**Genetic polymorphisms involved in mitochondrial metabolism and pancreatic cancer risk**

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**Running title:** Mitochondrion-related SNPs and pancreatic cancer risk

**Keywords:** Pancreatic cancer, genetic polymorphisms, mitochondrion, association, case-control study

**Financials supports.**

This work was supported by intramural funding of DKFZ (Federico Canzian), by Fondazione Tizzi ([www.fondazionetizzi.it](http://www.fondazionetizzi.it)) and by Fondazione Arpa ([www.fondazionearpa.it](http://www.fondazionearpa.it)) (Daniele Campa), by Ministry of Health of Czech Republic, NV 19‐03‐00097, and NV 19‐09‐00088 (Martin Lovecek), by Italian Ministry of Health grants (RC1803GA32) to the Division of Gastroenterology, Fondazione “Casa Sollievo della Sofferenza” IRCCS Hospital, San Giovanni Rotondo (FG), Italy and by the “5x1000” voluntary contribution (Francesca Tavano), by the Ministry of Health of the Czech Republic, Grant no. NV19‐08‐00113 (Pavel Souček) and by the Charles University project no. UNCE/MED/006 (to Viktor Hlaváč). The PDAC cases were obtained from the PancoBank (EPZ/Heidelberg, Germany; Ethical committee of the University of Heidelberg case numbers 301/2001 and 159/2002; Prof M. W. Büchler, Dr N. A. Giese, E. Soyka, M. Stauch, M. Meinhardt) supported by Bundesministerium für Bildung und Forschung (BMBF) grants (01GS08114,01ZX1305C, 01KT1506), Heidelberger Stiftung Chirurgie and Biomaterial Bank Heidelberg (Prof P. Schirmacher) supported by BMBF grant (01EY1101).

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**Disclosure of Potential Conflicts of Interest**

Dr Neoptolemos reports grants from NUCANA, grants from Heidelberger Stiftung Chirurgie, grants from Stiftung Deutsche Krebshilfe, outside the submitted work. The other authors declare no competing interests.

Words count: 786

Number of tables: 2

**Abstract**

**Background.** The mitochondrial metabolism has been associated with pancreatic ductal adenocarcinoma (PDAC) risk. Recent evidence also suggests the involvement of the genetic variability of the mitochondrial function in several traits involved in PDAC aetiology. However, a systematic investigation of the genetic variability of mitochondrial genome (mtSNPs) and of all the nuclear genes involved in its functioning (n-mtSNPs) has never been attempted.

**Methods.** We conducted a two-phase association study of mtSNPs and n-mtSNPs to assess their effect on PDAC risk. We analysed 35,297 n-mtSNPs and 101 mtSNPs in up to 55,870 individuals (12,884 PDAC cases and 42,986 controls). In addition, we also conducted a gene-based analysis on 1,588 genes involved in mitochondrial metabolism using MAGMA software.

**Results.** In the discovery phase we identified 49 n-mtSNPs and no mtSNPs associated with PDAC risk (P <0.05). In the second phase none of the findings were replicated. In the gene-level analysis we observed that three genes (*TERT*, *SUGCT* and *SURF1*) involved in the mitochondrial metabolism showed an association below the Bonferroni-corrected threshold of statistical significance (P =0.05/1588=3.1 x10-5).

**Conclusion.** Even thoughthe mitochondrial metabolism might be involved in PDAC aetiology,our results, obtained in a study with one of the largest sample sizes to date, show that neither n-mtSNPs nor mtSNPs are associated with PDAC risk.

**Impact.** This large case-control study does not support a role of the genetic variability of the mitochondrial function in PDAC risk.

**Introduction**

Overwhelming evidences suggest a central role for mitochondria in cellular metabolism and tumorigenesis. The mitochondrial metabolism, genetic variability and content have been associated with pancreatic ductal adenocarcinoma (PDAC) risk (1,2). In addition, statistically significant associations were identified between single nucleotide polymorphisms (SNPs) in the mitochondrial genome (mtSNPs), as well as SNPs situated in the nuclear genome but involved in mitochondrial metabolism (n-mtSNPs), and seven metabolic traits (3). Several of these traits, such as body mass index and type 2 diabetes, are strongly associated with PDAC risk.

