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INVESTIGATIVE REPORT

KRAS, *HRAS* and *EGFR* Mutations in Sporadic Sebaceous Gland Hyperplasia

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Sporadic sebaceous gland hyperplasia (SGH) is a benign skin lesion, with a high prevalence in the general population. Although SGH has been attributed to both extrinsic and intrinsic factors, the underlying genetic changes have not yet been characterized. Recently, *HRAS* and *KRAS* mutations have been identified in sebaceous naevus, a hamartoma sharing histological characteristics with SGH. Therefore we screened 43 SGH for activating mutations in *RAS* genes and other oncogenes. We identified a wide spectrum of mutually exclusive activating *HRAS* (8/43), *KRAS* (11/43) and *EGFR* mutations (7/31) in altogether 60% of the lesions investigated. A *RAS* and *EGFR* wildtype status was found in 15 normal sebaceous glands in the head and neck area. Our findings indicate that activating *HRAS*, *KRAS* and *EGFR* mutations play a major role in the pathogenesis of sporadic SGH. These results support the concept that SGH is a true benign neoplasm rather than a reactive hyperplasia. ***Key words: HRAS; KRAS; EGFR; sebaceous gland hyperplasia.***

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Sebaceous gland hyperplasia (SGH) is the most common lesion of sebaceous glands, which presents clinically as yellowish or skin-coloured umbilicated papule most commonly situated on the forehead, cheeks or nose of elderly individuals (1). Histologically, 4 or more mature sebaceous lobules localized in the upper dermis are attached to the central infundibulum of a sebaceous follicle, which opens to an umbilicated epidermal surface. The sebocytes comprising the lobules mostly show compact nuclei and multivacuolated cytoplasms except for 1 or 2 layers of peripheral basaloid, germinative cells (2, 3). It has been noted that categorizing SGH as "hyperplasias" may be inappropriate, as SGH do not involute clinically (4). SGHs have been attributed to both extrinsic factors, such as ultraviolet (UV) radiation, and chronic immunosuppression with cyclosporine as well as intrinsic factors, e.g. reduced androgen levels leading to a decreased cellular turnover in aged sebaceous glands (5). Genetic studies in transgenic mice have linked parathormone-regulated protein and *KRAS* with sebaceous gland alterations (6, 7). In humans the *BRAF* c.1799T>A mutation has been identified as contributor to the pathogenesis of SGH in a very small subgroup of patients belonging to MYH-associated polyposis pedigrees (8). The cause of sporadic human SGH has remained an enigma, however. Recently, activating post-zygotic *HRAS* and *KRAS* mutations have been identified in sebaceous naevi (9). These hamartomas share histological characteristics with SGH; however, they differ from SGH by their general breadth, papillomatous epidermal hyperplasia and frequent apocrine elements as well as their clinical course. In the light of these recent results we tested the hypothesis that SGH may not be mere hyperplasias, but true benign neoplasms, by screening sporadic SGH for activating mutations in RAS as well as other oncogenes.

MATERIALS AND METHODS

Sample acquisition

Biopsy material of a male adolescent with a pretreated organoid epidermal naevus clinically and histologically resembling linear SGH was the starting point of this study. Consequently 43 SGH were retrieved from the histological files of the Department of Dermatology, University of Regensburg, Germany. The SGH derived from 25 males and 18 females and were localized on the cheeks (20/43), the forehead (11/43), the nose (9/43) and the neck (3/43). The mean age of the patients at the time of biopsy/excision was 61 years. Various matched non-lesional tissues (overlying epidermis, unaffected sebaceous glands, various skin tumours, melanocytic naevi and other skin diseases) were available from 19/44 patients. Fifteen histologically normal sebaceous glands taken from the head and neck area from 15 elderly patients served as control. The study was performed according to the Declaration of Helsinki and was approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der Universität Regensburg, Zeichen 14-101-0001).

