Genetically determined telomere length is associated with pancreatic neuroendocrine neoplasms onset

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# Abstract

Telomere length (TL) is a potential indicator of cancer predisposition, however, the multitude of techniques used to measure it causes the results to be heterogeneous and, in some cases, controversial. In the last years, several studies adopted a strategy based on TL associated genetic variants to generate a polygenic score, often referred as teloscore, used in lieu of direct TL measurement. For pancreatic neuroendocrine neoplasms (PanNEN), this strategy has not been attempted yet. A teloscore was generated using 11 SNPs (*NAF1*-rs7675998, *ZNF676*-rs409627, *TERC*-rs10936599, *CTC1*-rs3027234, *PXK*-rs6772228, *DHX35*-rs6028466, *OBFC1*-rs9420907, *ZNF208*-rs8105767, *ACYP2*-rs11125529, *TERT*-rs2736100 and *ZBTB46*-rs755017) and 291 PanNEN cases and 1686 controls collected by the PANcreatic Disease ReseArch (PANDoRA) consortium were genotyped to analyse the association of the teloscore and its individual SNPs with the risk of developing PanNEN. An association between genetically determined long telomeres and the risk of developing PanNEN OR=1.99; CI 1.33-2.98; P=0.0008, for highest vs median (third) quintile was observed. In addition, two novel SNPs associated with PanNEN risk were identified: *ZNF676*-rs409627 (ORC/C\_vs\_G/G=2.3, CI 1.60-3.32, P=8.22×10-6) and *TERT*-rs2736100 (ORC/A\_vs\_C/C=2.09, CI 1.45-3.00, P=6.79×10-5). This study provides a clear indication of the involvement of telomere length in PanNEN risk, and the successful application of a polygenic score underlines the importance of identifying new genetic variants to better understand the aetiology of this rare disease.

# Introduction

Pancreatic neuroendocrine neoplasms (PanNENs) are rare neoplasms of the pancreas, with less than one new case per 100,000 individuals worldwide and an increasing trend in incidence observed in recent years, [1–3]. PanNET can be classified as functional or non-functional (NF). Of the former, the more common types being insulinoma, gastrinoma, glucagonoma and somatostatinoma [4]. However, the majority of PanNENs are NF and difficult to diagnose in early stages due to the lack of specific symptoms, and at the time of diagnosis metastases are reported in up to 50% of patients [5]. However, given a relatively indolent behaviour, the median survival of non-functional PanNENs is 66 months, and 1-, 5-, 10-year survival rates are 79.0, 51.8, and 38.1%, respectively [1]. Due to the relative rarity and low lethality, particularly compared to pancreatic ductal adenocarcinoma (PDAC), PanNENs have been understudied, resulting in a modest knowledge of the disease aetiology, with only a small number of epidemiological risk factors such as family history of any cancer and non-recent onset diabetes, which are also associated with increased risk of developing PDAC [6–9].

The current knowledge of the genetic background of PanNENs is scarce as well, since only few studies have been attempted [10–17]. Only one genome-wide association study (GWAS) has been conducted, where PanNENs were considered together with other NENs, however, it did not identify any risk locus at the conventional GWAS threshold of significance [18]. Recent evidence suggests a certain degree of overlap of risk variants between PanNENs and PDACs [16].

High penetrance causative germline mutations have been reported in the *MTYH*, *CHEK2*, *BRCA2*, *ATM*, *MAPKBP1*, *PIF1*, *CDKN1B* genes [3] that are principally implicated in three biological mechanisms: DNA repair, and chromatin remodelling. The maintenance of chromatin organisation is a recurrent aspect in PanNEN, in particular, the alternative lengthening of telomeres, which is partially driven by somatic mutations in two genes involved in telomere length (TL) regulation, the death domain associated protein (*DAXX)* and ATRX chromatin remodeler (*ATRX)* genes, present in 17-25% of PanNEN subjects [3,19–22].