A comprehensive study of the mitochondrial genome and n-mtSNPs in relation to PDAC has never been attempted, therefore we analysed the involvement of 101 mtSNPs and 35,297 n-mtSNPs in PDAC susceptibility in a multi-ethnic association study comprising almost 50,000 individuals.

**Materials and methods**

**Study design and populations**

We used a two-step approach. In the first phase we used the genotypes of 7,843 PDAC cases and 7,719 controls from the Pancreatic Cancer Cohort Consortium (PanScan) I, PanScan II and the Pancreatic Cancer Case-Control Consortium (PanC4) (reviewed in (1)) downloaded from dbGaP (study accession numbers phs000206.v5.p3 and phs000648.v1.p1; project reference #12644). We imputed the mitochondrial and nuclear genome as described in detail in (3) and (4) respectively, obtaining 101 SNPs for the mitochondrial and 7,509,345 SNPs for the nuclear genomes.

In the second phase (validation) we genotyped 3,638 PDAC cases and 3,332 controls of Caucasian descent from the PANcreatic Disease ReseArch (PANDoRA) (5) consortium and used the summary statistics of the Japan Pancreatic Cancer Research (JaPAN) consortium for an additional 2,039 PDAC cases and 32,592 controls of Asian descent (6).

**Nuclear gene and SNP selection**

We identified 1588 genes encoding for a mitochondrial localized protein, using two databases: Human MitoCarta 2.0 (<https://www.broadinstitute.org/mitocarta/mitocarta30-inventory-mammalian-mitochondrial-proteins-and-pathways>) and Integrated Mitochondrial Protein Index (<http://www.mrc-mbu.cam.ac.uk/impi>). For each gene we identified tagging SNPs (tSNPs) using Haploview software, for a total of 67,960 tSNPs.

**Data analysis**

Out of 67,960 tSNPs, 34,007 were found in the PanScan I-II and PanC4 dataset. Additionally, 1,290 proxies (linkage disequilibrium r2≥0.80) were included, for a total of 35,297 n-mtSNPs. All 101 mtSNPs were included in the analysis. In the first phase logistic regression, adjusted for sex, age and the 8 first principal components, was performed. In the second phase we selected for replication SNPs fulfilling the following criteria: MAF>0.05, P<5×10-4 considering all dbGaP data together, P<0.05 in each individual dataset and no LD with known PDAC risk loci. Genotyping in PANDoRA was performed with TaqMan technology (ThermoFisher Applied Biosystems, Waltham MA, USA). PANDoRA data were analysed by logistic regression adjusted for sex, age, and country of origin. Finally, we conducted a meta-analysis on 55,870 individuals from all datasets with either a fixed or a random effect model. We also conducted a gene-level analysis using the Multi-marker Analysis of GenoMic Annotation (MAGMA) software (7), and pathway enrichment analysis using the gProfiler g:GOSt tool (<https://biit.cs.ut.ee/gprofiler/gost>).

**Results**

In the first phase, we observed 49 independent n-mtSNPs showing an association with PDAC risk with P<0.05 in both PanScanI-II and PanC4 and in their pooled dataset. None of the mtSNPs met our criteria for replication and therefore we did not advance them to the following steps. Five n-mtSNPs (rs7676303, rs11717398, rs3845970, rs11130833, rs802933) were genotyped in the replication phase in PANDoRA and analysed in JaPAN. None of the five selected SNPs showed an association with PDAC in PANDoRA, except *FHIT-*rs3845970. In the meta-analysis we observed no significant result for any of the analysed SNPs. All results are shown in **table 1**.

In the MAGMA analysis of all the 1,588 genes, 110 genes showed an association with P<0.05, with three (*TERT, SUGCT* and *SURF1*) below the Bonferroni-corrected threshold (P=0.05/1,588=3.1x10-5) in at least one of the models used (as described in the **table 2**). A pathway enrichment analysis with gProfiler g:GOSt tool on these 110 genes showed that they are involved mainly in the mitochondrial metabolism without overlap with pancreatic or tumorigenic pathways.

