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

Giulia Peduzzi1\*, Manuel Gentiluomo1\*, Francesca Tavano2, Paolo Giorgio Arcidiacono3, Stefano Ermini4, Ludmila Vodičková5,6,7, Ugo Boggi8, Giulia Martina Cavestro9, Gabriele Capurso3,10, Luca Morelli11, Anna Caterina Milanetto12, Raffaele Pezzilli13, Rita T. Lawlor14, Silvia Carrara15, Martin Lovecek16, Pavel Souček7, Feng Guo17, Thilo Hackert18, Faik G. Uzunoğlu19, Maria Gazouli20, Andrea Párniczky21,22, Juozas Kupcinskas23, Maarten F. Bijlsma24, Bas Bueno-de-Mesquita25, Roel C. H. Vermeulen26, Casper H.J. van Eijck27, Krzysztof Jamroziak28, Renata Talar-Wojnarowska29, William Greenhalf30, Domenica Gioffreda2, Maria Chiara Petrone3, Stefano Landi1, Livia Archibugi3,10, Marta Puzzono9, Niccola Funel31, Cosimo Sperti32, Maria Liliana Piredda14, Beatrice Mohelnikova-Duchonova33, Ye Lu34,35, Viktor Hlaváč7, Xin Gao17, Martin Schneider18, Jakob R. Izbicki19, George Theodoropoulos36, Stefania Bunduc21,37, Edita Kreivenaite23, Olivier R. Busch38, Ewa Małecka-Panas29, Eithne Costello30, Francesco Perri2, Sabrina Gloria Giulia Testoni3, Giuseppe Vanella3,10, Claudio Pasquali12, Martin Oliverius39, Hermann Brenner17, Martin Loos18, Mara Götz19, Konstantinos Georgiou36, Bálint Erőss21, Evaristo Maiello40, Andrea Szentesi21,41, Francesca Bazzocchi42, Daniela Basso43, John P. Neoptolemos18, Péter Hegyi21,41, Vytautas Kiudelis23, Federico Canzian34#, Daniele Campa1#.

1 Department of Biology, University of Pisa, Pisa, Italy

2 Division of Gastroenterology and Research Laboratory, Fondazione IRCCS “Casa Sollievo della Sofferenza” Hospital, San Giovanni Rotondo, Italy

3 Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational & Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy

4 Blood Transfusion Service, Azienda Ospedaliero-Universitaria Meyer, Children's Hospital, Florence, Italy

5 Institute of Experimental Medicine, AS CR, Prague, Czech Republic

6 First Medical Faculty, Charles University Prague, Czech Republic, Prague, Czech Republic

7 Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic

8 Division of General and Transplant Surgery, Pisa University Hospital, Pisa, Italy

9 Gastroenterology and Gastrointestinal Endoscopy Unit, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientic Institute, Milan, Italy

10 Digestive and Liver Disease Unit, Sant'Andrea Hospital, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy

11 General Surgery Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

12 Department DISCOG - University of Padova, Clinica Chirurgica 1, Padua, Italy

13 Gastroenterology Unit, San Carlo Hospital, Potenza, Italy

14 ARC-NET, Centre for Applied Research on Cancer, University and Hospital Trust of Verona, Verona, Italy

15 Digestive Endoscopy Unit, Division of Gastroenterology, Humanitas Clinical and Research Hospital, Milan, Italy

16 Department of Surgery I, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Olomouc, Czech Republic

17 Clinical Epidemiology and Aging Research Division Head German Cancer Research Center (DKFZ), Foundation under Public Law, Heidelberg, Germany, Heidelberg, Germany

18 Department of General Surgery, University of Heidelberg, Heidelberg, Germany

19 Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

20 Laboratory of Biology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

21 Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary

22 Heim Pál National Pediatric Institute, Budapest, Hungary

23 Gastroenterology Department and Institute for Digestive Research, Lithuanian University of Health Sciences, Kaunas, Lithuania

24 Laboratory for Experimental Oncology and Radiobiology, Amsterdam University Medical Centers, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands

25 Former senior scientist, Dept. for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands

26 University of Utrecht, Utrecht, Netherlands

27 Department of Surgery, Erasmus Medical Center, Erasmus University, Rotterdam, Netherlands

28 Institute of Hematology and Transfusion Medicine, Warsaw, Poland

29 Department of Digestive Tract Diseases, Medical University of Lodz, Lodz, Poland

30 Institute for Health Research Liverpool Pancreas Biomedical Research Unit, University of Liverpool, Liverpool, United Kingdom

31 Department of Surgery, Unit of Experimental Surgical Pathology, Pisa University Hospital, Pisa, Italy

32 Department DISCOG - University of Padova, Clinica Chirurgica 3, Padua, Italy

33 Department of Oncology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Olomouc, Czech Republic

34 Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany

35 Medical Faculty Heidelberg, University of Heidelberg, Heidelberg, Baden- Württemberg, Germany

36 First Propaedeutic University Surgery Clinic, Hippocratio General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

37 Fundeni Clinical Institute, Bucharest, Romania

38 Department of Surgery, Cancer Center Amsterdam, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands

39 Department of Surgery, Faculty Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic

40 Department of Oncology, Fondazione IRCCS “Casa Sollievo della Sofferenza” Hospital, San Giovanni Rotondo, Italy

41 Centre for Translational Medicine, Department of Medicine, University of Szeged, Szeged, Hungary

42 Department of Surgery, Fondazione IRCCS “Casa Sollievo della Sofferenza” Hospital, San Giovanni Rotondo, Italy

43 Department DIMED - University of Padova, Padua, Italy

\* These authors share first position

# These authors share last position

**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).

**Corresponding author**

Daniele Campa

University of Pisa, Department of Biology, Via Derna 1, 56126 Pisa (PI), Italy

email: daniele.campa@unipi.it

phone: +39-050 2211510

fax: +39-050-2211501

**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.

**References**

1. Gentiluomo M, Canzian F, Nicolini A, Gemignani F, Landi S, Campa D. Germline genetic variability in pancreatic cancer risk and prognosis. Semin Cancer Biol. Elsevier Ltd; 2020;

2. Reyes-Castellanos G, Masoud R, Carrier A. Mitochondrial Metabolism in PDAC: From Better Knowledge to New Targeting Strategies. Biomedicines. 2020;8:270.

3. Kraja AT, Liu C, Fetterman JL, Graff M, Have CT, Gu C, et al. Associations of Mitochondrial and Nuclear Mitochondrial Variants and Genes with Seven Metabolic Traits. Am J Hum Genet. 2019;104:112–38.

4. Lu Y, Gentiluomo M, Lorenzo-Bermejo J, Morelli L, Obazee O, Campa D, et al. Mendelian randomisation study of the effects of known and putative risk factors on pancreatic cancer. J Med Genet. 2020;jmedgenet-2019-106200.

5. Campa D, Rizzato C, Capurso G, Giese N, Funel N, Greenhalf W, et al. Genetic susceptibility to pancreatic cancer and its functional characterisation: The PANcreatic Disease ReseArch (PANDoRA) consortium. Dig Liver Dis. 2013;45:95–9.

6. Lin Y, Nakatochi M, Hosono Y, Ito H, Kamatani Y, Inoko A, et al. Genome-wide association meta-analysis identifies GP2 gene risk variants for pancreatic cancer. Nat Commun. 2020;11.

7. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: Generalized Gene-Set Analysis of GWAS Data. Tang H, editor. PLOS Comput Biol. 2015;11:e1004219.

**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.