TL is a molecular trait associated with several diseases and cancers types, including PDAC [23], [24]. However, the estimation of effect of TL on cancer risk is prone to errors due to technical (e.g., the way the DNA is processed) and epidemiologic (e.g., stress, smoking, study design) confounders and to reverse causation bias. Therefore, a high degree of heterogeneity is present in the results reported with some studies reporting long telomere associated with risk, others reporting short telomere associated with risk and others finding non-linear, U-shaped or null associations [23,25–32]. TL is genetically determined, and 11 single nucleotide polymorphisms (SNPs) have shown a strong influence on this trait [23,33–35]. A polygenic score generated with those 11 SNPs, called “teloscore” [24,36] has been successfully used in susceptibility studies of several human traits [37,38], including cancer [23,36,39–45]. The advantage of using a genetic score is that it bypasses all the possible confounders, and it could give a more precise estimation of the causative association between TL and cancer risk. In fact, the studies conducted with genetic scores show more consistencies in the results indicating genetically longer determined telomere length as risk factors [23,36,43,46–48]**.**

Given that there are no reports on the effect of TL on PanNEN susceptibility this study aimed to understand the association of TL with the risk of developing PanNEN using the teloscore.

# Material and methods

## Study population

The present study analysed 291 PanNENs and 1686 controls collected within the PANcreatic Disease ReseArch (PANDoRA) study, a multicentric consortium consisting of 13 countries (Greece, Italy, Germany, Netherland, Denmark, Czech Republic, Hungary, Poland, Ukraine, Lithuania, the United Kingdom, Brazil and Japan) [49]. The cases and controls used in this study were from Italy, Germany Poland and United Kingdom. PanNEN cases were histologically confirmed, sporadic and not observed in the context of genetic syndromes. Controls were individuals from the general population, without any pancreatic disease at recruitment, individuals hospitalised for non-tumour related causes, or blood donors. The United Kingdom controls were obtained from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Data on sex, age and country of origin were collected for all participants. The Ethics Commission of the Medical Faculty of the University of Heidelberg approved the PANDoRA study protocol. In accordance with the Declaration of Helsinki, written informed consent was obtained from each participant. The details of the study population are shown in **table 1**.

## SNP selection

The teloscore was computed using 11 SNPs (*NAF1*-rs7675998, *ZNF676*-rs409627, *TERC*-rs10936599, *CTC1*-rs3027234, *PXK*-rs6772228, *DHX35*-rs6028466, *OBFC1*-rs9420907, *ZNF208*-rs8105767, *ACYP2*-rs11125529, *TERT*-rs2736100 and *ZBTB46*-rs755017) identified through genome-wide association studies (GWAS) that utilized TL as the outcome [23,33–35].

## Teloscore computation

The teloscore computation has been described in detail elsewhere [36]. Briefly it was calculated summing for each subject the products obtained multiplying the number of effect alleles (alleles associated with longer telomeres) by their effect size on telomere elongation expressed in base pairs. The estimate of the per-allele effect on TL for each SNP was obtained from the literature [23]. Not all the genotyped individuals reached a call rate (CR) of 100%, and for this reason, and to be able to compute comparable score values for all study subjects, we also considered average values for the score (using the teloscore value divided by the number of genotyped SNPs) an approach that was successfully used in other studies [36,37,50]. Finally, the teloscore was transformed into quintiles based on its distribution in the controls.

## Genotyping

For each sample, DNA was isolated from whole blood using a QIamp 96 DNA QIAcube HT Kit (Qiagen, Hilden, Germany). TaqMan technology (ABI, Applied Biosystems, Foster City, CA, USA) was used according to the manufacturer’s indications. The experiments were carried out in 384-well plates. Around 10% of the samples were duplicated in each plate to ensure genotyping quality. The concordance rate between the duplicated samples was checked after genotyping. Fluorescent signals of the genotyping assays were read on PCR plates by the QuantStudioTM 5 Real-Time PCR system (Thermofisher, Waltham, Massachusetts, USA) and the QuantStudio Design & Analysis Software.

## Statistical analysis

Hardy-Weinberg Equilibrium (HWE) was calculated in the controls using the Pearson chi2 test, considering a significance threshold of 0.05/11= 0.0045.