**Discussion**

The mitochondrial metabolism and content have been associated with PDAC risk, but a systematic investigation of the genetic variability of mitochondrial genome and of all the genes involved in its functioning has never been attempted. After conducting a meta-analysis, we did not observe any statistically significant finding at individual SNP level. Aggregating the SNPs in a multi-marker model we observed associations with two known PDAC risk genes (*TERT, SUGCT*)and anovel one (*SURF1*)that is involved in the biogenesis of the cytochrome c oxidase complex. However, the association was significant only with the model that relies on the most significant SNP, thus not adding much to what has been previously observed with the individual variants. Pathway enrichment analysis showed overlap only with mitochondrial pathways.

In conclusion, this study suggests no effect of the genetic variability in mitochondrial metabolism in relation to PDAC susceptibility.

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**Table 1.** Case-control analysis of the five candidate SNPs selected after the discovery phase of the study.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chromosome**  | **Gene** | **SNP** | **Alleles (M/m)** | **Phase** | **Total controls and cases** | **Additive model** |
| **OR (95% CI)** | **P-value** | **P-value Het** |
| 4 | *SPATA5* | rs7676303 | A/G | PanScan+PanC4 | 14,023 | **0.83 (0.74-0.92)** | **3.84×10-4** | **-** |
|   |   |   |   | PANDoRA | 6,763 | 0.97 (0.83-1.12) | 0.635 | - |
|   |   |   |   | JaPAN | - | - | - | - |
|   |   |  |  | Meta-analysis | 20,786 | **0.88 (0.80-0.96)** | **3.20×10-3** | 0.990 |
| 3 | *MRPS25* | rs11717398 | G/C | PanScan+PanC4 | 14,256 | **1.11 (1.05-1.16)** | **1.25×10-4** | **-** |
|  |  |  |  | PANDoRA | 6,749 | 0.95 (0.87-1.02) | 0.168 | - |
|  |  |  |  | JaPAN | 33,283 | 1.02 (0.90-1.14) | 0.715 | - |
|  |  |  |  | Meta-analysis | 54,288 | 1.03 (0.94-1.13) | 0.524 | **0.004** |
| 3 | *FHIT* | rs3845970 | C/A | PanScan+PanC4 | 14,270 | **0.92 (0.87-0.96)** | **8.84×10-4** | **-** |
|   |   |   |   | PANDoRA | 6,656 | **1.12 (1.03-1.22)** | **0.006** | - |
|   |   |   |   | JaPAN | 33,283 | 0.98 (0.91-1.06) | 0.682 | - |
|   |   |   |   | Meta-analysis | 54,209 | 0.99 (0.89-1.12) | 0.990 | **4.11×10-4** |
| 3 | *FHIT* | rs11130833 | C/T | PanScan+PanC4 | 14,257 | **0.91 (0.87-0.96)** | **6.15×10-4** | **-** |
|  |  |  |  | PANDoRA | 6,145 | 0.97 (0.89-1.05) | 0.407 | - |
|  |  |  |  | JaPAN | 33,283 | 0.98 (0.91-1.06) | 0.664 | - |
|  |  |  |  | Meta-analysis | 53,685 | **0.94 (0.90-0.97)** | **6.81×10-4** | 0.187 |
| 3 | *FHIT* | rs802933 | A/G | PanScan+PanC4 | 14,123 | **0.92 (0.88-0.97)** | **9.99×10-4** | **-** |
|   |  |   |   | PANDoRA | 6,087 | 1.06 (0.99-1.15) | 0.105 | - |
|   |   |   |   | JaPAN | 33,283 | 1.03 (0.93-1.13) | 0.552 | - |
|   |   |   |   | Meta-analysis | 53,493 | 0.99 (0.91-1.09) | 0.918 | **0.003** |

All analyses were adjusted by age, sex, and the first 8 principal components. Statistically significant results (P<0.05) are in bold. [M] major allele, [m] minor allele. Meta-analysis was performed applying the fixed-effects model or random-effects model for SNPs showing heterogeneity. [P-value Het] P-value for the heterogeneity test.

