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The phenotypic landscape of the *TP53* p.Arg337His mutation in pediatric cancers: a scoping review protocol

O panorama fenotípico da mutação *TP53* p.Arg337His em câncer pediátrico: um protocolo de revisão de escopo

El paisaje fenotípico de la mutación *TP53* p.Arg337His en cánceres pediátricos: un protocol de revisión del alcance

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Abstract
The *TP53* p.Arg337His is a founder mutation that exists at a very high frequency in Southern and Southeastern Brazil. Adrenocortical and plexus choroides carcinomas are highly associated with this variant. The present scoping review protocol aimed to map health-related literature searching for pediatric cancer related to the *TP53* p.Arg337His. Methods: A scoping review protocol is presented in this article, conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guideline. Six databases, an electronic repository, and additional sources were searched using keywords and text words. The review team consists of three independent screeners. Two screeners will do the initial title and abstract screening for all studies retrieved by the search strategy and then the full text screening phase. Reference lists of included studies will be screened, and data will be independently extracted by the review team. Results will be analyzed qualitatively and quantitatively. Ethics and dissemination: Ethical approval is not necessary, since the study does not involve human participants. Findings will be disseminated through publication at scientific journals and conferences.
Keywords: Li-Fraumeni syndrome; Genetic predisposition to disease; Neoplasms; Genetics; Child; Adolescent.

Resumo
A *TP53* p.Arg337His é uma mutação fundadora que existe em altíssima frequência no Sul e Sudeste do Brasil. Os carcinomas adrenocorticais e do plexo coróide estão altamente associados a esta variante. O presente protocolo de revisão de escopo teve como objetivo mapear a literatura relacionada à saúde buscando câncer pediátrico associado à variante *TP53* p.Arg337His. Métodos: Um protocol de revisão de escopo é apresentado neste artigo, conduzido de acordo com as diretrizes *Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR)*. Seis bases de dados, um repositório eletrônico e fontes adicionais foram pesquisadas usando palavras-chave, palavras de texto e busca manual. A equipe de revisão consiste em três avaliadores independentes. Dois avaliadores farão a triagem inicial de títulos e resumos de todos os estudos recuperados pela estratégia de busca, seguida, pela fase de triagem do texto completo. As listas de referências dos estudos incluídos serão analisadas e os dados serão extraídos de forma independente pela equipe de revisão. Os resultados serão analisados qualitativa e quantitativamente. Ética e divulgação: Não é necessária aprovação ética, uma vez que o estudo não envolve participantes humanos. Os resultados serão divulgados através de publicação em revistas e conferências científicas.
Palavras-chave: Síndrome de Li-Fraumeni; Predisposição genética para doença; Neoplasias; Genética; Criança; Adolescente.

Resumen
La *TP53* p.Arg337His es una mutación fundadora que existe con una frecuencia muy alta en el sur y sureste de Brasil. Los carcinomas adrenocorticales y de plexo coroideo están altamente asociados con esta variante. El presente

protocolo de revisión de alcance tuvo como objetivo mapear la literatura relacionada con la salud en busca de cáncer pediátrico relacionado con el *TP53* p.Arg337His. Métodos: En este artículo se presenta un protocolo de revisión de alcance, realizado de acuerdo con la directriz Elementos de informes preferidos para revisiones sistemáticas y extensión de metanálisis para revisiones de alcance (PRISMA-ScR). Se realizaron búsquedas en seis bases de datos, un repositorio electrónico y fuentes adicionales utilizando palabras clave y palabras de texto. El equipo de revisión consta de tres evaluadores independientes. Dos evaluadores realizarán la selección inicial de títulos y resúmenes de todos los estudios recuperados mediante la estrategia de búsqueda y luego la fase de selección del texto completo. Se examinarán las listas de referencias de los estudios incluidos y el equipo de revisión extraerá los datos de forma independiente. Los resultados se analizarán cualitativa y cuantitativamente. Ética y difusión: No es necesaria la aprobación ética, ya que el estudio no involucra participantes humanos. Los hallazgos se difundirán mediante publicaciones en revistas y congresos científicos.
Palabras clave: Síndrome de Li-Fraumeni; Predisposición genética a la enfermedad; Neoplasias; Genética; Niño; Adolescente.

