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ARTICLE

Lack of genetic homozygosity in prepubertal teratomas: divergent pathogenesis distinct from that of teratomas in adolescents

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Abstract

In adults, both immature and mature ovarian teratomas show frequent genetic homozygosity consistent with tumorigenesis involving germ cells after meiosis I. Investigation into genetic zygosity of various teratomas in children has been limited. Thirteen sacrococcygeal, 12 ovarian, and 3 testicular teratomas in children 18 years or younger were retrieved from our departmental archives and histologically reviewed. Tumor and paired normal tissues were microdissected and subjected to short tandem repeat (STR) genotyping. DNA genotyping was informative in 12 sacrococcygeal teratomas, 8 ovarian teratomas, and 3 testicular teratomas. Sacrococcygeal teratomas included seven mature teratomas, four immature teratomas, and one mixed germ cell tumor with patient age ranging from 0 days to 3 years. All but two patients were female. Ovarian teratomas included five mature and three immature teratomas with patient age ranging from 2 to 18 years. Testicular teratomas included two mature teratomas and one immature teratoma with patient age ranging from 3 months to 3 years. All sacrococcygeal, testicular, and ovarian teratomas in patients younger than 4 years showed no evidence of genetic homozygosity by STR genotyping. In contrast, all four ovarian teratomas in patients older than 9 years showed either partial or complete homozygosity. In conclusion, unlike adolescent and adult ovarian teratomas, prepubertal sacrococcygeal and gonadal teratomas lack genetic homozygosity, supporting the hypothesis that teratomas before puberty develop at an early stage of germ cell development different from that of teratomas in adolescents and adults.

Introduction

Extragonadal germ cell tumors, much like their counterparts arising in the ovary and testis, are believed to originate from germ cells that stalled during embryonic migration [1, 2]. The evidence for the germ cell origin of ovarian teratomas in adulthood is well supported by numerous molecular investigations [3–12]. However, epidemiologic and molecular genetic evidence has suggested that germ cell tumors in prepubertal children are a unique biological tumor category distinct from that of adolescents and adults.

According to a recent classification of pediatric germ cell tumors, they may be classified into two pathogenetic types [13, 14]. Type I germ cell tumors arise from germ cells at an early developmental stage with meiosis I failure. They are generally seen in children before puberty, mostly 0–4 years of age, and involve anatomic sites along the midline. They do not show gross genetic abnormalities detectable by karyotyping or array-based comparative genomic hybridization or fluorescence in situ hybridization [14]. In contrast, Type II germ cell tumors develop from germ cells in gonads (ovary and testis) at or after puberty and after meiosis I with failure of meiosis II [15]. The presence of isochromosome 12p is a common finding in postpubertal testicular germ cell tumors [1, 15–17]. In addition, they may show other complex genetic alterations [14]. More importantly, a significant majority of Type II teratomas display genetic homozygosity in the tumor tissue compared with the paired normal tissue [9, 11].

Sacrococcygeal teratoma is the most common extragonadal Type I germ cell tumor with an estimated incidence of 1:35,000–40,000 live births [16, 18]. These tumors

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frequently occur in females with a reported female-to-male ratio between 3:1 and 7:1 [2, 19]. Sacrococcygeal teratomas are most often mature; however, immature teratomas and mixed germ cell tumors can also occur. In contrast to Type II germ cell tumors, there has been only one study in 1994 assessing genetic homozygosity in pediatric sacrococcygeal teratomas using traditional karyotyping and restriction fragment length polymorphism (RFLP) analysis [2, 15, 16, 20]. Therefore, investigations using modern technology with more resolving power are needed to further elucidate the pathogenesis of pediatric teratomas at the genetic level. In this study, we investigated genetic zygosity in cohorts of pediatric teratomas arising from sacrococcygeal, ovarian, and testicular sites by short tandem repeat (STR) genotyping.

