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Genetic alterations landscape in paediatric thyroid tumours and/or differentiated thyroid cancer: Systematic review

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Abstract

Differentiated thyroid cancer (DTC) is a rare disease in the paediatric population (≤ 18 years old. at diagnosis). Increasing incidence is reflected by increases in incidence for papillary thyroid carcinoma (PTC) subtypes. Compared to those of adults, despite aggressive presentation, paediatric DTC has an excellent prognosis. As for adult DTC, European and American guidelines recommend individualised management, based on the differences in clinical presentation and genetic findings. Therefore, we conducted a systematic review to identify the epidemiological landscape of all genetic alterations so far investigated in paediatric populations at diagnosis affected by thyroid tumours and/or DTC that have improved and/or informed preventive and/or curative diagnostic and prognostic clinical conduct globally. Fusions involving the gene *RET* followed by *NTRK, ALK* and *BRAF,* were the most prevalent rearrangements found in paediatric PTC. *BRAF* V600E was found at lower prevalence in paediatric (especially ≤ 10 years old) than in adults PTC. We identified *TERT* and *RAS* mutations at very low prevalence in most countries. *DICER1* SNVs, while found at higher prevalence in few countries, they were found in both benign and DTC. Although the precise role of *DICER1* is not fully understood, it has been hypothesised that additional genetic alterations, similar to that observed for *RAS* gene, might be required for the malignant transformation of these nodules. Regarding aggressiveness, fusion oncogenes may have a higher growth impact compared with *BRAF* V600E. We reported the shortcomings of the systematized research and outlined three key recommendations for global authors to improve and inform precision health approaches, glocally.

Keywords Paediatric differentiated thyroid tumour · Genetic landscape · Actionable mutations · Precision medicine

1 Introduction

Differentiated thyroid cancer (DTC) is a rare disease in the paediatric population (≤ 18 years old. at diagnosis). Its incidence rate increased 1.1 per year from 1973 to 2006 and markedly increased from 2006 to 2013, especially in females and patients aged > 10 years. The increase in incidence rates was reflected by increases in incidence for papillary thyroid carcinoma (PTC) subtypes, being the classic PTC the most prevalent (58,6%), followed by the follicular subtype of PTC (18.9%) [1].

Compared to those of adults, paediatric DTC usually presents with more aggressive local disease and higher frequency of lymph nodes (50–75%) and distant metastasis (5–16%), being the lungs the most common site [2, 3]. It has been suggested that extra-thyroidal extension, younger age, and larger tumours (> 2 cm) are prognostic factors associated with worse prognosis [4, 5].

Despite this aggressive presentation, paediatric DTC has an excellent prognosis. Therefore, early identification of children who are at high risk of persistent or metastatic disease, and those children that may not need radioactive iodine (RAI) therapy, is a fundamental step in the therapeutic strategy. Remarkably, younger age at diagnosis (< 10 years of age) was found as an important risk factor for

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disease recurrence (i.e., increased rate and faster time) [6, 7]. Age (< 10 years at diagnosis), American Thyroid Association (ATA) high-risk level and poor response to therapy were found as significant negative prognostic factors for event-free survival [8].

As for adult DTC, integration of variables (i.e., prognostic markers) may offer additional help to estimate the risk of recurrence or persistent disease and, therefore, individualised management.

Recent European Thyroid Association (ETA) recommendations [4] and the first ATA guideline [9] endorsed that special recommendations, based on the differences in clinical presentation and genetic findings, are necessary for DTC management in this age group. However, the current evidence is insufficient to conclude that molecular testing of thyroid nodule or paediatric thyroid carcinoma tissue will help diagnosis or alter clinical management. Therefore, prospective studies are needed.

Although evidence suggests that *BRAF* V600E variant in a fine-needle biopsy may help PTC diagnosis and could be considered, *BRAF* V600E prevalence is considerably lower in children (mainly < 10 years of age) and was not found in some populations. In fact, the younger the age, the more important the role of fusions in the development of thyroid cancer in the paediatric age-tiers [10–19].

Due to the uncommonness of paediatric thyroid cancer and the observed difference in tumour biology and clinicopathological presentation, we believe that global evidence identification and synthesis would certainly help to outline the genetic differences among individuals from different populations, as well as validate the use of the variable (i.e., genetic findings) for prognostication and treatment decisions in paediatric age-tiers.

Therefore, we conducted a systematic review of available evidence published in peer-reviewed scientific journals to identify the epidemiological landscape of all genetic alterations so far investigated in paediatric populations (i.e. individuals ≤ 18 years of age) at diagnosis affected by thyroid tumours and/or DTC that have improved and/or informed preventive and/or curative diagnostic and prognostic clinical conduct (i.e. to guide the use of druggable targets, surgical therapeutic interventions and/or biochemical, imaging and further genetic alterations follow-up), globally. We have also investigated the epidemiological landscape of actionable targets from such genetic alterations identified, as well as key evidence gaps whose research and development must continue to produce new actionable information (as technology) and further enable adequate context-specific precision health approaches at the glocal level [20, 21] – i.e. developing strategies that are contextually relevant for local implementation but whose implementation could also be adapted at other global locations, given adequate health technology assessment [22].

2 Methodology

This systematic review was designed following a predefined protocol, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [23], which is registered in the PROSPERO database under the identification number: PROSPERO 2023 CRD42023446483 (PRISMA Checklist is available at the Supplementary File).

2.1 Eligibility criteria

This systematic review included systematic, non-systematic and rapid reviews, as well as peer-reviewed original articles, which discuss, comment and critically analyse how epidemiological data on molecular genetic alterations profiling of paediatric populations has been enabling precision health approaches, per country, to improve and/or inform diagnosis or prognosis of individuals affected by thyroid tumours and/or DTC. Therefore, we included (series of) case studies and cohort studies exemplifying mere molecular genetic alterations profiling in paediatric populations affected by thyroid tumours and/or DTC that did (or not) outline actionable targets and/or evidence gaps for improving and/or informing clinical for the purposes of precision health approaches. As such, specific familial predisposing genetic alterations, such as in the *RET* oncogene for Multiple Endocrine Neoplasia Type 2 (MEN2) was regarded as irrelevant and was discarded. Meanwhile, we incorporated qualitative evidence alongside a review of quantitative data when we found relevant evidence describing genotype–phenotype correlations that portrayed the diagnostic and/or prognostic roles of such molecular genetic alterations profiles per country, region or sub-region (or state).

