REVISED MANUSCRIPT - SHORT REPORT

Surprising genetic and pathological findings in a patient with giant bilateral periadrenal tumors: PEComas and mutations of *PTCH1* in Gorlin-Goltz syndrome

Peter Igaz[1,2 3*], Géza Tóth[4], Péter Nagy[5], Katalin Dezső[5], Péter István Turai[1,2,3], Márta Medvecz[6], Norbert Wikonkál[6], Gergely Huszty[7], László Piros[7], Erika Tóth[8], Anikó Bozsik[9,10], Attila Patócs[9,10,11], Henriett Butz[9,10,11]

[1]Department of Endocrinology, Faculty of Medicine, Semmelweis University, H-1083 Budapest, Hungary

[2]Department of Internal Medicine and Oncology, Faculty of Medicine, Semmelweis University, H-1083 Budapest, Hungary

[3]MTA-SE Molecular Medicine Research Group, Eötvös Loránd Research Network, H-1083 Budapest, Hungary

[4] Szt. Lázár Hospital, Department of Endocrinology, H-3100 Salgótarján, Hungary

[5]1st Department of Pathology and Experimental Cancer Research, Faculty of Medicine, Semmelweis University, H-1085 Budapest, Hungary

[6]Department of Dermatology, Venereology and Dermatooncology, Faculty of Medicine, Semmelweis University, H-1085 Budapest, Hungary

[7]Department of Transplantation and Surgery, Faculty of Medicine, Semmelweis University, H-1085 Budapest, Hungary

[8]Department of Surgical and Molecular Pathology, National Institute of Oncology, H-1122 Budapest, Hungary

[9]MTA-SE Hereditary Tumors Research Group, Eötvös Loránd Research Network, H-1089 Budapest, Hungary

[10]Department of Molecular Genetics, National Institute of Oncology, H-1022 Budapest, Hungary

[11]Department of Laboratory Medicine, Faculty of Medicine, Semmelweis University, H-1089 Budapest, Hungary

***Corresponding author:**

Dr. Peter Igaz MD MSc PhD DSc

Department of Endocrinology,

Department of Internal Medicine and Oncology, Faculty of Medicine, Semmelweis University

H-1083 Budapest, Korányi str. 2/a, Hungary

Phone/Fax: +36-1-266-0816

e-mail: igaz.peter@med.semmelweis-univ.hu

Keywords: Gorlin-Goltz syndrome; nevoid basal cell carcinoma syndrome; PEComa; PTCH1, somatic mutation, germline mutation, postzygotic

Word count (excluding title page, summary, references, acknowledgements and figure legends): 2000

Summary

Gorlin-Goltz syndrome (GGS) or nevoid basal cell carcinoma syndrome is a rare tumor-overgrowth syndrome associated with multiple developmental anomalies and a wide variety of tumors. Here, we describe a case of a 23-year-old male GGS patient with bilateral giant tumors adjacent to both adrenals that raised the suspicion of malignancy on imaging. Histological analysis of both surgically resected tumors revealed perivascular epitheloid cell tumors (PEComa) that were independent of the adrenals. Exome sequencing of the patient's blood sample revealed a novel germline heterozygous frameshift mutation in the *PTCH1* gene. As a second hit, a somatic five nucleotide long deletion in the *PTCH1* gene was demonstrated in the tumor DNA of both PEComas. To the best of our knowledge, this is the first report on PEComa in GGS, and this finding also raises the potential relevance of *PTCH1* mutations and altered sonic hedgehog signaling in PEComa pathogenesis. The presence of the same somatic mutation in the bilateral tumors might indicate the possibility of a postzygotic mutation that along with the germline mutation of the same gene could represent an intriguing genetic phenomenon.