Unconditional logistic regression analysis was performed to assess the association of the teloscore and the individual SNPs with the risk of developing PanNEN. The analysis of the teloscore was carried out using quintiles with the third quintile (median genetically gdTL) as reference. The association analysis for each SNP was performed according to an additive and co-dominant inheritance model with the major allele set as reference. All analyses were adjusted by sex, age, and country of origin.

## Bioinformatic tools

Several bioinformatics tools were used to assess the potential functional effects of the SNPs associated with the risk of developing PanNEN.

RegulomeDB (regulomedb.org, access date: 1/April/2021) [51] was used to determine if the regions where the SNPs are situated harbour transcription binding sites or other regulatory elements. RegulomeDB annotates genetic variants with predicted regulatory functions in the human genome, and generates a score to rank the variants in different class from 1 to 7, where 1 includes the variants associated with the maximum number of regulatory elements (i.e., eQTL + TF binding + matched TF motif + matched DNase Footprint + DNase peak), and 7 is the rank without information on possible regulatory element.

The Genotype-Tissue Expression (GTEx) portal (gtexportal.org, access date: 1/April/2021) was used to identify if a variant was an expression quantitative trait locus (eQTL) [52]. The LDtrait tool (ldlink.nci.nih.gov/?tab=ldtrait, access date: 1/April/2021) was used to identify if a variant (or variants in LD) was previously associated with a trait or disease in a GWAS. [53].

The 3D-genome Interaction Viewer and database (3DIV; <http://3div.kr>, access date 01/07/2021) was used to investigate epigenetic interactions of the selected variants and neighbouring genomic regions (2 Mb), in the pancreatic tissue.

# Results

## Association between gdTL and PanNEN risk

The average call rate of the SNPs used for statistical analysis was 98.8%. Concordance among duplicated samples was higher than 99%.

We observed that longer genetically determined telomeres were associated with an increased risk of developing PanNEN (OR=1.99, CI 1.33-2.98; P=0.0008) comparing the fifth quintile with the third quintile, which represent the median distribution. The results of the teloscore analyses are reported in **table 2.**

The analysis of the individual polymorphisms showed that *ZNF676*-rs409627-C and *TERT*-rs2736100-A were associated with an increased risk of developing PanNEN: *ZNF676*-rs409627-C (ORadditive=1.49, CI 1.23-1.8, P=3.5×10-5, ORC/C\_vs\_G/G=2.3, CI 1.60-3.32, P=8.22×10-6) and *TERT*-rs2736100-A (ORC/A\_vs\_C/C=2.09, CI 1.45-3.00, P=6.79×10-5). None of the other selected SNPs showed any statistically significant associations (**table 3)**.

Furthermore, the web tools (GTEx, RegulomeDB and LDtrait), identified *ZNF676*-rs409627 as an eQTL for three genes expressed in the pancreatic tissue: the vomeronasal 1 receptor 85 pseudogene (*VN1R85P*), zinc finger proteins 676 and 257 (*ZNF676*, *ZNF257*). RegulomeDB assigned to *ZNF676*-rs409627 a rank of 7 (no functional annotation). 3DIV tool did not identify any spatial chromatin interaction for *ZNF676*-rs409627.

*TERT-*rs2736100 is an eQTL for the telomerase reverse transcriptase (*TERT)* gene with the A allele associated with higher expression in the skin, according to GTEx. RegulomeDB assigns to *TERT-*rs2736100 a functional rank of 5 (SNP in a transcription factor binding site or in a DNase peak). Based on the 3DIV tool, *TERT-*rs2736100 interacts with two super-enhancer sequences 145-150Kb upstream from the *TERT* gene.

# Discussion

Although PanNEN is a rare disease, it is showing an increase in incidence in recent years [2]. Given its rarity, identifying risk factors is challenging, and the contribution of the genetic variability to the disease onset is still not completely understood.

