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Whole-exome sequencing identifies cancer-associated variants of the endo-lysosomal ion transport channels in the Saudi population

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A B S T R A C T

Background: Although national efforts are underway to document the genomic variability of the Saudi population relative to other populations, such variability remains largely unexplored. Genetic variability is known to impact the fate of cells and increase or decrease the risk of a variety of complex diseases including cancer forms. Therefore, the identification of variants associated with cancer susceptibility in Saudi population may protect individuals from cancer or aid in patient-tailored therapies. The *endo*-lysosomal ion transport genes responsible for cationic ion homeostasis within the cell. We screened 703 single-nucleotide polymorphisms (SNPs) of the *endo*-lysosomal ion transporter genes in the Saudi population and identified cancer-associated variants that have been reported in other populations.

Methods: Utilizing previously derived local data of Whole-Exome Sequencing (WES), we examined SNPs of *TPCN1, TPCN2, P2RX4, TRPM7, TRPV4, TRPV4,* and *TRPV6* genes. The SNPs were identified for those genes by our in-house database. We predicted the pathogenicity of these variants using *in silico* tools CADD, Polyphen-2, SIFT, PrimateAI, and FATHMM-XF. Then, we validated our findings by exploring the genetics database (VarSome, dbSNP NCB, OMIM, ClinVar, Ensembl, and GWAS Catalog) to further link cancer risk.

Results: The WES database yielded 703 SNPs found in *TPCN2, P2RX4, TRPM7, TRPV4,* and *TRPV6* genes in 1,144 subjects. The number of variants that were found to be common in our population was 150 SNPs. We identified 13 coding-region non-synonymous variants of the *endo*-lysosomal genes that were most common with a minor allele frequency (MAF) of ≥ 1 %. Twelve of these variants are rs2376558, rs3750965, rs61746574, rs35264875, rs3829241, rs72928978, rs25644, rs8042919, rs17881456, rs4987682, rs4987667, and rs4987657 that were classified as cancer-associated genes.

Conclusion: Our study highlighted cancer-associated SNPs in the *endo*-lysosomal genes among Saudi individuals. The allelic frequencies on polymorphic variants confer susceptibility to complex diseases that are comparable to other populations. There is currently insufficient clinical data supporting the link between these SNPs and cancer risk in the Saudi population. Our data argues for initiating future cohort studies in which individuals with the identified SNPs are monitored and assessed for their likelihood of developing malignancies and therapy outcomes.

1. Introduction

To understand the evolutionary history of human genetics and the incidence of diseases, we must understand the patterns of genetic variations occurring in human populations (Cavalli-Sforza, 1998). In order to study disease development, it is critical to investigate mutational patterns in genes that encode proteins disrupted in disease. Whole-Exome Sequencing (WES), used for genetic correlation analysis, can aid in the identification of molecular aberrations (Bick and Dimmock, 2011) (see Fig. 1 and Fig. 2).

The *endo*-lysosomal cation-selective channels; Two-Pore Channels (TPCs), Transient Receptor Potential channels (TRPs) and the ligand-gated ion channels receptors (P2XRs) adenosine triphosphate (ATP)-gated channels located in the *endo*-lysosomal regions within the cell and are involved in the cationic systems, such as calcium (Ca^{2+}) and magnesium (Mg^{2+}) homeostasis (Lloyd-Evans et al., 2008). Disturbances in these systems have been linked to tumorigenesis (Faris et al., 2019; Zhong et al., 2022).

We focused our investigation on the Single Nucleotide Polymorphisms (SNPs) of the following genes: two TPCs (*TPCN1* and *TPCN2*), three of the TRPs (*TRPM7*, *TRPV4*, and *TRPV6*) and *P2RX4*. The implication of these genes in cancer was prominent in the literature as their overexpression was shown to trigger epithelial-to-mesenchymal transition (EMT)-induced proliferation, migration, and invasion

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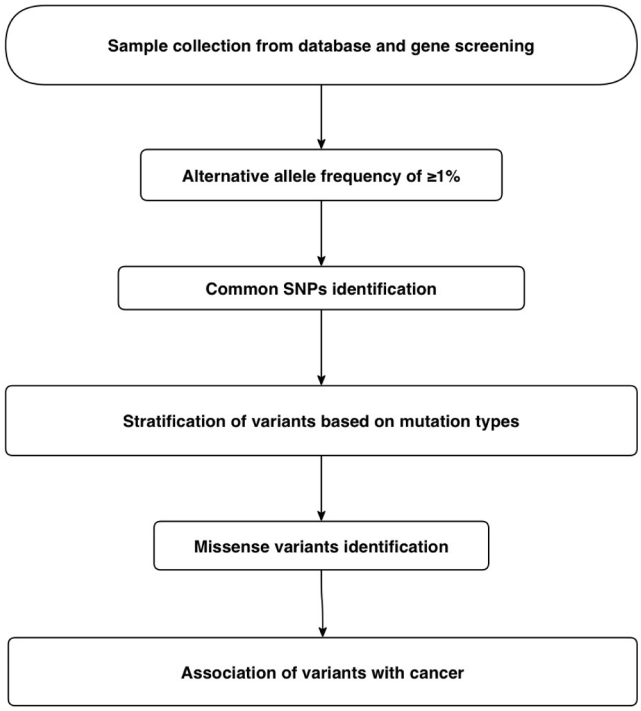

Fig. 1. Flowchart of study methodology. First, genes of interest were filtered by alternative allele frequency percentage. Then, the variants were filtered down based on mutation types. Lastly, the cancer-associated variants were identified.