Gorlin-Goltz syndrome (GGS) or nevoid basal cell carcinoma syndrome is a rare, autosomal dominantly inherited tumor-overgrowth syndrome associated with multiple developmental abnormalities and tumors. Typical manifestations of the syndrome include basal cell carcinomas, keratocystic odontogenic tumors, central nervous system calcifications, skeletal, ophtalmological, urogenital, gastrointestinal and heart anomalies (reviewed in detail by[1, 2]). A wide variety of different tumors were described in GGS such as central nervous system tumors (medulloblastoma, meningioma), cardiac fibromas, rhabdomyosarcoma and there are occasional reports of other tumors e.g. leiomyoma, leiomyosarcoma, schwannoma, lymphoma etc.[3]. To the best of our knowledge, perivascular epitheloid cell tumor (PEComa) has not yet been described as a manifestation of the syndrome.

GGS is caused by mutations of tumor suppressor genes involved in the sonic hedgehog (SHH) signaling pathway, most frequently in Patched 1 (*PTCH1*), and in approximately 5 % of cases suppressor of fused (*SUFU*) [2, 4]. Also, occasional variants in *PTCH2* have been found in individuals with GGS but these may not be conclusive [5].

Here, we report a case of giant bilateral retroperitoneal PEComas adjacent to the adrenals in a patient with a previously undescribed frameshift germline heterozygous *PTCH1* mutation. An additional somatic mutation, as a second hit has been demonstrated in the tumor DNA by having found the same somatic mutation of the *PTCH1* gene in both tumors. The pathogenic relevance of *PTCH1* mutations and altered SHH signaling has not yet been demonstrated in PEComa.

Case report

A 23-year-old male patient without actual complaints was referred to our center with recent imaging reports showing large bilateral adrenal tumors that were discovered accidentally. Abdominal ultrasound, computed tomography (CT) (**Figure 1a**) and magnetic resonance imaging (MRI) (**Figure 1b**) described large retroperitoneal, potentially adrenal tumors (left size: 12x12x7 cm, right size: 10x7x5

cm) of unusual morphology raising both the possibility of adrenocortical cancer and pheochromocytoma or other retroperitoneal neoplasm.

Both the patient and his mother were previously diagnosed with GGS at the Department of Dermatology, Venereal Diseases and Dermatooncology of Semmelweis University based on the clinical features of the syndrome (genetic diagnosis has not been done at that time yet). The patient fulfilled three major criteria of the syndrome including basal cell carcinoma of the skin before the age of 20 (first basal cell carcinoma removed at the age of 6), palmar or plantar pitting and a first degree relative (mother) [6]. He had a history of multiple cystic tumors removed from the maxilla (most probably keratogenic odontogenic tumors, but histology was not available).

Brain MRI revealed calcifications in the falx cerebri. Macrocephaly and hypertelorism were also noted. No cardiac or urogenital anomaly was found. Abdominal imaging did not reveal any tumors in the mother, who also had typical facial appearance (hypertelorism, macrocephaly), calcification of the falx cerebri and recurrent basal cell carcinomas.

The patient was normotensive, and the detailed hormonal work-up revealed no abnormalities. Pheochromocytoma could be excluded. ^{18}FDG-PET-CT (^{18}fluorodeoxyglucose-positron-emission-tomography CT) showed moderately increased tracer uptake in both tumors and again raised its potentially malignant behavior. No further tumor was shown on ^{18}FDG-PET-CT.

During open laparotomy, two separate hard tumors were found surrounding the root of the mesentery: the left adrenal gland could not be separated from the tumor, but the intact right adrenal could be easily detached. One year after the operation the patient is well, and there is no sign of tumor recurrence by abdominal MRI. No further treatment was necessary.

Materials and Methods

Immunohistochemistry

Immunohistochemical labeling was performed on the Leica Bond-Max autostainer (Leica Biosystems, Buffalo Grove, IL) using the Bond polymer refined detection kit (DS9800). The standard antibodies used are listed in **Supplemental Table 1.**

Genetic analysis

DNA was isolated both from the patient and his mother following their informed consent. DNA sequencing of disease-causing genes both in the peripheral blood and in tumor tissues was performed based on the Ethical approval by the Hungarian Health Science Council (ETT) (IV-4474-1/2021/EKU).

DNA isolation from peripheral blood and from tissue

Total DNA purification from whole blood was done by automated nucleic acid purification using QIAamp DNA Blood Mini Kit (Cat. No.: ID: 51104, Qiagen, Hilden, Germany) on a QiaCube Instrument. DNA quality and quantity was controlled by Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) and by standard gel electrophoresis.

