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Germline *TP53* noncoding variant (rs78378222) prevalence in cohorts of prostatic adenocarcinoma and benign prostatic hyperplasia: further evidence from southern Brazil and novel insights into its functional impact mediated by the circRNAs-miRNAs-*TP53* regulatory axis

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Abstract

Background

The *TP53* 3'UTR germline variant rs78378222 A > C has been associated with several tumors in European populations. It modifies both the polyadenylation signal (PAS) sequence and binding sites for specific miRNAs (miR-382-5p, miR-325-3p, and miR-125b; rs7837822-associated miRNAs) in the *TP53* 3'UTR, resulting in decreased p53 expression. Its prevalence is not yet fully known in admixed populations.

Methods and Results

Herein, the germline prevalence of rs7837822 was examined in 320 samples from two cohorts of patients diagnosed with prostatic adenocarcinoma (PAC, n = 153) and benign prostatic hyperplasia (BPH, n = 167) in southern Brazil. Additionally, circRNAs reported in the *circRNAdisease v2.0* database as previously validated "sponges" of rs7837822-associated miRNAs were retrieved, and circRNA differential expression analysis was performed based on PAC and BPH tissues using the GEO database. The variant allele was observed in 1/153 (0.65%) of PAC and in 1/167 (0.6%) of BPH cases, a lower frequency compared to the European prostate cancer cohorts. Interestingly, twenty circRNAs regulating rs78378222-associated miRNAs in other human tissues not related to the prostate gland were found, and two specific circRNAs were upregulated in PAC when compared with BPH tissues, namely hsa_circ_0001658 (derived from the *ARID1B* host gene; p = 0.0378) and hsa_circ_NR3C1 (p = 0.0114).

Conclusions

This is the first report investigating a novel functional aspect associated with this variant involving the circRNA-miRNA-*TP53* regulatory axis, and a hypothesis-generating framework for future experimental studies. Germline analyses, including larger Brazilian cohorts, should be undertaken to confirm our findings and determine whether screening for rs78378222 in non-cancerous (BPH) and cancerous prostate conditions is justified.

Introduction

Pathogenic germline variants in the tumor suppressor gene *TP53* are the underlying cause of Li-Fraumeni syndrome (LFS), which is characterized by increased early-onset cancer predisposition (Malkin et al., 1979; Petitjean et al., 2007). Although exonic regions were the main focus in previous studies, sequence variants in 5' and 3' untranslated regions (UTRs) have been recently explored and show promising potential for tumor-promoting activity (Stacey et al., 2011; Li et al., 2013; Diederichs et al., 2016; Deng et al., 2019) and disturbing of microRNA (miRNA) binding sites (Jardin *et al*., 2013). Sequence variants in the 3'UTR may have a great impact on protein expression since it contains polyadenylation regulatory sequences, controls mRNA stability, localization, and the efficiency of protein translation (Erson-Bensan et al., 2020).

Despite being increasingly studied, the contribution of 3'UTR noncoding variants to the inherited predisposition to cancer is poorly understood (Erson-Bensan *et al*., 2020). The first description of comprehensive molecular analyses of *TP53* UTR sequences was performed by Li and colleagues (2013) in a somatic context. However, two years earlier, a rare germline variant (rs78378222, NM_000546.5:c.*1175A > C) located within the sole polyadenylation signal (PAS) sequence of *TP53* 3'UTR was detected is a less extensive analysis in a germline context, showing a minor allele frequency (MAF) ranging from 0.003 to 0.044 in controls and cancer-affected individuals from European ancestry cohorts, respectively (Stacey et al., 2011). Importantly, a subsequent meta-analysis suggested that this variant confers susceptibility to general cancer (Wang et al., 2016). In parallel, independent case-control association studies reported that rs78378222[C] is a risk allele for different types of tumors, including prostate cancer (Deng et al., 2019; Egan et al., 2012; Zhou et al., 2012; Enciso-Mora et al., 2013; Diskin et al., 2014; Wang et al., 2015; Macedo et al., 2016; Zhao et al., 2016; Melin et al., 2017; Rafnar et al., 2018; Di Giovannantonio et al., 2021; Zhang et al., 2021).

Moreover, the presence or absence of this variant allele creates or disrupts binding sites for specific miRNAs that modulate p53 activity (Zhou et al., 2012; Zhao et al., 2016). In recent years, long non-coding RNAs such as circRNAs have gained attention due to their ability to regulate miRNA availability, mainly by acting as miRNA sponges (Misir et al., 2022). To date, the relationship between the rs78378222[C] variant allele's presence or absence and its functional impact regarding circRNA regulation has not been explored. This investigation represents a novel insight into indirect and upstream *TP53* regulation by circRNAs associated with this variant.

Interestingly, the prevalence of germline rs78378222[C] carriers in non-tumoral conditions, such as benign prostatic hyperplasia (BPH), has not yet been assessed. To date, a previous study from our research group is the only report that evaluated the rs78378222 germline frequency in cancer cohorts from the Brazilian population, and it focused on a sample from the southern and southeastern region of the country (Macedo et al., 2016).

Hence, this study aimed to determine the germline prevalence of the *TP53* rs7837822 (A > C) variant in cohorts of patients with prostatic adenocarcinoma (PAC) and BPH from southern Brazil. Moreover, we aimed to characterize the clinical features associated with variant-positive cases and further investigate functional evidence exploring the circRNA-miRNA-*TP53* 3'UTR regulatory axis regarding this variant.

Materials and Methods

Study subjects, sample types and ethical aspects

Patients diagnosed with prostate adenocarcinoma (PAC, n = 153) and benign prostatic hyperplasia (BPH, n = 167) enrolled at the Urology Service of Hospital de Clínicas de Porto Alegre were recruited for this prospective study. Pathological analyses confirmed typical adenocarcinoma histology in all prostate cancer cases, and peripheral blood samples were obtained from all participants. The patients were predominantly self-declared Caucasians/Euro-descendant and residents of the state of Rio Grande do Sul in the southern region of Brazil. The inclusion criteria to select patients and detailed ethnicity data were previously described (Neto et al., 2008; Zambra et al., 2013; Biolchi et al., 2012).

Informed consent was obtained from all PAC and BPH subjects. All analyses were previously approved by the ethical committee of HCPA, Brazil, under the Certificate of Presentation for Ethical Appreciation (CAAE) number 9346919900005327.

Molecular analyses

Genomic DNA extraction from peripheral blood leukocytes was performed through a salting-out procedure, as previously described (Miller et al., 1988). *TP53* rs7837822 genotyping was performed by real-time PCR using fluorescent allele-specific TaqMan probes (reference and catalog numbers C_102214636_10 and 4351379, respectively), according to the manufacturer's standard protocols (Applied Biosystems, Carlsbad, USA).