(Zhong et al., 2022; Nguyen et al., 2017; Sun and Yue, 2018; Müller et al., 2021; Cordier et al., 2021; Maynard et al., 2022). Blocking the activity of these proteins reduces the viability of cancer cells, thus indicating their application as potential druggable targets for cancer treatment. Previously published studies have identified the *TPCN2* variants rs3750965 and rs3829241 to be linked to tumor progression (Alharbi and Parrington, 2021). The American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., 2015) identify these *TPCN2* variants as benign, with the *TPCN2* variant rs72928978 as 'likely pathogenic'.

In this paper, we utilized WES to examine allele frequencies of cancer-associated *endo*-lysosomal ion transport gene variants in the Saudi population. We analyzed the exome (protein-coding region) sequence data for 1,144 of Saudi individuals and screened for common non-synonymous variants of *endo*-lysosomal ion transport genes (Table 1). By using public bioinformatic resources, we identified the variants rs2376558, rs3750965, rs61746574, rs35264875, rs3829241, rs72928978, rs25644, rs8042919, rs17881456, rs4987682, rs4987667, and rs4987657 as common variants in Saudi population that have been reported in other populations as cancer-associated variants (Fig. 2 and Table 2). As a pilot study, it provides a rationale for constructing follow-up cohort studies in which the association between these variants and cancer risk is thoroughly investigated in Saudi population.

2. Material and Methods

2.1. Study design and data collection

This study was based on a secondary data analysis of genomic data collected at King Faisal Specialist Hospital and Research Centre (KFSHRC) in Saudi Arabia, which procures participant samples from healthcare sectors across the country (both public and private hospitals). Recruited participants (n = 1,144) were either individuals suspected to carry rare genetic disorders (infants, children, and young adults) or their healthy parents (30 years and above) not reported to have cancer. The protocol utilized in this study was approved by the Research Ethical Committees and declared exempt from institutional review board (IRB) approval. Saudi participants (or legal guardians) gave written informed consent. Review Board (IRB) approval by (IRB# 2230016).

2.2. Genetic data processing and interpretation

2.2.1. Data processing

703 SNPs screened in total for the 6 *endo*-lysosomal genes *TPCN1* (n = 121) *TPCN2* (n = 169), *P2RX4* (n = 58), *TRPM7* (n = 185), *TRPV4* (n = 85), and *TRPV6* (n = 85) (Table 1. Supplementary). Minor allele frequency (MAF) was calculated for each SNP. MAF of 1 % or greater was considered common in the Saudi population. The reference allele is obtained from the human genome assembly hg19 (GRCh37). The allele frequency equation is adopted from the previously published work (Abouelhoda et al., 2016) and is calculated as follows: heterozygous status no./(samples no. – homozygous status no.).

2.2.2. Variants classification and pathogenicity prediction

The variant descriptions for nomenclature used here are rs#, chromosomal location, amino acid changes and substitution (>) for the common missense variants depicted in our paper. The mutation frequencies lower than 1 % were excluded. Metrics of pathogenicity for sequence variants were calculated by the *in silico* tools CADD (Kircher et al., 2014), Polyphen-2 (Adzhubei et al., 2010), SIFT (Kumar et al., 2009), PrimateAI (Sundaram et al., 2018), and FATHMM-XF (Rogers et al., 2018). The common variants were analyzed regardless of their classification according to ACMG guidelines (Richards et al., 2015), which could be annotated as Benign (B), Likely Benign (LB), Pathogenic (P), Likely Pathogenic (LP), and Uncertain Significance (VUS) (Table 3. Supplementary).

2.2.3. Disease association to the common variants of endo-lysosomal ion channels

To derive genotype-phenotype disease associations and variant annotation, known single nucleotide variants (SNVs) were derived from multiple databases and information sources; VarSome (Kopanos et al., 2019), the single-nucleotide polymorphism database of dbSNP NCBI (Sherry et al., 2001), Online Mendelian Inheritance in Man (OMIM) (Amberger et al., 2009), ClinVar (Landrum et al., 2016), Ensembl (Cunningham et al., 2021), and Genome-wide association studies (GWAS) Catalog (Sollis et al., 2023), and compared to the variants identified in our study. In addition, published literature obtained from search engines like PubMed and the genomic search engine MasterMind, was also considered as evidence for the phenotype associations (Table 4. Supplementary).

2.2.4. Comparison of the allele frequency between Saudi and global populations

The frequency scores for the in-house common variants were compared against the regional data resource GME Variome (Scott et al., 2016) along with the global resources of the 1000 Genomes Project (1kGP) (Auton et al., 2015) and Genome Aggregation Database (gnomAD) (Chen et al., 2022) (Table 2).

3. Results

3.1. Study population

We reported in this study the genomic sequences of 1,144 Saudi individuals that were recruited from KFSHRC in Saudi Arabia. 632 (55.24 %) of the population are male, 413 (36.1 %) are female and 99 (8.6 %) are unspecified. Their samples were subjected to WES for detecting disease-associated variants. Genes were selected and evaluated according to their role as *endo*-lysosomal ion channels specifically

in the cationic channel pathways. There were 703 genetic variants screened (Table 1. Supplementary), and 13 genes were selected from the set of 150 common SNPs (Table 2. Supplementary).

