Comprehensive profiling of the mutational landscape of hidradenoma papilliferum validates key role of alterations in the phosphoinositide 3-kinase/AKT pathway

https://doi.org/10.1093/bjd/ljaf257

Dear Editor, To date, genetic characterization of hidradenoma papilliferum (HP) has identified recurrent somatic mutations in *PIK3CA* and *AKT1*, with recurrent *PIK3R1* mutations seen in some cases without *PIK3CA* or *AKT1* mutations.[1–5] However, these studies used small sample sizes and/or analysed a limited number of genes; thus the mutational landscape of HP remains incomplete. Furthermore, the aetiology of HP is currently unclear; human papillomavirus (HPV) DNA has been detected in some anogenital HP lesions[6,7] but not others,[3,5,8] and HPV42 has recently been identified as a driver of digital papillary adenocarcinoma[9] – a cutaneous adnexal tumour that shows similar histological characteristics to HP. Thus, to comprehensively characterize the mutational landscape of HP, we collated a cohort of 68 HP cases, ascertained from 8 institutions across 7 countries; the tumours were all from the female anogenital region (predominantly the vulva; 87%).

The cohort was subdivided into cases that had tumour tissue with matched normal tissue ($n=35$; 'discovery' cohort), and cases that had tumour tissue only ($n=29$; 'validation'

cohort). Whole-exome sequencing was performed on the DNA from both cohorts, and pulldown RNA sequencing (RNAseq) was performed on tumour RNA from 60 cases (selected from both cohorts), with all sequencing data deposited in the European Genome and Phenome Archive.

Focusing on the discovery cohort, the tumour mutational burden of HP was low (median 0.270 mutations per megabase), and thus we were not able to identify any COSMIC mutational signatures. The most recurrently mutated genes were *PIK3CA* and *PIK3R1* (Figure 1a; mirrored in