Materials and methods

Case selection

Thirteen sacrococcygeal teratomas, 12 ovarian teratomas, and 3 testicular teratomas were collected from the departmental pathology archives at Yale School of Medicine. All available hematoxylin and eosin (H&E)-stained and immunohistochemical slides were reviewed by the authors (OLS, MD, and PH) to confirm the diagnosis and to assess tumor volume for downstream STR genotyping analysis. Teratomas with any immature elements were categorized as immature teratoma. Four of 12 ovarian teratomas were included in a previous study [11]. Demographic data were obtained by review of clinical records. This study was approved by the Institutional Review Board and informed consent was not required.

Tissue dissection and DNA extraction

Formalin-fixed, paraffin-embedded blocks containing distinct areas of teratoma and normal tissue (if available) were selected for each case. A H&E-stained section and additional unstained sections were created on glass slides from the formalin-fixed, paraffin-embedded tissue blocks. Areas of teratoma and normal tissue were confirmed by H&E-stained slide review and corresponding tissues from the unstained slides were scraped with a sterile scalpel into separate microcentrifuge tubes. DNA was extracted by hydrothermal pressure method of simultaneous deparaffinization and lysis of formalin-fixed paraffin-embedded tissue followed by conventional column purification to obtain high quality DNA [21].

Short tandem repeat (STR) genotype analysis

Tissue genotyping was performed using a methodology similar to our prior studies [11, 22]. The PowerPlex® 16 System (Promega Corporation, Madison, WI, USA) was used to perform multiplex polymerase chain reaction (PCR) at 15 STR loci. One microliter of the PCR product was mixed with 13 μL of Hi-Di and 0.5 μL sizing marker (GeneScan-500LIZ, Applied Biosystems, Inc.). Capillary electrophoresis of the product was performed on an ABI3130 platform. GeneMapper software, version 3.7 (Applied Biosystems, Inc., Foster City, CA, USA) was used for data collection and further analysis. The PCR products were identified by expected size range and fluorescent color. Genotyping data were reviewed and loci were deemed informative if two distinct alleles at a given locus were observed in the normal control tissue. The informative loci in teratoma tissue were then scored to determine if the locus was homozygous or heterozygous. Cases with homozygosity at all informative loci were considered to show complete homozygosity. As previously defined [11], cases with homozygosity involving more than 30% but not all informative loci were considered to represent partial homozygosity. Cases with no or less than 30% informative STR loci showing homozygosity were considered heterozygous.

Table 1 Clinicopathologic characteristics of cases with informative genotyping.

Case	Location	Age	Gender	Diagnosis
1	Sacrococcygeal	0 day	F	Immature teratoma
2	Sacrococcygeal	1 day	F	Immature teratoma
3	Sacrococcygeal	1 day	F	Immature teratoma
4	Sacrococcygeal	1 day	F	Mature teratoma
5	Sacrococcygeal	3 days	F	Immature teratoma
6	Sacrococcygeal	3 days	F	Mature teratoma
7	Sacrococcygeal	6 days	F	Mature teratoma
8	Sacrococcygeal	2 weeks	F	Mature teratoma
9	Sacrococcygeal	2 weeks	F	Mature teratoma
10	Sacrococcygeal	2 years	F	Mature teratoma
11	Sacrococcygeal	2 years	M	MGCT with MT & YST
12	Sacrococcygeal	3 years	M	Mature teratoma
13	Ovarian	2 years	F	Mature teratoma
14	Ovarian	3 years	F	Mature teratoma
15	Ovarian	4 years	F	Mature teratoma
16	Ovarian	4 years	F	Immature teratoma
17	Ovarian	9 years	F	Immature teratoma
18	Ovarian	11 years	F	Immature teratoma
19	Ovarian	16 years	F	Mature teratoma
20	Ovarian	18 years	F	Mature teratoma
21	Testicular	3 months	M	Immature teratoma
22	Testicular	1 years	M	Mature teratoma
23	Testicular	3 years	M	Mature teratoma

MT mature teratoma, *MGCT* mixed germ cell tumor, *YST* yolk sac tumor.