In silico analyses of the circRNAs-miRNAs-TP53 3`UTR regulatory axis and data expression from GEO dataset

To identify circRNAs that regulate miRNAs whose binding sites in the *TP53* 3'UTR may be affected by the rs78378222 variant (miR-382-5p, miR-325-3p, and miR-125b), a database of experimentally validated circRNA-miRNA-target interactions, circRNAdisease v2.0, was queried in the "Search by miRNA" dataset. The search criteria were filtered only by human species and not restricted by detection method or sample type (http://cgga.org.cn/circRNADisease/; Sun et al., 2023). The final list of circRNAs obtained through this search included nomenclature, disease-associated, expression pattern, and more details regarding each study from which the circRNA expression data were previously reported. In addition, the CircInteractome web tool was employed to explore another known function of circRNAs that is potentially interacting with RNA-binding proteins (RBPs) (https://circinteractome.nia.nih.gov/; Panda et al., 2018).

Ultimately, the GEO (Gene Expression Omnibus) database was queried to identify previous studies related to circRNA expression profiles, including PAC of different clinical stages and BPH sample tissues. This search allowed us to find a previous circRNA-seq analysis involving nine samples of PAC and three samples of BPH (GSE212215, Wang et al., 2023). Differential expression analysis of circRNAs was performed using the GEO2R interactive web tool.

Query in population databases and linkage disequilibrium analyses

The frequency of the rs78378222[C] variant allele was investigated in the following population databases: gnomAD v2.1.1 data set (GRCh37/hg19) (Karczewski et al., 2020), 1000 Genomes Project (Genomes Project et al., 2015), Exome Aggregation Consortium (ExAC) Browser (Karczewski et al., 2017), Trans-Omics for Precision Medicine (TOPMed) (Taliun et al., 2021), Fabulous Ladies Over Seventy (FLOSSIES) (Walsh et al., 2010), and Online Archive of Brazilian Mutations (ABraOM, SABE-WGS-1171 dataset) (Naslavsky et al., 2020; Naslavsky et al., 2017). Pairwise linkage disequilibrium of the rs78378222 variant with other *TP53* variants was accessed in the Ensembl database (https://www.ensembl.org/index.html), evaluating data from the 1000 Genomes project (Phase 3) for all the available populations.

Statistical analyses

Genotype and allele frequencies were estimated by simple counting. Clinical and molecular features of patients were assessed using descriptive statistics. SPSS® version 18 (SPSS® Inc., Chicago, IL, USA) was used for data handling and for all descriptive analyses.

Results

Clinical samples obtained from a total of 320 individuals diagnosed with PAC or BPH were included in this study. General clinical data according to the study groups are summarized in Table 1. PAC (n = 153) and BPH (n = 167) groups were predominantly composed of Caucasian self-identified ethnicity. The mean and median age at tumor/condition diagnosis was in the sixth decade of life in both PAC and BPH cohorts. Other specific clinical features (PSA levels and Gleason score) are presented in **Table S1**. All PAC tumors had a Gleason score assigned of 6 or higher (**Table S1**).

Table 1
Sample characterization and *TP53* rs78378222 (A > C) genotyping results from patients included in this study.

Characteristics and molecular features	PAC (n = 153)	BPH (n = 167)
Self-identified ethnicity		
N (%)[a]	98 (64)[a]	107 (64.1)[a]
White	82 (83.7)	104 (97.2)
Black	16 (16.3)	3 (2.8)
Age at diagnosis		
Mean, years (± SD)	64.3 (7.1)	66.8 (8.2)
Median, years (IR)	65 (9.2)	67 (9.5)
Genotype, N (%)		
AA	152 (99.3)	166 (99.4)
AC	1 (0.65)	1 (0.60)
CC	0	0
C allele frequency	0.0033	0.0029

PAC, prostatic adenocarcinoma; BPH, benign prostatic hyperplasia; SD, standard deviation; IR, interquartile range; NAP, not applicable.

[a] The percentage was calculated over the total number of genotyped samples for each study group, and over the number of cases for which the specified clinical data was available.

Allele and genotype frequencies of *TP53* rs78378222 in each group of analysis are shown in Table 1. The variant was identified in only one PAC-affected patient (germline frequency of heterozygous genotype 0.65%) and one BPH case (germline frequency of heterozygotes 0.6%). Representative plots of the experimental results of TaqMan genotyping are shown in **Figure S1**. Both heterozygotes identified in the PAC and BPH cohorts were self-identified as white males. Of particular interest, the PAC-affected patient harboring the variant had a family history of prostate cancer (affected father).

Importantly, homozygous individuals for the minor allele C were not identified in any of the study cohorts (Table 2). To better understand this finding, we queried updated frequency data of this variant (**Table S2**) and provided an overview of all case-control association analyses and functional evidence previously reported in the literature (**Table S3**). Among 18 initial search results addressing the rs78378222 variant, one review article was excluded as it mentions the variant but does not provide original data (Rice et al., 2016), while another study classified as a review remained in our analysis because it represents the first meta-analysis of the relationship between this variant and overall cancer risk (Wang et al., 2016). Additionally, a meta-analysis of GWAS datasets reporting new statistical data about rs78378222 and the risk of glioma subtypes (Melin et al., 2017) was included from its citation in one of the initial search results, totaling 18 articles in our final analysis. As depicted in Fig. 1, functional evidence from these studies demonstrates that different genotypes for the rs78378222 variant modulate p53 expression levels and function through two main molecular mechanisms: impairment of the polyadenylation efficiency of *TP53* transcripts, and influence on their negative regulation by certain miRNAs, such as miR-382-5p, miR-325-3p, and miR-125b. Given that it is a hypomorphic (i.e., multiple descriptions of p53 downregulation in clinical samples and cancer cell lines harboring the minor C-allele) and rare variant (MAF ranging from 0.002 to 0.02 in African and European populations, respectively), there are only a few reports of rs78378222[C/C] homozygotes in previous studies and different population databases (**Table S2**).

Table 2
Clinical and molecular findings from PAC and BPH-affected patients harboring the functional variant *TP53* rs78378222.

Identifier	Tumor/ condition	Gender	Ethnicity	Age at diagnosis (years)	Cancer FH[a]	PSA levels (ng/ml)	Gleason score, PAC
#1	BPH	Male	Caucasian	70	No	3.58	NAP
#2	PAC	Male	Caucasian	75	**Yes**[b]	6	6 (3 + 3)

NAP, not applicable; [a] Cancer FH, presence of cancer family history; [b] First-degree relative (father) with prostate cancer diagnosis.

Moreover, we investigated experimentally validated interactions between circRNAs and the three miRNAs of interest (miR-382-5p, miR-325-3p, and miR-125b) from the circRNAdisease database. A total of twenty circRNAs available in the database with previously validated interactions were identified, revealing changes in circRNA expression profiles across various diseases, including numerous cancers and, of special interest, some tumor types associated with Li-Fraumeni syndrome (Table 3). Interestingly, none of the twenty circRNAs exhibited an overlapping regulatory function with any of the miRNAs of interest. Additionally, we collected the host genes associated with each circRNA sequence, as well as the known or hypothesized molecular mechanisms reported by each miRNA-circRNA interaction, primarily emphasizing the circRNA's sponging action on miRNAs. Furthermore, as part of this *in silico* investigation based on another function related to circRNAs that is binding to RBPs, we identified the top three RBPs with the highest number of

circRNA-related interaction sites previously reported (Table 3). Among all RBPs found in this analysis, the specific RBP named EIF4A3 stands out as the most interacting with the circRNAs of interest.

