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TP53 PATHOGENIC VARIANTS RELATED TO CANCER

VARIANTES PATOGÉNICAS DE TP53 RELACIONADAS CON CÁNCER

Rosero C.Y.[1]*, Mejia L.G.[1], Corredor M.[2,3]

[1] Interdisciplinary Research Group in Health and Disease, Medicine Faculty, Universidad Cooperativa de Colombia, San Juan de Pasto, Nariño, Colombia.

[2] Genetics and Biochemistry of Microorganisms, Natural and Exact Sciences Faculty, Biology Institute, Universidad de Antioquia, Medellín, Colombia.

[3] Genetics, Regeneration and Cancer, GRC, Natural and Exact Sciences Faculty, Biology Institute, Universidad de Antioquia, Medellín, Colombia.

Corresponding author:
Carol Yovanna Rosero Galindo
carol.roserog@campusucc.edu.co

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ABSTRACT

TP53 or P53 is a tumor suppressor gene known as the "genome guardian", responsible for inducing cell response to DNA damage, by stopping the cell cycle in case of mutation, activating DNA repair enzymes, initiating senescence and activation of apoptosis. Mutations in the gene sequence can cause non-synonymous mutations or errors in the reading frame by insertion, deletion or displacement of nucleotides: *e.g.*, c.358A>G mutation in exon 4 and variants located in exons 9 and 10 of the TD domain. Therefore, in this review, we will see that changes in the reading frame, including the loss of one or two base pairs could prevent accurate transcription or changes in the structure and function of the protein, and could completely impair reparation function. These changes promote self-sufficiency in growth signaling, insensitivity to anti-growth signals, and evasion of apoptosis, resulting in limitless replication and induction of metastatic angiogenesis, generating as a consequence the proliferation of tumor, neoplastic, and lymphoid cells. Taking into account the importance of TP53 in the regulation of the cell cycle, the objective of this review is to update information related to the role of this gene in the development of cancer and the description of genetic variations.

Key words: Neoplasms, nuclear phosphoprotein p53, Tumor Suppressor, mutation, Clinvar, Uniprot

RESUMEN

TP53 o P53 es un gen supresor de tumores conocido como el "guardián del genoma", encargado de inducir la respuesta de la célula ante el daño del ADN, deteniendo el ciclo celular en caso de mutación, activando enzimas de reparación del ADN, iniciando el proceso de senescencia celular y activación de la apoptosis. Las mutaciones en la secuencia del gen pueden originar mutaciones no sinónimas o errores en el marco de lectura por la inserción, deleción o desplazamiento de nucleótidos: ejemplo, mutación c.358A>G en el exón 4 y variantes que se albergan en los exones 9 y 10 del dominio TD. Por lo tanto en esta revisión examinaremos cambios en el marco de lectura, incluyendo la pérdida de una o dos pares de bases, que podrían impedir la exacta transcripción o cambiar la estructura y función de la proteína o perjudicar completamente la función de reparación. Tales cambios promueven la auto-suficiencia en la señal de crecimiento, la insensibilidad a señales anti-crecimiento y la evasión de la apoptosis, lo que resulta en la replicación ilimitada y la inducción de angiogénesis metastásica, generando como consecuencia la proliferación de células tumorales, neoplásicas y linfoides. Teniendo en cuenta la importancia del TP53 en la regulación del ciclo celular, el objetivo de la presente revisión es actualizar la información relacionada con el papel de este gen en el desarrollo de cáncer y la descripción de las variaciones genéticas.

Palabras clave: Neoplasma, fosfoproteína nuclear p53, supresor de tumor, mutation, Clinvar, Uniprot.

TP53 IN THE DEVELOPMENT OF CANCER

Cancer is the result of the accumulation of multiple alterations in the genes that regulate cell growth and are considered critical for the progressive transformation of non-cancerous cells to malignant cells (Sánchez, 2006; Pierce, 2009; Herrera *et al.*, 2010; Risueño, 2012). Some alterations include point mutations, chromosome disruption, repair interruption, epigenetic alterations, and oncogene rearrangements as well as loss or alteration in the function of tumor suppressor genes (Roa *et al.*, 2000; Pierce, 2009).

Among the tumor suppressor genes most commonly altered in various cancers, the *tumor suppressor gene TP53* is notable. TP53 has been reported as a viable genetic marker for the diagnosis and prognosis of various types of tumors (Ramírez *et al.*, 2008). The TP53 gene product is a tumor suppressor protein that is also known as tumor protein P53, P53 cellular antigen tumor (UniProt), P53 phosphoprotein, P53 suppressor tumor, NY-CO13 antigen, or transformation-related protein 53 (TRP53). It corresponds to a crucial orthologous protein that prevents cancer in several organisms. Colloquially, it is termed the "guardian of the genome", because it prevents mutations and maintains genomic stability (Isobe *et al.*, 1986; Kern *et al.*, 1991; McBride *et al.*, 1986; Bourdon, 2007).

The International Cancer Genome Consortium established that TP53 is the most frequently mutated gene (>50%), indicating that it plays a crucial role in the prevention of cancer formation (Surget *et al.*, 2013).

STRUCTURE-FUNCTION RELATIONSHIP OF P53

TP53 is located on the short arm of chromosome 17 at position 17p13.1, extending more than 20 kb (20,000 bases, depending on the variant), with the first non-coding exon and a first long intron of 10 kb. The coding sequence covers from exon 2 to the initial part of exon 11 and codes for a 53 kDa nuclear phosphoprotein called P53 that is divided into three regions and domains, each with a specific function (Alpízar *et al.*, 2005; Rangel *et al.*, 2006; Gallego *et al.*, 2010; López, 2011). The conformation of the tetramer structure (Figure 1) and active regions of the protein (Figure 2) are presented below:

The p53 protein consists of five main domains:

1. The amino-terminal region, which carries the activation domains of transcription: AD1 and AD2 (amino acids 1–42:43–63).
2. The next region which contains many amino acid repeats of proline, called PRD, or a domain rich in proline (amino acids 64–91).
3. The central region (amino acids 101–306) which corresponds to the DNA-specific sequence binding domain (DBD), being the region where the highest number of mutations in human cancer has been recorded.
4. The carboxyl-terminal region, which contains the tetramer domain TD (amino acids 334–356), and
5. The basic or alkaline domain BD (amino acids 364–393); these domains participate in the formation of dimers and tetramers where the tetrameric complex is active in transcriptional regulation.

The conformation of the tetramer structure and active regions of the protein are presented in Figures 1 and 2.