Mutation analyses

DNA was isolated from manually microdissected sections of formalin-fixed paraffin-embedded tissues. Due to tissue limitations the following gradual approach was adopted: in a first step *HRAS*, *KRAS*, *NRAS*, *FGFR3* and *PIK3CA* mutations were analysed using SNaPshot assays (Applied Biosystems, Foster City, CA, USA), as described previously (9). To screen for mutations in other oncogenes, the OncoCarta Panel v1.0 (Sequenom, San

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Diego, California, USA) covering mutations in *ABL1, AKT1, AKT2, BRAF, CDK4, EGFR, ERBB2, FGFR1, FGFR3, FLT3, HRAS, JAK2, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA*, and *RET* was used for a subset of SGH being wildtype for the mutations mentioned above (10). Owing to DNA quantity limitations, only 4 samples were available for analysis with OncoCarta panel 1 and altogether 31 samples for succeeding direct sequencing of *EGFR* exon 21 or SNaPshot analysis of the BRAF c.1799T>A mutation respectively. Direct sequencing of EGFR exon 21 and SNaPshot analysis of BRAF c.1799T>A was performed as described previously (11, 12). Each mutation identified was confirmed by a second independent PCR.

Immunohistochemistry

Five SGH with a proven activating mutation in *HRAS, KRAS* or *EGFR*, 5 SGH and 5 normal sebaceous glands showing an *HRAS, KRAS* and *EGFR* wildtype status in the genetic analyses performed were evaluated for phosphorylated ERK using immunohistochemistry. Phospho-p44/42 MAPK (Erk1/2) Rabbit monoclonal antibody detecting phosphorylation at Threonin 202/ Tyrosine 204 (Cell Signaling Technology, Danvers, MA, United States, #4370, dilution 1:50) was applied according to the manufacturer's instructions. Isotype control was performed to rule out unspecific staining (Cell Signaling Technology, Danvers, MA, United States, #3900). The overall Phospho-p44/42 MAPK staining intensity (not the frequency of positive tumour cells) was scored 0 (negative), 1+ (weak), 2+ (strong), and 3+ (very strong) by 2 individual investigators.

RESULTS

The starting point of our study was an otherwise healthy male adolescent who presented to our clinic with Blaschko-linear yellowish umbilicated papules alternating with demarcated brownish plaques with verrucous surface on his left chest (Fig. 1A). Five years prior to presentation he had undergone 1-time curettage and CO_2-laser treatment of the lesion. Histopathology from a yellowish papule revealed a slightly atrophic epidermis and abundant mature sebaceous lobules lying high in the dermis. Assuming a pretreated sebaceous naevus we screened this lesion for RAS mutations and detected a heterozygous *HRAS* c.37G>C mutation in the sebaceous gland, whereas the overlying epidermis revealed a wildtype sequence at codon 13 (Fig. 1B). The apparent clinical and histological parallels of this pretreated lesion with linear SGH prompted us to speculate on a similar genetic basis of SGH and sebaceous naevus. Tissues from 43 patients with sporadic SGH were available for genetic analysis. Remarkably, sporadic SGH revealed a wide spectrum of mutually exclusive activating *HRAS* and *KRAS* hotspot mutations: *HRAS* c.182A>G (2/43), *HRAS* c.181C>A (1/43), *HRAS* c.182A>T (1/43), *HRAS* c.35G>A (3/43), *HRAS* c.37G>C (1/43), *KRAS* c.34G>T (1/43), *KRAS* c.35G>T (5/43) and *KRAS* c.35G>A (5/43) (Table I). In analogy to sebaceous naevi we did not find *NRAS*, *FGFR3* or *PIK3CA* hotspot mutations in the samples studied. Moreover, as previously shown in a smaller series (8), no *BRAF* c.1799T>A mutation could be detected in an analysis of 31 sporadic SGH. In order to identify additional oncogenes involved in the pathogenesis of SGH, we analysed 4 SGH being wildtype for *HRAS* and *KRAS* using the OncoCarta Panel v1.0. This Panel covers 238 mutations in 19 oncogenes and detected 3 *EGFR* c.2573T>G (p.(Leu858Arg)) mutations, which could be confirmed by direct sequencing. On the basis of these results, we sequenced *EGFR* exon 21 in 27 additional SGH, which revealed another 3 *EGFR* c.2573T>G mutations and 1 c.2573_2574TG>GT mutation in SGH being wildtype for *HRAS* and *KRAS*. Codon 858 is localized in the kinase domain of EGFR and represents a mutational hotspot in sporadic SGH. To sum up, we detected mutually exclusive *HRAS, KRAS* and *EGFR* mutations in 60% of the lesions investigated. The somatic character of the RAS and *EGFR* mutations identified could be proven, as overlying epidermis ($n=12$) (Fig. 2), matched normal sebaceous glands ($n=7$), matched dermal or melanocytic naevi ($n=3$), non-melanoma-skin cancer ($n=3$) and tissue from other skin diseases did not show the mutations identified in the respective lesional tissues. The specificity of *RAS* and *EGFR* mutations in sporadic SGH is substantiated by the RAS and *EGFR* wildtype status found in 15 normal sebaceous glands taken from the head and neck area from 15 elderly patients (Table II). To assess whether the identification of the aforementioned oncogenic mutations indicates activation of the MAPK pathway in sporadic SGH, we performed immunohistochemical staining for phospho-ERK in 5 sporadic SGH with and 5 sporadic SGH without identified oncogenic mutation. One normal sebaceous gland adjacent to SGH sample 27 and 5 normal seba-