1. Introduction

In Southern and Southeastern Brazil the *TP53* p.Arg337His variant is a germline mutation with a high prevalence (Achatz et al. 2007; Achatz & Zambetti. 2016; Frebourg et al. 2020; Kratz et al. 2021; Pinto & Zambetti. 2020). While it has been extensively associated with adrenocortical carcinoma and choroid plexus carcinoma in pediatric patients (Custodio et al. 2011; Custódio et al. 2013; Villani et al. 2011), emerging evidence suggests a broader tumor spectrum that remains incompletely characterized (Seidinger et al. 2010; Seidinger et al. 2015; Magalhães et al. 2019; Jeffers et al. 2021; Pinto et al. 2024). It is important to delineate this group of patients because of the surveillance for early tumor detection including annual whole-body and dedicated brain magnetic resonance imaging and pelvic-abdominal ultrasounds with careful complete physical examination has been shown to reduce mortality in individuals with Li–Fraumeni syndrome (Kratz et al. 2017; Villani et al. 2023). This scoping review aims to systematically map the literature on the tumor phenotypes associated with the *TP53* p.Arg337His variant in pediatric patients, providing a structured synthesis of available evidence to refine screening and surveillance strategies. By filling gaps left by previous reviews focusing primarily on adult populations or specific tumor types, our study will contribute to a more comprehensive understanding of the oncogenic potential of this variant in childhood and adolescence.

2. Methodology

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews and JBI Evidence Synthesis was conducted and no current or ongoing systematic reviews or scoping reviews on the topic were identified. The present scoping review protocol will be carried out following the guidelines from JBI manual for evidence synthesis (Aromataris *et al*. 2024). Additionally, the reporting of the text will adhere to an actualized PRISMA-ScR Checklist (Mattos *et al*. 2023).

2.1 Research Questions

The review question formulated is: “What tumor phenotypes are associated with the *TP53* p.Arg337His mutation in pediatric patients?”. Based on it, we used the PCC framework (Population, Concept and Context) to establish points of interest within this review question and help construct the search strategy for data identification (see Table 1).

Table 1. PCC framework

Descriptors	Description
Population	Pediatric patients (0~19 years) diagnosed with cancer and carriers of the *TP53* p.Arg337His mutation.
Concept	The *TP53* p.Arg337His mutation is related to a broad tumor heterogeneity in humans, especially in pediatric patients.
Context	The mutation of Portuguese ancestral origin at founder effect in the Brazilian population, *TP53* p.Arg337His, has an incidence of 1:300 in individuals at south and southeast regions of the country.

Source: Authors (2025).

2.2 Identifying relevant studies

The databases to be searched include Google Academic, Lilacs, MEDLINE (via Pubmed), Scopus, Web of Science, and Embase. Additionally, the *TP53* database from National Cancer Institute (https://tp53.cancer.gov) will also be assessed. The *TP53* database is the primary aggregate source of *TP53* variant data in literature. A compilation of all *TP53* p.Arg337His related articles will be downloaded in Excel format from *TP53* database, followed by a blinded evaluation of the articles by two reviewers. Given the substantial amount of information available on *TP53* mutations, including *TP53* p.Arg337His, this dataset will be instrumental in reinforcing both the qualitative and quantitative aspects pertaining to the review objective.

2.3 Eligibility

This review aims to cover the pediatric patient's tumor types of the *TP53* p.Arg337His mutation, utilizing the inclusion and exclusion criteria described below.

Inclusion criteria

The inclusion criteria encompass three interest points:

- Studies that include individuals aged between 0 and 19 years, as defined by the World Health Organization's description for pediatric patients diagnosed with cancer (World Health Organization. 2021).
- Studies that used sequencing methods to detect the *TP53* p.Arg337His mutation.

Exclusion

The exclusion criteria rely on two interest points:

- Studies including individuals carrying the *TP53* p.Arg337His variant without a cancer diagnosis will be excluded unless they provide relevant comparative data on penetrance, risk assessment, or predisposing factors that contribute to phenotypic characterization.
- Individuals carrying multiple *TP53* pathogenic variants, including *TP53* p.Arg337His, will be excluded from this review to maintain a clear focus on the phenotypic landscape specifically attributable to the *TP53* p.Arg337His variant alone. Given that multiple *TP53* mutations may have compounding effects, their inclusion could confound the analysis of this specific variant's impact on pediatric cancer susceptibility.

2.4 Search Strategy and Information Sources

Search strategy

The search strategy was developed by a research librarian and aims to identify both published and unpublished studies based on the established points of the PCC framework. A preliminary search of MEDLINE was conducted to identify relevant articles on the topic (see Table 2). The text words found in the titles and abstracts of these articles, along with the index terms used to describe them, were used to develop a comprehensive search strategy. This strategy will be tailored for

each database and information source included in the review. The final preliminary electronic search strategy was peer-reviewed using the PRESS Checklist (McGowan et al. 2016).