As a tumor suppressor, P53 is essential for preventing inappropriate cell proliferation and maintaining the integrity of the genome after genotoxic stress. Intracellular and extracellular stimuli such as DNA damage (including UV radiation, cytotoxic drugs, therapeutic chemical agents, and viruses), thermal shock, hypoxia, and oncogenic overexpression activate P53 protein as a regulatory mechanism to induce various biological responses (Bai and Zhu, 2006). Activation of P53 involves an increase in its protein level as well as qualitative changes through a broad post-translational modification, which results in activation of the P53-target gene complex; in this way, it acts as a sequence-specific transcription factor and regulates the expression of different genes that modulate various cellular processes in response to different types of stress. The genes activated by P53 are functionally diverse and participate in responses such as cell cycle control, cell survival, apoptosis, and senescence (Joerger, 2008).

In this context, the P53 protein can stop the cell cycle in phases G1 and G2 to provide additional time for cells to repair damage to the genome before entering the critical stages of DNA synthesis and mitosis. In the P53 signaling pathway in G1 (Figure 3), P21 protein blocks the cell cycle in the G1-S transition, joining the cyclin-CDK complexes (cyclin D/CDK4 and cyclin E/CDK2) responsible for driving the cell to the S-phase and avoiding activation of the transcription factor of the E2F family (elongation factor 2). By inhibiting the complexes, phosphorylation of RB (protein of retinoblastoma) is prevented; since this protein is necessary to start the S-phase, this blocks the progression of the cell cycle (Tomoak *et al.*, 2001; Ballesteros *et al.*, 2007). The genes involved in stopping the cycle in G2 are the *REPRIMO* and *14-3-3s*, members of a family of structural proteins. These genes sequester the cyclin B1-CDK1 complex outside the nucleus, which maintains the blockade in G2 Ballesteros *et al.*, 2007; Saavedra, 2015). The *14-3-3s* protein interacts with CDKs and can inhibit their activity to block the progression of the cell cycle; likewise, it regulates P53 and functionally increases its stability and reinforces its transcriptional activity (Zhang 2004). By contrast, the protein encoded by the target gene *GADD45* interacts with the CDC2 protein to block its kinase activity through the inhibitory

domain located in the central region of the protein (amino acids 65–84) that substantially contributes to the suppression of growth, thereby inducing arrest of the cell cycle (Saavedra, 2015).

As a guardian of the genome, P53 monitors cellular stress and, in tissues where stress can generate severe and irreparable damage, P53 can initiate apoptosis to eliminate damaged cells (Joerger, 2008; Harris, 1996) (Figure 3). The intrinsic or mitochondrial pathway of apoptosis is activated in response to DNA damage, a defective cell cycle, hypoxia, or other severe stress environments and is characterized by the release of pro-apoptotic molecules such as cytochrome C. The pathway is tightly regulated by a group of pro-apoptotic specific-tissue proteins, including BAX, NOXA, and PUMA, that act by promoting the release of cytochrome C from mitochondria to the cytoplasm (Yakovlev, 2004). After cytochrome C is released, it interacts with the activating factor of apoptosis activating proteases (APAF-1), which is also regulated by P53, to initiate a proteolysis cascade by proteins caspase (Rojas, 2009). Next, together with other mitochondrial proteins like SMAC/DIABLO that bind apoptosis inhibitory proteins (IAPs), it neutralizes their antiapoptotic activity, triggering a process of DNA fragmentation and cellular disorganization that leads to the death of the affected cell (Adrain and Creagh, 2001).

An alternative route through which P53 induces apoptosis via mitochondria is the activation of the expression of genes involved in increasing levels of reactive oxygen species like PIG3, an oxidoreductase enzyme that generates reactive oxygen species and whose expression is involved in the induction of apoptosis (Lee *et al*, 2010). By contrast, the extrinsic pathway, which promotes the sensitization of cells against signs of death, induces the expression of specific death receptors independently of the mitochondrial or intrinsic pathway; these death receptors include the FAS/APO-1/CD95 receptor and KILLER/DR5 receiver. The P53 protein also induces expression of the growth factor-3 interaction protein IGF1 (IGF1-BP3) that can bind to IGF-1 and IGF-2 (growth factors) and prevent its access to the IGFR1 receptor, thereby blocking signals from survival (Rojas, 2009).

In addition to the above-described functions, P53 mediates DNA repair processes and damage prevention through regulation of GADD45, P48, and DNA polymerase B (Uramoto *et al.*, 2006). GADD45 plays an important role in binding to damaged DNA and, in this way, makes it available to the repair machinery. In addition, its binding to PCN -a nuclear antigen of cells under repair, the subunit of DNA polymerase D- has been described, causing inhibition in DNA synthesis. P53 also regulates transcription of the *P53R2* gene, which plays a crucial role in DNA repair after DNA damage and encodes a small subunit of ribonucleotide reductase (RNR). This ribonucleotide reductase enzyme catalyzes the reduction of ribonucleotides diphosphate to the corresponding deoxyribonucleoside diphosphate, resulting in an equilibrium of the supply of dNTPs for DNA replication and repair (Uramoto *et al.*, 2006).

Lastly, P53 participates in the signaling pathway of cellular senescence (Figure 3), which comprises irreversible loss of the ability to divide, initiated in response to cell stress and damage. P53-induced senescence is the permanent arrest of the cell cycle, characterized by specific changes in gene expression. The activity of P53 and its expression levels increase when cells senesce. One cause of P53 activation seems to be an increase in the expression of P14, a tumor suppressor that stimulates P53 activity because it sequesters MDM2, which facilitates the degradation of the P53 protein. In this way, P14 prevents negative feedback regulation of P53 via MDM2. Another potential cause of increased P53 activity is the tumor suppressor of promyelocytic leukemia (PML), which interacts with an acetyltransferase (CBP/P300) that acetylates P53 and stimulates its activity (Bai and Zhu, 2006; Joerger, 2008).

In addition to these functions as a guardian of the genome, recent studies suggest that P53 controls additional processes that contribute to its primary function. Among these, P53 can modulate autophagy, alter metabolism, repress pluripotency and cell plasticity, and facilitate a form of iron-dependent cell death known as ferroptosis. The variety of P53 functions is anchored to its ability to control a large set of target genes (Kastenhuber and Lowe, 2017).

Cellular metabolism is controlled by P53 and is currently a focus of growing research interest. The set of metabolic target genes controlled by P53 affects many individual processes; it has been reported that P53 increases catabolism of glutamine, supports antioxidant activity, decreases lipid synthesis, increases oxidation of fatty acids, and stimulates gluconeogenesis. However, P53 may have opposite effects in the same metabolic processes, such as inhibiting glycolysis by attenuating glucose uptake or suppressing the expression of glycolytic enzymes in breast and lung cancer cells (Kastenhuber and Lowe, 2017).