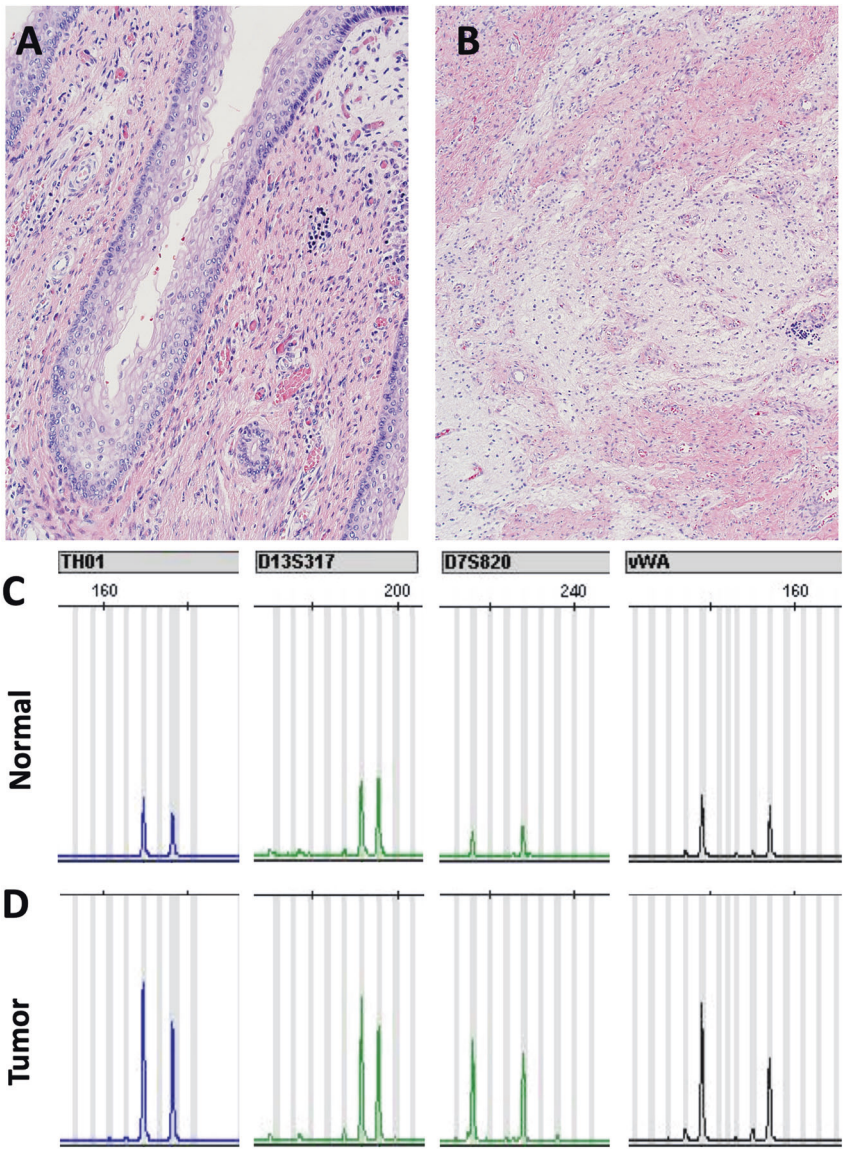

Fig. 1 Sacrococcygeal immature teratoma with heterozygosity in a 1-day-old female (case 3). a Area of the tumor with mature ectodermal elements (H.E., 200×). **b** Area of the tumor with mature neural elements (H.E., 100×). **c** Genotyping information with four informative (heterozygous) loci seen in normal tissue. **d** The sacrococcygeal teratoma displays heterozygosity at informative loci.