DNA was extracted from FFPE (formalin-fixed, paraffin embedded) blocks of both tumors and the intact left adrenal by using Maxwell RSC DNA FFPE Kit on Maxwell (Cat. No.: S1450, Madison, WI, USA) RSC Instrument as part of the routine molecular pathology diagnostics workflow.

Whole exome sequencing (WES) from peripheral blood

Library preparation was performed using Twist Human Core Exome library preparation with Twist mitochondrial panel (Cat. No.: 102026, Twist Bioscience, San Francisco, CA, USA) following the manufacturer's instruction. Subsequent sequencing was run on Novaseq Illumina platform (Illumina, San Diego, CA, USA) with an average coverage of 100x. Data were analyzed by applying Genome

Analysis Toolkit (GATK) Germline short variant discovery (SNPs + Indels) algorithm. Annotation of coding variants were done following American College of Medical Genetics and Genomics (ACMG) recommendations [7].

Multigene panel sequencing on FFPE DNA

Library preparation for targeted, next-generation sequencing (NGS) of 161 genes related to personalized tumor therapy with Oncomine™ Comprehensive Assay v3M (Cat. No.: A35805, Thermo Fisher Scientific) was performed on automated library and template prep on the Ion Chef Instrument (Cat. No.: 4484177, Thermo Fisher Scientific). NGS was run on Ion Torrent next-generation sequencing platform (Ion GeneStudio S5 System, Thermofisher Scientific, Waltham, MA, USA). Data were analyzed using Oncomine Knowledge Reporter Software (Cat. No.: A34298, Thermo Fisher Scientific).

Sanger validation and LOH (loss of heterozygosity) analysis

Targeted validation of the identified *PTCH1* variants was performed by traditional Sanger sequencing (Applied Biosystems 3031 Genetic Analyzer, Thermo Fisher Scientific) following PCR amplification. Primer sequences are presented in **Supplemental Table 2**.

Locus specific loss-of-heterogeneity (LOH) was tested as previously described [8]. Briefly, DNA from tumor tissues was used for PCR amplification by a Qiagen Multiplex PCR Kit (Qiagen). PCR product was purified by ExoSAP-IT™ reagents (Thermo Fisher Scientific), then purified amplicons were sequenced bidirectionally on an ABI3130 Genetic Analyzer (Applied Biosystems, Thermo Fisher Scientific) using a BigDye™ Terminator v.1.1 kit (Thermo Fisher Scientific).

Results

Histopathological analysis

Both tumors were found encapsulated and were completely removed. In case of the left side, an intact adrenal gland was found attached to the tumor. Histological examination revealed tumors on both sides consisting of spindle-cells resembling smooth muscle cells with eosinophilic cytoplasm (**Figure 1c**). Tumor cells were usually arranged in loose bundles, interspersed occasionally with lymphocytes. Mitotic figures were generally sparse. No necrosis was observed. Both tumors demonstrated almost diffuse strong immunoreactivity for smooth muscle actin, H-caldesmon (**Figure 1d**), desmin along with patchy labeling for HMB-45 and Melan-A (**Figure 1e**). The diagnosis of PEComa was thus established. Ki-67 immunohistochemistry revealed less than 1 % proliferating cells.

Genetic analysis

Due to the peculiar manifestation we performed exome sequencing followed by bidirectional Sanger sequencing of DNA isolated from the peripheral blood revealed a previously undescribed heterozygous frameshift mutation in exon 10 of the *PTCH1* gene both in the proband and his mother: NM_000264.3:c.1371delG (p.Met457Ilefs*34). No other pathogenic or likely pathogenic variant was identified in genes whose alterations should be reported by the ACMG (American College of Medical Genetics and Genomics) guideline[6].