Additionally, it has been reported that Wild-type P53 negatively regulates lipid synthesis and glycolysis in normal and tumor cells, and positively regulates oxidative phosphorylation and lipid catabolism. A polymorphism in the coding region of P53 in codon 72, which codes for either proline (P72) or arginine (R72), can affect the function of the protein. In response to DNA damage, the P72 variant of P53 predominantly triggers cell cycle arrest, whereas the R72 variant predominantly induces cell death or apoptosis. Despite these differences in function, the variant of codon 72 has not been systematically associated with cancer susceptibility. By contrast, this polymorphism is significantly associated with a higher body mass index and risk of diabetes in studies of humans (Gnanapradeepan *et al.*, 2018).

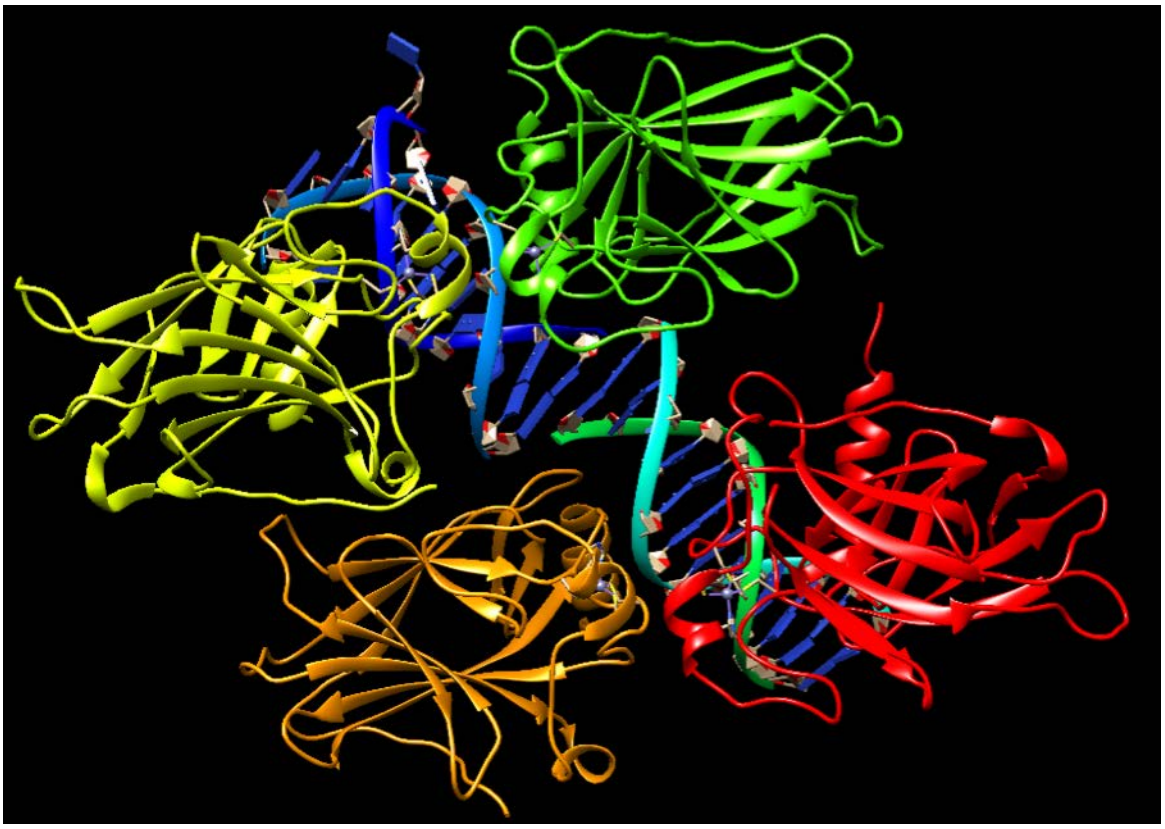

Figure 1. Formation of P53 tetramers on the DNA seen by Chimera 3,4. The structure of PDB (http://www.rcsb.org/pdb/), assembly 2AC0 developed by Kitayner *et al.*, 2006.

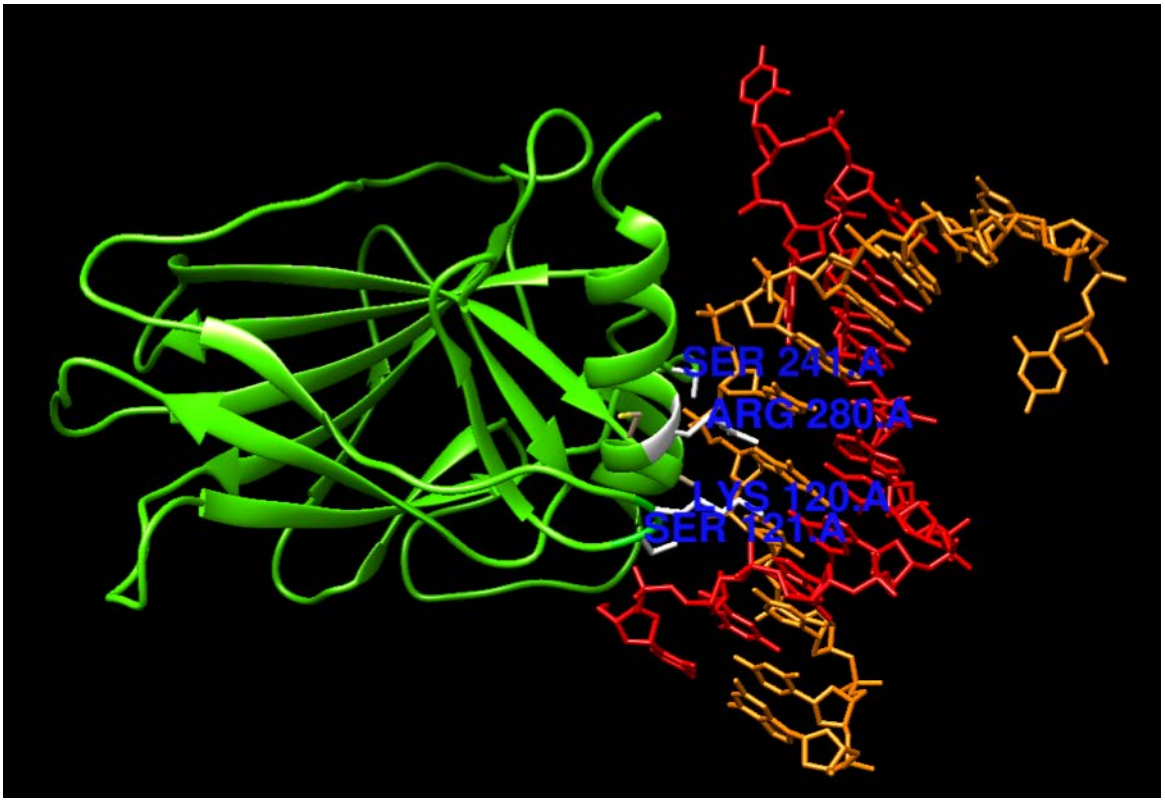

Figure 2. Some amino acids of the active protein domain with DNA, as seen by Chimera (Pettersen *et al.*, 2004) 3,4. Lysine-120 and Serine-121 (Zhao *et al.*, 2001; Joerger *et al.*, 2004), Serine-241 (Sjoeblom *et al.*, 2006; Rodrigues *et al.*, 1990); and Arginine 280 (Bartek *et al.*, 1990; Qin *et al.*, 2015).

