606	7	0	7	1	No	Yes
15812A	0.518	7	1	6	3	Yes	Yes
8618C	0.641	7	7	0	4	Yes	Yes
10114C	0.603	6	6	0	1	Yes	No
10128A	0.609	6	6	0	1	Yes	No
15312C	0.530	6	6	0	1	Yes	No
15617A	0.714	6	3	3	3	Yes	Yes
6150A	0.676	6	6	0	2	Yes	Yes
6723A	0.653	6	6	0	1	Yes	No
7119A	0.520	6	6	0	2	Yes	Yes
13129T	0.850	5	5	0	2	Yes	Yes

14334T	0.501	5	0	5	0	No	No
3434G	0.577	5	5	0	3	Yes	Yes

In this table, a description is given for variants with MutPred scores above 0.5 that have the most number of instances in the SABPA cohort data set. The MutPred score is given for each variants. The number of instances in the entire cohort, in the haplogroup L participants, and in the haplogroup MN participants are also given. Finally, the number of times a variant appears as a haplogroup defining variant on Phylotree (<http://www.phylotree.org>) is given, and whether a variant defines haplogroups within macro-haplogroup L or macro-haplogroup MN. Variants that only define either macro-haplogroup L or macro-haplogroup MN lineages, are shown in bold. MutPred: a pathogenicity score assigned to a variant using the MutPred program (mutpred.mutdb.org/about.html).

Supplementary variants

Gender	Mean 24 hour systolic ambulatory blood pressure measurement	Mean 24 hour diastolic ambulatory blood pressure measurement	HbA1C% (blood glucose measurement)	Consensus variants →
Male	147	102	10.1	719A 750G
Male	140	84	5.5	721C 750G
Female	117	75	5.7	597T 750G
Male	162	96	6.3	597T 750G
Female	160	98	5.7	750G 769A
Female	116	78	5.3	750G 769A
Female	151	78	5.7	750G 769A
Male	114	77	6.4	750G 769A
Female	110	64	5	750G 769A
Female	121	73	5.4	597T 750G
Female	144	90	5.5	597T 750G
Female	124	74	5.7	750G 769A
Female	145	89	6.1	750G 769A
Male	124	79	6	750G 1438G
Male	136	83	6.3	750G 769A
Female	123	73	5.8	750G 769A
Female	144	84	5.7	719A 750G
Female	131	71	5.7	597T 750G
Male	148	94	9.5	597T 709A
Female	120	70	6.3	597T 750G
Male	126	90	5.5	719A 750G
Male	145	93	6.1	750G 769A
Female	129	78	5.3	721C 750G
Male	154	94	6.2	750G 769A
Male	144	92	5.9	750G 769A
Female	113	73	5.4	597T 750G
Male	122	72	6.1	750G 769A
Female	130	82	5.5	750G 769A
Female	130	85	5.6	750G 769A
Male	130	84	5.5	719A 750G
Female	117	80	5.3	750G 769A
Female	111	72	5.2	750G 769A
Female	129	86	5.5	750G 769A
Female	126	81	5.6	750G 1438G
Female	111	73	5.5	750G 769A
Female	137	78	6.2	719A 750G
Female	119	79	5.4	719A 750G
Male	122	75	6	719A 750G
Male	154	103	6.8	750G 769A
Female	127	79	5.8	597T 750G
Female	122	68	5.2	750G 1438G
Male	131	87	5.5	750G 1438G