Exclusion criteria comprised publications regarding only adult populations (older than 18 years old) and familial differentiated and medullary thyroid cancers or anaplastic and poorly differentiated tumour types. We will also did not include publications describing epigenetic events (such as microRNA, LncRNA and methylation) or conference proceedings (as they comprise only abstract with no full-text available for analysis). Full-text eligibility exclusion criteria comprised publications that described only adult populations (older than 18 years old) and/or those describing both paediatric and young adult populations (older than 18 or 21 years of age), unless individual patient data for the paediatric population could be separately extracted. Finally, we also did not include publications that did not describe the mutational profile and/or location (country and/or (sub) region/state) and/or method for genetic alteration profiling and/or tumour type and status data.

2.2 Study outcomes

The main outcome of this study was the investigation of the epidemiological genetic alterations profile landscape of known and new diagnostic and prognostic targets amongst children and adolescents affected by thyroid tumours and/or DTC per country (and sub-region or state, where applicable – namely, Brazil, China and USA) and region (i.e., Asia, Europe, Middle-East, North America, South America and those induced by radiation due to nuclear environmental exposure – namely, Hiroshima/Nagasaki in 1945, Chernobyl in 1986 and Fukushima in 2011). More specifically, the primary outcomes combined differences in the prevalence of the following tumour variables: age at diagnosis (i.e., $0 \leq 10$ years of age or children, and $> 10 \leq 18$ years of age or adolescents), histological types (i.e., follicular thyroid adenoma [FTA] or carcinoma [FTC], papillary thyroid carcinoma [PTC], oncocytic thyroid adenoma [OTA] and carcinoma [OTC]), molecular biology and genomics methodological approaches for genetic alterations identification, number of patients, study design and aetiology (i.e., whether tumourigenesis and/or metastatic progression were sporadic, radiation-induced by the abovementioned environmental nuclear events, or therapy).

The secondary outcomes were related to each of the genetic alterations' diagnostic and prognostic role in terms of adequately informing differential clinical conduct amongst paediatric age-tiers and histological types, as well as their clinicopathological characteristics, therapeutics and relationship with survival outcome per country, region or sub-region (or state), namely: previous and/or other coexisting diseases, therapeutic (i.e., different types of surgery, radiotherapy, targeted-therapies and/or other) approaches, tumour size, lymph node metastasis (TNM-staging), follow-up period, distant metastasis, Initial Dynamic Risk Stratification (IDRS, to evaluate treatment response), final disease outcome (i.e., no evidence of disease (NED), progressing or death), actionable targets, evidence gaps, and findings, including barriers and facilitators, on how (actionable) diagnostic and/or prognostic molecular biomarkers are being implemented for specific populations within given locations (i.e., one or more institution(s), city(ies), sub-region(s)/state(s), country(ies), region(s)). Data on study limitations and funding support were also collected for study bias and conflict of interest evaluations.

2.3 Information sources

Relevant publications over the past thirty years (since 1995), describing and evaluating the diagnostic and/or prognostic role(s) of known and new (actionable) genetic alterations prevalence, and evidence gaps, in paediatric populations affected by thyroid tumours and/or DTC per country, were identified by searching the following electronic bibliographic databases: PubMed, EMBASE, The Cochrane Library, BVS, Google Scholar, and Web of Science. Searches were performed in English on 17 July 2023, using a combination of relevant terms such as 'paediatric thyroid tumours', 'paediatric differentiated thyroid cancer', 'molecular landscape' or 'genetic landscape' or 'mutational analysis' or 'genetic alterations identification', and they were adapted according to the bibliographic databases. There were no time or language restrictions. We did not include grey literature publications due to time constraints, as we were only able to search on Brazilian grey literature databases and it was not representative of all countries/regions whose peer-reviewed publications were included. However, we thoroughly examined bibliographies to manually include relevant studies meeting the eligibility criteria that were identified as primary studies on (non-) systematic literature reviews and original (primary) studies. We did not re-run searches on all databases just before the final analyses (only PubMed), because we finalised these on 28 August 2023. Therefore, there we no further studies to be retrieved for inclusion after such a short period (approximately 40 days).

2.4 Screening, data collection and analysis

Four reviewers independently screened titles and abstracts of publications as duos (JMC and YPC; INN and LS). Disagreements regarding eligibility of (full-text) studies were resolved by discussion and consensus (INN and LS duo) and/or by a fifth reviewer (MSAS for: JMC and YPC duo's title/abstract eligibility; both duos' full-text eligibility). Rayyan was used for study selection and conflicts' resolution.

Data was extracted by all five reviewers with all revising data extracted from documents, including information about location, study design, participants demographics and baseline characteristics, as well as numbers of events or measures of effect (primary and secondary outcomes), as previously detailed. Missing data was not included as study investigators were not contacted for unreported data or additional details. All extracted data was recorded on excel spreadsheets by all five reviewers that also synthesised findings. Full-text eligibility and data extraction occurred simultaneously due to time constraints for submission of systematic review manuscript for publication. Any disagreements were resolved by all five reviewers' consensus and/or JMC and/or MSAS.

2.5 Quality assessment of included studies

Quality assessment of the included original (primary) studies was conducted by four reviewers (MSAS, INN, YPC and JMC) using specific Critical Appraisal Checklist JBI Tools, developed by the Joanna Briggs Institute, Faculty of Health and Medical Sciences at the University of Adelaide, according to each study design. Each tool consists of six (Text or Opinion [24]), eight

(Case Reports [25]), ten (Case Series [26]), eleven (Cohort Studies [25]) or thirteen (Randomised Controlled Trials [27]) different questions that assess the methodological quality of each study, determining the extent to which the possibility of bias has been addressed in the study design, conduction and analysis. Each question was assessed by the four reviewers as 'Yes', 'No', or 'Unclear' and overall score comprised the percentual of 'Yes' answers.