3.2. High MAF and common variants endo-lysosomal ion channels in Saudi exomes

After dichotomizing SNPs based on allelic dominance, the more prevalent variants in the study population were seen as that 21.47 % (n = 150) of the tested variants to have a MAF of $\geq$ 1 % distributed as *TPCN1* (n = 13) *TPCN2* (n = 47), *P2RX4* (n = 22), *TRPM7* (n = 36), *TRPV4* (n = 11), and *TRPV6* (n = 21), while 2.1 % (n = 15) of the tested variants to have a MAF of $\geq$ 5 % distributed as *TPCN1* (n = 0) *TPCN2* (n = 9), *P2RX4* (n = 0), *TRPM7* (n = 3), *TRPV4* (n = 2), and *TRPV6* (n = 1) (Table 1. Supplementay Data).

3.3. Stratifying the common variants of endo-lysosomal ion channels

On the basis of common allele frequencies, we filtered the identified SNPs into 150 with a MAF of $\geq$ 1 %. Most of the coding region variants that probably could lead to a premature truncated protein, were as follows; common variants assigned as 13 for non-synonymous (missense); *TPCN1* (n = 0) *TPCN2* (n = 6), *P2RX4* (n = 1), *TRPM7* (n = 1), *TRPV4* (n = 1), and *TRPV6* (n = 4). While the non-coding *TPCN1* (n = 12) *TPCN2* (n = 37), *P2RX4* (n = 19), *TRPM7* (n = 32), *TRPV4* (n = 7), and *TRPV6* (n = 12). Synonymous was a total of 18 for all the *endo*-lysosomal genes; *TPCN1* (n = 1) *TPCN2* (n = 4), *P2RX4* (n = 2), *TRPM7* (n = 3), *TRPV4* (n = 3), and *TRPV6* (n = 5) (Table 2. Supplementary Data). No frameshift nor nonsense variants were observed in the common variants of the *endo*-lysosomal genes data obtained from our local WES database.

3.4. The common endo-lysosomal ion channels variants with missense variants

We identified 13 non-synonymous variants of the *endo*-lysosomal genes with an MAF of $\geq$ 1 %, (which is represented in percentage). The most frequently mutated genes were as follows: Six *TPCN2* variants:

