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A tumor profile in Patau syndrome (trisomy 13)

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Individuals with trisomic conditions like Down syndrome and Edwards syndrome are prone to certain types of malignancy. However, for Patau syndrome (constitutional trisomy 13), which occurs in 1/10,000–1/20,000 live births, the tumor profile has not been well characterized. An awareness of susceptibility to malignancies can improve care of affected individuals, as well as further our understanding of the contribution of trisomy to carcinogenesis. Therefore, we conducted an extensive review of the literature; we found 17 malignancies reported in individuals with Patau syndrome. These comprised eight embryonic tumors, three leukemias, two malignant germ cell tumors, two carcinomas, a malignant brain tumor, and a sarcoma. Benign tumors were mainly extragonadal teratomas. The small number of reported malignant tumors suggests that there is not an increased risk of cancer in the context of trisomy 13. The tumor profile in Patau syndrome differs from that observed in Edwards syndrome (trisomy 18) and Down syndrome (trisomy 21), suggesting that the supernumerary chromosome 13 could promote particular tumor formations as it does particular malformations. No general and direct relationships of tumor occurrence with organ weight, congenital malformations, histological changes, or presence of tumor suppressor genes on chromosome 13 were observed. However, some tumors were found in tissues whose growth and development are controlled by genes mapping to chromosome 13. Recent reports of successful outcomes following surgical treatment and adapted chemotherapy indicate that treatment of cancer is possible in Patau syndrome.

KEYWORDS
aneuploidy, cancer, cancer protection, carcinoma, Patau syndrome, teratoma, trisomy 13

1 | INTRODUCTION

Trisomy 13, or Patau syndrome, was first described in 1,656 (Pawelec, Dżugalik, Pietras, Bełza, & Latkowski, 2015) and genetically characterized more than 50 years ago (Patau, Smith, Therman, Inhorn, & Wagner, 1960). It occurs in 1/10,000–1/20,000 (Carey, 2010) newborns, and is associated with a particular distribution of malformations and profound neuro-developmental disabilities. Only 6–12% of infants with Patau syndrome survive beyond the first year of life (Janvier, Farlow, & Wilfond, 2012).

Similar to infants with Edwards syndrome (trisomy 18) or with Down syndrome (trisomy 21), individuals with Patau syndrome may develop malignancies and benign tumors (Satgé, Nishi, Sirvent, & Vekemans, 2016; Satgé et al., 1998). The type of tumors that occur in individuals with trisomy 13 are not well characterized. The identification of organs and tissues at risk for cancer in individuals with trisomy 13 should allow better clinical monitoring of infants. This information will also contribute to the understanding of oncogenesis in the context of constitutional supernumerary genetic material. Therefore, we aimed to evaluate the tumor profile of this condition by reviewing the literature and consulting the files of the Support Organization For Trisomy 13 and 18 and related disorders – Surgery Registry (SOFT-SR). We found that malignant tumors have been

reported only rarely in Patau syndrome and that the observed tumors have a unique distribution compared to the general population and to that observed in Edwards syndrome and Down syndrome (Satgé et al., 1998, 2016).

2 | MATERIALS AND METHODS

2.1 | Literature search

The literature search was conducted with the same methodology as we previously used for Edwards syndrome (Satgé et al., 2016). After an extensive review of the literature conducted on all autosomal constitutional trisomies (Satge & Van Den Berghe, 1996), one author (DS) followed the literature (PubMed) on tumors in Patau syndrome for 20 years. The search terms used were: Patau syndrome, trisomy 13, trisomy D, trisomy 13–15, neoplasms, cancer, and benign tumors. There were no language limitations or date limitations (i.e., before and after 1996). Partial trisomies were also included. We excluded hyperplasias and cysts. Case reports from Japan were searched on PubMed and on Igaku Chuo Zassi (Japanese Central Journal of Medicine), a search tool for medical articles written in Japanese and English. All articles found in Japanese or German were translated to English.

2.2 | Data from the SOFT-SR

Records of tumors in children with trisomy 13 were searched in the SOFT-SR. The SOFT has maintained a Surgery Registry (SOFT-SR) since 1989. Parents voluntarily report surgeries or procedures that were performed for their child on the SOFT membership registration form, and if further surgeries occur, report them to SOFT using an unreported surgery form. SOFT-SR provides information for families wanting surgery for their child and is a resource for researchers studying trisomy 13 or trisomy 18. Surgery tables listing diagnoses and surgery names are available for public viewing from the SOFT website at www.trisomy.org. Parents often contact SOFT for further information.