The methodological quality of secondary studies (systematic reviews and meta-analysis) was assessed by MSAS using AMSTAR 2 [28] to assign 'Yes', 'No' or 'Partial Yes' on ten questions, and further six questions specific to meta-analysis. Similarly, the overall score comprised the percentual of 'Yes' answers. Each study was rated by the four reviewers as: 'red' or 'low-level of confidence (overall score 0–25% 'Yes' answers); 'yellow' or 'moderate-level of confidence' (overall score 26–50% 'Yes' answers); 'green' or 'high-level of confidence' (overall score 51–75% 'Yes' answers); 'blue' or 'excellent-level of confidence' (overall score 76–100% 'Yes' answers). A sample of each type of study was assessed by at least two reviewers (MSAS and any other reviewer). The rest were assessed by one of the four reviewers. Discrepancies were resolved by discussion amongst all four reviewers. The four reviewers consensually decided to use JBI Text and Opinion Tool [24] to conduct critical assessment of Non-systematic Literature Reviews included, and further discount 25% in the overall score for neither conducting a systematic, rapid nor scoping review, nor a qualitative evidence synthesis, case series, cohort nor a randomised controlled study. However, when non-systematic literature reviews also presented case reports or series, the four reviewers decided to use JBI Case Reports [25] and Case Series [26] Tools for critical assessment, respectively.

2.6 Data synthesis

Quantitative outcomes regarding genetic alterations landscape was collated by region, country (sub-region or state for Brazil, China and USA) and age-tier, according to histological type and specific genetic alteration, as well as method for identification and/or (clinical and/or analytical) validation (as summarised in Supplementary Table 1). We calculated prevalence of specific genetic alterations by adding sub-region/state, then country and regional percentual of investigated positive and negative findings reported by each included study's population sample. Since this is a meta-aggregative systematic review [29], and we did not necessarily find evidence on all quantitative and qualitative secondary outcomes, as previously described, these were textually discussed, when relevant, according to regional and country (and sub-region or state for Brazil, China and USA) epidemiological genetic alterations' profiles.

3 Findings

3.1 Study selection and characteristics

The search strategies for all aforementioned electronic bibliographic database retrieved 3,511 results. After excluding 959 duplicates, 2,552 studies were formally screened against eligibility criteria. Among those, we included 543 studies for full-text screening against eligibility criteria. From these, we included 160 studies, which includes 5 by manual selection through reference lists regarding primary studies' data that fell under the eligibility criteria. We included 17 Case Reports [30–46], 67 Case Series [47–113], 56 Cohort Studies [11, 13, 14, 114–166], 1 Randomised Controlled Trial [167], 17 Non-Systematic Reviews [10, 12, 15–19, 168–177] and 2 Systematic Reviews and Meta-analysis [178, 179]. The selection flowchart of the research, outlining reasons for exclusion, is presented in Fig. 1.

3.2 Genetic alterations landscape global findings for sporadic, radiation-induced by nuclear environmental events and/or therapy-exposed paediatric thyroid tumours and DTC

The first question of our systematic review regarded the epidemiological landscape of genetic alterations in paediatric thyroid tumours and/or DTC that are sporadic, radiation-induced by nuclear environmental events and/or therapy-exposed. Therefore, we have summarised all epidemiological genetic alterations (mutations and fusions) identified and/or (clinically and/or analytically) validated per region and country (and sub-region or state for Brazil, China and USA) in Supplementary Table 1. These studies' findings have several implications. First, in those state/countries that have implemented comprehensive testing methods to identify genetic alterations, they were able to uncover the unique alterations of paediatric thyroid nodules and DTC, including less prevalent novel gene fusions and SNVs, such as *DICER1* and other new players. Remarkably, in most studies, neoplasms (i.e., benign, and malignant neoplasms) harbouring *DICER1* mutations SNVs were most of follicular subtype of PTCs, FTCs and FTA. None had extrathyroidal extension, lymph node or distant metastasis. Although the precise role of *DICER1* is not fully understood, it has been hypothesised that additional genetic alterations, similar to that observed for *RAS* gene, might be required for the malignant transformation of these nodules. A common finding across the countries was that in paediatric DTC, fusion alterations, most commonly involving *RET* and *NTRK*, have the highest association with invasive disease, lymph node involvement and distant metastases (mainly to the lung) while BRAF V600E is uncommon in PTC patients with less than 10 years of age, which present a more aggressive phenotype than those children with > 10–18 years of age.