While investigating tumor tissue, locus specific LOH (with copy number loss) could not be confirmed, and multigene panel NGS of the tumor tissue DNA including 161 tumor-related genes showed only *PTCH1* alterations: beside the 50% allele frequency of the above germline mutation (NM_000264.3:c.1371delG; p.Met457Ilefs*34), a 5 nucleotide deletion has also been documented with a 20% allele frequency NM_000264.3:c.2796_2800delCGCGT, p.Ala933Cysfs*24 according to the Human Genome Variation Society (HGVS) nomenclature) on the left side tumor with 50% tumor cell

ratio, whereas the same 5-nucleotide deletion has been found on the right side tumor with a 10% allele frequency with 40% tumor cell ratio. Bidirectional Sanger sequencing confirmed both the germline and somatic mutations. The multigene panel could not identify any other genetic alteration except for the germline variant with 47.26% variant allele frequency in the adjacent normal adrenal tissue.

Discussion

Perivascular epitheloid cell tumors (PEComas) are rare mesenchymal tumors displaying both melanocytic and smooth muscle differentiation [9, 10]. Angiomyolipomas are among the most common form of PEComas, but there are several uncommon forms, as well. Retroperitoneal localization has recently been established as the third most frequent, but altogether rare PEComa localization [11].

Our case highlights a unique clinical pathology of bilateral giant retroperitoneal PEComas in a patient with an obviously pathogenic and previously unreported germline mutation in *PTCH1*. To the best of our knowledge, this is the first case of PEComa in a patient with a germline *PTCH1* mutation suffering from GGS. We have not found data on PEComa in GGS at any location in general. The bilateral appearance of the tumor was highly suggestive of the pathogenic relevance of the documented germline genetic alteration.

A case of bilateral cystic adrenal lymphangiomas in GGS has been described [12]. Rare cases of adrenal PEComa including malignant tumors have been documented without clinical suspicion for GGS [13, 14]. In our case, however, despite the vicinity of both adrenal glands, the retroperitoneal PEComas were ultimately found to be independent of the adrenals. The presented case is a further example of the imaging difficulties associated with adrenal (periadrenal) tumors.

There are two main molecular routes in PEComa pathogenesis: i. loss of the *TSC1/TSC2* (tuberous sclerosis complex subunit 1 and 2) tumor suppressor complex resulting in an increased

mTORC1 (mammalian target of rapamycin complex 1) signaling; ii. genetic rearrangements, including fusion genes of the transcription factor *TFE3* (transcription factor binding to IGHM enhancer 3)[10]. Altered SHH signaling has not yet been revealed as a pathogenic route in PEComa pathogenesis.

The detected novel one base deletion (c.1371delG) causes a frameshift and consequently a premature stop codon leading to protein truncation. Frameshift mutations in *PTCH1* are common in GGS[15]. The ACMG classification of this variant is pathogenic[7].

The presence of another somatic five base deletion leading to protein truncation suggests the loss-of-function of *PTCH1*, demonstrating the pathogenic relevance of *PTCH1* mutations in the patient's PEComa. Unfortunately, *cis* and *trans* localization of the identified variants cannot be investigated as only FFPE specimens were available for genetic test.

PTCH1 is a major component of SHH that is involved in the regulation of organogenesis and tumorigenesis of numerous organs[16]. The relevance of altered SHH signaling or *PTCH1* mutations in PEComas, however, has not been previously demonstrated and thus our case is the first reported case raising this potential association.

The presence of the same somatic mutation of *PTCH1* in both tumors is intriguing. We hypothesize that a postzygotic somatic mutation could be responsible for this phenomenon analogous to the recent findings in Wilms tumor[17, 18], where phylogenetic analysis pointed at the potential origin of somatic mutations (clonal expansions) in the primordial kidney tissue before lateralization [17]. (**Figure 2**) The same somatic mutation of the disease causing *RET* protooncogene has also been detected in bilateral pheochromocytomas and a medullary thyroid cancer of a multiple endocrine neoplasia type 2 patient[19]. In our case, the young patient inherited a germline *PTCH1* mutation, and might have acquired a postzygotic somatic mutation before lateralization that resulted in the development of bilateral PEComas. Additionally, somatic mosaicism with the same mutation in different tissue types has also been described related to *PTCH1* gene[20].