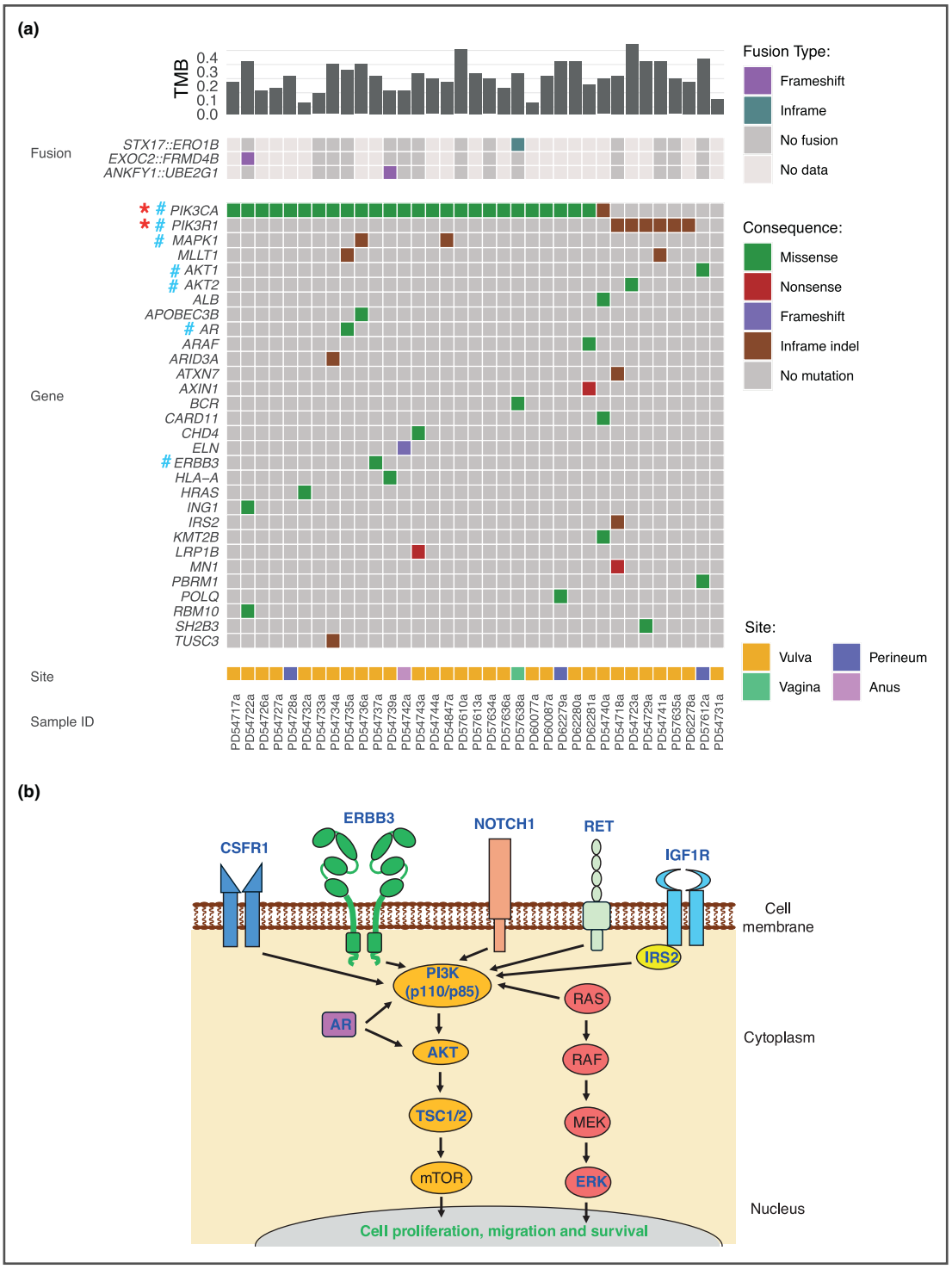

Figure 1 Overall mutational landscape of hidradenoma papilliferum. (a) The 'discovery cohort' ($n=35$). Tumour mutational burden (TMB) is shown as mutations per megabase. The oncoplot panel shows OncoKB database cancer genes for which a mutation was present in at least one sample. Asterisks (in red) indicate significantly mutated genes and hashtags (in light blue) indicate genes in the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signalling pathway. (b) Schematic diagram showing the PI3K/AKT/mTOR signalling pathway and associated pathways and interactors. Blue text indicates the translated proteins of genes that were altered (somatic mutations or germline variants) in the hidradenoma papilliferum (HP) cohort. *MAPK1* encodes ERK2 (shown as ERK).

the validation cohort), which encode the p110α catalytic and p85α regulatory subunits of the phosphatidylinositol 3-kinase (PI3K) enzyme. In both cohorts, the *PIK3CA* mutations were located at known 'activating/oncogenic' hotspots (p.H1047R/L and p.E545K). Similarly, all but one of the *PIK3R1* mutations occurred at known hotspots that were predicted to be 'likely oncogenic'. Using two different algorithms to identify genes under positive selection in the tumours, both *PIK3CA* and *PIK3R1* were found to be significantly mutated, and thus represent candidate driver genes of HP. Furthermore, co-mutation and mutual exclusivity analysis found that *PIK3CA* and *PIK3R1* mutations were mutually exclusive.

The PI3K enzyme is a key part of the PI3K/AKT/mammalian target of rapamycin (mTOR) intracellular signalling pathway responsible for driving cell proliferation, migration and survival. Considering both cohorts, we identified recurrent mutations in key members of this pathway, specifically *PIK3CA*, *PIK31R* and *AKT1* (and a single tumour with an *AKT2* mutation). Other mutated cancer genes with a link to this pathway included receptors/receptor-associated proteins that signal via the PI3K/ATK/mTOR pathway (*ERBB3*, *IRS2*), or are members of pathways that crosstalk with the PI3K/AKT/mTOR pathway (*AR* and *MAPK1*; Figure 1b). Of these four genes, only *AR* has been previously reported as mutated in HP.[5]

Using the discovery cohort, we performed the first copy number (CN) analysis of HP and found a very quiet landscape with no recurrent chromosomal gains or losses, and the tumours were all diploid (Figure S1; available at https://doi.org/10.6084/m9.figshare.29395838.v1). Taken together, this strongly suggests that CN alterations are not driver events in HP. Using the RNAseq data, a total of five different fusion genes were identified (Figure 1a). However, given that these fusions were found in tumours with somatic *PIK3CA* or *AKT1* mutations, and the fusions were only found in one tumour sample each, it would suggest they are not driver events. As a potential role for HPV in HP pathogenesis remains unclear, we looked for the presence of any viruses in our tumour sequencing reads. Using an algorithm that searches for short segments of viral sequences ('minimizers'), we did not find a significant presence of minimizers belonging to the HPV genera (*Alphapapillomavirus*, *Betapapillomavirus* or *Gammapapillomavirus*).

Sequencing of normal tissue in our discovery cohort allowed for investigation of putative pathogenic germline variants in HP. Focusing on known cancer-predisposition genes with variants of moderate-to-severe functional impact, the most commonly altered genes were *ARID1B* and *CEBPA* (3 of 35, 9% of cases each). Importantly, there was a patient carrying a ClinVar 'pathogenic' variant, specifically PD54740 (a frameshift deletion in *NF1* at p.L1877X). There were also patients with mutations in members of the PI3K/AKT/mTOR signalling pathway (*TSC1/2*), mutations in receptors that signal through this pathway (*CSFR1*, *NOTCH1*, *RET*, *IGF1R*) or mutations in members of other pathways that crosstalk with this pathway (*MAPK1*; Figure 1b).