3 | RESULTS

Here we present a summary of the reported tumors found in individuals with Patau syndrome. The scientific literature through 2016 was reviewed. Individuals with Patau syndrome have been documented to have embryonic tumors, germ cell tumors, leukemia, carcinomas and adenomas, cerebral tumors, sarcomas, non-cutaneous mesenchymal tumors, and cutaneous tumors (summarized in Table 1).

3.1 | Embryonic tumors

Eight embryonic tumors have been reported in individuals with trisomy 13. These comprise three neuroblastomas, two nephroblastomas, one hepatoblastoma, one retinoblastoma, and one rhabdomyosarcoma.

Three neuroblastomas, the most frequent extracranial embryonic tumor in the general population, have been reported in infants with trisomy 13 at autopsy. A 2-month-old boy with a phenotype strongly suggesting Patau syndrome died from enterocolitis and had a 2 cm left adrenal neuroblastoma and liver metastases (Stage IV-S) (Mittelbach & Szekely, 1935). A 2-day-old infant girl with constitutional trisomy 13 had a bilateral in situ neuroblastoma. Her sister (without trisomy) died at 3 years of age from a left adrenal neuroblastoma (Feingold, Gheradi, & Simons, 1971). Another in situ neuroblastoma was found in a 34-week-old premature infant girl with trisomy 13 who died 4 days after birth (Nevin, Dodge, & Allen, 1972).

Nephroblastoma (or Wilms tumor) is the second most frequent extracranial embryonic tumor in infants in the general population; it was observed in two children with trisomy 13. The first child was a 16-month-old boy treated for a stage I nephroblastoma. At 4 years and 10 months of age he was still alive with a series of constitutional chromosomal anomalies associated with Wilms tumor and without other medical details (Olson, Hamilton, & Breslow, 1995). The second child was a 4-year-old boy whose nephroblastoma was revealed by gross hematuria (Sweeney & Pelegano, 2000). His triphasic nephroblastoma was resected from the left part of a horseshoe kidney. The family decided not to treat the tumor. The child died of aspiration pneumonia at 5 years of age. Additionally, abnormal nephrogenic rests (Feingold et al., 1971; Keshgegian & Chatten, 1979; Moerman, Fryns, van der Steen, Kleczkowska, & Lauweryns, 1988) and nephroblastomatosis, which designates diffuse and multifocal nephrogenic rests (Traub et al., 2006), have been observed in the kidneys of fetuses and infants with trisomy 13 more frequently than in euploid offspring. Nephrogenic rests may undergo neoplastic transformation into nephroblastomas. The molecular analysis of nephroblastomatosis foci from a 24-week-old fetus with trisomy 13 showed loss of the Wilms tumor gene (*WT1*) and biallelic expression of insulin growth factor 2 (IGF2), characteristics of Wilms tumor (Traub et al., 2006).

One hepatoblastoma has been reported in an individual with trisomy 13. It was discovered by an ultrasound follow-up of a 15-month-old girl whose mother had been treated with insulin during pregnancy. The stage I epithelial and mesenchymal type hepatoblastoma was completely resected. The girl received four courses of doxorubicin as adjuvant chemotherapy and granulocytic colony stimulating factor (G-CSF). She experienced grade III hematology toxicity requiring transfusions. Cisplatin was omitted from treatment due to its risk of ototoxicity and nephrotoxicity. She was in remission 8 months after the diagnosis of her malignancy (Shah, Tran, Randolph, Mascarenhas, & Venkatramani, 2014; Zhou, Ranganathan, Venkatramani, Gomulia, & Wang, 2013). She died at 3 years 2 months in her sleep from apnea.

One definitive retinoblastoma was reported in an individual with trisomy 13 (Gilbert & Opitz, 1982). Foci of retinal dysplasia with numerous rosettes are regularly observed after careful histological examination of the eyes of fetuses and infants with trisomy 13 (François, 1968; Michon, Borges, & Tso, 1991; Moerman et al., 1988). These foci may be confused with retinoblastoma (Chan, Lakshminrusimha, Heffner, & Gonzalez-Fernandez, 2007). Since the experienced team reporting this retinoblastoma in trisomy 13 also described individuals with retinal dysplasia in the same book chapter, we consider

TABLE 1 Reported malignant tumors in fetuses, infants, children, and young adults with trisomy 13