Unfortunately, we cannot prove this hypothesis, as we cannot retrieve normal retroperitoneal (non-adrenal) tissue from the patient that might also contain the somatic mutation. Based on their very low proliferative rate (Ki-67 <1%), histological features, similar sizes and location, a metastatic relation between the tumors seems to be improbable.

In conclusion, we report the first case of giant bilateral retroperitoneal PEComas in a patient suffering from Gorlin-Goltz syndrome and raise the pathogenic link of *PTCH1* mutation and altered sonic hedgehog signaling in the pathogenesis of PEComa. Moreover, the same somatic mutation in the bilateral tumors might represent another clue in the pathogenesis of bilateral tumors, in this case alongside with germline mutation of the same gene.

Funding: Hungarian National Research, Development and Innovation Office (NKFIH) grants K134215 to Dr. Peter Igaz and K125231 to Attila Patocs. The study was also financed by the Higher Education Institutional Excellence Program--- of the Ministry of Human Capacities in Hungary, within the framework of the molecular biology thematic program of the Semmelweis University. Henriett Butz is a recipient of Bolyai Research Fellowship of the Hungarian Academy of Sciences.

Acknowledgements: The Department of Internal Medicine and Oncology and the Department of Dermatology, Venereology, and Dermatooncology, Semmelweis University are Reference Centres of the European Reference Networks (ERN) on rare endocrine diseases and skin, respectively. The Department of Endocrinology at the Department of Internal Medicine and Oncology is a Research Center of Excellence of the European Network for the Study of Adrenal Tumors (ENS@T).

Author contributions: Research conception (P.I.), manuscript writing (P.I., H.B.), molecular studies (H.B., A.P., A.B., E.T., P.I.T.), pathology/immunohistochemistry (P.N., K.D.), clinical management (P.I., G.T., M.M., N.W., G.H., L.P.).

Competing interests: The authors have no conflicts of interest to report.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in Journal of Medical Genetics and any other BMJ products and to exploit all rights, as set out in our licence.