Table 3
circRNAs previously validated targeting miRNAs whose binding sites are associated with rs78378222 A > C location in the *TP53* 3`UTR (data extracted from circRNAdisease v2.0).

Human miRNA	circRNA targeting this miRNA (circBase ID or variant nomenclatures)	Host Gene	Associated disease	Detection method	circRNA expression status	Molecular mechanism and/or biological function and/or main findings about the circRNA	Sample type	Top RNA-binding protein interaction sites with the cirRNA	Reference study (PMID)
hsa-miR-382-5p	hsa_circ_0005397	*RHOT1*	Pancreatic cancer	Microarray, RT-qPCR	UP	miRNA sponge of miR-382-5p	tissue	EIF4A3 (7), PTB (2), AGO2 (1)	27997903
	has_circ_DICER1	*DICER1*	Brain glioma [a,b]	RT-qPCR	UP	miRNA sponge of miR-382-5p, promoting the cell viability, migration, and tube formation	cell line, PDX	N/A	30621721
	hsa_circ_0001658	*ARID1B*	Osteosarcoma [a]	RT-qPCR	UP	miRNA sponge of miR-382-5p, while positively modulate the expression of YB-1, promoting the proliferation and metastasis	tissue	EIF4A3 (78), FUS (11), PTB (11)	31758574
	hsa_circ_0008285	*CDYL*	Colorectal cancer [b]	RT-qPCR	DOWN	miRNA sponge of miR-382-5p, forming a miR-382-5p/PTEN axis and inhibiting colorectal cancer cell proliferation and migration	tissue, cell line	EIF4A3 (4), FMRP (4), HuR (4)	32423803
	hsa_circ_0000190	*CNIH4*	Stomach cancer	RT-qPCR	DOWN	miRNA sponge of miR-382-5p. Circ_0000190 suppressed gastric cancer (GC) progression. ZNRF3 was a target of hsa-miR-382-5p, and hsa-miR-382-5p accelerated the proliferation, motility and restrained the ferroptosis of GC cells partly via regulating ZNRF3.	tissue, cell line, PDX	AGO2 (9), AGO1 (4), EIF4A3 (4)	35037032
	hsa_circ_NEK6	*NEK6*	Lung non-small cell carcinoma [b]	RT-qPCR	UP	miRNA sponge of miR-382-5p, contributing to fortify the expression of breast carcinoma amplified sequence 2 (BCAS2) in non-small cell lung cancer (NSCLC). Silencing of circ_NEK6 could effectively suppress NSCLC cell proliferation, migration and invasion	tissue, cell line, PDX	N/A	34663267
	hsa_circ_0008309	*CUL3*	Oral squamous cell carcinoma	RNA-Seq, RT-qPCR	DOWN	Evidence of hsa_circ_0008309-hsa-miR-136-5P/hsa-miR-382-5P-ATXN1 regulatory axis	tissue, cell line	AGO2 (9), EIF4A3 (3), FMRP (2)	30344795

N/A, not available; PDX, Patient derived xenograft model; UP= upregulation; DOWN= downregulation.

[a] Tumor types associated with classical spectrum phenotype of the Li-Fraumeni syndrome (LFS). The five core LFS-related cancers are adrenocortical carcinomas (ACC), breast cancer, central nervous system (CNS) tumors, osteosarcomas, and soft-tissue sarcomas [Evans & Woodward 2021, PMID: 32984917].

[b] Tumor types previously associated with the studied allele variant *TP53* rs78378222[C]. This allele variant was previously found to confer significantly increased risk for developing these tumor types.

Human miRNA	circRNA targeting this miRNA (circBase ID or variant nomenclatures)	Host Gene	Associated disease	Detection method	circRNA expression status	Molecular mechanism and/or biological function and/or main findings about the circRNA	Sample type	Top RNA-binding protein interaction sites with the cirRNA	Reference study (PMID)
	hsa_circ_NR3C1	*NR3C1*	age related macular degeneration	RNA-Seq, RT-qPCR	DOWN	miRNA sponge of miR-382-5p, sequestering its activity	tissue	N/A	32017889
	hsa_circ_AP2A2	*AP2A2*	Hemangioma	RT-qPCR	UP	miRNA sponge of miR-382-5p, forming a hsa_circ_AP2A2/hsa-miR-382-5p/VEGFA regulatory axis, promoting proliferation, colony formation, migration, and invasion	Tissue, cell line	N/A	32091151
	hsa_circ_0000467	N/A	Colorectal cancer [b]	Microarray, RT-qPCR	UP	miRNA sponge of miR-382-5p, up-regulating EN2 expression (target of this miRNA). In addition, the depletion of circ_0000467 expression was found to impede the multiplication, migration, invasion, and epithelial-mesenchymal transition (EMT) processes in colorectal carcinoma cells	tissue, cell line	AGO2 (6), AGO1 (2), EIF4A3 (2)	33685351
hsa-miR-125b	hsa_circ_PVT1	*PVT1*	Stomach cancer, acute lymphoblastic leukemia	RNA-Seq, RT-qPCR	UP	miRNA sponge of hsa-miR-125b, promoting proliferation of tumor cells	tissue, cell line	N/A	27986464
hsa-miR-125b	hsa_circ_0000516	*RPPH1*	Thyroid gland papillary carcinoma	Microarray, RT-qPCR	UP	miRNA sponge of hsa-miR-125b	tissue	AGO2 (1), EIF4A3 (1)	28288173
	hsa_circ_0056288	*GLI2*	Osteosarcoma [a]	RT-qPCR	UP	miRNA sponge of hsa-miR-125b-5p, promoting proliferation, migration and invasion of tumor cells	tissue, cell line	AGO2 (5), EIF4A3 (1)	28695772
	hsa_circ_0086996	*RECK*	Osteosarcoma [a]	RT-qPCR	UP	miRNA sponge of hsa-miR-125b-5p; circ_0086996 knockdown significantly suppressed cell proliferation, migration, and invasion	tissue, cell line	EIF4A3 (27) AGO2 (2), FUS (2)	33053498
	hsa_circ_VAPA	*VAPA*	Stomach cancer, psoriasis	RT-qPCR	UP	miRNA sponge of hsa-miR-125b-5p, and hsa-miR-125b-5p could target STAT3 in the gastric cancer (GC) cells. Moreover, CircVAPA depletion	tissue, cell line, PDX	N/A	33642823

N/A, not available; PDX, Patient derived xenograft model; UP= upregulation; DOWN= downregulation.