Tumor type	#	Age and mode of discovery	Treatment and outcome
Embryonic tumors			
Neuroblastoma	3	f 34w-2m AF	No
Nephroblastoma	2	1y 4m & 4y	One: treatment not indicated The other: surgery, other treatments, declined by parents[a]
Hepatoblastoma	1	15m USF	Surgery, chemotherapy[b,c]
Retinoblastoma	1	NI AF	No
Embryonic rhabdomyosarcoma	1	3y CF	Surgery, chemotherapy[d]
Malignant germ cell tumors			
Extragonadal	1	f 16w AF	No
Ovarian	1	13y CF	Surgery, chemotherapy[e]
Leukemia			
Myeloid leukemia	2	NB AF & 9m CF	Chemotherapy, DOD[f]
Leukemia NOS	1	NI	NI
Carcinoma			
Adrenal carcinoma	1	2w AF	No
Colon carcinoma	1	NB AF	No
Brain cancer			
Pilocytic astrocytoma	1	5y MRIF	No treatment, parents declined[g]
Sarcoma			
Bladder sarcoma	1	26y	DOD 4 months after discovery, treatment not indicated
Total	17		

f, fetus; w, weeks; m, months; y, years; AF, autopsy finding; USF, ultrasound finding; CF, clinical findings; MRIF, magnetic resonance imaging finding; DOD, dead of disease; NI, not indicated; NB, newborn.
[a]Dead from another cause 1 year later.
[b]Dead from another cause 2 years after treatment.
[c]Also recorded in the SOFT-SR.
[d]Outcome not indicated.
[e]No information on follow up.
[f]Old observation when chemotherapy was not very efficient.
[g]Alive and well at 7 years old.

that their diagnosis of retinoblastoma is accurate and not the result of a confusion with retinal dysplasia (Gilbert & Opitz, 1982). Another observation of a retinal mass suggestive of retinoblastoma was reported in a 28-day-old neonate with trisomy 13. However, we did not include this case due to the lack of a definitive diagnosis (François, 1968). A retinoblastoma was reported in a 19-month-old child with de novo partial trisomy 13 due to a complex karyotype including an X;13 translocation. However, since the individual's phenotype suggested a partial 13q deletion and not a 13q triplication, the authors hypothesized that the interstitial deletion and X-chromosome inactivation were responsible for the tumor (Dries, Baca, Truss, & Dobin, 2003).

Finally, an embryonic rhabdomyosarcoma of the bladder was discovered in a 3-year-old boy. He had a partial trisomy of the long arm of chromosome 13: der(13)t(13;13)(p11.2-q22.1). The stage III tumor was surgically resected and re-classified as a group III post-operative stage tumor. Combination chemotherapy reduced the tumor's size (Kanemasa et al., 2014).

3.2 | Germ cell tumors

With eight reported cases, germ cell tumors, mainly extragonadal benign germ cell teratomas, are the second group of tumors found in individuals with trisomy 13. A sacrococcygeal teratoma has been reported in a newborn girl from Central Africa with clinical features of trisomy 13 (Lubala et al., 2015). A second sacrococcygeal teratoma was excised in a 3-day-old girl from Turkey (Dorum, Köksal, Özkan, Karakaya, & Akgül, 2016). A juxtarectal cystic teratoma was found in a 12-day-old girl with Patau syndrome and t(13;22) translocation (Hodes, Cole, Palmer, & Reed, 1978). The same publication reported multiple dermoid cysts of the posterior pelvis in another infant with trisomy 13, which could be considered a kind of teratoma. However, we did not include it in this review given the lack of details on the tumor (Hodes et al., 1978). A large immature teratoma of the neck was observed in a 16-week-old fetus with cleft palate and limb malformations. Her karyotype indicated a constitutional trisomy 13 with centric inversion of chromosome 9 (Dische & Gardner, 1978). She also had multiple tumor foci in the liver that could be metastases to the liver rather than an exceptional double neck-liver teratoma. A child with trisomy 13 and a non-specified teratoma was briefly cited in a study of germ cell tumors (Marsden, Birch, & Swindell, 1981). A 24-week-old polymalformed fetus with trisomy 13 had a large mature intraoral teratoma (Yapar, Ekici, & Gökmen, 1995). The umbilical cord of a 17-week-old fetus with trisomy 13 and exomphalos contained a large tridermal immature teratoma without a malignant component (Hargitai et al., 2005). In addition, a 19-year-old girl with trisomy 13 was treated for a 10 cm left ovarian dysgerminoma that was revealed by abdominal distension. She received three courses of chemotherapy with cisplatin, bleomycin, and vinblastin starting at half doses that were gradually increased. No relapse was noted at the end of the three courses (Kikuchi et al., 1999).