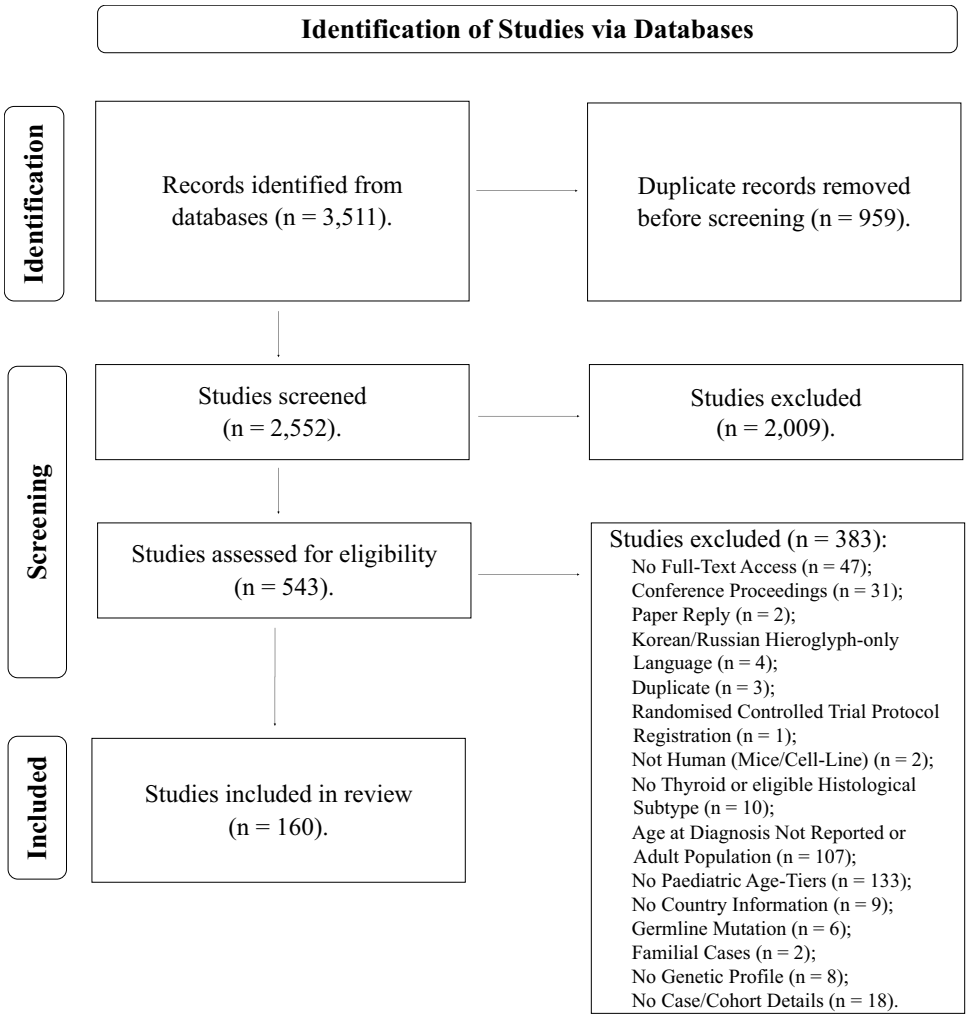

Fig. 1 Systematic review flow chart of records identification and study screening

Those studies that assessed mainly for genetic alterations identified in adults, performed in most countries, although showed a more limited genetic landscape, support a significantly lower rate of the *BRAF* V600E mutation in PTC in paediatric patients than in adults and that *RAS* and *TERT* mutations do not contribute significantly to PTC tumourigenesis. Although it has generated a *BRAF* and *RAS*-score (BRS) for paediatric thyroid carcinoma [121], the authors also agree that it will be essential to generate the transcriptional signatures of the most prevalent fusions found such as *RET, NTRK* and *BRAF* (mainly in Brazil).

This global epidemiological landscape can enable us to better understand the populations' geographical and age variations for detection of actionable targets such as tyrosine-kinase inhibitors (TKIs such as *NTRK, RET, ALK* and *BRAF)* that could benefit from targeted therapy for those patients presenting progressive disease. It is important to be able to indicate selective TKIs for these patients, although this is a completely infrequent situation in paediatric thyroid cancer, and we could hypothesise on the usefulness of such an approach when these patients reach adult age and have RAI therapy refractory progressive thyroid cancer.

As such, we have also visually summarised the genetic alterations profiles' landscape in the Fig. 2 world map.

3.3 Actionable genetic alterations landscape for sporadic, radiation-induced by nuclear environmental events and/or therapy-exposed paediatric thyroid tumours and DTC

The second question of our systematic review regarded the epidemiological landscape of actionable genetic alterations in paediatric thyroid tumours and/or DTC that are sporadic, radiation-induced by nuclear environmental events and/or radiation therapy-exposed. We present findings per region and country (and sub-region or state for Brazil, China and USA). Our goal was to identify all such genetic alterations that have improved and/or informed preventive and/or curative diagnostic and prognostic clinical conduct (i.e. to guide the use of druggable targets, surgical therapeutic interventions and/or biochemical, imaging and further genetic alterations follow-up), globally (Supplementary Findings).