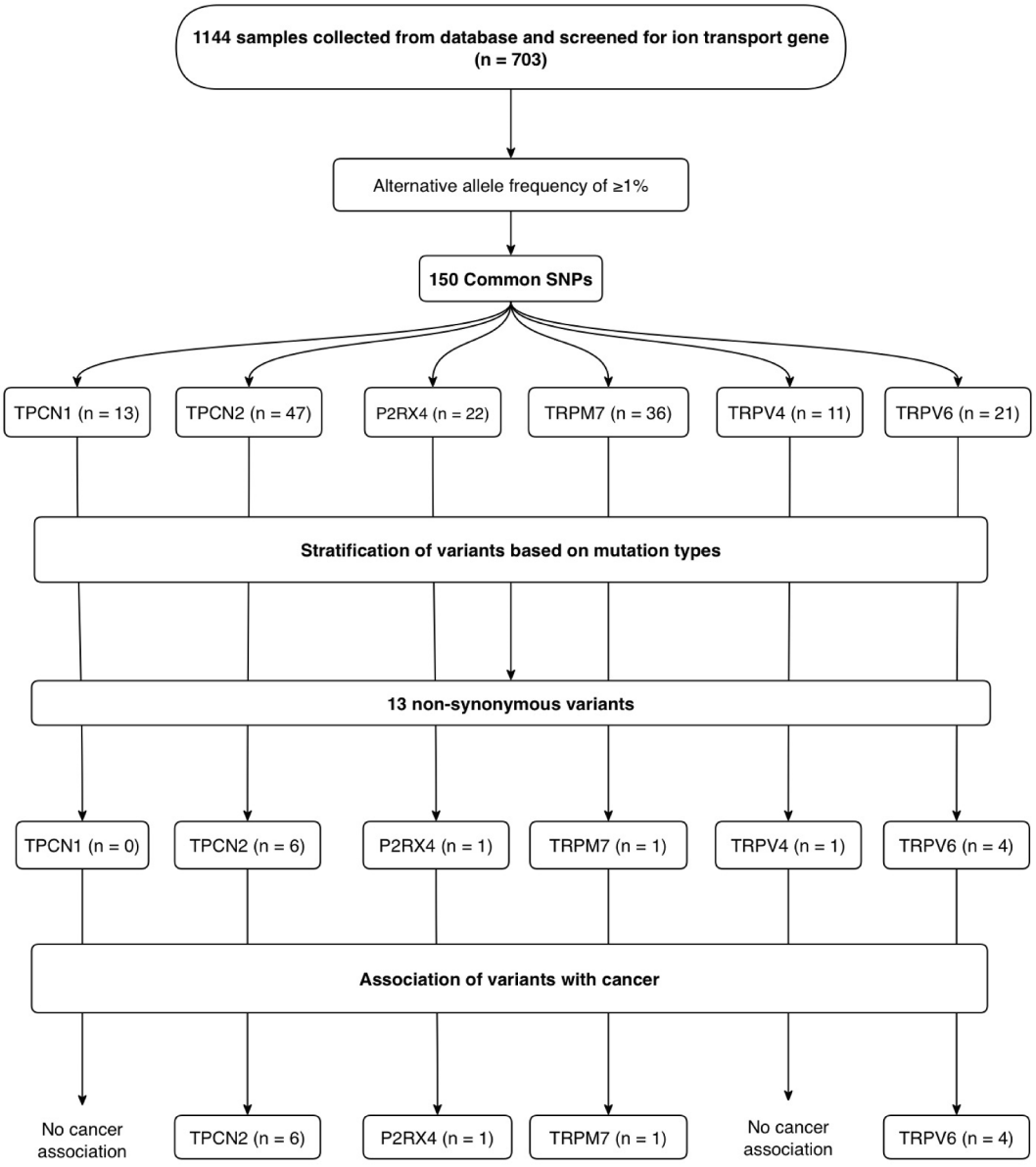

Fig. 2. The selection process of the variants studied. Data analyzed from 1,144 subjects identified 703 SNPs in relevant genes. These variants were filtered to 150 according to their MAF. Only non-synonymous variants were further investigated (n = 13 variants). Variants associated with cancer were identified in this study.

Table 1
The most common non-synonymous variants based on MAF in Saudi Population. Comparison between local, regional, and global databases.

Gene symbol	Chromosome Coordinates (GRCh37)	Polymorphism	Position of the polymorphism	Genotype (Alleles)	Zygosity prevalence in studied population (%)		Minor Allele Frequency (MAF)	Frequency Allele		
					Homozygosity	Heterozygosity		GME (Middle Eastern and Central Asian population)	1kGP	gnomAD (Exome)
TPCN2	chr11:68851414	rs2376558	Leu564Pro	TC	87.5	7.167832168	0.91083914	0.9566	0.25	0.8658
	chr11:68840160	rs3750965	Lys376Arg	AG	17.13286713	42.3951049	0.383304209	0.3497	0.29	0.2871
	chr11:68840399	rs61746574	Gly387Asp	GA	5.506993007	32.77972028	0.218968526	0.1947	0.09	0.1162
	chr11:68846399	rs35264875	Met484Leu	AT	1.748251748	21.5034965	0.125	0.1676	0.10	0.1579
	chr11:68855363	rs3829241	Gly734Glu	GA	2.447552448	19.40559441	0.121503495	0.2225	0.18	0.2887
	chr11:68831364	rs72928978	Val219Ile	GA	0.524475524	5.244755245	0.031468533	0.0672	0.04	0.09423
P2RX4	chr12:121666646	rs25644	Ser258Gly	AG	3.234265734	22.11538462	0.142919585	0.1208	0.18	0.1657
TRPM7	chr15:50878630	rs8042919	Thr1482Ile	GA	1.31	11.53	0.070804194	0.0877	0.08	0.08471
TRPV4	chr12:110252547	rs3742030	Pro19Ser	GA	0.96	12.5	0.072115384	0.0652	0.04	0.03653
TRPV6	chr7:142583330	rs17881456	Ser18Ala	AC	94.31818182	0.34965035	0.944930077	N/A	N/A	N/A
	chr7:142569596	rs4987682	Met721Thr	AG	2.097902098	15.9965035	0.100961536	0.0946	0.19	0.09192
	chr7:142572908	rs4987667	Met418Val	TC	1.486013986	15.90909091	0.094405591	0.09113	0.19	0.09048
	chr7:142574913	rs4987657	Cys197Arg	AG	1.486013986	15.2972028	0.091346152	0.0957	0.19	0.09030

Table 2
Cancer-reported non-synonymous variants arranged based on allele frequency.

Gene symbol	Polymorphism	Position of the polymorphism	Genotype (Alleles)	Minor Allele Frequency (MAF)	Previously reported cancer-association in literature, ClinVar, and Ensembl
TPCN2	rs2376558	Leu564Pro	TC	0.91083914	Gallbladder cancer (García et al., 2020), ovarian carcinoma (Castellarin et al., 2013), and gastrointestinal stromal tumors (Pang et al., 2019).
	rs3750965	Lys376Arg	AG	0.383304209	Decrease metastatic cancer risk (Alharbi and Parrington, 2021), ovarian carcinoma (Castellarin et al., 2013), gastrointestinal stromal tumors (Pang et al., 2019), renal cell carcinoma (Patel et al., 2022), and pancreatic acinar cell carcinoma (Furukawa et al., 2015).
	rs61746574	Gly387Asp	GA	0.218968526	Breast cancer (Haiman et al., 2013).
	rs35264875	Met484Leu	AT	0.125	Breast, colon, prostate, and malignant hematological cancers and low risk of cancer metastasis (Alharbi and Parrington, 2021), colorectal adenoma (Chen et al., 2016), skin cancer (Alharbi and Parrington, 2019), Gastrointestinal stromal tumors (Pang et al., 2019).
	rs3829241	Gly734Glu	GA	0.121503495	Skin cancer (Alharbi and Parrington, 2019), and gastric adenomas (Lim et al., 2016).
	rs72928978	Val219Ile	GA	0.031468533	Renal cell carcinoma (Patel et al., 2022), and gastrointestinal stromal tumors (Pang et al., 2019).
P2RX4	rs25644	Ser258Gly	AG	0.142919585	Prostate cancer (Alharbi and Parrington, 2021), and gastrointestinal stromal tumors (Pang et al., 2019).
TRPM7	rs8042919	Thr1482Ile	GA	0.070804194	Breast cancer (Shen et al., 2014), and colorectal cancer (Dai et al., 2007).
TRPV6	rs17881456	Ser18Ala	AC	0.944930077	Gastrointestinal stromal tumors (Pang et al., 2019).
	rs4987682	Met721Thr	AG	0.100961536	Prostate cancer progression (Wissenbach et al., 2001).
	rs4987667	Met418Val	TC	0.094405591	Prostate cancer progression (Wissenbach et al., 2001).
	rs4987657	Cys197Arg	AG	0.091346152	Prostate cancer progression (Wissenbach et al., 2001).