3.3 | Leukemia

Leukemia has been reported in three individuals with trisomy 13. Myeloid leukemia was found in a premature stillborn boy with trisomy 13 at autopsy (Schade, Schoeller, & Schultze, 1962). The second individual was a 9-month-old girl with partial trisomy 13 who developed myeloid leukemia (Zuelzer, Thompson, & Mastrangelo, 1968). Despite several treatments she died following cerebrospinal dissemination. The child's maternal grandmother was suspected to be

in the early stages of a chronic lymphocytic leukemia. Most recently, a study of neonatal tumors indicated that an infant with leukemia had a duplication of chromosome 13q (Parkes et al., 1994).

3.4 | Carcinomas and adenomas

Carcinomas are very rare in children and exceptional in neonates (Satgé, Philippe, Ruppe, Levy, & Walter, 1988). Nonetheless, two individuals with trisomy 13 have been reported. A 4 × 3 × 3 cm adrenal carcinoma was found in a 15-day-old infant at autopsy (Nevin et al., 1972). A pea size adenosquamous carcinoma in the anorectal junction was discovered in a full term neonate. This tumor had numerous mitoses, and the capsule was invaded. However, no metastasis was found (Isaacs, 1987). Additionally, two benign epithelial tumors were observed after autopsy of fetuses with trisomy 13. The first tumor was a microcystadenoma in the pancreas of a normal weight 7-day-old infant (Hashida, Jaffe, & Yunis, 1983). The other was a 1 cm adenomyoma on the head of the pancreas in a 36-week-old girl (Moerman et al., 1988).

3.5 | Cerebral tumors

Only one low-grade malignancy and two benign tumors of the central nervous system (CNS) have been reported in infants and children with trisomy 13. A 5-year-old girl with trisomy 13 with translocation (46,XX der(13;3)(q10;q10) + 13) and severe intellectual impairment, but no major cardiac or brain anomalies, had a 1.5 cm right cerebellar lesion observed by magnetic resonance imaging (MRI) suggestive of a pilocytic astrocytoma. Due to imaging results suggesting a low-grade tumor and parental decision, a surgical resection was not performed. The child remained in good health at 7 years of age (Omar, Ahmad, El Bashir, & Al Jaber, 2009). An interhemispheric tubulonodular lipoma of the corpus callosum was found at the autopsy of a newborn with trisomy 13 who died 5 min after birth (Wainwright, Bowen, & Radcliffe, 1995). After examination of the temporal bone of a 6-month-old girl with trisomy 13, a benign tumor was found in the right seventh nerve. The tumor-associated skeletal muscle and nerve fibers was presented as a teratoma (Maniglia, Wolff, & Herques, 1970). However, the tumor did not show aspects of a true germ cell tumor and could have been a choristoma, a type of malformative tumor. Finally, minute neuroglioblastic proliferations in the cerebellum of a premature neonate with trisomy 13 have been observed, which could be considered as in situ tumors (Feingold et al., 1971).

3.6 | Sarcomas and non-cutaneous mesenchymal tumors

In addition to the embryonic rhabdomyosarcoma of the bladder cited above, a small round cell sarcoma of the left part of the neck was diagnosed in a 26-year-old man with trisomy 13. The tumor enlarged and destroyed his cervical vertebrae. The man died 4 months after his diagnosis. His treatment was not indicated (Tanaka et al., 2014). Multiple hemangiomas of the lung have been observed in a 42-day-old girl with partial trisomy 13 (46,XX ter(13;13)(q10;q10) +13) who died from acute bacterial sepsis (Quijano & Drut, 2007).

3.7 | Cutaneous tumors

Benign vascular cutaneous tumors, mainly hemangiomas but also port wine stains and telangiectatic nevus, are frequently observed involving the skull and face of newborns with Patau syndrome. These tumors occur in 27–56% of individuals with complete trisomy 13 and in 11–44% of individuals with trisomy 13 mosaicism (Petry et al., 2013; Wieser, Wohlmuth, Rittinger, Fischer, & Wertaschnigg, 2015). They were previously reported with the generic term hemangioma. Hemangiomas treated with propranolol in an 11-month girl with trisomy 13 showed a good regression tendency (Wieser et al., 2015). Preauricular tags, which are small facial appendages, are sometimes reported (Pachajoa & Meza Escobar, 2013; Wieser et al., 2015). A small sacral appendage of unknown histology was observed in a 2-month-old infant with mosaic trisomy 13 (Pachajoa & Meza Escobar, 2013). Whole body congenital milia corresponding to keratin filled cysts have been described in two other infants with trisomy 13 (Nakai, Okuzawa, Katoh, & Kishimoto 2010; Torrelo et al., 2010).