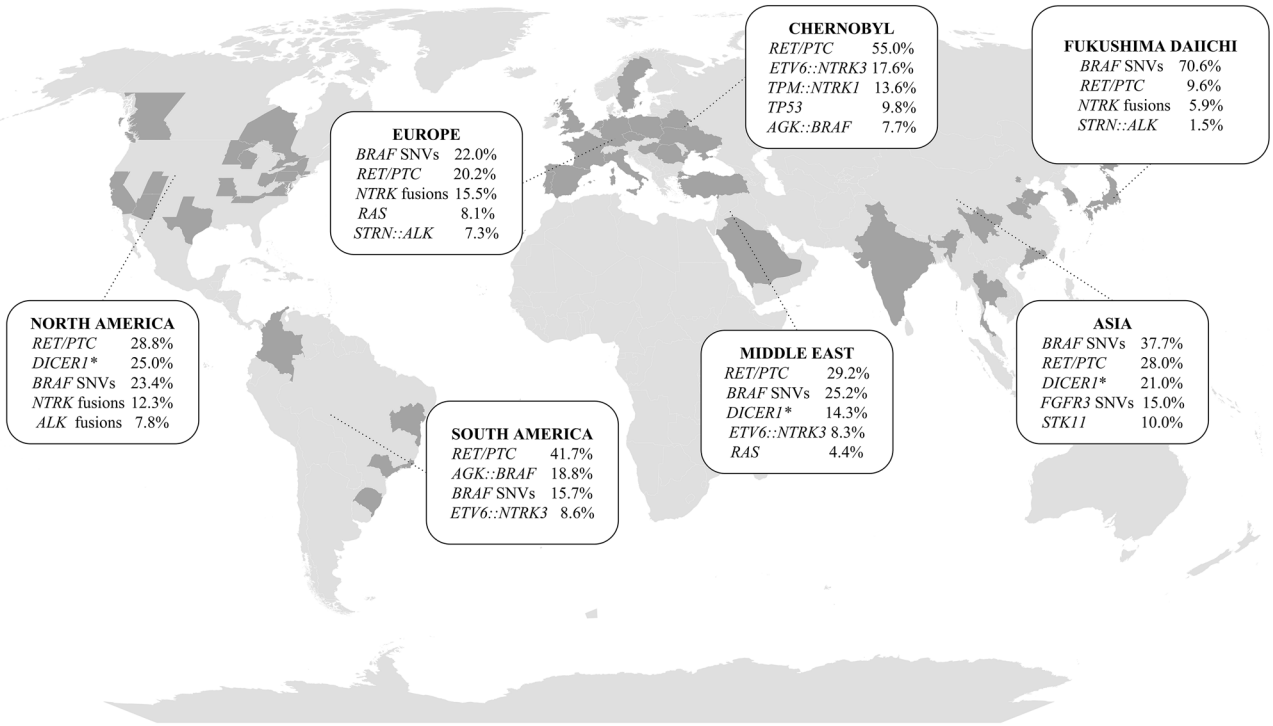

Fig. 2 The global epidemiological landscape of genetic alterations in sporadic, radiation-induced by environmental nuclear events and/or therapy-exposed paediatric thyroid tumours and/or DTC is shown. SNVs, Single Nucleotide Variants. *SNVs found in benign and malignant thyroid neoplasia

3.4 Evidence gaps in (actionable) genetic alterations for sporadic, radiation-induced by nuclear environmental events and/or therapy-exposed paediatric thyroid tumours and DTC

The third question of our systematic review regarded any key evidence gaps in the epidemiological landscape of (actionable) genetic alterations in paediatric thyroid tumours and/or differentiated thyroid cancer. Here, we present findings per region and country (and sub-region or state for Brazil, China and USA). Our overall goal with these three questions was to identify unresolved issues in paediatric thyroid tumours and DTC management that could be tackled by the establishment of new (actionable) information (as technology) research, development and implementation that can enable adequate context-specific precision health approaches, glocally [20, 21].

3.5 Asia

Across all Chinese sub-regions, evidence gaps we identified referred to larger amount of research, development and implementation (for both clinical and analytical validity evaluation) work to define clinical utility, elucidate biological mechanisms, and explore the potential of *TERT* promoter mutations as therapeutic targets in thyroid cancer [127], as well as of *BRAF* V600E mutation's role in risk stratification and management of children and adolescent PTC, for the purposes of updating current ETA and ATA guidelines [17, 178, 179]. There is no such evidence for fusion oncogenes in PTCs such as *RET/PTC*, especially regarding therapy-induced tumourigenesis. Nevertheless, *RET/PTC* was reported to be present in benign adenomas and also in Hashimoto thyroiditis tissues [15]. Bridging the gap between evidence generation and its implementation remains key, since preliminary reports of targeted therapy in paediatric patients with DTC with progressive disease have shown encouraging results, as well as the possible association of hyperthyroidism and PTC in resistance to thyroid hormone. Therefore, adequately-designed clinical trials must be conducted [19], also to explore the long-term effects of medication [44].

In terms of evidence gaps identified in India, we observed that whole-exome-sequencing or other more advanced molecular biology and genomics methodological approaches could be explored to unravel further genetic biomarkers for aggressiveness in paediatric PTC [119]. As for adults, *BRAF* V600E mutations has been associated with RAI-therapy refractoriness in childhood DTCs. However, data concerning its association with other aggressive features in paediatric cases are quite heterogeneous, and further studies are needed [179].

The evidence gaps we identified across the Republic of Korea referred to the aetiology of age-associated genetic alterations that remains unexplained, although chromosomal rearrangements have a strong association with exposure to ionizing radiation, as thyroid cells of young children may be more susceptible to its effects and/or lose key factors in the DNA repair machinery, leading to uncoupled double-stranded breaks and translocation with partner genes. Children with oncogenic fusion PTCs presented with more advanced-stage disease (especially, lung metastasis and a higher risk for recurrence or persistence) than did those with *BRAF* V600E PTC [135, 136]. Furthermore, *DICER1* SNVs have been identified in benign and malignant thyroid neoplasms. However, the pathogenesis associated with progression of a normal thyroid to benign neoplasms and then to malignant transformation, has not yet been fully established. Therefore, further studies are needed to better understand this distinct pathogenesis [67]. As for *DICER1*, *STK11* has also been identified as a coexisting well-known driver mutation hot-spot, whose role in tumorigenesis needs to be better investigated [117].

Regarding study limitations, in China, we observed that qualitative and quantitative analyses of genotype–phenotype association of these genetic alterations with the various clinicopathological characteristics described have not yet been done. Furthermore, a retrospective design to the included studies may signify insufficient number of cases and/or incomplete data for cases, as well as short follow-up period. This may be due to the rarity of thyroid cancer in the paediatric population. Nevertheless, large-sample, multicentre prospective studies are also needed to investigate any potential differences between children and adolescents with PTC across China and or Asia, regionally [134, 159]. Whereas in India, Chakraborty et al. [119] outlined that longer duration prospective studies must be conducted to evaluate progression-free or overall survival in *BRAF* V600E mutations, as well as other genetic alterations often found in paediatric DTCs, such as *RET/PTC* rearrangement in radiation-induced DTCs and *PAX8/PPARγ* fusion, as previous studies have shown high rates of such translocations in India. In the Republic of Korea, we observed that the small number of cases and the possible selection bias of some studies [34, 117, 135] make definitive conclusions difficult to draw. Most prominently, the lack of individual data available on genetic alterations and clinicopathological correlations remained as a limitation across several regional studies, preventing comparisons between different paediatric age-tiers as well as with other young adult and adult age groups. We would like to outline the gold-standard for individual patient data reporting as implemented by Lee et al. (2021).

Finally, we found little information regarding funding support to investigate potential conflicts of interests across all Chinese sub-regions. However, we observed that most studies that reported funding support were either based in Beijing [127, 128], Hiroshima, Nagasaki or Fukushima [15], mainly funded by the public rather than the private sector [159]. In India, Chakraborty et al. [119] received public sector funding. We identified that most studies received financial support by several Korean Ministries, therefore, the public sector [34, 67, 117, 136].