TL has been extensively investigated in relation to cancer risk, with very heterogenous results [23,25–32]. Given the heterogeneous results, a novel approach based on polygenic risk scores of SNPs associated with telomere length has been successfully employed to assess the causative relation between gdTL and risk of the onset several cancer types. In this study an association between longer gdTL and increased susceptibility to PanNET has been observed. The individuals in the 5th quintile of gdTL (longest telomeres) showed a two-fold increased chances of developing PanNEN compared to individuals in the 3rd quintile that represent an approximation of the median distribution of TL in the population.

Long telomeres can increase the risk of cancer development not by altering DNA mutation rate directly, but by delaying senescence, increasing the number of mitotic cycles and therefore increasing the chance of acquiring a deleterious mutation and finally undergoing malignant transformation [54]. The observation that longer gdTL are associated with increased risk is in general agreement with what observed for other tumours such as multiple myeloma, myeloproliferative diseases, melanoma, lung and prostate cancer [23,36,43,45,47,55–59]. These observations suggest that is not TL itself that represents a risk factor, but rather the innate ability of dividing more, that is associated with longer gdTL, that increases the risk of developing cancer. Our results, therefore, switch the focus from the measured length, that can be modified by the environment, to the predisposition to have longer telomeres, that can increase the risk regardless of the different environmental factors.

The effect of the individual SNPs was also assessed, considering that many variants associated with TL are pleiotropic and functional. Two polymorphisms showed an association that remained significant after correction for multiple testing. We observed that *TERT*-rs2736100 A/C heterozygotes had an increased risk of developing PanNEN compared with the C/C homozygotes.

This polymorphism is located in an intron of the *TERT* gene that is actively involved in telomere length maintenance [60].In particular, the A allele is associated with long telomeres, with an estimated increase of 102 bp per allele [35]. *TERT*-rs2736100 is a pleiotropic variant associated with many human phenotypes, including several cancers [25,26,28,30–32,61,62]. Interestingly, the A allele of *TERT*-2736100 was also associated with increased risk of developing PDAC [24]. This observation is intriguing considering that the two diseases seem to share only a modest portion of risk loci [16]. Even though this variant is one of the most studied in the human genome, it is hard to explain the molecular mechanism of the associations across a plethora of phenotypes, considering that the variant is not an eQTL, and it does not seem to harbour regulatory or functional potential. A possible explanation could be that *TERT*-rs2736100 is just a proxy for the variant that is responsible for the widespread associations. Fine-mapping studies on multiple cancer types aimed at uncovering low frequency and rare variants are warranted to understand better the mechanistic link of the associations identified through the association studies.

The association between *ZNF676*-rs409627 and risk of developing PanNEN was also observed. All the annotation tools used in our study suggest no functional relevance for this polymorphism. In contrast with *TERT*-rs2736100, *ZNF676*-rs409627 is not reported as a pleiotropic variant, and it seems to be specifically associated with TL. This evidence suggests that the effect observed is mediated only by TL, highlighting its importance in PanNEN aetiology. The C allele of *ZNF676*-rs409627 that is associated with increased risk is also associated with longer TL (with an estimated increase of 103.2 bp per allele) [34]. Although the role played by these polymorphisms in the regulation of telomere length and especially in the predisposition to develop cancer remains unknown, the concordance between the directions of the effect reported with the alleles increasing the risk, associated with longer telomeres, and longer telomere associated with increased risk is a clear, although indirect indication of the link between genetic variability, telomere length and PanNEN occurrence.

One of the strengths of the study is represented by the use of genetic variants in lieu of PCR-based methods, thus avoiding potential bias due to technical and epidemiologic confounders.

A potential limitation of the study is the sample size that could lead to overestimation of the effect of the genetic variants. However, considering the rarity of this disease, the sample size of 291 PanNEN makes this study one of the largest reported so far. Finally, both associations that we report remain significant after Bonferroni correction, making them unlikely to be spurious findings.

In conclusion, the results obtained in this study provide for the first time a clear indication of the involvement of gdTL in PanNEN risk and underline the importance of identifying new genetic variants and using them to generate new tools such as polygenic scores to further our understanding of the etiopathogenesis of rare and understudied diseases such as PanNEN.