[a] Tumor types associated with classical spectrum phenotype of the Li-Fraumeni syndrome (LFS). The five core LFS-related cancers are adrenocortical carcinomas (ACC), breast cancer, central nervous system (CNS) tumors, osteosarcomas, and soft-tissue sarcomas [Evans & Woodward 2021, PMID: 32984917].

[b] Tumor types previously associated with the studied allele variant *TP53* rs78378222[C]. This allele variant was previously found to confer significantly increased risk for developing these tumor types.

Human miRNA	circRNA targeting this miRNA (circBase ID or variant nomenclatures)	Host Gene	Associated disease	Detection method	circRNA expression status	Molecular mechanism and/or biological function and/or main findings about the circRNA	Sample type	Top RNA-binding protein interaction sites with the cirRNA	Reference study (PMID)
						inhibited proliferation, migration, and invasion and increased apoptosis of GC cells.			
	hsa_circ_0001806	*CSPP1*	Hepatocellular carcinoma	RT-qPCR	UP	miRNA sponge of hsa-miR-125b to up-regulate hexokinase II (HK2) expression, promoting hepatocellular carcinoma (HCC) cell proliferation, migration and glycolysis and inhibited cell apoptosis	tissue, cell line, PDX	EIF4A3 (6), HuR (3)	34664737
	has_circ_101491	N/A	Brain glioma [a,b]	RT-qPCR	UP	miRNA sponge of hsa-miR-125b-5p, forming a circ101491/hsa-miR-125b-5p/EDN1 regulatory axis. Additionally, circ101491 overexpression promoted viability, invasion and migration of glioma cells both in vivo and in vitro	tissue, cell line	N/A	36796652
	hsa_circ_0026070	*ARF3*	Encephalitis	RT-qPCR	UP	Up-regulating hsa-miR-125b, which mitigates TNF-alpha-induced inflammatory damage	cell line	AGO2 (52), EIF4A3 (31), HuR (34)	32329660
	hsa_circ_LAS1L	*LAS1L*	Acute Myocardial Infarction	RT-qPCR	DOWN	miRNA sponge of hsa-miR-125b, inhibiting the activation, proliferation and migration of cardiac fibroblasts, and promoting apoptosis	cell line	N/A	31950540
hsa-miR-325-3p	hsa_circ_0069313	*PACRGL*	Oral squamous cell carcinoma [b]	RT-qPCR	UP	miRNA sponge of miR-325-3p; has_circ_0069313 induces oral scamous cell carcinoma (OSCC) immunity escape via the miR-325-3p-Foxp3 axis in both OSCC cells and Treg cells.	tissue, cell line	AGO2 (19), EIF4A3 (13), HuR (12)	35575762

N/A, not available; PDX, Patient derived xenograft model; UP= upregulation; DOWN= downregulation.

[a] Tumor types associated with classical spectrum phenotype of the Li-Fraumeni syndrome (LFS). The five core LFS-related cancers are adrenocortical carcinomas (ACC), breast cancer, central nervous system (CNS) tumors, osteosarcomas, and soft-tissue sarcomas [Evans & Woodward 2021, PMID: 32984917].

[b] Tumor types previously associated with the studied allele variant *TP53* rs78378222[C]. This allele variant was previously found to confer significantly increased risk for developing these tumor types.

Given that some circRNAs have been demonstrated to influence microRNA expression in certain Li-Fraumeni-related cancers and other tumor types, we also examined data from a specific circRNA-seq database (GSE212215) of prostatic tumors, including PAC and BPH tissue samples (**Table S4**). Among all circRNAs analyzed, two of them were differentially expressed when comparing the two studied groups. The first circRNA was associated with the host gene *ARID1B* ($p = 0.0378$), and the second was linked to *NR3C1* ($p = 0.0114$). Both were significantly overexpressed in the PAC samples.

Lastly, we investigated whether other variants in the *TP53* gene would be differentially co-inherited with rs78378222 in different populations (Table 4). Pairwise linkage disequilibrium data were available only in European ancestry populations, because this variant was not genotyped in other populations at the time of the 1000 Genomes project. The rare noncoding variant rs35850753 (MAF = 0.005), mapping to the 5'UTR of the Δ133 isoform of *TP53*, exhibited a strong linkage disequilibrium with the studied variant, having higher r^2 correlation values in the UK, Italy, and Finland populations. In contrast, rs17884306, a low-frequency 3'UTR variant recently identified in elderly individuals from southeastern Brazil (ABraOM database, MAF = 0.03) (Naslavsky et al., 2020), had estimated r^2 values with rs78378222 below 0.3, suggesting that both *loci* are not in linkage disequilibrium in the European populations analyzed.

Table 4
Pairwise linkage disequilibrium data by population regarding rs78378222 (focus variant) and other variants of interest in the *TP53* gene.

Description of population [a]	*TP53* variant [b]	Chromosomal location	Gene region	r^2 [g]	D' [h]
Finnish (Finland)	rs1042522 [c]	17:7676154	Exon 4	0.071875	1.00
Finnish (Finland)	rs1642785 [d]	17:7676483	Intron 2	0.065430	1.00
Iberian populations (Spain)	rs17884306 [e]	17:7668783	3'UTR	0.158805	1.00
Toscani (Italy)				0.196244	1.00
British (England and Scotland)				0.217876	1.00
Utah residents (USA) with Northern and Eastern European ancestry				0.106598	1.00
Finnish (Finland)				0.294406	1.00
Iberian populations (Spain)	rs35850753 [f]	17:7675353	5'UTR	0.115553	1.00
Toscani (Italy)				**0.497652**	1.00
British (England and Scotland)				**1.000000**	1.00
Utah residents (USA) with Northern and Eastern European ancestry				0.246193	1.00
Finnish (Finland)				**0.484375**	1.00

[a] This table gathers information from the 1000 Genomes Phase 3-based linkage disequilibrium (LD) plots and tables obtained from Ensembl database.

[b] For other variants of interest in *TP53* not mentioned above, such as rs121912664 (Brazilian founder pathogenic variant c.1010G > A p.Arg337His, widely referred as R337H) and rs17878362 (16-bp duplication polymorphism in intron 3, or PIN3), there was no pairwise LD data in a given population for the following reasons: minor allele frequency close or equal to 0; they do not have enough genotypes to calculate LD values; and estimated r^2 values are below 0.05 and have been filtered out.

[c] *TP53* c.215C > G (p.Pro72Arg) is a very common functional missense variant (minor allele frequency, MAF = 0.6), also known as Pro72Arg.

[d] *TP53* c.74 + 38C > G is a common intronic variant (MAF = 0.4), also known as PIN2 polymorphism (intron 2).

[e] *TP53* c.*826G > A is a low frequency noncoding variant (MAF = 0.06) recently identified in the population of the southeastern region of Brazil (ABraOM database, MAF = 0.03).