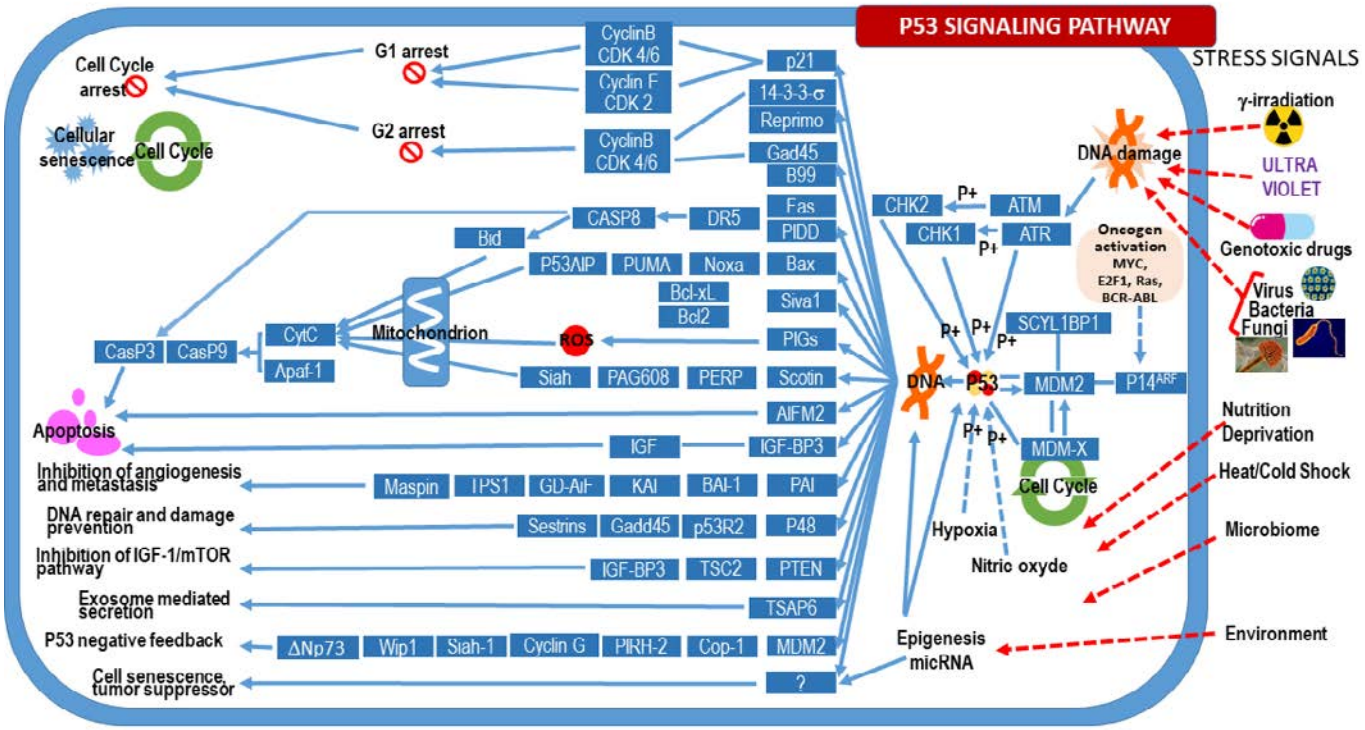

Figure 3. Scheme of signaling pathways of the p53 protein. Taken from the KEGG database assembled by the Keneshisa laboratory. Reworked in, Cell Designer 4.4 of System Biology Institute (Funahashi *et al.,* 2003). The inclusion of virus, bacteria, fungi, epigenesis, micRNA, unknown gene (?) and its pathway to cell senescence, tumor suppressor target are original of this article and is not found in the KEGG database, which is supported by current publications (Bhardwaj *et al.* , 2015; Yang & Lu, 2015).

VARIATIONS

Since the implementation of Sanger sequencing and with the advent of NGS (Next Generation Sequencing) technologies, thousands of tumors have been sequenced, generating information on the prevalence and kind of TP53 mutations in various types of cancer (Bouaoun *et al.*, 2016).

Most mutations in TP53 occur in the central DNA-binding domain and result in an inactivation of the function as a transcription factor. In experimental contexts, some non-synonymous mutations have been associated with a dominant-negative inhibition of the wild p53 protein and/or gain of oncogenic function in the absence of the normal p53 protein (Quintela *et al.*, 2001; Donehower *et al.*, 2019). Likewise, such mutations often make p53 resistant to proteolytic degradation by ubiquitin ligases E3, such as MDM2, ensuring high levels of stable mutant p53 protein (Donehower *et al.*, 2019).

Current evidence indicates that alterations of P53 at the gene level occur late in the pathogenesis of cancer and that the most frequent mechanism of inactivation corresponds to mutation of one allele followed by loss of the remaining allele through deletion on chromosome band 17p (Gallego *et al.*, 2010; Donehower *et al.*, 2019). Other less frequent mechanism includes mutations of both TP53 alleles or mutation of one allele and retention of the second wild-type allele. A homozygous TP53 deletion is a rare event, possibly due to its close relationship with genes essential for the cell (*e.g.*, POLR2A) (Donehower *et al.*, 2019). As a result, TP53 gene alterations are useful signals of many types of cancer in humans (Roa *et al.*, 2002). Likewise, in a recent study using exome sequencing in twelve types of cancer, TP53 was the most frequently mutated gene in most cancer types studied (Duffy *et al.*, 2017).

In this regard, analysis of important neoplasms of lung, breast, colon, stomach, and other organs indicates that TP53 mutations are the most common genetic abnormalities in human cancer. To date, multiple variants of TP53 have been analyzed to understand the molecular mechanisms of cancer initiation and progression. Studies have been conducted in various populations where cancer is recurrent and are initially based on SNPs selection (Hao *et al.*, 2013).

The mutations reported for TP53 gene are collected in different databases. The main compendium is the International Agency for Research on Cancer (IARC), which includes three types of data: somatic mutations, germline mutations, and polymorphisms. Importantly, it has been reported that more than 50% of human neoplasms present somatic mutations in TP53, with a registry of approximately 21,512 somatic mutations and 283 germline mutations in all types of cancer (Oliver *et al.*, 2002; Rangel *et al.*, 2006).