3.8 | Diagnosis and treatment

Among the 17 cancers, eight were discovered at autopsy in fetuses and newborns between 16 weeks of gestation and 2 months of age. In eight of the nine other malignancies tumors were detected because of symptoms such as hematuria (Sweeney & Pelegano, 2000), cutaneous purpura (Zuelzer et al., 1968), fever (Tanaka et al., 2014), and abdominal distention (Kikuchi et al., 1999). For others, a systematic ultrasound discovered the malignancy (Omar et al., 2009; Shah et al., 2014). Among benign tumors, observation of teratomas was made at systematic autopsy (Hodes et al., 1978) and by intrauterine ultrasound or MRI (Dische & Gardner, 1978; Hargitai et al., 2005; Yapar et al., 1995), but rarely at birth (Lubala et al., 2015). At the time of discovery none of the tumors were large.

Six children with a malignancy received complete or partial treatment and others received no treatment. For the 26-year-old man with small round cell sarcoma of the neck, there was no indication of treatment. He died 4 months after diagnosis (Tanaka et al., 2014). The parents of a 5-year-old child with a low-grade glioma pilocytic astrocytoma decided against treatment. The child was still alive with no major complication from her tumor at 7 years of age (Omar et al., 2009). Five children were surgically treated; three of them received chemotherapy. Chemotherapy was not given for a stage I nephroblastoma (Olson et al., 1995). The parents of a second child with another nephroblastoma decided against postsurgical chemotherapy, and the child died from another cause at 5 years old, 1 year after the diagnosis of his tumor (Sweeney & Pelegano, 2000). For hepatoblastoma, an infant received four courses of doxorubicin (240 mg/m^2) and experienced a grade III hematological toxicity with *Escherichia coli* infection. She was in remission 8 months after diagnosis (Shah et al., 2014). An embryonic stage III rhabdomyosarcoma of the bladder

diagnosed at 3 years of age was treated by combination chemotherapy (not detailed), which reduced the tumor size (Kanemasa et al., 2014). For an ovarian dysgerminoma, a 19-year-old woman with trisomy 13 received surgery and three courses of chemotherapy with half doses of cisplatin, bleomycin, and vincristine, which were gradually increased. At the end of the three courses of chemotherapy no relapse was observed (Kikuchi et al., 1999). Chemotherapy with methotrexate, cyclophosphamide, vincristine, and prednisone in succession for myeloid leukemia in a 9-month-old girl was not effective (Zuelzer et al., 1968). Radiotherapy was not given to any of these patients.

3.9 | Data from the SOFT-SR

As of January 2017, 158 children with full trisomy 13, and 36 children with mosaic trisomy 13 were reported to have undergone 550 (22%) and 36 (4.6%) of the surgeries, and procedures registered in the SOFT-SR, respectively. One child treated for hepatoblastoma was described above (Shah et al., 2014; Zhou et al., 2013). Two other children were treated for a sacrococcygeal teratoma. One received an operation at 9 weeks of age for a sacrococcygeal teratoma that was visible at birth (Figure 1) and had since increased in size, changed colors, and caused pain. The girl is currently 6 years old and has intestinal issues with chronic constipation. The teratoma seems to recur. The child's great aunt has been treated for breast cancer. The second child was born at 31 weeks of gestation. She was operated on at 4.7 years old for a sacrococcygeal teratoma and again at 7.8 years old because of tumor recurrence. Her grandmother died at 52 years of age from a breast cancer that was diagnosed at 48 years old.

FIGURE 1 Picture of the sacrococcygeal teratoma. [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

4.1 | Tumor frequency and distribution

The 16 malignancies reported in the literature during a 56-year period (1960–2016) and an old observation in 1933 do not suggest an excess of cancer, in individuals with Patau syndrome, a condition affecting 1/10,000–1/20,000 newborns (Carey, 2010). In six studies reporting 143 subjects with trisomy 13 and indicating clinical features, not a single cancer was observed (Baty, Blackburn, & Carey, 1994; Hodes et al., 1978; Lin et al., 2007; Moerman et al., 1988; Petry et al., 2013; Taylor, 1968). Similarly, a study on birth defects associated with cancer found no malignancy among a cohort of 237 live born infants with trisomy 13, accounting for 178 years of follow up (Botto et al., 2013). Some cases in our review come from studies of malignancies (Olson et al., 1995; Parkes et al., 1994) and from autopsy studies (Gilbert & Opitz, 1982; Isaacs, 1987); the others are from case reports. The paucity of case reports could suggest there is no excess of cancer since a malignancy observed in a genetic condition is more likely to be published.