[f] *TP53* c.376-117G > A is a rare noncoding variant (MAF = 0.005) that maps to 5'UTR of the Δ133 isoform of *TP53*. It has been previously reported as a germline variant in linkage disequilibrium with rs78378222, and both variants were robustly associated with risk of neuroblastoma in different populations (Diskin et al., 2014; PMID: 24634504).

[g] The correlation between a pair of loci. It varies from 0 (loci are in complete linkage equilibrium) to 1 (loci are in complete linkage disequilibrium and coinherited).

[h] The difference between the observed and the expected frequency of a given haplotype. If two loci are independent (i.e. in linkage equilibrium and therefore not coinherited at all), the D' value will be 0.

Discussion

The prevalence of rs78378222[C] variant was reported in a few studies worldwide; however, no previous study analyzed cancerous and non-cancerous clinical samples from the same tissue. Thus, exploring its prevalence in both conditions may help understand the variant's role in the context of benign growth and carcinogenesis involving prostate tissue. Herein, we identified a low germline prevalence of rs78378222[C] in PAC and BPH patients (0.65% and 0.6%, respectively). This low prevalence of rs78378222[C] carriers observed in each of the cohorts, as well as in the overall sample of the current study (2/320, 0.63%), are slightly similar to the carrier frequency of about 1.2% (14/1,171) recently reported in a Brazilian repository of whole-genome sequencing data (ABraOM, SABE-WGS-1171 dataset) (Naslavsky et al., 2020; Naslavsky et al., 2017). On the other hand, the germline frequency of heterozygotes in our PAC cohort was much smaller than that obtained in the study conducted by Stacey and colleagues (2011) in European and North American populations (reaching up to 3%). They also found a significant association of this variant with prostate cancer (OR = 1.44, 95% CI = 1.24 to 1.68) (Stacey et al., 2011).

A higher germline frequency (3–4%) of rs78378222[C] was found in tumor-affected individuals with European ancestry (Stacey et al., 2011) in the population database gnomAD v2.1.1. In contrast, a lower frequency (~ 0,3%) is found in population controls with Latino and African ancestry. The variability in rs78378222[C] allele frequencies was also verified in a previous study from our group focusing on South Brazilian populations (Macedo et al., 2016). Although we did not perform a refined ancestry analysis of the patients included in this study, we speculate that the lower prevalence found in our work might be explained by the probable European origin of the rs78378222[C] allele, which is evidenced by its higher frequency in European ancestry populational databases, and the population of southern Brazil has a high heterogeneous genetic constitution with a predominant tri-hybrid composition (European, African and Native American) (Marrero et al., 2005; Souza et al., 2019). In addition to the heterogeneity, south and southeast Brazilian regions are of particular interest due to the high prevalence of another functional *TP53* variant in the general population (~ 0,3%, the highest value ever described for a *TP53* germline variation), the germline founder pathogenic variant c.1010G > A (rs121912664), commonly known as R337H or p.(Arg337His) (Pinto et al., 2004; Custódio et al., 2013; Achatz et al., 2016). This variant has been consistently associated with the LFS phenotype. Interestingly, in our previous analyses, rs78378222[C] carriers were not found in a group of LFS patients harboring germline *TP53* pathogenic variants (n = 130) but were detected at a high frequency in patients with the LFS phenotype but no identifiable coding *TP53* pathogenic variants (7/129, 5.4%) (Macedo et al., 2016).

The rarity and location of the variant rs78378222 A > C raises concern about its functional role. However, rare sequence variants (MAF < 0.05) located in regulatory, noncoding regions of the genome have been proposed to contribute to the “missing heritability” in cancer (Bodmer et al., 2010). Independent studies showed association of rs78378222 A > C variant with susceptibility to prostate cancer, colorectal adenomas, brain tumors (mainly glioma and neuroblastoma), esophageal squamous cell carcinoma, uterine leiomyoma, soft-tissue sarcoma, non-melanomatous skin cancer and general cancer predisposition in different populations (Stacey et al., 2011; Deng et al., 2019; Wang et al., 2016; Zhou et al., 2012; Enciso-Mora et al., 2013; Diskin et al., 2014; Wang et al., 2015; Melin et al., 2017; Rafnar et al., 2018; Di Giovannantonio et al., 2021). This broad association with malignant neoplasms is supported by functional analyses indicating that the presence of the minor allele C results in altered post-transcriptional *TP53* regulation (Stacey et al., 2011; Li et al., 2013; Deng et al., 2019; Macedo et al., 2016; Zhao et al., 2016; Zhang et al., 2021).

To provide a more complete overview of the rs78378222 A > C functional role and case-control association findings, we reviewed eighteen original articles that evaluated the functional consequences related to this variant. There is evidence that the A-to-C transition changes the canonical sequence of *TP53* PAS from AATAAA to AATACA, leading to impaired *TP53* mRNA 3'-end processing, production of aberrant transcripts, and decreased expression levels of both *TP53* mRNA and p53 protein. Reduced p53 levels were identified in cancer cell lines, animal model tissues, and many different human clinical specimens (normal and tumor tissue samples) from rs78378222[A/C] heterozygotes (Stacey et al., 2011; Li et al., 2013; Deng et al., 2019; Wang et al., 2016; Diskin et al., 2014; Macedo et al., 2016).

Remarkably, a more recent work described significant enrichments of uncleaved, improperly terminated “run-on” *TP53* transcripts in cancer cell lines carrying the C-allele compared with the A-allele (Zhang et al., 2021). Moreover, in a group of patients with wild-type *TP53* tumors from the TCGA cohort, those with the minor C-allele have significantly worse progression-free interval, overall survival, and treatment response to radiotherapy compared to those without the minor allele. Together, these data reinforce our previous hypothesis that rs78378222 confers susceptibility to different tumors through a mechanism of reduction in *TP53* dosage (haploinsufficiency) (Macedo et al., 2016).

Furthermore, the presence of the C-allele hinders negative *TP53* regulation exerted directly by specific miRNAs (rs78378222-associated miRNAs). Specifically, it creates a binding site for miR-382-5p and compromises the miR-325-3p site, promoting p53 downregulation, as demonstrated in miRNA expression analyses from a mouse model harboring the variant (Zhou et al., 2012). Another study involving functional experiments in epithelial cells demonstrated that the C-allele introduces a miR-125b targeting site in the *TP53* 3'UTR mRNA (Zhao et al., 2016). In line with these previous findings, in the present study, we conducted an *in silico* analysis regarding the potential effect of rs78378222 on the indirect regulation of p53 expression by circRNAs. Their complete role is still unknown, but strong evidence has demonstrated their ability to act as miRNA sponges (Misir et al., 2022). Moreover, it is widely described that circRNA activity as a modulator of gene and protein expression is an emerging topic within non-coding RNAs, especially as candidate biomarkers in prostate cancer (as reviewed in Shu et al., 2025), in which, in the last five years, only 30 studies have focused on this research question.