3.6 Europe

The evidence gaps we identified across all European countries referred to the need for further studies, particularly in regions where paediatric populations are poorly studied or without described tumour molecular profile. Few studies (i.e., first studies) did not report the *RET* fusion partners and, therefore, to calculate the real prevalence of the individual *RET* fusions was not achievable. Furthermore, follicular thyroid tumours are still very under-studied [97, 141]. Investigating novel gene fusions and assessing alterations already described in small subsets may help the better understanding of tumour's molecular landscape, enabling robust correlations and clinical applications [11, 32, 71, 137, 141]. Lastly, studies exploring the distribution of genetic alterations across distinct foci of primary tumour and metastasis are necessary to uncover its application in target therapies for metastatic tumours [55].

Within the Czech Republic, evidence gaps revolved around the need to underscore: the mechanism of *RET/PTC1*ex9 formation [32] and other fusion genes by RNA in paediatric populations to assess any potential correlations between certain fusion genes and clinical-pathological features, and compared those with adult population, especially in PTC [11, 146]; the clinical impact and prognostic importance of *RAS* mutations in FTA, as well as the role of pathogenic variants found in *PTEN* or *PIK3CA* genes, which have been found in paediatric PTCs [146]. In France, we identified the need for new studies investigating a potential post-Chernobyl molecular signature in thyroid tumours comparison purposes with sporadic tumours samples analysed [79]. Evidence gaps in Germany related to: the role of Gsα mutation in paediatric populations [45]; and carefully designed studies to identify potential correlation between *RET/PTC* rearrangements and clinical behaviour or nodal metastasis [95]. In the Netherlands, studies outlined the need for more in depth investigation on kinase inhibitors and their so far limited efficacy leading to resistance and severe side effects [99]. In Poland, evidence gaps related to: further investigation on the influence of the novel mutation at codon 31 of *KRAS* oncogene on the development of PTC [59]; larger samples analyses as the TCGA study [84]. Evidence gaps that we identified in Portugal related to the putative role of *EWSR1::FLI1* gene rearrangement in the neoplastic development of PTC,

which outlined the small series of positive cases as a study limitation that should be tackled [77, 122]. In Sweden, we identified the need to identify additional gene fusions in FTC additionally to the well-described *PAX8/PPARγ* fusion gene and other less common fusion events such as *THADA* [141]. In the United Kingdom, we also identified the need for larger sample size studies to adequately identify each of the known *RET* translocations [102].

Regarding study limitations, in the Czech Republic, we observed the limited number of paediatric samples [146] and that no functional analysis of novel fusion genes have been performed [11]. In Germany, one study outlined several confounding variables when analysing PTC histology, irrespective of Belarusian patients' age [148]. Italian authors outlined that: resolution power of early CGH investigations was extremely limited and should be tackled [144]; case series bias lies in the limited number of paediatric cases and the controversial 'wait and see' approach used in Italian Classification Thyroid system [92]; the nCounter analysis displayed an important technical limitation for *NTRK3* fusion detection and that the lack of clinical follow-up data is a serious limitation to also investigate the real impact of different molecular and pathological PTC characteristics in the prognostic risk stratification of patients [137]. Dutch studies mainly discussed small sample sizes of studies comparing different histological subtypes and their association with the outcome of different molecular backgrounds stratified by the histological subtype [99]. Whereas Polish studies outlined that biased and small [60] samples have prevented de facto genotype–phenotype association studies not only for *BRAF* and *TERT*p mutations [156] but also *RAS*, *PAX8/PPARγ*, *RET/PTC1*, and *RET/PTC3* rearrangements [84]. One Swedish study also outlined the small sample size [41].

Finally, regarding information on funding support to investigate potential conflicts of interests, we observed that all studies were funded by the public sector in the Czech Republic [11, 32, 146], Germany [148], Italy [69, 92, 137], the Netherlands [99, 145], Poland [59, 60, 84, 97, 156], Portugal [77], Sweden [41, 104, 141], and the UK [102]. Whereas certain studies also received funding from the private sector in France [79], Italy [126], and Portugal [121].

3.7 Middle East

The current knowledge about sporadic paediatric PTCs at the molecular level is limited due to the scarcity of relatively small cohorts focusing on these aspects. The status of fusion oncogenes and their correlation with disease-free survival (DFS) is not addressed in paediatric PTCs. Therefore, regarding evidence gaps, we identified the need for larger and more comprehensive studies to better understand the genetic characteristics and genotype–phenotype correlations of paediatric PTCs, shedding light on their genomic landscape [78]. Additionally, the prognostic significance of the *BRAF* V600E mutation remains unclear in paediatric patients with thyroid cancer [149]. This highlights the need for further research to determine the impact of this mutation on the prognosis and clinical outcomes of paediatric thyroid cancer cases.

In Saudi Arabia, we identified a need for prospective larger samples studies [17] deploying additional identification methods to fixed panels that exclude other important genes, such as *PAX8/PPARγ*, *THADA* fusion genes, and *EIF1AX* mutations [116]. Moreover, different demographic and racial characteristics, distinct of methods of diagnosis and molecular analysis, resulting in high heterogeneity of the sample [115] and cross-sectional and retrospective previous studies [178] may have compromised the ability to demonstrate causality. Studies evaluating only point mutations in 'target genes/exons' that are not frequently mutated in paediatric thyroid cancer do not allow for clinical-pathological associations [48]. Although certain non-systematic literature reviews have been thoroughly developed, some are lacking a few references and did not outline clear pharmaceutical actionable genetic targets, even though they synthesised large amounts of genetic alterations prevalence per country [10].

In Turkey, retrospective studies with relatively small sample sizes have prevented the correlation between *BRAF* V600E mutation and recurrence or response to treatment [130].

Finally, we found no information regarding funding support to investigate potential conflicts of interests across all Middle East countries analysed.