**Table 2.** Significant results (P <0.05) of the analysis performed with MAGMA.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Chr** | **N° SNPs** | **PSNPwise\_Top1** | **PSNPwise\_mean** | **PMulti** |
| *TERT* | 5 | 18 | 7.94×10ˉ⁷ | 1.75×10ˉ⁶ | 6.10×10ˉ⁸ |
| *SUGCT* | 7 | 894 | 9.17×10ˉ⁷ | 1.60×10ˉ³ | 2.64×10ˉ⁶ |
| *SURF1* | 9 | 13 | 1.21×10ˉ⁵ | 3.22×10ˉ³ | 9.35×10ˉ⁵ |
| *MRPS25* | 3 | 47 | 1.74×10ˉ³ | 1.10×10ˉ⁴ | 1.29×10ˉ⁴ |
| *HSCB* | 22 | 44 | 2.80×10ˉ⁴ | 5.50×10ˉ⁴ | 1.80×10ˉ⁴ |
| *PNPO* | 17 | 20 | 1.26×10ˉ³ | 1.05×10ˉ⁴ | 1.97×10ˉ⁴ |
| *GLS* | 2 | 102 | 5.20×10ˉ³ | 4.37×10ˉ⁴ | 2.94×10ˉ⁴ |
| *MIEF1* | 22 | 19 | 3.53×10ˉ³ | 5.85×10ˉ⁴ | 5.55×10ˉ⁴ |
| *TYMS* | 18 | 65 | 7.81×10ˉ³ | 1.40×10ˉ³ | 1.11×10ˉ³ |
| *ATP5F1EP2* | 13 | 4 | 2.27×10ˉ⁴ | 7.93×10ˉ³ | 1.18×10ˉ³ |
| *RPUSD2* | 15 | 18 | 1.75×10ˉ³ | 1.98×10ˉ³ | 1.38×10ˉ³ |
| *NIPSNAP1* | 22 | 57 | 4.72×10ˉ³ | 3.93×10ˉ³ | 1.89×10ˉ³ |
| *ETFBKMT* | 12 | 58 | 6.11×10ˉ³ | 3.06×10ˉ³ | 2.33×10ˉ³ |
| *PKM* | 15 | 43 | 8.71×10ˉ³ | 3.77×10ˉ³ | 3.35×10ˉ³ |
| *PYROXD2* | 10 | 161 | 1.22×10ˉ² | 3.70×10ˉ³ | 3.90×10ˉ³ |
| *TSTD3* | 6 | 40 | 6.93×10ˉ³ | 8.47×10ˉ³ | 4.73×10ˉ³ |
| *COQ6* | 14 | 46 | 3.43×10ˉ³ | 2.90×10ˉ² | 5.02×10ˉ³ |
| *MRPL44* | 2 | 18 | 1.48×10ˉ² | 5.72×10ˉ³ | 5.08×10ˉ³ |
| *OGDH* | 7 | 163 | 8.39×10ˉ³ | 9.73×10ˉ³ | 5.27×10ˉ³ |
| *WDR31* | 9 | 63 | 1.37×10ˉ² | 6.50×10ˉ³ | 5.29×10ˉ³ |
| *BID* | 22 | 93 | 1.44×10ˉ² | 8.51×10ˉ³ | 5.30×10ˉ³ |
| *ARGLU1* | 13 | 22 | 4.83×10ˉ³ | 2.17×10ˉ² | 5.46×10ˉ³ |
| *DAOA* | 13 | 110 | 2.83×10ˉ³ | 2.82×10ˉ² | 5.49×10ˉ³ |
| *NCEH1* | 3 | 162 | 2.02×10ˉ³ | 6.43×10ˉ² | 6.71×10ˉ³ |
| *FAM195A* | 16 | 8 | 8.09×10ˉ³ | 9.23×10ˉ³ | 6.80×10ˉ³ |
| *ASS1* | 9 | 122 | 1.32×10ˉ² | 1.29×10ˉ² | 7.24×10ˉ³ |
| *RMDN3* | 15 | 27 | 8.50×10ˉ³ | 2.00×10ˉ² | 7.31×10ˉ³ |
| *PARS2* | 1 | 36 | 2.22×10ˉ² | 5.58×10ˉ³ | 7.32×10ˉ³ |