Since the rs78378222 variant was previously described as altering binding sites for those miRNAs, which results in altered p53 levels, herein we explored for the first time the circRNA-miRNA-*TP53* regulatory axis associated with the presence of rs78378222[C]. As a new subject, little data and comprehensive literature were available to make a more robust analysis; thus, our goal was to provide novel insights into the functional effects of the indirect regulation and modulation of p53 by circRNAs, as well as to demonstrate the need for future experimental validation studies bringing the circRNA-miRNA importance regarding the molecular pathology aspects in tumor samples harboring the variant. Herein, we found a set of previously reported circRNAs (n = 20) as sponges of rs78378222-associated miRNAs from the *circRNAdisease* database. However, it is important to consider that none of these circRNA-miRNA interactions were validated in prostate gland-related tissues and/or cell lines. Importantly, the additional analysis shown in **Table S4** from the GSE212215 dataset allowed the validation of our *circRNAdisease* findings, highlighting two of the twenty circRNAs, namely hsa_circ_0001658 (derived from the *ARID1B* host gene) and hsa_circ_NR3C1 (*NR3C1* host gene), as the most significantly dysregulated circRNAs (the only ones with a significant p-value < 0.05), specifically upregulated in PAC tumors compared to BPH.

In this context, *ARID1B* is previously described as a tumor suppressor gene and often harbors inactivating mutations, with more reports associated with breast tumors. Its inactivation can lead to abnormal chromatin closure, which prevents the expression of tumor suppressor genes (*CDKN1A* and *CDKN2A*), thereby promoting the proliferation of breast cancer cells and evasion of apoptotic mechanisms (Stephens et al., 2012). However, to our knowledge, no previous findings have correlated the tumor suppressor role of this protein with prostatic tumorigenesis or association with deregulated circRNA expression. In parallel, it was found that the *NR3C1* gene encodes a nuclear hormone receptor, acting as a transcription factor that modulates gene expression across different tissues (Gu et al., 2017). Moreover, *NR3C1* was recently identified as a potential biomarker for clinical outcomes in metastatic

prostate cancer from a large-scale gene expression data study, along with some key miRNAs (miR-548c-3p and miR-582-5p), and its downregulation was observed to improve the prostate cancer patient survival rate (Shinawi et al., 2022).

Ultimately, linkage disequilibrium analyses identified that the *TP53* 3'UTR variant studied here and rs35850753, another rare germline variant mapped to the 5'UTR of the Δ133 isoform of *TP53*, are preferentially co-inherited in certain European populations. This 5' UTR variant is an oncogenic short isoform lacking the N-terminus, shown to have a dominant-negative effect whereby it inhibits the tumor-suppressive functions of full-length *TP53* (Fujita et al., 2009; Slatter et al., 2011). An estimated r^2 correlation value of 1 was observed in the British/UK population, indicating that both *loci* are in complete linkage disequilibrium in this population. Interestingly, these two noncoding variants have been robustly associated with risk of neuroblastoma in African and European ancestry cohorts (Diskin et al., 2014).

Conclusion

In summary, despite the low frequency of the rs78378222[C] allele found in our BPH and PAC cohorts, this is the largest study to date evaluating this germline-noncoding *TP53* functional variant in Brazilians, and it represents the first report of the minor C-allele frequency in a non-tumoral condition (BPH). Remarkably, we also provided a comprehensive and integrative overview of all functional implications of this hypomorphic allele described so far. In this context, this is the first study to explore a novel functional aspect associated with this variant involving the circRNA-miRNA-*TP53* regulatory axis. Overall, these *in silico* circRNA-related analyses expand the current understanding of the field by unraveling potential biological mechanisms that warrant further investigation, generating new research perspectives and serving as a foundation for future hypothesis-driven experimental studies. Further studies genotyping rs78378222 in larger cohorts of PAC and BPH patients from distinct regions of Brazil should be undertaken to confirm our findings and determine if screening for this *TP53* 3'UTR variant is justified in the Brazilian population, as well as additional analyses should be performed to validate the functional impact of the rs78378222[C] in the indirect regulation of p53 expression by the circRNAs reported here.

Abbreviations

3'UTR – 3' untranslated region

5'UTR – 5' untranslated region

ABraOM - Online Archive of Brazilian Mutations

BPH - benign prostatic hyperplasia

CI - Confidence interval

CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico

ExAC - Exome Aggregation Consortium

FLOSSIES - Fabulous Ladies Over Seventy

FIPE - Fundo de Incentivo à Pesquisa

GWAS - genome-wide association study

HCPA - Hospital de Clínicas de Porto Alegre

LFS - Li-Fraumeni syndrome

MAF - minor allele frequency

miRNA - microRNA

OR - Odds ratio

PAC - prostatic adenocarcinoma

PAS - polyadenylation signal

PSA - Prostatic specific antigen

TCGA - The Cancer Genome Atlas

TOPMed - Trans-Omics for Precision Medicine

UK - United Kingdom

Declarations

Conflict of interest

The authors declare that they have no competing interests that are relevant to the content of this article.

Ethical approval

The study received approval from the Research Ethics Committee of Hospital de Clínicas de Porto Alegre, Brazil, and it was carried out in accordance with the relevant guidelines and regulations of this ethical committee. The experiments were conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consent to participate in the study.

Consent to publish

Written informed consent for the publication of clinical details was obtained from all study participants.

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Author Contribution

IAV, ISB, FSLV, GSM, and PA-P performed the conception and design of the study; IAV, GDV, EHP, BVF, TFA, YMAR, BSC, LMD, and GSS performed the experiments; IAV, GDV, TWK, BVF, NB, GS, BRS, MBS, RMS, TFA, and KNM performed the bioinformatic analyses; IAV, GDV, EHP, TWK, BVF, NB, GS, BRS, MBS, RMS, TFA, YMAR, BSC, LMD, GSS, KNM, and CR performed the data analyses; IAV, GDV, EHP, TWK, BVF, NB, GS, BRS, MBS, and RMS performed the literature review to write the discussion; IAV, GDV, EHP, TWK, BVF, NB, GS, BRS, MBS, RMS, CR, ISB, FSLV, GSM, PA-P wrote and revised the manuscript; all authors read and approved the final version.

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Data Availability

All data generated or analyzed during this study are included in this published article.