rs2376558_T > C (91 %), rs3750965_G > A (38 %), rs61746574_G > A (21 %), rs35264875_A > T (12 %), rs3829241_G > A (12 %), and rs72928978_G > A (3 %), followed by four TRPV6 variants: rs17881456_A > C (94 %), rs4987682_A > G (10 %), rs4987667_T > C (9 %), and rs4987657_A > G (9 %). The rest of the *endo*-lysosomal genes had one non-synonymous variant for each *P2RX4* (rs25644_A > G, 14 %), *TRPM7* (rs8042919_G > A, 7 %), and *TRPV4* (rs3742030_G > A, 7 %), while *TPCN1* had no non-synonymous variants. Their allele frequencies as seen in the local exomes dataset along with the global databases are presented in Table. 1.

3.5. Common variants of endo-lysosomal ion channels as cancer susceptibility genes in Saudi population

The 13 common non-synonymous variants were predicted for pathogenicity score by CADD (Kircher et al., 2014), Polyphen-2 (Adzhubei et al., 2010), SIFT (Kumar et al., 2009), PrimateAI (Sundaram et al., 2018), and FATHMM-XF (Rogers et al., 2018) and annotated as benign while only two deleterious variants (rs72928978 and rs25644) were predicted to be damaging and benign, respectively. rs72928978 is annotated in ACMG guidelines (Richards et al., 2015) as 'Likely Pathogenic' with a scaled score of ≥ 20 which in turn predicts it as one of the top 1 % of deleterious variants in human genome. We applied the dbSNP NCBI (Sherry et al., 2001), OMIM (Amberger et al., 2009), ClinVar (Landrum et al., 2016), and Ensembl (Cunningham et al., 2021) databases for the classification of the clinical implication for each SNP obtained from our local WES analysis. All associated phenotypes and complex diseases are listed for each common non-synonymous variant of the studied genes (Table 4 Supplementary Data). Subsequently, we filtered our 13 common non-synonymous variants down to those associated with cancer risk in other populations. A total of 12 variants that have been reported in the literature as cancer-associated (Table 2).

4. Discussion

Genetic variability, particularly non-synonymous variants, can impact the biological processes of the cell and increase cancer risk (Horak et al., 2022). Here we performed an expanded analysis of exome sequencing data from 1,144 Saudi individuals not reported to have cancer (Table 1. Supplementary Data). Saudi population is known to have high consanguinity rates (Alkuraya, 2014). Therefore, these results can be representative to the population. WES analysis revealed 703 polymorphisms associated with different diseases. These variants have been reported in the literature to be associated with different phenotypes/diseases (Table 4. Supplementary Data). We identified 13 missense variants of the *endo*-lysosomal genes that were most common with a MAF of $\geq$ 1 % (Fig. 3 and Table 1.).

The *endo*-lysosomal ion channels TPCs and TRP are in the *endo*-lysosomal regions within the cell. Both superfamilies have been implicated in cancer when disrupted (Faris et al., 2019; Zhong et al., 2022). To assess the allocation of the *endo*-lysosomal transport genes, we analyzed our in-house database and compared it with the publicly available genome databases. After screening the SNPs of our genes of interest, we compared our common missense SNVs in our local database with the regional Greater Middle East (GME) Variome project (Scott et al., 2016) and the global resources 1kGP (Auton et al., 2015) and gnomAD (Chen et al., 2022) (Table 1.).

The TPCs are *endo*-lysosomal voltage-gated, cation-selective ion channels and their genes, named *TPCN1* and *TPCN2*, are located at 12q24.13 and 11q13.3 respectively (NCBI gene ID: 53,373 and 219931). They control the release of Ca^{2+} from the endosomes and lysosomes. TPC1 is mainly expressed in the endosomes, while TPC2 ion channel is located predominately in lysosomes (Favia et al., 2014). The role of TPCs in regulating Ca^{2+} signaling has been established in cancer. Recent evidence has emerged that the overexpression of these channels is implicated in tumorigenesis and metastasis (Nguyen et al., 2017; Faris et al., 2019; Brailoiu et al., 2009). An increase in TPC activity was correlated with cancer progression. The inhibition of the function/expression of both TPC1 and TPC2 affected cellular proliferation, adhesion, and migratory signals in several cancers in vitro and in vivo (Nguyen et al., 2017; Sun and Yue, 2018; Müller et al., 2021). Analyses from previous reports provided evidence that amplification of genes located at 11q13-q14 has been associated with cancer (Wilkerson and Reis-Filho, 2013; Xu et al., 2010).