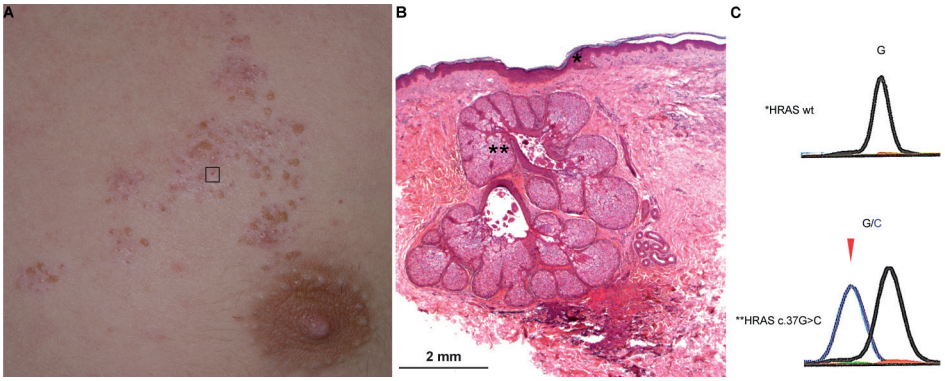


Fig. 1. Clinical, histological and genetic findings of a sebaceous naevus 5 years after curettage and CO_2 laser treatment. (A) Blaschko-linear yellowish umbilicated papules alternating with brownish, verrucous plaques. (B) Histological evaluation showed prominent sebaceous lobules (**) lying high in the dermis and a slightly atrophic overlying epidermis (*). (C) The *HRAS* c.37G>C mutation (*bottom*) was detected in the sebaceous gland (**), however, not in the overlying epidermis (*). Peaks indicate the DNA antisense strand of the *HRAS* gene.

Table I. HRAS, KRAS *and* EGFR *mutations in sporadic sebaceous gland hyperplasia*