In addition to the electronic search strategy, a hand-searching process will be conducted simultaneously using the most frequently identified terms from the electronic search results. This approach aims to capture sources that may not be consistently indexed across articles, thus avoiding potential omissions in coverage. Sources identified through hand-searching will be clearly distinguished from those identified through electronic search strategy in the presentation of data. Furthermore, the reference list of all included sources of evidence will be screened for additional studies.

Table 2. Previous Search Strategy.

Database	Search Strategy
Medline	("genes, p53"[MeSH Terms] OR "TP53"[Title/Abstract] OR "p.Arg337His"[Title/Abstract] OR "R337H"[Title/Abstract] OR "Tumor Suppressor Protein p53"[mh]) ("cancer*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract] OR "neoplasms"[MeSH Terms] OR "neoplas*"[Title/Abstract] OR "onco*"[Title/Abstract] OR "malign*"[Title/Abstract]) ("adolescent"[mesh] OR "child"[mesh] OR "infant"[mesh] OR infant disease*[tiab] OR ("childhood"[tiab] AND disease*[tiab]) OR adolescen*[tiab] OR "babies"[tiab] OR "baby"[tiab] OR "boy*"[tiab] OR "boyhood"[tiab] OR "girlfriend"[tiab] OR "girlhood"[tiab] OR child*[tiab] OR "girl*"[tiab] OR infan*[tiab] OR juvenil*[tiab] OR "kid"[tiab] OR "minors"[tiab] OR minors*[tiab] or neonat*[tiab] OR neo-nat*[tiab] OR newborn*[tiab] OR new-born*[tiab] OR paediatric*[tiab] OR peadiatric*[tiab] OR pediatric*[tiab] OR perinat*[tiab] OR preschool*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR school*[tiab] OR teen*[tiab] OR "toddler*"[tiab] OR "underage*"[tiab] OR "under-age"[tiab] OR youth*[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR infan*[tiab] OR child*[tiab] OR adolescen*[journal] OR "young"[journal])
Result	4812

Source: Authors (2025).

Source selection

The search selection team consists of three independent screeners. The initial phase encompasses the search process, wherein all identified citations will be collected and uploaded into RAYANN, followed by duplicate entries removal by one screener (CBTF) (Ouzzani et al. 2016). The intermediate phase involves the screening of titles and abstracts of the remaining sources by two screeners (ACES and GLC), based on the established keywords. Unrelated studies will be excluded.

The final phase involves a thorough full-text analysis of the selected sources, assessing them against the inclusion criteria by two screeners (ACES and GLC). Reference lists of included studies will also be screened. The full-text data retrieval of all potentially eligible articles will be independently screened. Disagreements between reviewers regarding eligibility will be resolved by a third member of the research team (CBTF). Cohen's kappa coefficient will be used to test interrater reliability (Cohen. 1960). Reasons for the exclusion of sources at any phase will be documented and reported in the scoping review. Results will be analyzed both qualitatively and quantitatively. The review will consider any study type, including those published on any date and in any language.

2.5 Data synthesis

To capture detailed information of each study, a draft chart form (see Figure 1) has been developed at the protocol stage to aid the collecting and sorting of key information from the selected articles, following the guidelines from JBI manual (Aromataris & Munn. 2020). It will be tested and refined during the full-text screening. The extracted data will encompass specific details about the participants, concept, context, study methods and key findings pertinent to the review question/s, as

number of individuals with and without the context and the geographic location of each one when provided. Additional information such as authors name, year of publication and type of study will also be retrieved. If additional categories emerge during data extraction, they will be incorporated into the extraction tool as identified.