A comparison with the general population where nearly one child in 300 children will develop cancer (Scheurer, Bondy, & Gurney, 2011) is difficult because the mean life expectancy is currently around 1 month in Patau syndrome (Petry et al., 2013). However, using the same literature search method, 2.6 times more cancers were found in individuals with Edwards syndrome (44 cancers) than were found in individuals with Patau syndrome (17 cancers) (Satgé et al., 2016). This suggests cancer does not appear more frequently in individuals with Patau syndrome compared to those with Edwards syndrome (trisomy 18) because Edwards syndrome also occurs two to three times more frequently (1/6,000–1/8,000 births) (Carey, 2010) than Patau syndrome. Conversely, Down syndrome (trisomy 21) is associated with an increased risk of leukemia, particularly in infancy and early childhood (Satgé et al., 1998).

At first glance, the tumor distribution in patients with Patau syndrome does not seem to differ from that in the general population. In this review individuals with Patau syndrome had embryonic tumors, leukemias, malignant germ cell tumors, and cerebral tumors. The occurrence of two carcinomas and two benign epithelial tumors of the pancreas, both exceptional in newborns (Satgé et al., 1988), raises the question of whether individuals with Patau syndrome have an increased vulnerability to tumor development in epithelial tissue. Benign and malignant germ cell tumors appear more frequent than expected since two sacrococcygeal teratomas in the files of the SOFT-SR can be added to the eight cases mentioned in this review.

This review does not have the power of an epidemiological study for establishing a complete tumor profile in Patau syndrome; however, we believe it provides an acceptable first evaluation of this question. The same method was used for Down syndrome (Satgé et al., 1998), and its results were confirmed by epidemiological studies during the following decades (Hasle, Friedman, Olsen, & Rasmussen, 2016; Patja, Pukkala, Sund, Iivanainen, & Kaski, 2006; Sullivan, Hussain, Glasson, & Bittles, 2007). Additionally, since the method used is similar to that for

Down syndrome (Satgé et al., 1998) and for Edwards syndrome (Satgé et al., 2016), and is conducted by the same researchers, the tumor profile of these three syndrome may be more easily compared.

With only 17 malignancies it is difficult to compare the tumor profile of Patau syndrome to the tumor profile of Edwards syndrome and of Down syndrome. We may, however, observe that the distribution of benign and malignant tumors in Patau syndrome is wider compared to the other two conditions. For instance, embryonic tumors were more frequently seen in Patau syndrome, and carcinomas have not been observed in infants and children with Edwards syndrome or Down syndrome.

4.2 | Tumors, organ weight, and congenital malformations

Interesting observations can be made between fetal organ weight and tumor distribution in Patau syndrome. First, an increase of fetal kidney weight has been reported in trisomy 13 by different researchers (Barr, 1994; Fujinaga, Shepard, & Fitzsimmons, 1990; Marin-Padilla, Hoefnagel, & Benirschke, 1964). This overgrowth of renal tissue could be linked with two Wilms tumors found in children with Patau syndrome (Olson et al., 1995; Sweeney & Pelegano, 2000). A second noticeable observation is the increase in fetal adrenal weight and fetal adrenal cellularity in Patau syndrome (Naeye, 1967), and a very unusual case of corticoadrenal carcinoma (Nevin et al., 1972). Additionally, Marin-Padilla et al. (1964) observed an increased weight of pancreases from two fetuses that we could link to benign tumors found in pancreases of newborns with Patau syndrome (Hashida et al., 1983; Moerman et al., 1988). For germ cell tumors and leukemia a correlation with organ weight is not possible.