Peter Igaz

References

1. Kiwilsza M, Sporniak-Tutak K: **Gorlin-Goltz syndrome--a medical condition requiring a multidisciplinary approach**. *Medical Science Monitor* 2012, **18**(9):Ra145-153.
2. Bresler SC, Padwa BL, Granter SR: **Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome)**. *Head and Neck Pathology* 2016, **10**(2):119-124.
3. Lo Muzio L: **Nevoid basal cell carcinoma syndrome (Gorlin syndrome)**. *Orphanet Journal of Rare Diseases* 2008, **3**:32.
4. Foulkes WD, Kamihara J, Evans DGR, Brugières L, Bourdeaut F, Molenaar JJ, Walsh MF, Brodeur GM, Diller L: **Cancer Surveillance in Gorlin Syndrome and Rhabdoid Tumor Predisposition Syndrome**. *Clinical Cancer Research* 2017, **23**(12):e62-e67.
5. Smith MJ, Evans DG (2021) **PTCH2 is not a strong candidate gene for gorlin syndrome predisposition**. *Familial Cancer*, on-line ahead of print doi:10.1007/s10689-021-00269-7
6. Kimonis VE, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ, Bale AE, Bale SJ: **Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome**. *American Journal of Medical Genetics* 1997, **69**(3):299-308.
7. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee: **Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology**. *Genetics in Medicine* 2015, **17**(5):405-424.
8. Butz H, Papp J, Bozsik A, Krokker L, Pócza T, Oláh E, Patócs A: **Application of Multilayer Evidence for Annotation of C-Terminal BRCA2 Variants**. *Cancers* 2021, **13**(4).
9. Thway K, Fisher C: **PEComa: morphology and genetics of a complex tumor family**. *Annals of Diagnostic Pathology* 2015, **19**(5):359-368.
10. Utpatel K, Calvisi DF, Köhler G, Kühnel T, Niesel A, Verloh N, Vogelhuber M, Neu R, Hosten N, Schildhaus HU, Dietmaier W, Evert M: **Complexity of PEComas : Diagnostic approach, molecular background, clinical management**. *Der Pathologe* 2020, **41**(Suppl 1):9-19.
11. Touloumis Z, Giannakou N, Sioros C, Trigka A, Cheilakea M, Dimitriou N, Griniatsos J: **Retroperitoneal perivascular epithelioid cell tumours: A case report and review of literature**. *World Journal of Clinical Cases* 2019, **7**(21):3524-3534.
12. Mortelé KJ, Hoier MR, Mergo PJ, Ros PR: **Bilateral adrenal cystic lymphangiomas in nevoid basal cell carcinoma (Gorlin-Goltz) syndrome: US, CT, and MR findings**. *Journal of Computer Assisted Tomography* 1999, **23**(4):562-564.
13. Lau SK: **Malignant PEComa of the adrenal gland**. *Pathology, Research and Practice* 2012, **208**(2):113-117.
14. Pant L, Kalita D, Chopra R, Das A, Jain G: **Malignant Perivascular Epithelioid Cell Tumor (PEComa) of the Adrenal Gland: Report of a Rare Case Posing Diagnostic Challenge with the Role of Immunohistochemistry in the Diagnosis**. *Endocrine Pathology* 2015, **26**(2):129-134.
15. Martinez MF, Romano MV, Martinez AP, González A, Muchnik C, Stengel FM, Mazzuoccolo LD, Azurmendi PJ: **Nevoid Basal Cell Carcinoma Syndrome: PTCH1 Mutation Profile and Expression of Genes Involved in the Hedgehog Pathway in Argentinian Patients**. *Cells* 2019, **8**(2).
16. Jeng KS, Chang CF, Lin SS: **Sonic Hedgehog Signaling in Organogenesis, Tumors, and Tumor Microenvironments**. *International Journal of Molecular Sciences* 2020, **21**(3).
17. Coorens THH, Treger TD, Al-Saadi R, Moore L, Tran MGB, Mitchell TJ, Tugnait S, Thevanesan C, Young MD, Oliver TRW, Oostveen M, Collord G, Tarpey PS, Cagan A, Hooks Y, Brougham M, Reynolds BC, Barone G, Anderson J, Jorgensen M, Burke GAA, Visser J, Nicholson JC, Smeulders N, Mushtaq I, Stewart GD, Campbell PJ, Wedge DC, Martincorena I, Rampling D, Hook L, Warren AY, Coleman N, Chowdhury T, Sebire N, Drost J, Saeb-Parsy K, Stratton MR,

Straathof K, Pritchard-Jones K, Behjati S: **Embryonal precursors of Wilms tumor**. *Science (New York, NY)* 2019, **366**(6470):1247-1251.
18. Foulkes WD, Polak P: **Bilateral Tumors - Inherited or Acquired?** *The New England Journal of Medicine* 2020, **383**(3):280-282.
19. Akama H, Noshiro T, Kimura N, Shimizu K, Watanabe T, Shibukawa S, Nakai S, Miura W, Ito S, Miura Y: **Multiple endocrine neoplasia type 2A with the identical somatic mutation in medullary thyroid carcinoma and pheochromocytoma without germline mutation at the corresponding site in the RET proto-oncogene**. *Internal Medicine* 1999, **38**(2):145-149.
20. Ikemoto Y, Takayama Y, Fujii K, Masuda M, Kato C, Hatsuse H, Fujitani K, Nagao K, Kameyama K, Ikehara H, Toyoda M, Umezawa A, Miyashita T: **Somatic mosaicism containing double mutations in PTCH1 revealed by generation of induced pluripotent stem cells from nevoid basal cell carcinoma syndrome**. *Journal of Medical Genetics* 2017, **54**(8):579-584.

Legends for figures

Figure 1.

Imaging and histological (20x magnification) features of the bilateral periadrenal retroperitoneal PEComas. **a.** coronal post-contrast CT image, **b.** coronal T2-weigthed MRI image, **c.** hematoxylin eosin staining, **d.** H-caldesmon immunohistochemistry, **e.** Melan A immunohistochemistry.

Figure 2.

Schematic illustration of the potential relevance of germline and somatic *PTCH1* mutations in the pathogenesis of bilateral PEComas in our case. The Figure was created with BioRender.com.