| *PHYKPL* | 5 | 99 | 2.65×10ˉ² | 6.98×10ˉ³ | 7.71×10ˉ³ |
| **Gene** | **Chr** | **N° SNPs** | **PSNPwise\_Top1** | **PSNPwise\_mean** | **PMulti** |
| *SERHL2* | 22 | 59 | 1.23×10ˉ² | 9.44×10ˉ³ | 7.80×10ˉ³ |
| *PSMB3* | 17 | 30 | 1.96×10ˉ² | 7.20×10ˉ³ | 8.08×10ˉ³ |
| *RAD51* | 15 | 59 | 1.15×10ˉ² | 1.98×10ˉ² | 8.58×10ˉ³ |
| *GPX1* | 3 | 2 | 1.64×10ˉ² | 5.27×10ˉ³ | 8.63×10ˉ³ |
| *NDUFA11* | 19 | 55 | 6.68×10ˉ³ | 2.57×10ˉ² | 1.02×10ˉ² |
| *MRPS6* | 21 | 93 | 1.31×10ˉ² | 4.30×10ˉ² | 1.10×10ˉ² |
| *SLC25A12* | 2 | 237 | 1.88×10ˉ² | 2.00×10ˉ² | 1.13×10ˉ² |
| *SLC25A47* | 14 | 16 | 1.03×10ˉ² | 1.55×10ˉ² | 1.18×10ˉ² |
| *PDHA2* | 4 | 8 | 1.22×10ˉ² | 1.67×10ˉ² | 1.22×10ˉ² |
| *BBC3* | 19 | 10 | 2.83×10ˉ² | 8.51×10ˉ³ | 1.23×10ˉ² |
| *CPT2* | 1 | 27 | 3.76×10ˉ² | 1.07×10ˉ² | 1.36×10ˉ² |
| *DNAJC28* | 21 | 15 | 7.50×10ˉ³ | 6.60×10ˉ² | 1.51×10ˉ² |
| *SLC9B2* | 4 | 34 | 2.50×10ˉ² | 1.98×10ˉ² | 1.53×10ˉ² |
| *AKR1B15* | 7 | 97 | 5.61×10ˉ³ | 8.17×10ˉ² | 1.60×10ˉ² |
| *TRMT5* | 14 | 6 | 4.28×10ˉ² | 9.49×10ˉ³ | 1.68×10ˉ² |
| *MSRB2* | 10 | 48 | 2.07×10ˉ² | 2.61×10ˉ² | 1.78×10ˉ² |
| *PRKCA* | 17 | 1525 | 6.89×10ˉ² | 1.24×10ˉ² | 1.82×10ˉ² |
| *FDX1L* | 19 | 27 | 7.34×10ˉ³ | 9.83×10ˉ² | 1.85×10ˉ² |
| *C19orf12* | 19 | 58 | 5.25×10ˉ³ | 0.152 | 2.00×10ˉ² |
| *UBE2H* | 7 | 385 | 8.49×10ˉ² | 1.69×10ˉ² | 2.09×10ˉ² |
| *VARS* | 6 | 16 | 7.26×10ˉ³ | 9.60×10ˉ² | 2.09×10ˉ² |
| *NDUFB3* | 2 | 33 | 0.102 | 1.50×10ˉ² | 2.15×10ˉ² |
| *AASS* | 7 | 92 | 1.56×10ˉ² | 5.84×10ˉ² | 2.20×10ˉ² |
| *COX16* | 14 | 119 | 4.02×10ˉ² | 2.24×10ˉ² | 2.27×10ˉ² |
| *SLMO2* | 20 | 16 | 4.78×10ˉ² | 2.22×10ˉ² | 2.29×10ˉ² |
| *C2orf47* | 2 | 15 | 3.09×10ˉ² | 2.34×10ˉ² | 2.34×10ˉ² |
| *PYCARD* | 16 | 1 | 2.34×10ˉ² | 2.34×10ˉ² | 2.34×10ˉ² |
| *PCK2* | 14 | 11 | 4.40×10ˉ² | 1.76×10ˉ² | 2.35×10ˉ² |