3.8 North America

The evidence gaps that we identified in Canada revolved around the need for more research on children with *CCDC6::RET*-driven tumours being younger than those with *BRAF* V600E-driven tumours (mean age 10.1 vs. 14.5 years) to verify the hypothesis of whether tumours arising in young (pre-/peri-pubertal) children constitute a biologically and genomically unique category [96]. Regarding information on funding support to investigate potential conflicts of interests, we observed that most studies were financed by the public and third sector [40, 96] as well as the private sector [40].

Nearly 30 studies were published across 14 states in the USA, predominantly in Philadelphia. Evidence gaps that were acknowledged across all US states referred to the need for further studies using comprehensive molecular testing byNext Generation Sequencing (NGS) in all patients with unresectable or progressive and/or symptomatic distal disease that is unresponsive to standard therapy of surgery and radioactive iodine, especially including targetable oncogenic drivers including: *NTRK1-3*, *RET* and *ALK* gene fusions, *BRAF* mutations, and *MET* overexpression/fusion [88].

In Maryland, we identified the need for prospective studies with larger samples from more than one institution to allow meaningful statistical analysis after focused NGS targeting known genomic alterations in thyroid cancers broadly [90]. In the Tennessee, authors outlined the need to underscore the precise role of *DICER1* in thyroid oncogenesis, suggesting a potential additional hits hypothesis required for nodule transformation [61]. In Wisconsin, we identified the need for further research on the genetics of paediatric PTC as a way of better stratifying patients and identifying subgroups that could safely be treated with subtotal thyroidectomy [129]. In New York, evidence gap evolved around the need for larger sample sizes to compile a variety of tumour types to identify oncogenic fusions, especially *NTRK* fusions [143], whereas, in Washington-DC, the target was *RAS* mutations involved in the extrathyroidal spread of PTC [124], while in Connecticut, authors discussed whether their small samples studies would influence the prevalence of *NTRK1/NTRK3* fusions in PTCs [88].

In Pennsylvania, studies investigating *BRA*F positive tumours, with decreased expression of the *NIS* and nodal and/or distant metastases, also outlined the need for further research into *RAS* and *PAX8/PPARγ* mutations' potential association with less aggressive disease, as patients would be able to undergo less aggressive adjunctive treatments [53]. Also, we identified the need for further investigations deploying NGS as a cost-effective approach with high throughput and parallel sequencing to analyse larger numbers of genetic variations in small volume samples in studies aiming to underscore evidence that paediatric thyroid cancer is likely biologically different than adult thyroid cancer. Still in Pennsylvania, we identified the need for larger sample studies to further determine whether *DICER1* mutations are somatic or germline [153], as well as for clearly underscoring the pathological pathways through which *ETV6::NTRK3*, *TPR::NTRK1*, *RET/PTC and PAX8/PPARγ* gene fusions may increase the susceptibility to chromosomal fragility in paediatric radiation therapy-induced PTC [147]. Finally, tumours with no identified genetic alteration in the miRInform thyroid test should use a more comprehensive panel [125].

In Texas, we identified evidence gaps relating to the need for prospective and larger studies evaluating the benefits of molecular testing in paediatric thyroid lesions bearing *TERT* promoter rearrangements to verify if they play a role in paediatric thyroid carcinomas. Furthermore, it may be important to verify whether age (> 11–18 years of age) may play a role in the frequency discrepancies of *RAS* mutations in paediatric thyroid cancers, or if this finding is simply incidental [118].

Regarding study limitations, we identified sampling bias in retrospective studies around Tennessee – especially for patients of racial or ethnic minority groups, as well as investigations at high-volume centres with established thyroid expertise, both of which may produce results that cannot be generalisable to different settings and/or underserved communities. Furthermore, although comprehensive testing methods to detect unique genetic alterations in paediatric thyroid tumours have been implemented, certain targets may be refined to underscore key genomic and clinicopathologic findings to help with targeted therapy in the case of progression following treatment with radioactive iodine or in the neoadjuvant setting. It may also help prevent diagnostic surgeries in paediatric populations with more aggressive disease and expand the understanding of the genetic mechanisms of thyroid tumours in children [61].

In Wisconsin, we identified potential bias in COLD-PCR methodology used in DNA samples extracted from paraffin-embedded tissue from a retrospective review with a small sample size, as well as rarity of patient follow-up data, which makes association with recurrence unclear [129].

Finally, in Missouri, we outline that, beyond limitations related to retrospective analyses, *BRAF* mutation analysis in PTC through PCR–RFLP, which can generate both false positive and false negative results, should be avoided. Also, investigators should also test for other common mutations, such as the *RET/PTC* rearrangement that often occurs in paediatric PTC and can enrich diagnosis and prognosis informing tumour management [50].

Regarding information on funding support to investigate potential conflicts of interests, we observed that most US-based studies received support by both the public and private sectors [13, 18, 61, 75, 88, 90, 124, 125, 125, 129, 142, 147, 147, 151, 153, 167].

3.9 South America

Regarding evidence gaps, one of the main drawbacks of the Brazilian studies is that they are retrospective analysis, which lacks a proper follow-up for all the patients [112, 180]. This may limit the accuracy and completeness of the findings. Moreover, the rarity of this disease in the paediatric population limits the number of patients included in the studies, especially for cases under 10 years of age at diagnosis, making it challenging to gather a larger number of cases [58]. Colombian paediatric PTC patients have been tested only for point mutations (*BRAF* V600E, *DICER1, NKX2-1, NTRK1, PTEN, RAS* and *TSHR*), demonstrating a frequency of 6.3% *BRAF* V600E in the studied population and none for all the other tested mutations [56]. Evidence gaps related to the need for further studies on: how the patients evolve; if their response to RAI therapy was complete; exploring wider known genetic alterations; registering more clinical data to unveil possible familial clustering and risk factors [56].

Both in Brazil and Colombia, we identified the need for studies to investigate quite heterogeneous data concerning

BRAF mutations association with aggressive features in paediatric cases. Also, both qualitative and quantitative analyses of the association of these events with various clinicopathological characteristics should be conducted [179].