The role of somatic TP53 mutations in the steep rise in cancer rates with aging has not been investigated at a population level (Richarson, 2013). This relationship was quantified by using the International Agency for Research on Cancer (IARC) TP53 and GLOBOCAN cancer databases. TP53 mutations are associated with the aging-related rise in cancer incidence rates. However, preneoplastic TP53 mutations do not confer a growth advantage in gastric tumors and the evidence is less convincing than in other types of cancer (Morgan *et al.*, 2003).

TP53 variations databases: ClinVar

The ClinVar database is a recent initiative of the NCBI (National Center for Biotechnology Information) for collecting information on variants with clinical relevance to support a molecular diagnosis by genotype-phenotype association from real patient data. ClinVar database provides a file of associations between variants of medical importance and phenotypes for multiple genes, including the TP53 tumor suppressor (Landrum *et al.*, 2013).

In ClinVar, the interpretation of variation in sequences depends on a classification system standardized by two associations: The American College of Medical Genetics and Genomics and The Association for Molecular Pathology (ACMG). Currently, this system allows classification of a variant as pathogenic when the molecular consequences lead to a loss of function in that gene associated with a certain disease (Richards *et al.*, 2015).

For the TP53 gene, 298 pathogenic mutations have been reported concerning hereditary cancer, predisposition to syndromes, Li-Fraumeni Syndrome, adenocarcinomas, and osteosarcomas (ClinVar database). Within the coding region of the gene, around 60% of pathogenic mutations are concentrated in the area between exons 5 and 8, affecting the DBD domain involved in DNA recognition and binding. TP53 mutations within the domain affect its function, particularly when they occur within the so called hotspots that correspond to points necessary for protein function, such as DNA contact (codons 248 and 273) or stability (codons 175, 249, and 282) (Petitjean *et al.*, 2007) (Table 1).

Approximately 5% of mutations reported in exon 4 are involved in the PRD domain necessary for complete suppressive activity of P53, which participates in the induction of apoptosis (Rangel *et al.*, 2006). Among these, the clinical significance of mutation c.358 A>G for exon 4 remains uncertain and, therefore, there is a classification conflict as a pathogenic variant (Table 1).

Finally, around 6% of mutations are reported in exons 9 and 10 of the TD domain (Table 1), which is responsible for the oligomerization of P53 molecules. Variation in this domain can interfere with the formation of the dimer and tetramer.

Non-synonymous mutations can cause functional inactivation due to the generation of truncated monomers that are unable to establish the correct contacts, whereas synonymous mutations can affect the structure and dynamics of dimer stabilization during protein formation (Castaño *et al.*, 1996). Therefore, these variants may be involved in the loss of P53 function in malignant cells (Rangel *et al.*, 2006; López, 2011).

Mutations in non-coding regions have not been as widely studied as mutations in coding sequences despite the finding that many SNPs in the TP53 gene are in intronic regions (Marsh *et al.*, 2001). Variants have been reported in intronic regions for TP53 as: variant c.994-1G>A in intron 9, c.920-1G>A in intron 8, and c. 101-2A>G in intron 10 (Table 1). These mutations in non-coding regions can affect splicing sites, which lead to truncated protein products or reduced protein levels. The transition from A to G in intron 10, which eliminates a splicing acceptor site and causes a frameshift (change in reading frame), was recently reported in a pediatric adrenocortical tumor (Ming *et al.*, 2012). It has been proposed that intronic variation influences susceptibility to cancer via regulation of gene expression, splicing, or mRNA stability, and these polymorphisms may be in linkage disequilibrium with other functional polymorphisms that could increase the risk of cancer (Sprague *et al.*, 2007).

Most studies of TP53 have only examined exons 5–8, in which missense mutations are most common, without considering that exons 2–4 and 9–11 also present many deletions and insertions. ClinVar has reported 135 pathogenic deletions in the TP53 gene. These deletions can cause disruptions in the reading frame during translation because the number of deleted nucleotides is not anmultiple of three (The sequence Ontology Browser), then the sequence of amino acids translated from the mutated gene changes from the point of the deletion (Castaño *et al.*, 1996). Of note, in Li-Fraumeni syndrome, pathogenic deletions of 1 bp have been reported in codons 178 and 317 (Table 1).

To date, 46 pathogenic duplications have been identified. Some duplications generate a change in the reading frame during translation (frameshift variant), resulting in an effect similar to that caused by deletions. Other duplications constitute an intronic mutation in the acceptor splicing site (splice acceptor variant). In this sense, a mutation in the splicing regulatory region can result in deleterious effects in the splicing process of mRNA precursors (Ward *et al.*, 2010), consequently producing a different RNA and a non-functional protein. Of note, in addition to the duplications, pathogenic insertions in ovarian neoplasms and hereditary cancer predisposition syndrome have been identified (Table 1).

Of the total of TP53 variants reported as pathogenic, approximately 35% are punctual (point mutations), with a single change of nucleotide base. Concerning the known molecular consequences, most of the identified point mutations result in a unique amino acid change

that typically alters the binding of P53 to DNA. These missense mutations inactivate the gene protein product by not allowing its binding to DNA, making it incapable of activating its target genes (Rangel *et al.*, 2006).

Additionally, a smaller percentage of TP53 variants correspond to nonsense mutations, *i.e.*, the substitution of one base for another that gives rise to a stop codon, causing premature termination of protein synthesis and, consequently, the formation of a protein truncated at the point of mutation. Studies have noted that the variation c.637C>T in codon 213 (Arg213Ter) is the most frequent nonsense mutation in various cancers, including colorectal (41% of all nonsense mutations), gastric (33%), and breast cancer (21%), because codon 213, which consists of a CpG dinucleotide, is the main methylation target and the nonsense mutation results in the endogenous deamination of 5-methylcytosine to thymine. It has been suggested that this dinucleotide, besides being an endogenous pro-mutagenic factor, could be a preferential target for exogenous carcinogenic chemicals (Shuyer *et al.*, 1998).

In summary, the variants reported here demonstrate that access to knowledge and interpretation of variants of clinical importance are relevant to a better understanding of diseases. The current research focused on identification of biomarkers is intended to improve molecular knowledge about the specific cellular mechanisms that cause or drive tumor transformation within the enormous complexity of cancer. Important variations in the TP53 tumor suppression gene have been identified in humans and their patterns can show great differences not only between tumor types but also between different populations depending on genetic variability and environmental factors (Vaiva *et al.*, 2009). Among these variants, those identified as pathogenic typically result in a single amino acid change that alters the binding of P53 to DNA, induce a change in the reading frame (frameshift), or cause premature interruption of translation leading to inactivation of the protein.