| *ATP5E* | 20 | 10 | 4.25×10ˉ² | 2.37×10ˉ² | 2.42×10ˉ² |
| **Gene** | **Chr** | **N° SNPs** | **PSNPwise\_Top1** | **PSNPwise\_mean** | **PMulti** |
| *POLDIP2* | 17 | 10 | 5.83×10ˉ³ | 1.86E-01 | 2.44×10ˉ² |
| *NQO1* | 16 | 40 | 5.67×10ˉ² | 2.17×10ˉ² | 2.52×10ˉ² |
| *TOMM40L* | 1 | 9 | 4.83×10ˉ² | 1.90×10ˉ² | 2.58×10ˉ² |
| *CYB5R3* | 22 | 107 | 2.13×10ˉ² | 4.95×10ˉ² | 2.61×10ˉ² |
| *TRIM42* | 3 | 66 | 6.48×10ˉ³ | 0.212 | 2.61×10ˉ² |
| *CLIC1* | 6 | 1 | 2.70×10ˉ² | 2.70×10ˉ² | 2.70×10ˉ² |
| *APTX* | 9 | 88 | 1.16×10ˉ² | 0.129 | 2.75×10ˉ² |
| *CCS* | 11 | 13 | 0.111 | 1.33×10ˉ² | 2.76×10ˉ² |
| *MFF* | 2 | 102 | 5.05×10ˉ² | 2.96×10ˉ² | 2.77×10ˉ² |
| *SLC8A3* | 14 | 512 | 0.276 | 6.57×10ˉ³ | 2.79×10ˉ² |
| *MCAT* | 22 | 20 | 5.60×10ˉ² | 2.32×10ˉ² | 2.84×10ˉ² |
| *TACO1* | 17 | 2 | 1.92×10ˉ² | 4.60×10ˉ² | 2.88×10ˉ² |
| *GSR* | 8 | 119 | 2.98×10ˉ² | 4.96×10ˉ² | 2.89×10ˉ² |
| *GPT2* | 16 | 40 | 0.105 | 1.92×10ˉ² | 2.93×10ˉ² |
| *ADCK4* | 19 | 56 | 9.89×10ˉ² | 1.81×10ˉ² | 3.14×10ˉ² |
| *SLC25A27* | 6 | 28 | 2.51×10ˉ² | 6.75×10ˉ² | 3.26×10ˉ² |
| *SPATA5* | 4 | 1024 | 8.91×10ˉ³ | 2.09E-01 | 3.29×10ˉ² |
| *TMEM160* | 19 | 9 | 2.72×10ˉ² | 4.70×10ˉ² | 3.32×10ˉ² |
| *ENOSF1* | 18 | 187 | 5.57×10ˉ² | 3.79×10ˉ² | 3.38×10ˉ² |
| *PPP1R15A* | 19 | 29 | 1.86×10ˉ² | 9.33×10ˉ² | 3.43×10ˉ² |
| *PET117* | 20 | 169 | 8.41×10ˉ² | 2.32×10ˉ² | 3.47×10ˉ² |
| *FXN* | 9 | 258 | 6.33×10ˉ² | 4.39×10ˉ² | 3.54×10ˉ² |
| *ANKRD61* | 7 | 17 | 8.10×10ˉ² | 2.26×10ˉ² | 3.62×10ˉ² |
| *SUCLG1* | 2 | 90 | 2.00×10ˉ² | 0.183 | 3.66×10ˉ² |
| *TOMM40* | 19 | 41 | 7.64×10ˉ² | 2.36×10ˉ² | 3.69×10ˉ² |
| *AHCYL1* | 1 | 17 | 4.04×10ˉ² | 5.07×10ˉ² | 3.73×10ˉ² |
| **Gene** | **Chr** | **N° SNPs** | **PSNPwise\_Top1** | **PSNPwise\_mean** | **PMulti** |
| *ATP13A1* | 19 | 49 | 7.27×10ˉ² | 3.44×10ˉ² | 3.74×10ˉ² |
| *TMEM11* | 17 | 38 | 5.28×10ˉ² | 4.21×10ˉ² | 3.75×10ˉ² |