References

1. Achatz MI, Zambetti GP (2016) The Inherited p53 Mutation in the Brazilian Population Maria. Cold Spring Harbor Laboratory Press
2. Biolchi V, Neto BS, Koff W, Brum IS (2012) Androgen receptor CAG polymorphism and the risk of benign prostatic hyperplasia in a Brazilian population. Int Braz J Urol 38(3):373–379
3. Bodmer W, Tomlinson I (2010) Rare genetic variants and the risk of cancer. Curr Opin Genet Dev [Internet] 20(3):262–267 Disponível em:. http://dx.doi.org/10.1016/j.gde.2010.04.016
4. Custódio G, Parise GA, Filho NK, Komechen H, Sabbaga CC, Rosati R et al (2013) Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. J Clin Oncol 31(20):2619–2626
5. Deng Q, Hu H, Yu X, Liu S, Wang L, Chen W et al (2019) Tissue-specific microRNA expression alters cancer susceptibility conferred by a TP53 noncoding variant. Nat Commun [Internet] 10(1):1–13 Disponível em:. http://dx.doi.org/10.1038/s41467-019-13002-x
6. Di Giovannantonio M, Harris BHL, Zhang P, Kitchen-Smith I, Xiong L, Sahgal N et al (2021) Heritable genetic variants in key cancer genes link cancer risk with anthropometric traits. J Med Genet 58(6):392–399
7. Diederichs S, Bartsch L, Berkmann JC, Fröse K, Heitmann J, Hoppe C et al (2016) The dark matter of the cancer genome: aberrations in regulatory elements, untranslated regions, splice sites, non-coding RNA and synonymous mutations. EMBO Mol Med 8(5):442–457
8. Diskin SJ, Capasso M, Diamond M, Oldridge DA, Conkrite K, Bosse KR et al (2014) Rare variants in TP53 and susceptibility to neuroblastoma. J Natl Cancer Inst 106(4):7–10
9. Egan KM, Nabors LB, Olson JJ, Monteiro AN, Browning JE, Madden MH et al (2012) Rare TP53 genetic variant associated with glioma risk and outcome. J Med Genet 108(10):420–421
10. Erson-Bensan AE (2020) RNA-biology ruling cancer progression? Focus on 3'UTRs and splicing. Cancer Metastasis Rev 39(3):887–901

11. Fujita K, Mondal AM, Horikawa I, Nguyen GH, Sohn JJ, Bowman ED et al (2009) p53 isoforms, Δ133p53 and p53β, are endogenous regulators of replicative cellular senescence. Nat Cell Biol 11(9):1135–1142
12. Genomes Project, Auton A, Abecasis GR, Altshuler DM, Durbin RM, Bentley DR et al (2015) A global reference for human genetic variation, vol 526. Nature. Nature Publishing Group, pp 68–74
13. Gu Y, Deng B, Kong J, Yan C, Huang T, Yang J et al (2017) Functional polymorphisms in NR3C1 are associated with gastric cancer risk in Chinese population. Oncotarget 8:105312–105319. 10.18632/oncotarget.22172
14. Jardin Fabrice, Coiffier B, Becquerel H, Civils H, Lyon DE (2013) TP53 and outcome in DLBCL: not only the coding region. Vol. 121, NUMBER
15. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q et al (2020) The mutational constraint spectrum quantified from variation in 141,456 humans. Nature 581(7809):434–443
16. Karczewski KJ, Weisburd B, Thomas B, Solomonson M, Ruderfer DM, Kavanagh D et al (2017) The ExAC browser: Displaying reference data information from over 60 000 exomes. Nucleic Acids Res 45(D1):D840–D845
17. Li Y, Gordon MW, Xu-Monette ZY, Visco C, Tzankov A, Zou D et al (2013) Single nucleotide variation in the TP53 3' untranslated region in diffuse large B-cell lymphoma treated with rituximab-CHOP: A report from the International DLBCL Rituximab-CHOP Consortium Program. Blood 121(22):4529–4540
18. Macedo GS, Araujo Vieira I, Brandalize AP, Giacomazzi J, Inez Palmero E, Volc S et al (2016) Rare germline variant (rs78378222) in the TP53 3′ UTR: Evidence for a new mechanism of cancer predisposition in Li-Fraumeni syndrome. Cancer Genet [Internet] 209(3):97–106 Disponível em:. http://dx.doi.org/10.1016/j.cancergen.2015.12.012
19. Malkin D, Li FP, Strong LC, Fraumeni JF, Nelson CE, Kim DH et al (1979) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250(4985):1233–8
20. Marrero AR, das Neves Leite FP, de Almeida Carvalho B, Peres LM, Kommers TC, da Cruz IM et al (2005) Heterogeneity of the genome ancestry of individuals classified as White in the state of Rio Grande do Sul, Brazil. Am J Hum Biology 17(4):496–506
21. Melín BS, Barnholtz-Sloan JS, Wrensch MR, Johansen C, Il'yasova D, Kinnersley B et al (2017) Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. Nat Genet 49(5):789–794
22. Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Research, vol 15. C I R L Press Limited
23. Misir S, Wu N, Yang BB (2022) Specific expression and functions of circular RNAs. Cell Death Differ 29:481–491. https://doi.org/10.1038/s41418-022-00948-7
24. Naslavsky MS, Scliar MO, Yamamoto GL, Yu Ting Wang J, Zverinova S, Karp T et al (2020) Whole-genome sequencing of 1,171 elderly admixed individuals from the largest Latin American metropolis (São Paulo, Brazil). Wagner CS Magalhães [Internet]. 10:24 Disponível em:. https://doi.org/10.1101/2020.09.15.298026
25. Naslavsky MS, Yamamoto GL, de Almeida TF, Ezquina SAM, Sunaga DY, Pho N et al (2017) Exomic variants of an elderly cohort of Brazilians in the ABraOM database. Hum Mutat 38(7):751–763
26. Neto BS, Koff WJ, Biolchi V, Brenner C, Biolo KD, Spritzer PM et al (2008) Polymorphic CAG and GGC repeat lengths in the androgen receptor gene and prostate cancer risk: Analysis of a Brazilian population. Cancer Invest 26(1):74–80
27. Panda AC, Dudekula DB, Abdelmohsen K, Gorospe M (2018) Analysis of Circular RNAs Using the Web Tool CircInteractome. Methods Mol Biol 1724:43–56. 10.1007/978-1-4939-7562-4_4
28. Petitjean A, Mathe E, Kato S, Ishioka C, Tavtigian SV, Hainaut P et al (2007) Impact of Mutant p53 Functional Properties on TP53 Mutation Patterns and Tumor Phenotype: Lessons from Recent Developments in the IARC TP53 Database. Hum Mutat 28(6):622–629
29. Pinto EM, Billerbeck AEC, Villares MCBF, Domenice S, Mendonça BB, Latronico AC (2004) Founder effect for the highly prevalent R337H mutation of tumor suppressor p53 in Brazilian patients with adrenocortical tumors. Arq Bras Endocrinol Metabol 48(5):647–650
30. Rafnar T, Gunnarsson B, Stefansson OA, Sulem P, Ingason A, Frigge ML et al (2018) Variants associating with uterine leiomyoma highlight genetic background shared by various cancers and hormone-related traits. Nat Commun 9(1):3636
31. Rice T, Lachance DH, Molinaro AM, Eckel-Passow JE, Walsh KM, Barnholtz-Sloan J et al (2016) Neuro-oncology practice: Understanding inherited genetic risk of adult glioma - A review. Neurooncol Pract 3(1):10–16
32. Shu X, Wang J, Chen D, Li Y, Shi Y, Chen H et al (2025) The roles and function of circular RNA in prostate cancer. Gene 971:149801
33. Slatter TL, Hung N, Campbell H, Rubio C, Mehta R, Renshaw P et al (2011) Hyperproliferation, cancer, and inflammation in mice expressing a Δ133p53-like isoform. Blood 117(19):5166–5177
34. de Soluza AM, Resende SS, de Sousa TN (2019) Cristiana Ferreira Alves de Brito. A systematic scoping review of the genetic ancestry of the Brazilian population. Genet Mol Biology Press 42(3):495–508
35. Stacey SN, Sulem P, Jonasdottir A, Masson G, Gudmundsson J, Gudbjartsson DF et al (2011) A germline variant in the TP53 polyadenylation signal confers cancer susceptibility. Nat Genet 43(11):1098–1103
36. Stephens P, Tarpey P, Davies H et al (2012) The landscape of cancer genes and mutational processes in breast cancer. Nature 486:400–404. https://doi.org/10.1038/nature11017
37. Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R et al (2021) Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature 590(7845):290–299