Results

From the initial cohorts of teratomas, STR genotyping was informative in 12 sacrococcygeal teratomas, 8 ovarian teratomas, and 3 testicular teratomas. Five initial cases were excluded due to PCR amplification failure or poor DNA quality extracted from the tumor tissue.

The clinical and pathological characteristics of the 23 cases with informative genotyping data are presented in Table 1. The age of the patients at presentation ranged from 0 days to 3 years (mean = 7 months) for sacrococcygeal teratomas (ten females and two males), 2 to 18 years (mean = 8.4 years) for ovarian teratomas and 3 months to 3 years (mean = 17 months) for testicular teratomas.

Histologically, among sacrococcygeal teratomas, seven cases were mature teratomas, four were immature teratomas, and one was a mixed germ cell tumor. The patients with immature teratoma ranged in age from 0 days to 3 days (mean = 1 day) and the patients with mature teratoma ranged in age from 1 day to 3 years (mean = 8.8 months). Mature teratomatous elements were most frequently mature ectoderm and mature neural tissue types (Fig. 1). Four immature teratomas harbored various amount of immature neuroectodermal elements. One sacrococcygeal mixed germ cell tumor (case 11) showed mature teratoma admixed with yolk sac tumor component characterized by the endodermal sinus growth pattern and the presence of Schiller–Duval bodies (Fig. 2).

For ovarian teratomas, five cases were mature teratomas and three cases were immature teratomas. The patients with mature teratoma ranged in age from 2 years to 18 years (mean = 8.6 years) and those with immature teratoma ranged in age from 4 years to 11 years (mean = 8 years). In addition to the mature teratoma component, varying amount