| *UHRF1BP1* | 6 | 228 | 0.100 | 2.98×10ˉ² | 3.77×10ˉ² |
| *SYBU* | 8 | 275 | 0.131 | 1.82×10ˉ² | 3.78×10ˉ² |
| *PSEN1* | 14 | 171 | 1.14×10ˉ² | 2.39E-01 | 3.85×10ˉ² |
| *NDUFAF1* | 15 | 36 | 4.89×10ˉ² | 5.12×10ˉ² | 3.87×10ˉ² |
| *SLC25A34* | 1 | 9 | 4.98×10ˉ² | 4.12×10ˉ² | 3.93×10ˉ² |
| *HAGH* | 16 | 171 | 5.13×10ˉ² | 5.18×10ˉ² | 3.96×10ˉ² |
| *MYH10* | 17 | 221 | 4.63×10ˉ² | 7.78×10ˉ² | 3.97×10ˉ² |
| *UQCR10* | 22 | 14 | 4.32×10ˉ² | 4.32×10ˉ² | 4.06×10ˉ² |
| *G0S2* | 1 | 7 | 2.61×10ˉ² | 7.31×10ˉ² | 4.07×10ˉ² |
| *ACO2* | 22 | 57 | 3.38×10ˉ² | 8.58×10ˉ² | 4.09×10ˉ² |
| *RPL30* | 8 | 16 | 0.101 | 2.48×10ˉ² | 4.10×10ˉ² |
| *NDUFS8* | 11 | 4 | 0.104 | 1.94×10ˉ² | 4.10×10ˉ² |
| *GSTM4* | 1 | 22 | 0.101 | 2.69×10ˉ² | 4.19×10ˉ² |
| *SLC25A13* | 7 | 235 | 8.76×10ˉ² | 4.06×10ˉ² | 4.28×10ˉ² |
| *ACOT2* | 14 | 20 | 5.65×10ˉ² | 4.20×10ˉ² | 4.28×10ˉ² |
| *UBE3B* | 12 | 143 | 6.47×10ˉ² | 5.64×10ˉ² | 4.31×10ˉ² |
| *MRPL49* | 11 | 8 | 4.95×10ˉ² | 4.72×10ˉ² | 4.35×10ˉ² |
| *SLC25A37* | 8 | 256 | 9.34×10ˉ² | 3.90×10ˉ² | 4.57×10ˉ² |
| *FOXRED1* | 11 | 22 | 7.12×10ˉ² | 4.54×10ˉ² | 4.81×10ˉ² |
| *PTPN11* | 12 | 44 | 2.92×10ˉ² | 0.128 | 4.88×10ˉ² |
| *C15orf48* | 15 | 2 | 4.93×10ˉ² | 4.86×10ˉ² | 4.89×10ˉ² |
| *PAPSS2* | 10 | 235 | 3.72×10ˉ² | 0.119 | 4.90×10ˉ² |
| *MTG2* | 20 | 110 | 9.47×10ˉ³ | 0.361 | 4.92×10ˉ² |
| *COQ4* | 9 | 23 | 1.19×10ˉ² | 0.269 | 4.94×10ˉ² |

Only genes that had P<0.05 in at least of one model are reported. The three models are: 1) SNP-wise Mean, 2) SNP-wise Top 1 and 3) Multi model. The two SNP-wise models examine the individual SNPs present in the gene and subsequently combine the resulting P values of the SNPs into a gene test statistic, while the multi model runs the basic models (SNP-wise) and combines the resulting P-values into an aggregated P-value for the gene.