38. Wang X, Huang R, Yu J, Zhu F, Xi X, Huang Y, Zhang C, Hu H (2023) Identification of differentially expressed circRNAs in prostate cancer of different clinical stages by RNA sequencing. Sci Rep 13(1):21175. 10.1038/s41598-023-48521-7
39. Wang Y, Xue-Song Wu J, He T, Ma W, Lei Z-Y, Shen (2016) A novel TP53 variant (rs78378222 A > C) in the polyadenylation signal is associated with increased cancer susceptibility: evidence from a meta-analysis. Oncotarget 7(22):32865
40. Walsh T, Lee MK, Casadei S, Thornton AM, Stray SM, Pennil C et al (2010) Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. Proc Natl Acad Sci U S A 107(28):12629–12633
41. Zambra FMB, Biolchi V, Brum IS, Chies JAB (2013) CCR2 and CCR5 genes polymorphisms in benign prostatic hyperplasia and prostate cancer. Hum Immunol [Internet] 74(8):1003–1008 Disponível em:. http://dx.doi.org/10.1016/j.humimm.2013.04.031
42. Zhang P, Kitchen-Smith I, Xiong L, Stracquadanio G, Brown K, Richter PH et al (2021) Germline and somatic genetic variants in the p53 pathway interact to affect cancer risk, progression, and drug response. Cancer Res 81(7):1667–1680
43. Zhi-Yan, Sun et al (2023) circRNADisease v2.0: an updated resource for high-quality experimentally supported circRNA-disease associations. Nucleic Acids Res gkad949. https://doi.org/10.1093/nar/gkad949
44. Zhao Y, Li X, Zhu S (2016) Rs78378222 polymorphism in the 3'-untranslated region of TP53 contributes to development of age-associated cataracts by modifying microRNA-125b-induced apoptosis of lens epithelial cells. Mol Med Rep 14(3):2305–2310
45. Zhou L, Yuan Q, Yang M (2012) A functional germline variant in the P53 polyadenylation signal and risk of esophageal squamous cell carcinoma. Gene [Internet] 506(2):295–297 Disponível em:. http://dx.doi.org/10.1016/j.gene.2012.07.007

Figures

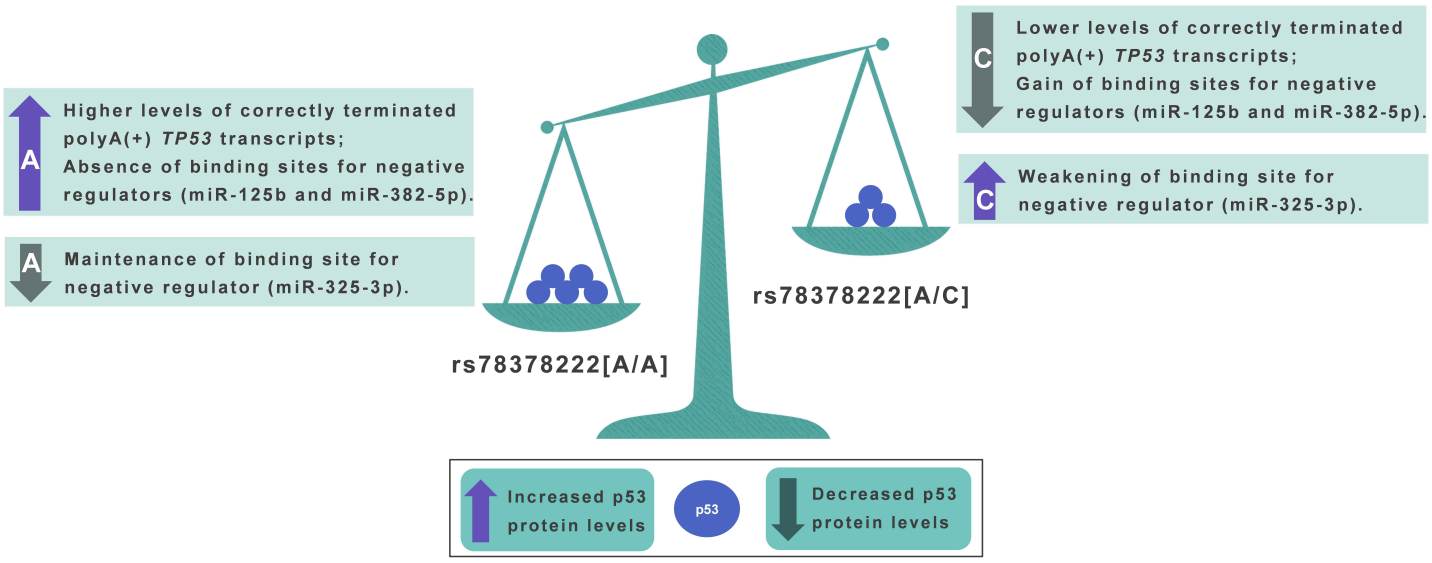


Figure 1

Overview of functional findings regarding the rs78378222[C] variant allele. Previous studies have hypothesized that the different genotypes for this noncoding variant (AA and AC, since homozygotes for the minor allele have rarely been described so far) influence the global balance of *TP53* transcript and p53 protein expression levels. First, rs78378222[C] was found to disrupt the sole polyadenylation signal sequence of *TP53*, which has been confirmed by detection of correctly terminated polyA(+) mRNAs predominantly derived from the wild-type allele (A), and decreased p53 levels in rs78378222[A/C] heterozygotes. More recent studies demonstrated that presence of the C minor allele also impacts the negative regulation exerted by miRNAs in the *TP53* 3'UTR mRNA, creating binding sites for miR-125b and miR-382-5p, as well as compromising a miR-325-3p site. All functional evidence mentioned here were reported by Stacey et al., 2011; Li et al., 2013; Macedo et al., 2016; Zhao et al., 2016; Deng et al., 2019 and Zhang et al. 2021.

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