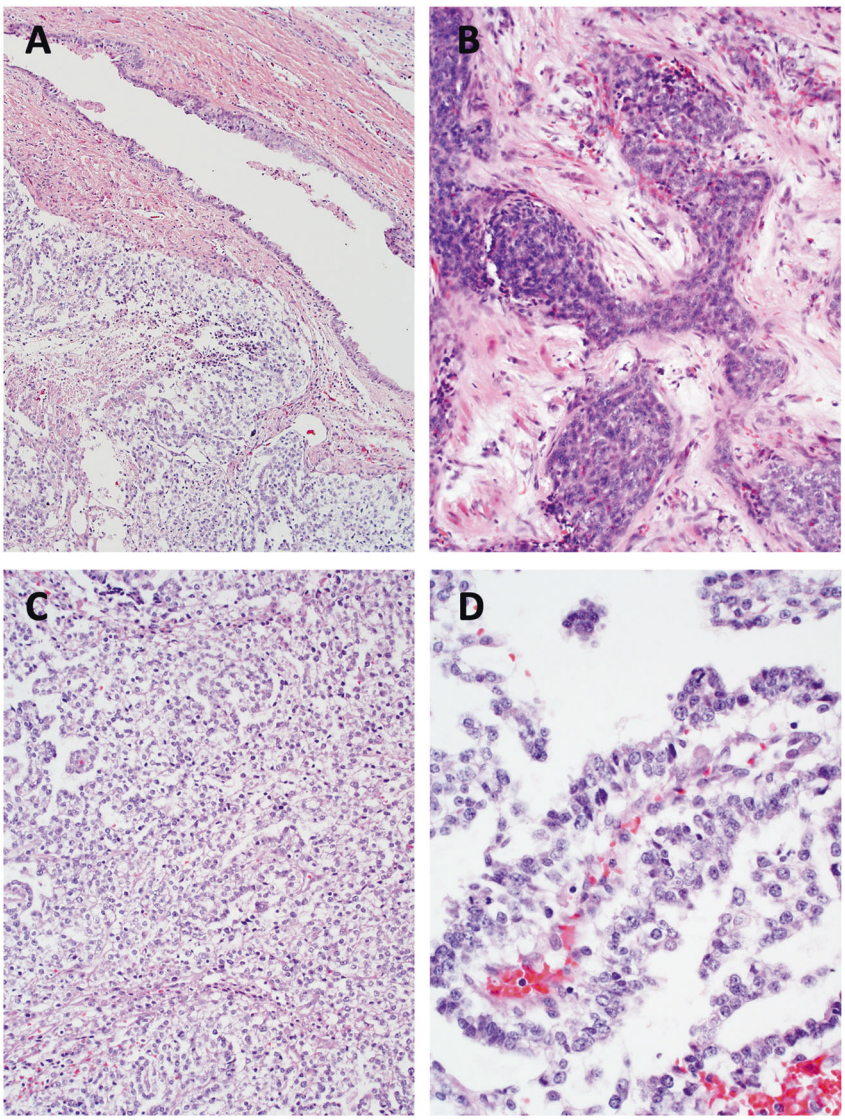

Fig. 2 Sacrococcygeal mixed germ cell tumor with mature teratoma and yolk sac tumor components in a 2-year-old male (case 11). a Area of the tumor with mature elements (H.E., 100×). **b**, **c** Two different morphologies of yolk sac tumor (H.E., 200×). **d** Endodermal sinus pattern with a Schiller–Duval body (H.E., 400×).

of immature neuroectodermal elements was seen in the immature teratomas (Fig. 3).

Among three testicular teratomas, two were mature teratomas and one was an immature teratoma. The patients with mature teratoma were 1 and 3 years old. The patient with an immature teratoma was 3 months of age and histologically the tumor showed immature neuroectodermal tissue with adjacent mature teratomatous elements (case 21, Fig. 4).

Table 2 presents details of the genotyping data of 23 informative pediatric teratomas. The cases with available normal tissue for comparison displayed 5–14 heterozygous STR loci in the corresponding normal tissue. All sacrococcygeal teratomas were found to be heterozygous, as were all ovarian teratomas in patients 4 years of age or younger. All four ovarian teratomas in patients aged 9–18 years demonstrated genetic homozygosity including one case of complete homozygosity and three cases of partial homozygosity. All three testicular teratomas were heterozygous. The summary of genotyping data by tumor location and patient age is shown in Table 3.

Discussion

In this STR genotyping study assessing genetic homozygosity, all sacrococcygeal, testicular, and ovarian teratomas in patients younger than 4 years showed genetic heterozygosity. In contrast, all ovarian teratomas in patients older than 9 years demonstrated either partial or complete homozygosity. As a majority of adult ovarian teratomas reveal homozygosity, our data indicate that teratomas in the prepubertal age group likely arise from germ cells at an early stage of maturation, distinct from adolescent teratomas that arise from germ cells at a later stage of development.