Sample No.	Sex	Localization	*HRAS*	*KRAS*	*EGFR*	*FGFR3*	*PIK3CA*	*BRAF*	IHC
1	F	Nose	wt	wt	na	wt	wt	na	
2	M	Neck	wt	wt	na	wt	wt	na	
3	M	Nose	wt	c.34G>T[b,c]	na	wt	wt	na	
4	M	Nose	wt	wt	wt	wt	wt	wt	
5	F	Cheek	wt	wt	na	wt	wt	na	
6	F	Nose	c.182A>G[a,b]	wt	wt	wt	wt	wt	
7	F	Neck	c.181C>A[a]	wt	na	na	wt	na	
8	M	Cheek	wt	c.35G>T[b]	wt	wt	wt	wt	
9	F	Cheek	wt	wt	na	na	wt	na	
10	M	Nose	wt	wt	wt	wt	wt	wt	
11	M	Cheek	c.35G>A[a]	wt	na	na	wt	na	
12	F	Forehead	wt	wt	wt	wt	wt	wt	
13	M	Cheek	wt	wt	wt	wt	wt	wt	
14	M	Cheek	wt	wt	wt	wt	wt	wt	
15	F	Forehead	wt	c.35G>T[a,b]	wt	wt	wt	wt	
16	F	Nose	wt	wt	wt	wt	wt	wt	
17	M	Nose	c.182A>T	wt	na	na	na	na	
18	M	Forehead	wt	c.35G>T[a]	wt	wt	wt	wt	
19	M	Cheek	wt	wt	c.2573T>G[a,c]	wt	wt	wt	
20	M	Forehead	c.35G>A[a]	wt	na	na	wt	na	
21	M	Cheek	wt	c.35G>A[a]	na	na	wt	na	
22	F	Cheek	wt	wt	na	na	wt	na	
23	F	Cheek	wt	c.35G>T[a]	wt	wt	wt	wt	
24	M	Cheek	wt	wt	na	na	na	na	
25	F	Forehead	wt	c.35G>A[a]	wt	wt	wt	wt	2
26	M	Nose	wt	wt	wt	wt	wt	wt	3
27	F	Cheek	wt	wt	c.2573T>G[a,c]	wt	wt	wt	2
28	M	Nose	wt	c.35G>A[b,c]	wt	wt	wt	wt	
29	F	Cheek	wt	wt	c.2573T>G	wt	wt	wt	2
30	F	Forehead	wt	wt	c.2573T>G	wt	wt	wt	
31	M	Cheek	wt	wt	wt	wt	wt	wt	2
32	F	Neck	wt	c.35G>A[b,c]	wt	wt	wt	wt	2
33	M	Cheek	wt	wt	wt	wt	wt	wt	3
34	M	Forehead	c.182A>G[b,c]	wt	wt	wt	wt	wt	
35	M	Cheek	c.35G>A[b]	wt	wt	wt	wt	wt	
36	F	Forehead	wt	wt	c.2573T>G[a]	na	wt	wt	
37	M	Cheek	wt	c.35G>T[c]	wt	wt	wt	wt	
38	F	Forehead	wt	c.35G>A	wt	wt	wt	wt	
39	M	Cheek	c.37G>C	wt	wt	wt	na	wt	3
40	M	Cheek	wt	wt	c.2573_2574TG>GT	wt	wt	wt	
41	M	Cheek	wt	wt	c.2573T>G	wt	wt	wt	
42	F	Forehead	wt	wt	wt	wt	wt	wt	2
43	M	Forehead	wt	wt	wt	wt	wt	wt	1

For the analysis of 19 delineated *RAS* hotspot mutations, 11 known *FGFR3* hotspot mutations and 5 previously described hotspot mutations in *PIK3CA*, we used the respective established SNaPshot® assays. *EGFR* Exon 21 was directly sequenced. Control tissue, [a]being adjacent epidermis, [b]tissue distant from the SGH or [c]matched normal sebaceous glands was analysed using the respective methods mentioned above. Samples analysed by OncoCarta panel 1 are highlighted in **bold**.

na: not available; wt: wild type; IHC: immunohistochemistry (1 = weak, 2 = strong, 3 = very strong).

ceous glands from the 15 control group patients served as check. Whereas levels of ERK phosphorylation of all 10 sporadic SGH samples were categorized as strong (+2) or very strong (+3), irrespective of their mutation status, the normal sebaceous glands stained negative or weakly for phospho-ERK (Tables I and II, Fig. 3).