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# Tables

Table 1 Characteristics of the study population.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Germany** | **Italy** | **Poland** | **U.K.** | **Total** |
| controls | 131 | 1330 | 91 | 134 | 1474 |
| Median age at recruitment, years (1st–3rd quartile) | 57 (54-61) | 63 (51-73) | 64 (23-71) | 64 (55-73) | 63 (52-73) |
| male | 62 | 785 | 44 | 79 | 830 |
| female | 69 | 545 | 47 | 55 | 644 |
| cases | 33 | 196 | 15 | 47 | 291 |
| Median age at diagnosis, years (1st–3rd quartile) | 55 (49-65) | 59 (48-69) | 52 (48-59) | 59 (50-71) | 57 (49-67) |
| male | 21 | 91 | 7 | 25 | 144 |
| female | 12 | 105 | 8 | 22 | 147 |
| Functional status |  |  |  |  |  |
| Yes | 2 | 45 | 3 | 6 | 56 |
| No | NA | 103 | 7 | NA | 110 |
| Unknown | 31 | 48 | 5 | 41 | 125 |
| Grade, G (WHO) |  |  |  |  |  |
| G1 and G2 | 7 | 125 | 3 | 22 | 157 |
| G3 | 3 | 10 | 2 | 1 | 16 |
| Unknown | 23 | 61 | 10 | 24 | 118 |
| Stage (ENETS) |  |  |  |  |  |
| I/II/III | 12 | 87 | 8 | NA | 107 |
| IV | 4 | 56 | 2 | NA | 62 |
| Unknown | 17 | 53 | 5 | 47 | 75 |
|  |  |  |  |  |  |

Table 2 Association between teloscore and risk of developing PanNEN.

|  |  |  |
| --- | --- | --- |
| Teloscore quintilesa | OR (95% CIb | Pvalue b |
| 1st | 1.20 (0.77-1.87) | 0.430 |
| 2nd | 1.15 (0.74-1.79) | 0.534 |
| 3rd | (reference) | - |
| 4th | 1.53 (1.01-2.31) | **0.045** |
| 5th | 1.99 (1.33-2.98) | **8×10-4** |

All analyses were adjusted for age, sex and country of origin. The bold p-value is statistically significant (<0.05).

a Quintiles were calculated using the distribution of the teloscore in the controls.

b Odds ratio, confidence intervals and p values obtained using the third quintile (median gdTL) as reference group. The first quintile represents the shortest gdTL; the fifth quintile represent the longest gdTL.