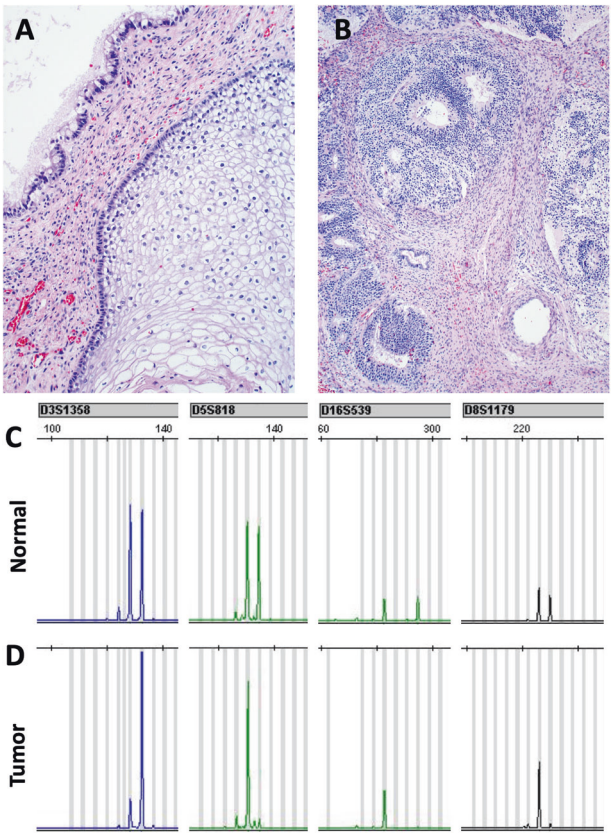

Fig. 3 Ovarian immature teratoma with partial homozygosity in an 11-year-old patient (case 18). a Area of the tumor with mature elements (H.E., 200×). **b** Foci of immature neuroectodermal elements (H.E., 100×). **c** Genotyping data with four informative loci seen in normal tissue. **d** The ovarian teratoma displays homozygosity at these informative loci.

In a female embryo, primordial germ cells migrate initially, 4 weeks after conception, along the body midline and then laterally to the gonad, i.e., the ovary, and differentiate into oogonia with a diploid biparental/heterozygous genome (46, 2N). Meiosis begins in oogonia with homologous chromosomes undergoing genomic reduplication and crossover recombination to form heterozygous primary oocytes (46, 2N, 4C) by 5 months of fetal life, and they remain dormant in the prophase of meiosis I until puberty. Therefore, all of the germ cell precursors in prepubertal females are arrested at prophase of meiosis I with heterozygous biparental genome. Once puberty begins, at each ovulation, meiosis I resumes in a primary oocyte leading to two daughter cells, each containing only one homolog (homozygous) from each of the 23 pairs of chromosomes (23, 1N, 2C). While one of the daughter cells degenerates to the polar body, the other one undergoes meiosis II leading to centromeric division into two daughter cells, each containing one chromatid of each chromosome and one of which eventually further develops into mature ovum (23, 1N, 1C) and the other one becomes the second polar body. The oocyte only completes the second meiosis during fertilization [23, 24]. The process is different in males with meiosis beginning at the onset of puberty and continuing throughout life.

With few exceptions, almost all pure teratomas including mature and immature ones have a diploid 46, XX karyotype. Early studies based on enzymatic polymorphism, karyotyping and RFLP analyses found the presence of frequent genetic homozygosity involving centromeric regions and sporadic heterozygosity involving distal chromosomal regions in most adult mature teratomas, suggesting adult teratomas (Type II teratomas) developed from germ cells that have completed the first meiosis but failed the second meiotic division [6, 9, 25]. A homozygous haploid karyotype was documented in a malignant sacrococcygeal teratoma with poorly differentiated carcinomatous and sarcomatous components in a 65-year-old woman [20]. Recent molecular and genetic studies of adult ovarian teratomas have further supported this hypothesis [11, 26] that the genetic zygosity of teratomas is often distinct from the heterozygous genome in somatic cells.

Sacrococcygeal teratomas are the most common extragonadal germ cell tumors. The majority (80%) of these tumors are diagnosed in infants less than 1 year of age [1]. They also show a female predominance with a female-to-male ratio of 3:1 to 7:1 [2, 19]. Most sacrococcygeal teratomas are mature, although immature teratomas and mixed germ cell tumors do occur. Corroborating the literature, the majority of sacrococcygeal tumors in our study were mature teratomas with a female-to-male ratio of 5:1, and all patients were younger than 3 years of age. According to Pierce et al. [13], sacrococcygeal teratoma is the most common Type I germ cell tumor that develops from germ cells before the completion of meiosis I. Type I germ cell tumors are primarily seen in children before puberty and involve anatomic sites along the midline. In contrast to the numerous genetic zygosity studies of Type II ovarian teratomas, only one previous study investigated genetic homozygosity in pediatric sacrococcygeal teratomas using centromeric heteromorphisms and RFLP markers [2], in which the absence of genetic homozygosity was found in all 17 cases. STR genotyping method was chosen in our study because of its high resolving power for genetic homozygosity assessment. The absence of genetic homozygosity (complete or partial) was found in all patients younger than 4 years of age including 12 sacrococcygeal teratomas (7 mature, 4 immature, and 1 mixed teratoma and yolk sac tumor), 4 ovarian teratomas (3 mature and 1 immature), and 3 testicular teratomas (2 mature and 1 immature). Given the frequent finding of genetic homozygosity in adult ovarian teratomas, our data in pediatric teratomas provide new evidence in support of the proposed pathogenesis of Type I teratoma that both extragonadal and gonadal teratomas in prepubertal