A link between congenital malformations and childhood cancer is still debated (Botto et al., 2013). Our review found only a few tumors that developed in various organs, making it difficult to find a direct relationship. A large study including 4,698 infants with trisomy 13 (Pont et al., 2006) indicated the most frequent malformations were in eyes or ears (49.5 times higher that of the general population), the oropharyngeal region (228.6 times), the central nervous system (CNS) (91.8 times), and the cardiovascular system (79.2 times). Two malignant tumors, one in the CNS and the other in the eye, and two benign tumors of the CNS were included in the review. Furthermore, the risk of malformation in the gastrointestinal tract was increased 29-fold while only two cancers (liver and rectal) and two benign tumors of the pancreas were reported. Additionally, the risk for genitourinary malformations was increased 14-fold, while only two renal tumors were reported in the review. On the basis of this study, there is not a clear link between malformation and cancer in individuals with trisomy 13.

4.3 | Correlation with histological changes

Abnormalities in tissue architecture are observed in organs of fetuses and infants with trisomy 13. A relationship with benign and malignant tumors and these dysplasias may be hypothesized. Nephrogenic rests, which share many chromosomal defects with nephroblastoma, are considered as possible precursors of this renal cancer (Traub et al., 2006). Nodular renal blastema is observed more frequently in trisomy 13 than in euploid fetuses and neonates (Fujinaga et al., 1990; Keshgegian & Chatten, 1979) and may be related to the two nephroblastomas found in this review (Olson et al., 1995; Sweeney & Pelegano, 2000). Similarly, the observation of disorders of the liver parenchyma and excess of liver parenchyma proliferation in individuals with trisomy 13 (Marin-Padilla et al., 1964) could be linked to the hepatoblastoma reported in a child with Patau syndrome (Shah et al., 2014; Zhou et al., 2013). For benign tumors, the microcystadenoma and the adenomyoma found in the pancreases of neonates with Patau syndrome may be seen as a tumor form of the dysplastic developmental anomaly very common in and considered as specific to Patau syndrome (Hashida et al., 1983; Moerman et al., 1988). Similarly, it is possible to speculate that the prominent cerebral dysplasia observed in individuals with trisomy 13 and which has been suspected to increase the risk of childhood cerebral tumors (Yachnis, Rorke, & Trojanowski, 1994) may have favored the onset of a pilocytic astrocytoma found in a girl with Patau syndrome (Omar et al., 2009). Finally, retinal dysplasia, which is frequent in Patau syndrome (Moerman et al., 1988), could be related to the retinoblastoma reported in an infant with trisomy 13 (Gilbert & Opitz, 1982). A possible link between tissue dysplasia and cancer formation remains to be clarified.

4.4 | Correlation with extra genetic material

Since cancer is considered a genetic disease (Vogelstein & Kinzler, 2004), tumors observed in Patau syndrome are suspected to be related to the excess of genetic material on the supernumerary chromosome 13. From a cytogenetic point of view, no clear difference in tumor type and distribution is observed between individuals with full, free, and complete trisomy 13 compared to those with partial trisomy 13 (Kanemasa et al., 2014; Quijano and Drut, 2007; Zuelzer et al., 1968), to those with translocations (Hodes et al., 1978; Omar et al., 2009; Parkes et al., 1994), or to those with trisomy 13 mosaicism (Pachajoa & Meza Escobar, 2013). However, cutaneous hemangiomas are more frequent in individuals with trisomy 13 compared to those with mosaicism (Wieser et al., 2015). The unique distribution of cancers and benign tumors in Patau syndrome compared to Edwards syndrome (Satgé et al., 2016) and to Down syndrome (Satgé et al., 1998) suggests that genes mapping to chromosome 13, rather than a general mechanism linked to aneuploidy, are responsible for the tumor profile. The trisomic state that induces a characteristic aneuploidy response pattern common to the three trisomies (Dürrbaum et al., 2014) does not explain the differences between these three conditions. A supernumerary chromosome 13 is rarely found in myeloblastic leukemias (<2% of cases) in euploid individuals (Baer & Bloomfield, 1992; Herold et al., 2014). Interestingly, the two leukemias in individuals with trisomy 13 that are reported here are myeloblastic leukemias (Schade et al., 1962; Zuelzer et al., 1968).