Table 3 Association between individual SNPs and risk of developing PanNEN.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **Chr** | **Pos** | **Gene** | **Genotype (n.con/n.cas)** | **S. model** | **OR** | **95%CI** | **P** |
| rs11125529 | 2 | 54248729 | *ACYP2* | C/C (1143/198) | Additive | 1.08 | (0.78-1.49) | 0.64 |
|  |  |  |  | C/A (168/34) | C/A vs C/C | 1.07 | (0.70-1.63) | 0.75 |
|  |  |  |  | A/A (27/6) | A/A vs C/C | 1.20 | (0.48-2.98) | 0.7 |
|  |  |  |  |  |  |  |  |  |
| rs6772228 | 3 | 58390292 | *PXK* | T/T (1342/272) | Additive | 0.73 | (0.41-1.31) | 0.29 |
|  |  |  |  | T/A (69/13) | T/A vs T/T | 0.84 | (0.45-1.57) | 0.59 |
|  |  |  |  | A/A (7/0) | A/A vs T/T | na | na | na |
|  |  |  |  |  |  |  |  |  |
| rs10936599 | 3 | 169774313 | *MYNN* | C/C (839/162) | Additive | 0.97 | (0.79-1.20) | 0.8 |
|  |  |  |  | C/T (492/100) | C/T vs C/C | 1.05 | (0.80-1.38) | 0.73 |
|  |  |  |  | T/T (114/18) | T/T vs C/C | 0.84 | (0.49-1.42) | 0.51 |
|  |  |  |  |  |  |  |  |  |
| rs7675998 | 4 | 163086668 | *MIR4454* | G/G (839/173) | Additive | 0.97 | (0.78-1.20) | 0.77 |
|  |  |  |  | G/A (528/90) | G/A vs G/G | 0.82 | (0.62-1.09) | 0.18 |
|  |  |  |  | A/A (86/22) | A/A vs G/G | 1.24 | (0.75-2.06) | 0.4 |
|  |  |  |  |  |  |  |  |  |
| rs2736100 | 5 | 1286401 | *TERT* | C/C (409/44) | Additive | 1.20 | (0.98-1.48) | 0.08 |
|  |  |  |  | C/A (680/151) | C/A vs C/C | 2.09 | (1.45-3.00) | **6.79×10-5** |
|  |  |  |  | A/A (264/39) | A/A vs C/C | 1.37 | (0.86-2.18) | 0.18 |
|  |  |  |  |  |  |  |  |  |
| rs9420907 | 10 | 103916707 | *OBFC1* | A/A (984/191) | Additive | 1.06 | (0.84-1.34) | 0.6 |
|  |  |  |  | A/C (425/72) | A/C vs A/A | 0.89 | (0.66-1.20) | 0.46 |
|  |  |  |  | C/C (52/16) | C/C vs A/A | 1.69 | (0.94-3.05) | 0.08 |
|  |  |  |  |  |  |  |  |  |
| rs3027234 | 17 | 8232774 | *CTC1* | C/C (817/165) | Additive | 0.93 | (0.75-1.15) | 0.5 |
|  |  |  |  | C/T (530/108) | C/T vs C/C | 1.03 | (0.78-1.35) | 0.84 |
|  |  |  |  | T/T (100/14) | T/T vs C/C | 0.69 | (0.39-1.25) | 0.23 |
|  |  |  |  |  |  |  |  |  |
| rs8105767 | 19 | 22032639 | *ZNF208* | A/A (758/159) | Additive | 0.95 | (0.78-1.15) | 0.59 |
|  |  |  |  | A/G (519/91) | A/G vs A/A | 0.81 | (0.61-1.07) | 0.14 |
|  |  |  |  | G/G (144/30) | G/G vs A/A | 1.07 | (0.69-1.65) | 0.77 |
|  |  |  |  |  |  |  |  |  |
| rs409627\* | 19 | 22176638 | *ZNF676* | G/G (582/79) | Additive | 1.49 | (1.23-1.80) | **3.50×10-5** |
|  |  |  |  | G/C (663/105) | G/C vs G/G | 1.17 | (0.85-1.61) | 0.33 |
|  |  |  |  | C/C (219/68) | C/C vs G/G | 2.30 | (1.60-3.32) | **8.22×10-6** |
|  |  |  |  |  |  |  |  |  |
| rs6028466 | 20 | 39500359 | *DHX35* | G/G (1258/253) | Additive | 0.77 | (0.51-1.16) | 0.21 |
|  |  |  |  | G/A (159/27) | G/A vs G/G | 0.85 | (0.55-1.32) | 0.47 |
|  |  |  |  | A/A (13/0) | A/A vs G/G | na | na | na |
|  |  |  |  |  |  |  |  |  |
| rs755017 | 20 | 63790269 | *ZBTB46* | A/A (945/114) | Additive | 0.86 | (0.54-1.37) | 0.53 |
|  |  |  |  | A/G (147/16) | A/G vs A/A | 0.73 | (0.41-1.32) | 0.30 |
|  |  |  |  | G/G (15/3) | G/G vs A/A | 1.23 | (0.32-4.61) | 0.76 |

Chr: chromosome; Pos: position on chromosome (GRCh38); Gene: gene mapping closest to the SNP: n.con: number of controls; n.cas: number of cases; S. model: genetic model used in the analysis; OR: odds ratio; CI: confidence interval; p-values in bold are statistically significant (p<0.05).