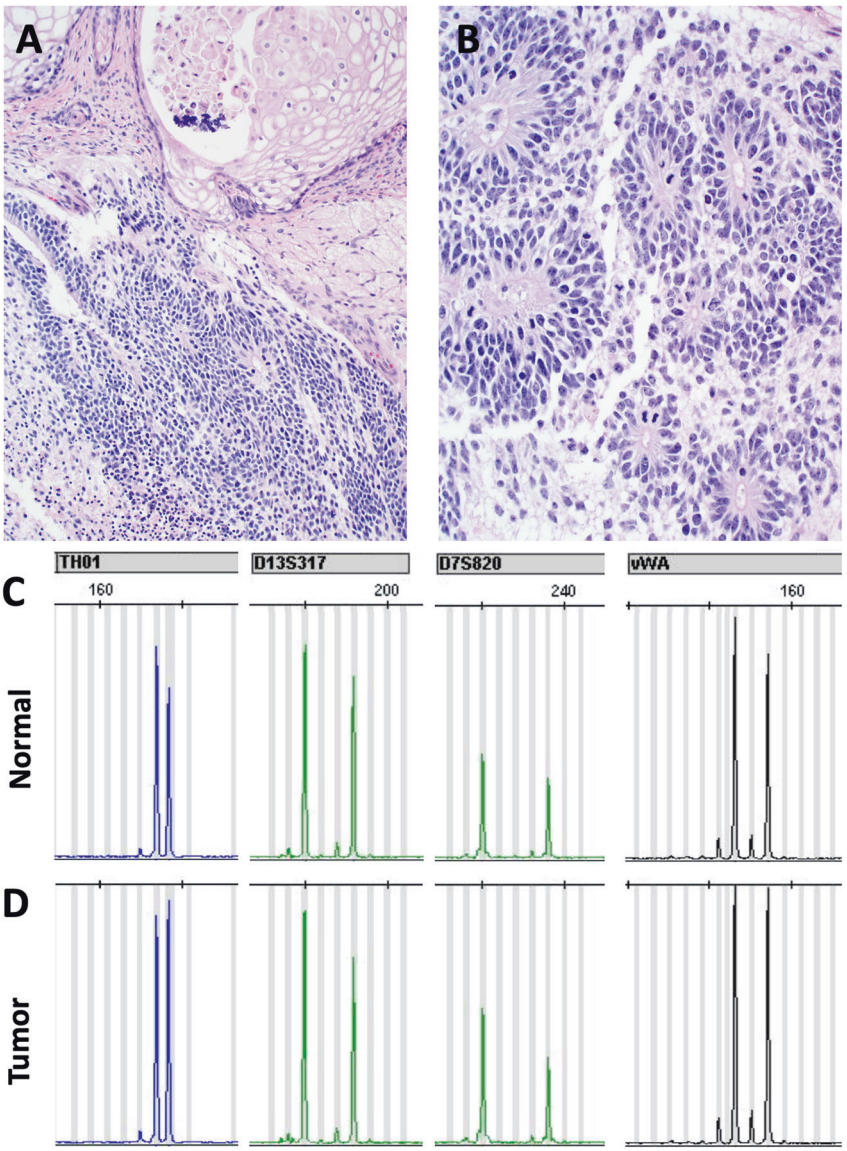

Fig. 4 Testicular immature teratoma with heterozygosity in a 3-month-old patient (case 21). a Area of the tumor with mature and immature elements (H.E., 200×). **b** Immature neuroepithelial tubules with scattered mitoses are easily seen (H.E., 400×). Four informative loci are heterozygous in normal tissue (**c**) with matching heterozygosity seen in the testicular teratoma (**d**).

children arise from germ cells before the completion of meiosis I.