P53 variations databases: Uniprot

According to the Universal Protein Resource (UniProt) database, a total of 1363 variants have been reported for the TP53 gene. In UniProt, TP53 variants associated with a disease are described by the amino acid change, the abbreviation of the associated disease, the effect (s) of the variation on the protein, and the cell and/or organism if known (Table 2). It should be noted that polymorphisms associated with human diseases have been validated in the dbSNP NCBI database. However, polymorphisms of a single amino acid caused by a change of a single nucleotide are relatively rare and have very low frequencies to be reported in the dbSNP.

Variation in TP53 occurs in conditions like Barrett's metaplasia, in which the stratified squamous epithelium normally in the lower part of the esophagus is replaced by a metaplastic columnar epithelium. This condition develops as a complication in approximately 10% of patients with chronic gastroesophageal reflux disease and predisposes patients to the development of esophageal adenocarcinoma. In addition, TP53 variants have been reported in Li-Fraumeni Syndrome (LFS), a hereditary, autosomal dominant disorder that predisposes patients to cancer.

Four types of cancer represent 80% of tumors occurring in carriers of a TP53 germline mutation, namely breast cancer, bone and soft tissue sarcomas, brain tumors, and adrenocortical carcinomas. Less common tumors include papilloma and choroidal plexus carcinoma before age 15; rhabdomyosarcoma before age 5; and leukemia, Wilms' tumor, malignant phyllode tumor, colorectal cancer, and gastric cancer (Table 2).

Under normal conditions, P53 protein is expressed at low levels. However, the P53 pathway is activated by any stress that alters the progression of the normal cell cycle or induces mutations to the genome leading to the transformation of a normal cell into a cancer cell (Bourdon, 2007). Therefore, P53 is considered to play an important role in maintaining the integrity of the genome; hence, loss of P53 function would allow the survival of genetically damaged cellular elements, eventually leading to tumor cell transformation (Rangel *et al.*, 2006).

Two general types of P53 mutations have been described: contact and conformational. The contact mutation proteins largely maintain the conformation of the wild-type folded protein, since the specific residues that are mutated are unable to bind to P53-specific DNA promoter sites. The conformational mutations (also known as structural mutations) cause protein destabilization, decrease its melting temperature, and decrease deployment at physiological temperatures. Mutations in P53 may result in the loss of its function as a tumor suppressor or an increase in oncogenic activity (Duffy *et al.*, 2017).

Current evidence indicates that alterations of P53 at the gene level occur late in the pathogenesis of cancer and that the most frequent mechanism of inactivation corresponds to mutation of one allele followed by the deletion of the remaining allele (Gallego *et al.*, 2010). As a result, TP53 gene alterations are useful signals of many types of cancer in humans (Roa *et al.*, 2002). Likewise, in a recent study using exome sequencing in twelve types of cancer, P53 was the most frequently mutated gene in most cancer types studied (Duffy *et al.*, 2017).

Table 1. Information of some mutations relevant to the TP53 gene reported in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar).

P53 DOMAIN	EXON	RSID	VARIATION	TYPE	PROTEIN CHANGE	CLINICAL SIGNIFICANCE	CONDITION
DBD DOMAIN	5 -8	rs11540652	c.743G>T	SNV	p.Arg248Leu	Likely Pathogenic	Hereditary cancer-predisposing syndrome, Uterine Carcinosarcoma, Transitional cell carcinoma of the bladder, Neoplasm of brain, Squamous cell lung carcinoma, Brainstem glioma ...(19)
		rs11540652	c.743G>C	SNV	p.Arg248Pro	Likely Pathogenic	Li-Fraumeni syndrome, Ovarian Serous Cystadenocarcinoma, Multiple myeloma, Adenocarcinoma of stomach, Uterine Carcinosarcoma...(21)
		rs11540652	c.743G>A	SNV	p.Arg248Gln	Pathogenic/Likely Pathogenic	Li-Fraumeni syndrome 1, Hereditary cancer-predisposing syndrome, Sarcoma, Acute myeloid leukemia, Neoplasm of the breast...(32)
		rs121912651	c.742C>G	SNV	p.Arg248Gly	Likely Pathogenic	Uterine Carcinosarcoma,Pancreatic adenocarcinoma, Neoplasm of the breast, Neoplasm of the large intestine, Squamous cell lung carcinoma...(22)
		rs121912651	c.742C>T	SNV	p.Arg248Trp	Pathogenic	Li-Fraumeni syndrome 1, Hereditary cancer-predisposing syndrome, Acute myeloid leukemia, Lung adenocarcinoma, Glioblastoma...(31)
		rs1555525498	c.741_742 delinsTT	INDEL	p.Arg248Trp	Likely Pathogenic	Li-Fraumeni syndrome
		rs28934576	c.818G>A	SNV	p.Arg273His	Pathogenic/Likely Pathogenic	Li-Fraumeni syndrome 1, Anaplastic thyroid carcinoma, Hereditary cancer-predisposing syndrome, Squamous cell lung carcinoma, Adenocarcinoma of stomach...(31)
		rs28934576	c.818G>C	SNV	p.Arg273Pro	Pathogenic/Likely Pathogenic	Hereditary cancer-predisposing syndrome, Multiple myeloma, Adrenocortical carcinoma, Pancreatic adenocarcinoma, Malignant melanoma of skin...(22)
		rs28934576	c.818G>T	SNV	p.Arg273Leu	Pathogenic	Pancreatic adenocarcinoma, Neoplasm of brain, Squamous cell carcinoma of the head and neck, Chronic lymphocytic leukemia, Neoplasm of the large intestine...(22)
		rs121913343	c.817C>A	SNV	p.Arg273Ser	Pathogenic/Likely Pathogenic	Lung adenocarcinoma, Glioblastoma, Ovarian Serous Cystadenocarcinoma, Chronic lymphocytic leukemia, Malignant neoplasm of body of uterus...(21)
		rs121913343	c.817C>G	SNV	p.Arg273Gly	Pathogenic	Ovarian Neoplasms, Li-Fraumeni syndrome
		rs28934578	c.524G>T	SNV	p.Arg175Leu	Conflicting Interpretations of Pathogenicity	Hereditary cancer-predisposing syndrome, Li-Fraumeni syndrome
		rs28934578	c.524G>A	SNV	p.Arg175His	Pathogenic	Li-Fraumeni syndrome 1, Hereditary cancer-predisposing syndrome, Malignant tumor of esophagus, Neoplasm, Neoplasm of the breast...(10)
		rs138729528	c.523C>T	SNV	p.Arg175Cys	Conflicting Interpretations of Pathogenicity	Pancreatic adenocarcinoma, Malignant melanoma of skin, Lung adenocarcinoma,Adenocarcinoma of stomach, Medulloblastoma...(20)
		rs138729528	c.523C>G	SNV	p.Arg175Gly	Pathogenic/Likely Pathogenic	Neoplasm of the large intestine, Malignant neoplasm of body of uterus, Transitional cell carcinoma of the bladder, Brainstem glioma, Hepatocellular carcinoma...(20)
		rs786202525	c.532del	DEL	p.His178fs	Pathogenic	Li-Fraumeni syndrome 1, Hereditary cancer-predisposing syndrome, Ovarian Neoplasms
		rs786202514	c.511_515dup	DUP	p.Val173fs	Pathogenic	Hereditary cancer-predisposing syndrome
		rs730882018	c.216dup	DUP	p.Val73fs	Pathogenic	Li-Fraumeni-like syndrome, Hereditary cancer-predisposing syndrome, Li-Fraumeni syndrome
		rs587782609	c.155_157dup	DUP	p.Trp53Ter	Pathogenic	Hereditary cancer-predisposing syndrome
		rs1567546889		INS	p.Ser303fs	Pathogenic	Ovarian Neoplasms
		rs1555525226	c.842_843insG	INS	p.Asp281fs	Pathogenic	Hereditary cancer-predisposing syndrome
PRD DOMAIN	4	rs1057520003	c.373A>C	SNV	p.Thr125Pro	Likely Pathogenic	Neoplasm of the large intestine, Squamous cell carcinoma of the head and neck, Transitional cell carcinoma of the bladder, Malignant melanoma of skin, Neoplasm of the breast...(16)
		rs1567555667	c.338T>G	SNV	p.Phe113Cys	Likely Pathogenic	Ovarian Neoplasms
		rs1057519997	c.332T>G	SNV	p.Leu111Arg	Likely Pathogenic	Adenocarcinoma of stomach, Chronic lymphocytic leukemia, Squamous cell lung carcinoma, Hepatocellular carcinoma… (4)
		rs1057519997	c.332T>A	SNV	p.Leu111Gln	Likely Pathogenic	Squamous cell lung carcinoma, Adenocarcinoma of stomach, Malignant melanoma of skin, Hepatocellular carcinoma, Neoplasm of the breast…(3)
		?		INDEL	p.Arg110Pro	Pathogenic	Li-Fraumeni syndrome
		rs11540654	c.329G>C	SNV	p.Arg110Pro	Pathogenic/Likely Pathogenic	Hereditary cancer-predisposing syndrome, Li-Fraumeni syndrome
		rs11540654	c.329G>T	SNV	p.Arg110Leu	Pathogenic/Likely Pathogenic	Li-Fraumeni syndrome, Hereditary cancer-predisposing syndrome, Ovarian Neoplasms
		rs1064796722	c.326T>G	SNV	p.Phe109Cys	Likely Pathogenic	Ovarian Neoplasms
		rs1057523496	c.325T>G	SNV	p.Phe109Val	Likely Pathogenic	not provided
		rs587781504	c.314G>T	SNV	p.Gly105Val	Likely Pathogenic	Ovarian Neoplasms
		rs1060501195	c.313G>A	SNV	p.Gly105Ser	Likely Pathogenic	Hereditary cancer-predisposing syndrome
		rs121912661	c.105G>T	SNV	p.Leu35Phe	Pathogenic	Carcinoma of pancreas