Finally, regarding information on funding support to investigate potential conflicts of interests, we observed that most Brazilian studies have been financed by the public sector [38, 58, 83, 112].

3.10 Nuclear environmental events: Chernobyl and Fukushima

As for Europe and the USA, the evidence gaps we identified revolved around more and better prospective larger sample sizes studies. In Belarus, we identified the need for studies investigating structural differences between the various rearranged forms of *RET,* specifically in solid variant of PTC in Chernobyl-exposed paediatric populations – a rare finding in either children or in the adult population – that is poorly characterised from both a biological behaviour and patient prognosis perspectives [75, 85, 86]. Differences of *RAS* mutations prevalence that might be related to age, environmental or genetic factors, or techniques used should also be further investigated [94]. TK/EC expression indicating the presence of *RET/PTC* rearrangements should also be further characterised [164]. Further analyses of *TP53* mutations need to be performed paediatric PTC without radiation history [157], especially codons 167 and 183 to investigate whether they are radiation-specific targets [109]. A matched control (age and region) would be necessary to ascertain whether the exposure to radioactive isotopes has really caused an increase in the prevalence of *RET* rearrangements, particularly *RET/PTC3,* to verify whether this is linked primarily to the nature of the carcinogenic agent or to the child's age [158].

In Ukraine, evidence gaps related to the need for further studies addressing all driver oncogenes and other cancer genes at the genomic and transcriptomic levels to determine whether the phenotype and prognosis of the *BRAF* V600E-positive radiogenic PTCs will be acquiring patient age-related changes similarly to those described in sporadic PTCs [107].

Japanese evidence gaps regarded the need for further studies also outlining the clinicopathological significance of *BRAF* or *TERT* promoter mutations and their prognostic impact via advanced methods such as whole-exome-sequencing. [76]. Furthermore, given the low frequency of both child PTC and the *ETV6::NTRK3* fusion, it remains unclear whether the impact of genetic alteration in PTCs varies with geographic diversity. As the increase of thyroid cancer after radiation exposure might require a relatively long period of time following the 2011 Fukushima disaster, it is important to accumulate detailed data regarding both sporadic and possible radiation-related PTCs in Japan [39]. Finally, it is important to verify any differences in genetic alteration between paediatric and adult FTCs, which have been this far poorly investigated in Fukushima radiation exposed paediatric populations [43].

Regarding study limitations, we would like to outline that sample size has been an issue for all Chernobyl and Fukushima studies and a Ukraine discussion regarding the detection of *RET/PTC* rearrangements via automated FISH analysis approach, which provides reliable results in higher cell numbers. Nevertheless, results indicate a genetic heterogeneity since only subpopulations of tumour cells carried the *RET/PTC* rearrangement [132].

Finally, we found little information on funding support to investigate potential conflicts of interests for nuclear environmental events studies. Nevertheless, we observed that all Brazilian studies received funding exclusively from the public sector [154]. German studies received financial support from the public sector [33, 152]. Japanese studies received funding from third, private and public sectors [39, 70, 76]. One Ukrainian study received funding from the third and public sectors [107]. One US-based study received funding from both public and private sectors [72, 75].

4 Final remarks

We have outlined three key recommendations for global authors as means of improving evidence generation and use in the implementation of genetic alterations identification and follow-up strategies to improve and/or inform the management of sporadic, radiation-induced by nuclear environmental events and/or therapy-exposed children and adolescents (diagnosed until 18 years of age) with thyroid tumours and/or DTC.

From the full-text studies that did not meet eligibility criteria, 133 studies from all investigated regions collected age data but did not report genotype–phenotype correlation and/or epidemiological data (Supplementary References A). Therefore, our first recommendation for authors is to stratify results by age groups (i.e. children, adolescents, young adults, adults and elderly populations) and/or report data for individual patients' age at diagnosis as supplementary/additional files.

From the full-text studies that did not meet eligibility criteria, 9 studies did not report individual country and/or sub-region or state (Supplementary References B) epidemiological data regarding genotype–phenotype correlations, following our eligibility criteria. For those studies analysing populations from more than one country and/or sub-region or state that did not report individual country and/or sub-region or state epidemiological data regarding genotype–phenotype data according to age-ranges and or individual patient data between zero and 18 years of age (inclusive) at diagnosis, we replicated the same data for all countries listed in the study. This is somewhat imprecise

but close enough at regional level, as those studies analysing population samples from more than one country and/or sub-region or sate belonged to the same region and/or country, respectively. Therefore, our second recommendation for authors is to report results per location as specific as possible (i.e. individual data for each city, sub-region or state, country, especially when analysing population samples from a group of countries and/or sub-region or state).

More generally, a wide variety of studies from all investigated countries did not adequately report positive and negative findings investigated, the methodologies deployed for such investigation, specific genetic alterations identified per histological type and/or aetiology. Therefore, our final recommendation for authors is to always report each genetic alteration investigated, whether you find them or not, by which specific methodological approach for such identification and/or (clinical and/or analytical) validation, as well as from which type of histological lesion caused by specific aetiology. Further descriptions in terms of clinicopathological characteristics, therapeutics and relationship with survival outcome per genetic alteration are also key for tackling implementation barriers and/or evaluating context-specific facilitators at other global locations.

Finally, as a short-term future perspective, such an approach will enable the development of novel genetic/genomic tests from data that has been validated following each country's specific genetic alterations landscape. This is of key importance for cost-effective implementation of precision medicine goals at the local level worldwide.

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Author contributions MSAS and JMC made substantial contributions to the conception or design of the work; MSAS, INN, YPC, LS and JMC made substantial contributions to the acquisition, analysis, or interpretation of data; MSAS, INN, YPC, LS and JMC drafted the work or revised it critically for important intellectual content; all authors approved the version to be published; and MSAS, INN, YPC, LS and JMC agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations

Competing interest All authors declare no direct or indirect financial or non-financial competing interests that are directly or indirectly related to the work submitted for publication.

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