Isochromosome 12p is a common abnormality in post-pubertal testicular germ cell tumors. In contrast, sacrococcygeal and ovarian teratomas in prepubertal populations generally lack isochromosome 12p, except those with malignant nonteratomatous components, notably yolk sac tumor [1, 27, 28]. It is noted that isochromosome 12p was not found in a recent study of pediatric sacrococcygeal teratomas with yolk sac tumor component [15]. Moreover, both pure mature and immature teratomas without a yolk sac tumor component in patients under age of 5 generally show normal genetic profile without gross chromosomal and genomic aberrations in array-based CGH studies [29, 30]. Overall, these previous studies using chromosome in situ hybridization and array-based CGH further support the notion that teratomas in patients before puberty (Type I) are genetically distinct from teratomas in adolescents and adults (Type II).

While our current study provides important insights into the pathogenesis of pediatric germ cell tumors, it is not without limitations. The number of pediatric sacrococcygeal, ovarian, and testicular teratomas considered in this study is relatively small. Further work considering a larger number of cases would be an important next step. Also, STR genotyping examines a limited number of polymorphic loci; additional studies using single nucleotide polymorphism arrays or next-generation sequencing technology will likely further elucidate the genetics of pediatric teratomas.

In conclusion, this is the first report of using STR genotyping to investigate the presence of genetic homozygosity in pediatric teratomas. In contrast to the presence of

frequent genetic homozygosity in postpubertal (adolescent) teratomas, prepubertal teratomas lack genetic homozygosity. Our data provide strong evidence to support the existence of two genetic pathways in the development of pediatric teratomas that involve germ cells at different stages of maturation.

Table 2 Pediatric teratoma genotyping result of informative cases.

Case	Diagnosis	Number of heterozygous alleles[a]	Interpretation
1	IT	8/9	Heterozygous
2	IT	5/5	Heterozygous
3	IT	6/6	Heterozygous
4	MT	5/5	Heterozygous
5	IT	11/12[b]	Heterozygous
6	MT	7/7	Heterozygous
7	MT	10/13[b]	Heterozygous
8	MT	12/12	Heterozygous
9	MT	8/8	Heterozygous
10	MT	9/9	Heterozygous
11	MGCT with MT & YST	10/10	Heterozygous
12	MT	9/9	Heterozygous
13	MT	9/10	Heterozygous
14	MT	9/11	Heterozygous
15	MT	5/6	Heterozygous
16	IT	7/9	Heterozygous
17	IT	6/14	Partial homozygosity
18	IT	5/9	Partial homozygosity
19	MT	0/12	Complete homozygosity
20	MT	5/8	Partial homozygosity
21	IT	12/12	Heterozygous
22	MT	7/9	Heterozygous
23	MT	9/9	Heterozygous

IT immature teratoma, *MT* mature teratoma, *MGCT* mixed germ cell tumor, *YST* yolk sac tumor.

[a]The denominator in each case is the number of informative alleles; that is, the number of heterozygous alleles in normal tissue.

[b]No molecular data is available for normal tissue.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Table 3 Summary of genotyping data by tumor location and patient age (informative cases only).

Tumor location	Patient age	Heterozygosity	Partial homozygosity	Complete homozygosity	Percentage with homozygosity (%)
Sacrococcygeal	≤3 years	12	0	0	0
Ovarian	≤4 years	4	0	0	0
Ovarian	9–18 years	0	3	1	100
Testicular	≤3 years	3	0	0	0

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