P53 DOMAIN	EXON	RSID	VARIATION	TYPE	PROTEIN CHANGE	CLINICAL SIGNIFICANCE	CONDITION
TD DOMAIN	9 -10	rs876659384	c.976G>T	SNV	p.Glu326Ter	Pathogenic	Hereditary cancer-predisposing syndrome, Li-Fraumeni syndrome, Ovarian Neoplasms
		rs863224500	c.973G>T	SNV	p.Gly325Ter	Pathogenic	Li-Fraumeni syndrome
		rs764735889	c.949C>T	SNV	p.Gln317Ter	Pathogenic/Likely Pathogenic	Hereditary cancer-predisposing syndrome, Li-Fraumeni syndrome
		rs758194998	c.1034C>T	SNV	p.Ser345Leu	Conflicting Interpretations of Pathogenicity	Hereditary cancer-predisposing syndrome
		rs1567545268	c.1028T>A	SNV	p.Ile343Lys	Uncertain Significance	Li-Fraumeni syndrome
		rs554738122	c.1009C>T	SNV	p.Arg337Ter	Conflicting Interpretations of Pathogenicity	Hereditary cancer-predisposing syndrome, Li-Fraumeni syndrome 1
		rs730882019	c.455dup	DUP	p.Pro153fs	Pathogenic	Li-Fraumeni syndrome 1, Hereditary cancer-predisposing syndrome
		rs1567546196	c.949del	DEL	p.Gln317fs	Pathogenic	Li-Fraumeni syndrome, Ovarian Neoplasms
		rs1567542146	c.1014_1015insT	INS	p.Glu339Ter	Pathogenic	Ovarian Neoplasms
INTRONIC REGION		rs11575997		SNV		Pathogenic	Li-Fraumeni syndrome
		rs11575997	c.993+1G>A	SNV	Splice Donor Variant	Pathogenic	Li-Fraumeni syndrome, Ovarian Neoplasms
		rs1131691033	?		Splice Donor Variant	Pathogenic	Hereditary cancer-predisposing syndrome
		rs587781702	c.920-1G>A	SNV	Splice Donor Variant	Pathogenic	Hereditary cancer-predisposing syndrome, not provided, Ovarian Neoplasms
		rs587781702	c.920-1G>T	SNV	Splice Donor Variant	Pathogenic	Hereditary cancer-predisposing syndrome, Ovarian Neoplasms
		rs1555525040	c.917_919+10del	DEL	Splice Donor Variant	Pathogenic	Li-Fraumeni syndrome
		rs1131691016	c.919+2T>A	SNV	Splice Donor Variant	Pathogenic	Hereditary breast and ovarian cancer syndrome
		rs1131691039	c.919+1G>A	SNV	Splice Donor Variant	Pathogenic	Li-Fraumeni syndrome 1
		rs878854073	c.673-1G>T	SNV	Splice Donor Variant	Pathogenic	Li-Fraumeni syndrome
		rs878854073	c.673-1G>A	SNV	Splice Donor Variant	Pathogenic	Hereditary cancer-predisposing syndrome
		rs1555525585	c.673-2A>G	SNV	Splice Donor Variant	Pathogenic	Li-Fraumeni syndrome,Ovarian Neoplasms

Table 2. Most important mutations by position (amino acid substitutions) reported in UniProt database (https://www.uniprot.org/uniprot/) for the p53 gene associated with a disease.