There are 6 common non-synonymous variants in exons of *TPCN2*

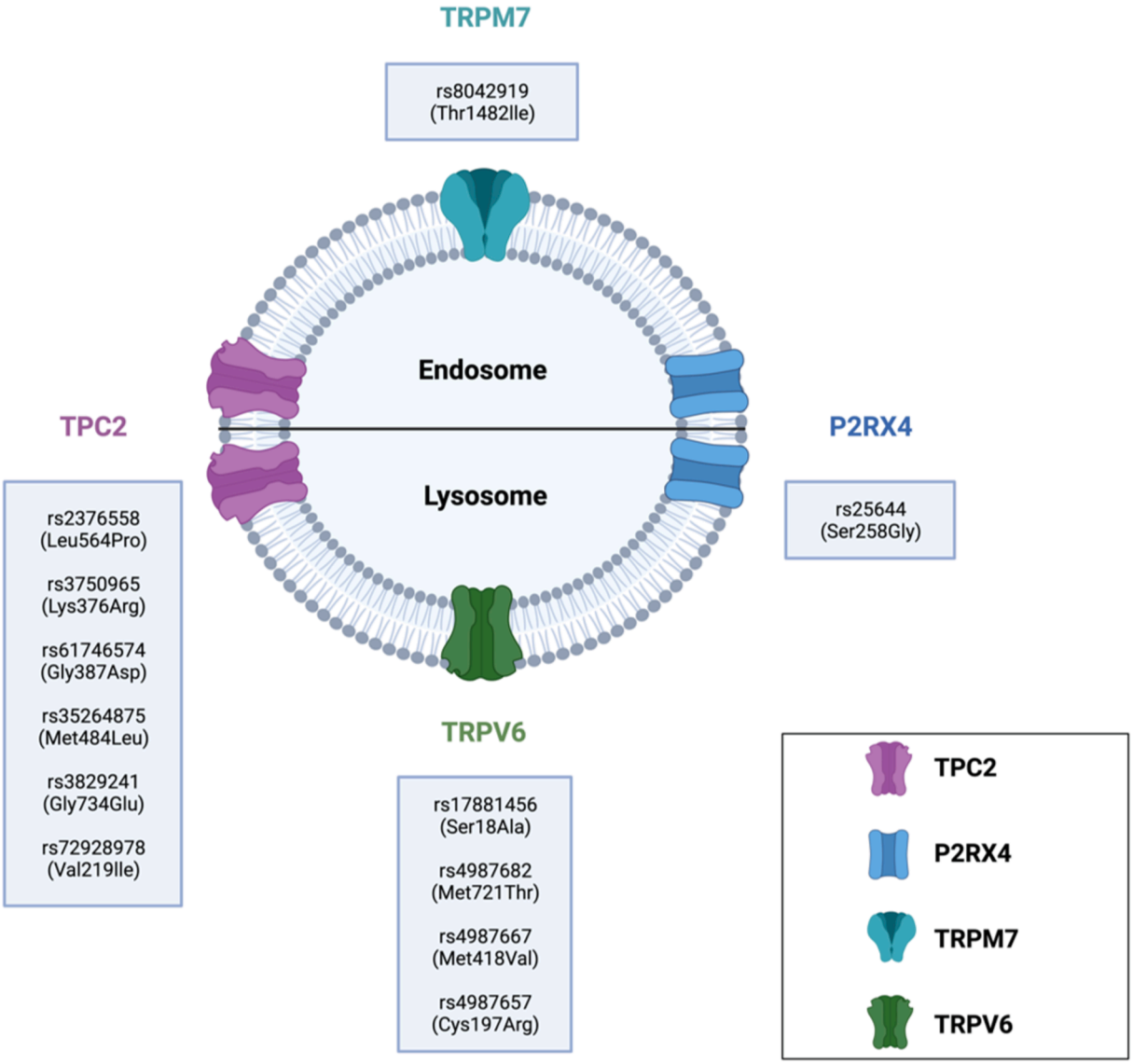

Fig. 3. Endo-lysosomal ion channels with their respective SNPs. Both TPC2 and P2RX4 are found in lysosomes and endosomes, while TRPM7 and TRPV6 are in the endosomes and lysosomes, respectively. Created with BioRender.com.

identified by our WES analysis (Table 1). The first variant with the highest MAF is rs2376558 which is a missense with a transversion of T to C causing Leu564Pro substitution (rs2376558). The second variant is rs3750965 which is an SNV causing missense with a transversion of A to G. This substitution led to the replacement of lysine with arginine (Lys376Arg) (rs3750965). In a similar WES analysis study done by Pang *et al.* (2019) both rs3750965 and rs2376558 have showed high MAF in patients with gastrointestinal stromal tumors (Pang et al., 2019). rs2376558 was observed to have a moderate impact as a variant linked to congenital pouch colon (Mathur et al., 2018). Moreover, patients with renal cancer (both papillary and clear cell renal cell carcinoma) have had GWAS studies showing significance in MAF for rs3750965 (Patel et al., 2022). Furukawa *et al.* (2015) anticipated that loss of wild-type allele of the rs3750965 variant in pancreatic acinar cell carcinoma patients can lead to the formation of tumor phenotype (Furukawa et al., 2015). Furthermore, rs2376558 variant was found to be common SNP in ovarian carcinoma patients (Castellarin et al., 2013). García *et al.* (2020) have characterized the genomic profile for metastatic gallbladder cancer cell lines for multiple genes having alterations, two of the identified mutations were rs2376558 and rs3750965 (García et al., 2020).