From a genic point of view, we could not find a clear correlation between the tumors observed in individuals with trisomy 13 and the two well established tumor suppressor genes that map to chromosome 13, *RB1*, and *BRCA2*. We hypothesize that the triplicated tumor suppressor genes *RB1* and *BRCA2* should provide enhanced protection against retinoblastoma and breast cancer, respectively. However, this review found one (Gilbert & Opitz, 1982) and possibly two (François, 1968) individuals with trisomy 13, and retinoblastoma. Since females with Patau syndrome typically do not reach late adulthood, a possible protection against breast cancer cannot be evaluated. Nonetheless, some interesting correlations between genes on chromosome 13 involved in organ development and cancers of these organs in infants with Patau syndrome may be noted. The *CDX2* gene, encoding a homeobox transcription factor involved in intestinal development (Silberg, Swain, Suh, & Traber, 2000), has been considered as both a tumor suppressor gene and as an oncogene for colon cancer (Salari et al., 2012). It could be related to the occurrence of a neonatal colon cancer (Isaacs, 1987). Two genes mapping to chromosome 13 *FLT3*, a hematopoietic regulator (He et al., 2014), and *FOXO1A*, a transcription factor (Dong et al., 2006), are frequently overexpressed in myeloid leukemia (Herold et al., 2014), raising the suspicion of their possible role in the onset of leukemia observed in the individuals in this review (Parkes et al., 1994; Schade et al., 1962; Zuelzer et al., 1968). Additionally, the two pancreatic benign tumors (Hashida et al., 1983; Moerman et al., 1988) reported here could be linked to the *BDX1* gene on chromosome 13. This gene is involved in early pancreatic development and has been shown to promote pancreatic ductal carcinoma (Yu et al., 2016). Although it is known that anomalies found in constitutional trisomies result from complex genetic interactions between genes on the supernumerary chromosome and also with genes on other chromosomes (Liu, Filippi, Roy, & Roberts, 2015), the gene dosage effect remains a main hypothesis to correlate a phenotypic trait such as tumor formation and a gene on the supernumerary chromosome.

4.5 | Treatment options

Many children with trisomy 13 die shortly after birth. On this basis it has been considered that these children should not be offered treatment, as was previously proposed for children with Down syndrome (Lantos, 2016). Survival rates, neurocognitive deficits, and the burden of treatment are three factors used to make a treatment decision (Lantos, 2016). A Canadian study conducted from 1991 to 2012 indicated that 12.9% of the 174 children with Patau syndrome survived their first birthday; 20% of them had a surgical treatment (Nelson, Rosella, Mahant, & Guttmann, 2016). Although children with trisomy 13 have neurocognitive deficits, no one can know with certainty what an infant is thinking (Lantos, 2016). Indeed, Lantos reminds us that children with trisomy 13 smile and laugh, and are not in pain. Similarly, a large study of the experience of parents of children with trisomy 13 and trisomy 18 who were engaged with parental support groups in Canada described these children as happy with their parents (Janvier et al., 2012). The cancers and benign tumors found in individuals with trisomy 13 are discovered at an early stage and, therefore, are accessible to treatment. Chemotherapy was successfully adapted for a young woman with trisomy 13 and ovarian dysgerminoma by starting treatment with lower drug doses. For treatment of an infant with hepatoblastoma, cisplatin was omitted from the treatment plan to avoid risks linked to ototoxicity and nephrotoxicity (Kikuchi et al., 1999; Shah et al., 2014). These examples demonstrate that survival after cancer treatment is possible for children with trisomy 13. Along with Lantos (2016), we propose that "if survival rates are not too low, neurocognitive impairment not total, and treatment not so burdensome to become inhumane parental values should drive decisions about treatment" (Lantos, 2016). A similar position has been proposed for children with trisomy 18 (Satgé et al., 2016). Treatment decisions should consider the advice of a multidisciplinary team comprising, at the least, a pediatric oncologist, pediatric surgeon, geneticist, pediatric neurologist, and medical ethicist.

The oldest person with full trisomy 13 in the SOFT SR lived 35 years and had a number of minor medical procedures reported to the registry.

5 | CONCLUSION

This is the first extensive review of tumors in Patau syndrome. The data of the SOFT-SR reveal few tumors in individuals with trisomy 13 suggesting that tumor frequency is not increased compared to euploid infants and children. A tumor profile in Patau syndrome, with a wide distribution of various tumor types in various tumor sites, early carcinoma cases, and overrepresentation of extragonadal teratomas, differs from that found in Edwards syndrome and in Down syndrome. It indicates that, beyond common mechanisms, the natural model of constitutional trisomy favors, for each chromosome, specific types of malignant and benign neoplasms. In the small study of tumors presented here, direct correlations with organ weight, congenital malformations, histological changes, or chromosome 13 oncogene and tumor suppressor genes could not be made. However, tumors occurred in organs and tissues whose growth, development, and differentiation are controlled by genes mapping to chromosome 13. It is important for the medical community to publish observations of tumors in individuals with trisomy 13 to allow a better medical follow-up and a better understanding of carcinogenesis in Patau syndrome.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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