POSITION	AA CHANGED	DESCRIPTION	ID	REFERENCES
110–110	R → L	In family cancer not coincident with LFS; Germinal mutation and in sporadic cancer; somatic mutation; does not induce SNAI1 degradation.	VAR_005861	Lim *et al.*, 2010
133–133	M → T	In LFS; Germinal mutation and in sporadic cancer; somatic mutation. Corresponds to variant rs28934873.	VAR_005875	Law *et al.*, 1991
151–151	P → S	In LFS; Germinal mutation and in sporadic cancer; somatic mutation. Corresponds to variant rs28934874.	VAR_005895	Caamano *et al.*, 1993
152–152	P → L	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005897	Casson *et al.*, 1991
163–163	Y → C	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_033035	Sjoeblom *et al.*, 2006; Chanock *et al.*, 2007
175–175	R → H	In LFS; Germinal mutation and in sporadic cancer; somatic mutation; does not induce SNAI1 degradation; reduces interaction with ZNF385A. Corresponds to variant rs28934578	VAR_005932	Lim *et al.*, 2010; Casson *et al.*, 1991; Sjoeblom *et al.*, 2006; Das *et al.*, 2007; Frebourg *et al.*, 1995; Varley *et al.*, 1995
193–193	H → R	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005948	Sjoeblom *et al.*, 2006; Frebourg *et al.*, 1995
213–213	R → P	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_036506	Sjoeblom *et al.*, 2006
220–220	Y → C	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005957	Caamano *et al.*, 1993; Van Rensburg *et al.*, 1998
241–241	S → F	In LFS; Germinal mutation and in sporadic cancer; somatic mutation. Corresponds to variant rs28934573.	VAR_005969	Sjoeblom *et al.*, 2006; Rodrigues *et al.*, 1990
245–245	G → C	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005972	Srivastava *et al.*, 1990; Audrezet *et al.*, 1996
245–245	G → D	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005973	Srivastava *et al.*, 1990; Audrezet *et al.*, 1996
245–245	G → S	In LFS; Germinal mutation and in sporadic cancer; somatic mutation. Corresponds to variant rs28934575	VAR_005974	Audrezet *et al.*, 1996
245–245	G → V	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005975	Hollstein *et al.*, 1990
248–248	R → Q	In LFS; Germinal mutation and in sporadic cancer; somatic mutation. Corresponds to variant rs11540652	VAR_005983	Caamano *et al.*, 1993; Sjoeblom *et al.*, 2006; Frebourg *et al.*, 1995; Hollstein *et al.*, 1990
248–248	R → W	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005984	Sjoeblom *et al.*, 2006; Malkin *et al.*, 1990; Audrezet *et al.*, 1996
252–252	L → P	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005988	Malkin *et al.*, 1990
258–258	E → K	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005991	Malkin *et al.*, 1990

POSITION	AA CHANGED	DESCRIPTION	ID	REFERENCES
272–272	V → L	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005992	Felix *et al.*, 1992
273–273	R → C	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005993	Sjoeblom *et al.*, 2006; Chanock *et al.*, 2007; Frebourg *et al.*, 1995; Van Rensburg *et al.*, 1998
273–273	R → H	In LFS; Germinal mutation and in sporadic cancer; somatic mutation; suppresses sequence-specific DNA binding; does not induce SNAI1 degradation. Corresponds to the variant rs28934576.	VAR_005995	Lim *et al.*, 2010; Caamano *et al.*, 1993; Casson *et al.*, 1991; Sjoeblom *et al.*, 2006; Rodrigues *et al.*, 1990; Malkin *et al.*, 1992; Somers *et al.*, 1992; Azuma *et al.*, 2002; Chehab *et al.*, 1999
273–273	R → L	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_036509	Sjoeblom *et al.*, 2006
275–275	C → Y	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_005998	Frebourg *et al.*, 1995
278–278	P → L	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_006003	Hollstein *et al.*, 1990
278–278	P → S	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_006004	Sjoeblom *et al.*, 2006; Van Rensburg *et al.*, 1998; Hollstein *et al.*, 1990
280–280	R → K	In family cancer not coincident with LFS; Germinal mutation and in sporadic cancer; somatic mutation; has no effect on the interaction with CCAR2	VAR_006007	Bartek *et al.*, 1990; Qin *et al.*, 2015
282–282	R → Q	In family cancer not coincident with LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_045387	Nimri *et al.*, 2003; Tu *et al.*, 2008
282–282	R → W	In LFS; Germinal mutation and in sporadic cancer; somatic mutation; does not induce SNAI1 degradation. Corresponds to variant rs28934574.	VAR_006016	Lim *et al.*, 2010; Audrezet *et al.*, 1996
292–292	K → I	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_015819	Gueran *et al.*, 1999
309–309	P → S	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_006038	Azuma *et al.*, 2002
325–325	G → V	In LFS; Germinal mutation. Corresponds to variant rs28934271.	VAR_006039	Malkin *et al.*, 1992
337–337	R → C	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_006041	Ribeiro *et al.*, 2001
337–337	R → H	In LFS; Germinal mutation and in sporadic cancer; somatic mutation.	VAR_035016	Ribeiro *et al.*, 2001
366–366	S → A	In family cancer not coincident with LFS; Germinal mutation and in sporadic cancer; somatic mutation. Corresponds to variant rs17881470.	VAR_022317	Ribeiro *et al.*, 2001

PERSPECTIVES IN TREATMENT

Currently, with the rise of next-generation sequencing and high throughput proteomics mass spectrometry, the study of different types of cancer has allowed the characterization of a series of mutations as potential drivers in the development of this pathology. Among the mutated genes in cancer, TP53 hosts variants that occur with a high frequency.

From a therapeutic perspective, the goal is looking for the mutant P53 protein to be the target of treatments. However, the fact that mutants are diverse in form and function means that therapies must be directed with a large number of molecules that are selective to the various mutants of P53 and in turn do not affect the functioning of the wild form, a fact that has made difficult the application or successful outcome of treatments. In this sense, recently small interference RNAs (siRNAs) have been developed for many targets that can silence the expression of the mutated protein satisfactorily and that are also selective for a single nucleotide, so that they can be applied to multiple P53 mutants. Recently, Ubby *et al.* (2019), generated specific siRNAs for four of the six mutational hotspot of P53, which were able to silence only the mutant alleles without having an impact on the expression of the wild protein, representing an important advance in the treatment of around 10% of all types of cancer and highlighting the importance of the identification of variants in this gene. Recently *in vitro* hPSC stem cells line engineering with stable integration of CRISPR/Cas9 (Ihry *et al.*, 2018) found that the lethal response to that double-strand breaks was *P53/TP53* dependent, such that the efficiency of precise genome engineering in hPSCs with a wild-type P53 gene was severely reduced. The results of Ihry *et al.* (2018) indicate that Cas9 toxicity creates an obstacle to the high-throughput use of CRISPR/Cas9 for genome engineering and screening in these stem cells. The new small interference RNAs (siRNAs) and CRISPR/Cas9 therapy tools scenario is still a challenge, and new discoveries are expected for the development of this urgent therapy.

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