The third variant is rs61746574 where in the NCBI, this non-synonymous variant had a substitution of G to A (rs61746574). In our study, rs61746574 has a high MAF of 21 %, while in Haiman *et al.* (2013), have shown that statistically significant MAFs in native Hawaiian (MAF: 4.59 %) and Latino (MAF: 12.83 %) population with breast cancer (Haiman et al., 2013). The fourth most common *TPCN2* variant is rs35264875, which is reported as a missense variant with A substituted to T, which leads to the amino acid change Met484Leu (M484L) (rs35264875). A previous study investigated the connection between the survival of bladder cancer patients and the rs35264875 variant (Shivakumar et al., 2017). Nevertheless, WES has identified the variant rs35264875 in benign colorectal adenoma samples (Chen et al., 2016). Alharbi *et al.* (2021) employed the UK Biobank resource and identified SNPs that showed the association between the variants (rs3750965 and rs35264875) and human cancer. These variants of the *endo*-lysosomal ion channel TPCN2 assume the risk of cancer, recurrence, malignancy, and metastasis. They have concluded that *TPCN2* gene when overexpressed will trigger tumorigenesis, while when underexpressed, it will enhance metastatic phenotypes (Alharbi and Parrington, 2021). However, there are differences in the expression of *TPCN2* gene between primary and metastatic cancers was detected as the gene being significantly lower in advanced stages (D'Amore et al., 2020). As seen with the presence of the rs3750965 variant, where a protective effect against cancer was observed, it had a low risk of developing cancer at a global level. Nonetheless, the same study showed that it causes malignancy risk of oral cancer and an increased risk of recurrence susceptibility in patients with prostate and rectal cancer (Alharbi and Parrington, 2021). The fifth *TPCN2* variant in our study is the rs3829241 that has the G substituted to A with the consequence of turning gly734-to-glu amino acid (Gly734Glu) (rs3829241). Somatic rs3829241 was also present in five patients with gastric adenomas (Lim et al., 2016). Both these polymorphisms (rs35264875 and rs3829241) contribute to the increased expression of *TPCN2* which can increase the susceptibility to skin cancer (Alharbi and Parrington, 2019).

The last *TPCN2* variant studied here is rs72928978, which has a G to A substitution at Val219Ile (rs72928978). With protein PolyPhen-2 prediction of possibly damaging variant (0.746) while the effect on protein not yet established. In Patel *et al.* (2022) both rs72928978 and rs35264875 have shown significance in MAF in papillary renal cell carcinoma patients (Patel et al., 2022). The variants rs2376558, rs35264875, rs72928978, rs25644 (*P2RX4*), and rs17881456 (*TRPV6*) have been observed by WES in patients with gastrointestinal stromal tumors and exhibited high MAF (Pang et al., 2019).

The ligand-gated ion channels receptors (P2XRs) are cationic ATP-gated receptors with 7 subunits (Illes et al., 2021). *P2RX4* (or P2X4 receptor) is located at chromosome 12q24.31 (NCBI gene ID: 5025) is known to have a function in neuropathic pain (Illes et al., 2021) but recent discoveries have linked it to cancers such as prostate cancer (Wang et al., 2023). Targeting *P2RX4* pharmacologically reduced cancer pain (Zhang et al., 2020;161:105106.). Furthermore, similar to the rest of the genes covered here, *P2RX4* is an attractive target as potential cancer biomarker where its overexpression has been linked to cell migration, invasion, and metastasis by EMT in prostate cancer cells (Maynard et al., 2022). The common variant found in our Saudi population *P2RX4* homozygous missense variant rs25644 as A being substituted with G and the amino acid consequence of Ser242Gly (rs25644). It has been seen to be associated with a high risk of prostate cancer but a low risk of cancer recurrence. The overexpression of *P2RX4* was seen to correlate with cancer development and when inhibited with a pharmacological inhibitor, caused growth-inhibition (Alharbi and Parrington, 2021) (Table 2).

TRPs are a group of cation channels with diverse functions involving Ca^{2+} release. The TRP channel superfamily has multiple subfamilies, and our focus is on both TRPM (melastatin) and TRPV (vanilloid) (Gees et al., 2010). *TRPM7* is one of the TRPM subfamilies, a divalent cation-selective ion channel with permeability to both Ca^{2+} and Mg^{2+} (Gees et al., 2010). It is located at chromosome 15q21 (NCBI gene ID: 54822). They are ubiquitously found in almost all tissues and are known for the regulation of Ca^{2+} concentration (Pedersen and Stock, 2013). The interrelation between *TRPM7* and cancer is evident in published literature as covered in the review by Yee *et al.* (Yee, 2017). The proliferation, apoptosis, migration, and invasion in breast cancer were linked to *TRPM7* with overexpression leading to poor prognosis in breast cancer patients (Cordier et al., 2021). Su *et al.* (2019) further validated the findings in vitro and established the *TRPM7* modulation of cell proliferation, migration, and invasion of colorectal cancer through the regulation of the EMT (Su et al., 2019). Overexpression of *TRPM7* was reported in human cell lines such as gastric, lung, ovarian, colorectal, and breast cancer cell lines (Gautier et al., 2016). The rs8042919 variant with the amino acid isoform Thr1482Ile of the *TRPM7* gene was identified in other populations with the risk of polyps (adenomas) progression to colorectal cancer. In addition to the presence of this polymorphism, the increase in Ca/Mg intake has been seen to lead to the increased risk of developing adenoma and hyperplastic polyps (Dai et al., 2007). Similarly, studies confirmed the presence of overexpressed *TRPM7* in colorectal cancer (Su et al., 2019; Pugliese et al., 2020). As *TRPM7* was found to control Mg^{2+} homeostasis and the overexpression of such gene is involved in the resistance of drugs in cancer cells (Castiglioni et al., 2015). Other studies have listed *TRPM7* as one of the genes captured by sequencing in 92 breast cancer patients (Agarwal et al., 2015) (Table 2).