Figure 1. Data Extraction Tool

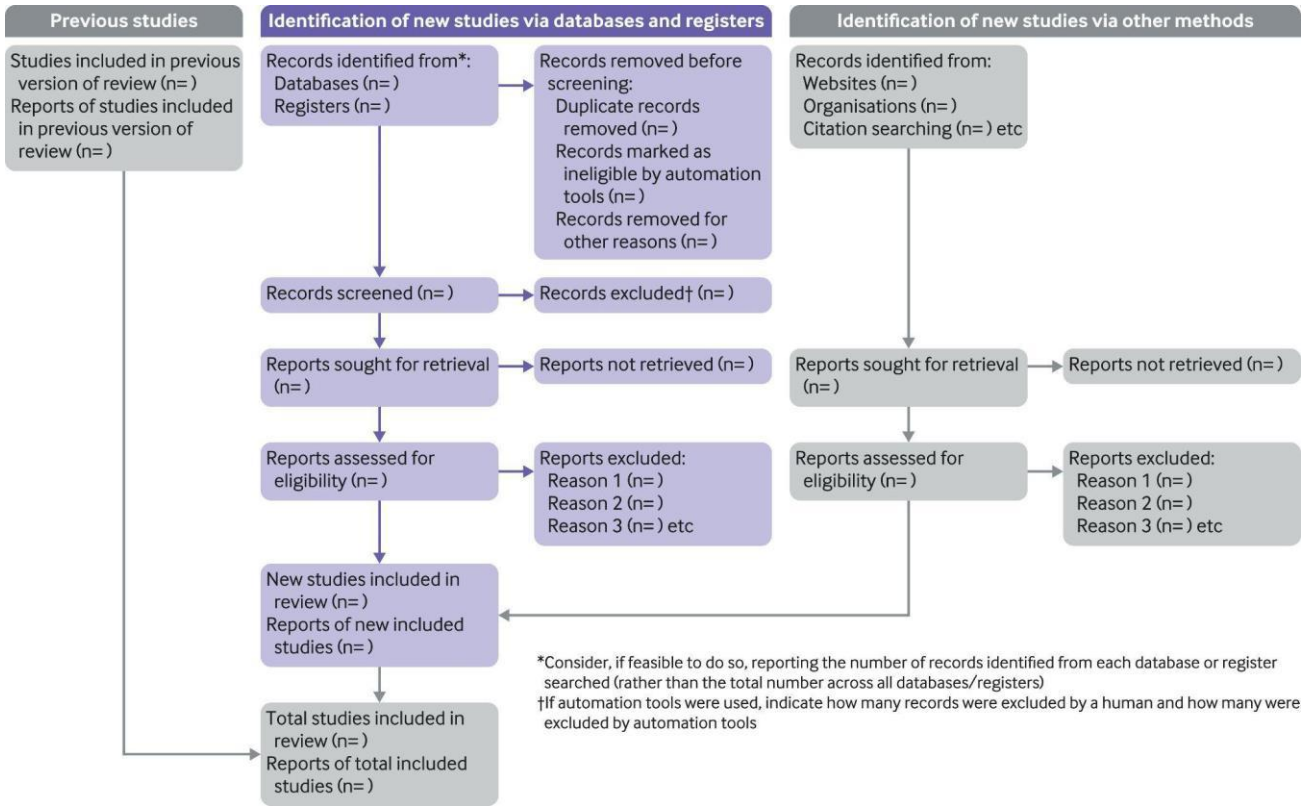
General Information	Author Completing This Form	
	Source Citation	
	Author name	
	Year of publication	
	Doi	
	Study ID (review control)	
	Type of data	
Eligibility	Study report Context, Concept and Population Criteria ?	
	Study eligible for inclusion ?	
	Reason for Exclusion	
Methodology	Aim of study	
	Study design	
	Geographic location	
	Study period	
	Inclusion criteria	
	Exclusion criteria	
	Screening Methodology to p.R337H	
Results	Number of Subjects Negative to p.R337H	
	Number of Subjects Positive to p.R337H	
	Tumor Phenotypes in Subjects Positive to p.R337H	

Source: Authors (2025).

2.6 Collating, summarizing and reporting the results

The process of study inclusion and exclusion will be fully reported in the final scoping review and presented in a PRISMA flow diagram (see Figure 2). In order to create a useful summary of data, tabulated results with descriptive information about the studies assessed such as year of publication, authors name, type of study, and geographic region of patients, will be provided. Qualitative analysis as the word cloud method, conducted on IRaMuTeQ software, will present the words following their respective frequencies of occurrence (Souza et al. 2018). Furthermore, the tables and the diagram will be accompanied by narrative text that describes the results and their alignment with the research objective.

Figure 2. Prisma flow diagram.



Source. Page et al (2021).

All data extracted from included studies will be made available in a publicly accessible repository (e.g., Open Science Framework from COS (COS) or Zenodo) upon publication of the scoping review (Foster & Deardorff. 2017). Data will include extracted tumor types, patient demographics, and relevant methodological details from each study.

3. Perspectives and Dissemination

The following scoping review protocol is intended to clarify cancer phenotypes related to *TP53* p.Arg337His. The findings will enhance patient care by elucidating the phenotypic manifestations associated with specific mutation, thereby facilitating the determination of optimal follow-up strategies. The results may be disseminated through professional networks, conference presentations, and publications, with the potential to influence clinical practice.

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