DISCUSSION

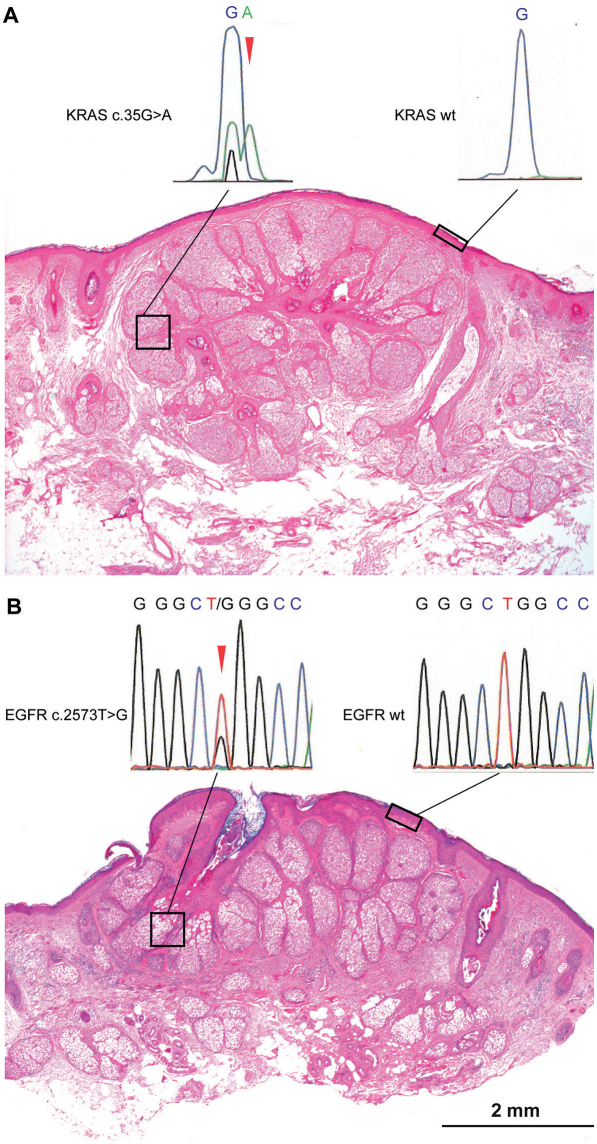
The results of this study strongly support the conclusion that activating mutations in the EGFR-RAS-MAPK pathway play a pivotal role in the pathogenesis of sporadic SGH. Our index patient and observations from animal models had prompted us to speculate on a pathogenic role of the EGFR-RAS-MAPK-pathway in sporadic SGH. For example, enlarged sebaceous glands had been demonstrated in DSK5 mice, (13) a mutant line characterized by an activating mutation in the kinase domain of the *EGFR* gene. This mutation results in a ligand-independent constitutive activation of EGFR (14). Moreover, *KRAS* c.35G>A has been found to induce SGH in a Cre-inducible mouse model (7). Despite these recent insights into the pathophysiology of sebaceous gland tumours, the genetic basis of sporadic human SGH has remained an enigma.

To the best of our knowledge, this is the first study to offer a detailed mutational analysis of sporadic human SGH. We identified a wide spectrum of mutually

Table II. HRAS, KRAS *and* EGFR *mutation status in normal sebaceous gland hyperplasia*

Sample No.	Sex	Localization	*HRAS*	*KRAS*	*EGFR*	IHC
1	F	Temple	wt	wt	wt	
2	M	Temple	wt	wt	wt	
3	F	Cheek	wt	wt	wt	0
4	F	Temple	wt	wt	wt	
5	M	Nose	wt	wt	wt	
6	M	Forehead	wt	wt	wt	0
7	F	Cheek	wt	wt	wt	
8	M	Neck	wt	wt	wt	
9	M	Nose	wt	wt	wt	1
10	M	Forehead	wt	wt	wt	
11	M	Forehead	wt	wt	wt	
12	M	Cheek	wt	wt	wt	0
13	F	Temple	wt	wt	wt	
14	M	Nose	wt	wt	wt	
15	M	Nose	wt	wt	wt	1

wt: wild type; IHC: immunohistochemistry. 0 = negative, 1 = weak.



exclusive *HRAS, KRAS* and *EGFR* mutations in 60% of the lesions investigated. Of note, no *NRAS, FGFR3*, *PIK3CA* and *BRAF* mutations could be detected in the samples analysed. As different from sebaceous adenomas or carcinomas, SGH are not indicative of Muir Torre syndrome and due to previous reports showing a very low frequency of microsatellite instability in sporadic SGH, (15) microsatellite instability was not assessed in our series. With respect to the mutated genes identified, the mutational profile of sporadic SGH resembles that of sebaceous naevi (9). However, contrary to the rather homogenous mutational pattern in sebaceous naevi, sporadic SGH reveal a wide spectrum of *HRAS* and *KRAS* mutations. An analogous phenomenon has already been observed in keratinocytic epidermal naevi and seborrhoeic keratoses. Both are benign epidermal skin tumours being histologically almost identical; however, the spectrum of *FGFR3* and *RAS* mutations is markedly more diverse in seborrhoeic keratoses than in keratinocytic epidermal naevi (16). In some of the sporadic SGH, the same *HRAS* and *KRAS* mutations have been detected as in sebaceous naevi, e.g. *HRAS* c.35G>A, *HRAS* c.37G>C, *KRAS* c.35G>T and *KRAS* c.35G>A (9). The yet existing phenotypic difference may be explained by the cell types affected by the mutation as well as the timepoint at which the mutation occurs in the respective cells. Despite the proposed role of UV irradiation in the pathogenesis of sporadic SGH, none of the mutations identified showed a UV signature (17). Our findings, together with the observation that EGFR as well as the extracellular signal-regulated kinases are activated in skin cells following UV-irradiation, (18) argue for an indirect rather than a direct role of UV irradiation in the pathogenesis of sporadic SGH. The fact that a proportion of sporadic SGH in this study did not show any oncogenic mutation, yet strong immunopositivity for pERK indicating MAPK-pathway activation may be explained in 3 ways: first, other genes within the EGFR-RAS-MAPK-pathway, which were not covered by the assays used in this study, might be involved in the pathogenesis of SGH. Secondly, mutations within the genes investigated might have been missed, as not all exons of *EGFR* could be sequenced and not the full range of mutations is covered by the respective SNaPshot assays used. Furthermore, due to tissue limitations not all samples could be analysed