TRPV1-6 are of the TRP vanilloid channels, that are permeable to both $Ca2^{+}$ and Na^{+} (Peng et al., 1999). *TRPV4* and *TRPV6* are involved in many cell processes (Rosenbaum and Islas, 2023) and are located at chromosomes 12q24.11 and 7q34 respectively (NCBI gene ID: 59,341 and 55503). The missense variant rs3742030 encoding the *TRPV4* gene shows G substituted to A with an amino acid consequence of Pro19Ser (rs3742030). This *TRPV4* polymorphism was seen to be associated with lung function (Obeidat et al., 2011) and hyponatremia (Tian et al., 2009). Both *TRPV4* and *TRPV6* have been implicated in cancer, by impairing Ca^{2+} homeostasis, and are considered as a target for treatment (Zhong et al., 2022). There has been a strong correlation between overexpressed *TRPV4* and *TRPV6* and prostate cancer with indications of poor prognosis (Thebault et al., 2006; Borgström et al., 2021) (Table 2). Nonetheless, the *TRPV4* variant rs3742030 has not been directly associated with cancer (Table 1). The lack of association may suggest that the assessed variant is not of major importance for the prognosis or identification of diseases or that it is a novel variant that has not yet been explored.

The three non-synonymous SNPs, found at the *TRPV6* gene, rs4987657, rs4987667, and rs4987682 have been found to be associated with the progression of prostate cancer (Wissenbach et al., 2001)

(Table 2). rs17881456 variant has not been implicated in any disease except for the study implicating this variant in gastrointestinal stromal cancer (Pang et al., 2019). There are two non-synonymous variants identified in our investigations of genes that are located in close proximity to *TPCN1* (*TRPV4* located at 12q24.11, *P2RX4* located at 12q24.31, and *TPCN1* located at 12q24.13) (Cunningham et al., 2021). The non-synonymous variants rs25644 and rs3742030 of *P2RX4* and *TRPV4* genes, respectively. These genes are located on the same chromosome 12, this could have an impact on the carcinogenicity of such genes by influencing both *TPCN1* and *TPCN2* expression. All this evidence sheds light on the importance of investigating the molecular mechanism and role of TPCs, TRPs, and P2RX in cancer cell function and prospective treatments.

The GME Variome project covers six GME regions highlighting both consanguinity and diversity of the subregional population and providing WES data from 2,497 subjects (Scott et al., 2016). Even with the existence of such a project, it is important to note that there is a lack of representation of the Middle Eastern and Central Asian areas in global datasets. In our study, the Saudi population showed an expected slight difference in allele frequency compared to GME databases (Table 1) highlighting the need for regional as well as local identification of common variants that can aid in the association to phenotypes and diseases such as cancer.

Our analysis makes use of the fact that the seemingly healthy individuals could carry cancer-risk variants, in which they need a follow-up to further investigate the possibility of developing cancer. This raises a question regarding the clinical utility of such variants as diagnostic genetic cancer biomarkers and/or aid in the development of pharmacological personalized anticancer therapies. With the advancement of science and technology, patient-tailored pharmacotherapy is feasible. This study provides insight into the ever-expanding knowledge of variants in Saudi population. We uncovered 13 common non-synonymous variants that not only can contribute to cancer risk but also can influence therapy outcomes. Understanding the pharmacogenomic impact of these variants can affect clinical decisions and prospective tailored cancer therapy, which can lead to optimized cancer patient treatment plans. In fact, the impact of these variants might not directly affect drug action. It is plausible that the effect can be indirect through influencing cancer aggressiveness which negatively decreases therapy efficiency. Unfortunately, there is a lack of information regarding the impact of these variants on anticancer therapies. Thus, further studies with the aid of both pharmacists and researchers are needed to test the pharmacogenomic implications of these variants that can later be utilized in a clinical setting.

Our study substantially added valuable information about the prevalence of cancer-associated variants in the examined genes in the Saudi population. However, our study suffered from several limitations due to the nature of the design of secondary data analysis-based examinations. The association between the identified non-synonymous variants and the likelihood of developing cancer in Saudi individuals was not investigated. Thus, constructing future case-control cohort studies in which such associations are thoroughly examined is highly warranted. Furthermore, the sample size obtained from the in-house WES database could be of smaller size that might not adequately represent the Saudi population. However, our report is considered the largest study in which *endo*-lysosomal ion transport gene variants were assessed among Saudi individuals. Additionally, we were not able to acquire the age nor the gender of all the participating individuals, which made it difficult to statistically designate those parameters in this study.

5. Conclusion

In summary, our study aimed to investigate the distribution of *endo*-lysosomal ion transport gene variants, focusing on cancer-associated variants, in the Saudi population. Utilizing genomic data at KFSHRC, we examined SNPs of *TPCN1*, *TPCN2*, *P2RX4*, *TRPM7*, *TRPV4*, *TRPV4*, and *TRPV6* genes. We validated our findings by examining the link between these variants and cancer using VarSome, dbSNP NCB, OMIM, ClinVar, Ensembl, and GWAS databases. We identified 12 common cancer-associated non-synonymous variants with an MAF $\geq$ 1, rs2376558, rs3750965, rs61746574, rs35264875, rs3829241, rs72928978, rs25644, rs8042919, rs17881456, rs4987682, rs4987667, and rs4987657 in the Saudi population. Our pilot study paves the road for future cohort studies in which the impact of these variants on cancer risk and treatment outcomes in the Saudi population is investigated.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2024.101961.

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