Fig. 2. Histological findings and corresponding *RAS* SNaPshot multiplex assay chromatograms/DNA sequence chromatograms of sporadic SGH. (A) Sample 25 shows abundant mature sebaceous lobules lying high in the dermis as well as an atrophic epidermis. A heterozygous *KRAS* c.35G>A mutation was detected in the sebaceous gland, whereas overlying epidermis revealed a wildtype sequence at codon 12. Peaks indicate the DNA antisense strand of the *KRAS* gene. (B) In sample 36 sebaceous lobules are attached to the central infundibulum of a sebaceous follicle, whose canal opens to an umbilicated epidermal surface. DNA sequence chromatograms show a heterozygous *EGFR* c.2573T>G mutation in the lesional tissue and a wildtype sequence at *EGFR* codon 858 in the overlying/adjacent epidermis.

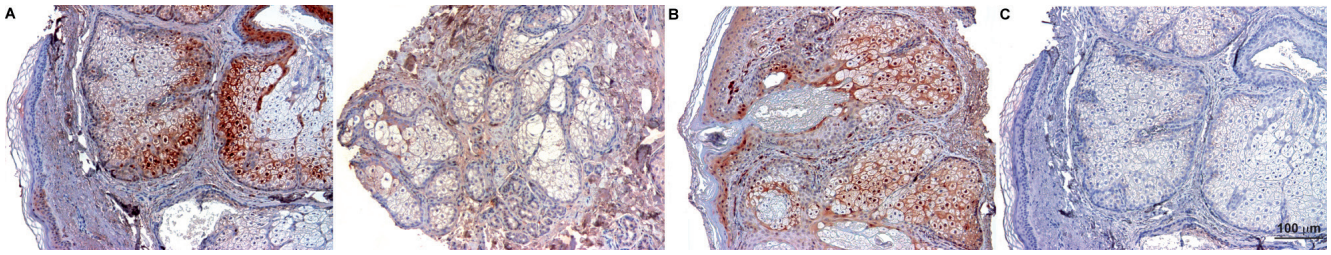


Fig. 3. Representative pERK1/2 staining in sporadic sebaceous gland hyperplasia (SGH) and matched normal sebaceous glands. (A) SGH sample 27 shows strong pERK1/2 staining (*left*) whereas pERK1/2 staining is very weak in the adjacent normal sebaceous glands (*right*). (B) SGH sample 31 also shows strong pERK1/2 staining. (C) Isotype control.

for all aforementioned genes. Thirdly, extrinsic factors leading to a constant activation of the RAS-MAPK-pathway may also induce SGH. Cyclosporin A, for example, has been shown to significantly increase the level of activated GTP-bound Ras, (19) and to induce SGH in patients under long-term treatment (20).

In summary, this study expands the spectrum of benign skin lesions harbouring *HRAS, KRAS* and *EGFR* mutations (21, 22) and sheds light on the pathogenic mechanisms underlying sporadic human SGH. Moreover, our data provide molecular support for the previously postulated hypothesis that sporadic SGH may be benign neoplasms rather than a form of hyperplasia. Further studies are needed to determine whether other sebaceous neoplasms (sebaceous adenoma and carcinoma) may harbour a similar mutational profile as sporadic SGH.

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The authors declare no conflicts of interest.

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