In summary, our comprehensive characterization of the genomic landscape of a large cohort of HP has identified *PIK3CA* and *PIK3R1* as mutually exclusive driver genes, and confirmed a key role for the alteration of genes in the PI3K/AKT/mTOR signalling pathway in driving this tumour type.

Saamin Cheema,[1] Louise van der Weyden,[1] Kim Wong,[1] Martin Del Castillo Velasco-Herrera,[1] Jamie Billington,[1] Ian Vermes,[1] Elizabeth Anderson,[1] Laura Allen,[1] Nicolas de Saint Aubain,[2] Michiel P J van der Horst,[3] Ahmed K Alomari,[4,5] Carolin Mogler,[6] Carlos Monteagudo,[7] Derek Frew,[8] Steven D Billings,[8] Mark J Arends,[9] Ingrid Ferreira,[1] Thomas Brenn[10,11] and David J Adams[1]

[1]Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, UK

The complete list of author affiliations is available in File S1 (see Supporting Information).

Correspondence: David J. Adams. Email: da1@sanger.ac.uk

Funding sources: This study was funded by the Medical Research Council (UK) (MR/V000292/1) and the Wellcome Trust (220540/Z/20/A).

Conflicts of interest: The authors have no competing or financial interests to declare.

Data availability: The sequencing data are available in the European Genome and Phenome Archive repository (https://www.ebi.ac.uk/ena/browser/home) under the study accessions EGAD00001015481 for whole-exome data, and EGAD00001015480 for RNA sequencing data.

Ethics statement: Ethical approval for the use of all patient samples in this project was obtained by a local committee at the institution of origin and from Research Governance at the Wellcome Sanger Institute. This study is part of the DERMATLAS Project that has been approved by the National Health Service Health Research Authority (Research Ethics Committee reference: 21/PR/1024, Integrated Research Application System project ID: 304621).

Patient consent: The study is anonymized linked and patient consent was given for inclusion of their tissue samples and associated clinical metadata in the study.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

References

1 Liau JY, Lan J, Hong JB *et al.* Frequent PIK3CA-activating mutations in hidradenoma papilliferums. *Hum Pathol* 2016; **55**:57–62.
2 Goto K, Maeda D, Kudo-Asabe Y *et al. PIK3CA* and *AKT1* mutations in hidradenoma papilliferum. *J Clin Pathol* 2017; **70**:424–7.
3 Pfarr N, Sinn HP, Klauschen F *et al.* Mutations in genes encoding PI3K-AKT and MAPK signaling define anogenital papillary hidradenoma. *Genes Chromosomes Cancer* 2016; **55**:113–19.

4 Konstantinova AM, Vanecek T, Martinek P *et al.* Molecular alterations in lesions of anogenital mammary-like glands and their mammary counterparts including hidradenoma papilliferum, intraductal papilloma, fibroadenoma and phyllodes tumor. *Ann Diagn Pathol* 2017; **28**:12–18.
5 Pfarr N, Allgäuer M, Steiger K *et al.* Several genotypes, one phenotype: *PIK3CA/AKT1* mutation-negative hidradenoma papilliferum show genetic lesions in other components of the signalling network. *Pathology* 2019; **51**:362–8.
6 Kazakov DV, Mikyskova I, Kutzner H *et al.* Hidradenoma papilliferum with oxyphilic metaplasia: a clinicopathological study of 18 cases, including detection of human papillomavirus. *Am J Dermatopathol* 2005; **27**:102–10.
7 Birge O, Bakır MS, Karadag C *et al.* Hidradenoma papilliferum of the hymen: a case report. *J Med Case Rep* 2021; **15**:162.
8 Kazakov DV, Nemcova J, Mikyskova I *et al.* Human papillomavirus in lesions of anogenital mammary-like glands. *Int J Gynecol Pathol* 2007; **26**:475–80.
9 Leiendecker L, Neumann T, Jung PS *et al.* Human papillomavirus 42 drives digital papillary adenocarcinoma and elicits a germ cell-like program conserved in HPV-positive cancers. *Cancer Discov* 2023; **13**:70–84.

NO COMPROMISE, JUST CLEARANCE

Bimzelx®▼ (bimekizumab) offers the opportunity for complete, fast, and lasting skin clearance and proven PsA efficacy [1–7]

68.2% (n=238/349)

of patients with PsO achieved **PASI 100 at Week 16**

(vs 1.2% placebo [n=1/86], p<0.0001)*** [2]

75.9% (n=265/349)

of patients with PsO achieved **PASI 75 at Week 4**

(vs 1.2% placebo [n=1/86], p<0.0001)*** [2]

76.9% (N=52)†

of patients with PsO achieved **PASI 100 at 5 years**[3]

51.5% (n=222/431) and **50.6%** (n=135/267)

of biologic-naïve and TNFi-IR PsA patients achieved **ACR 50 at Week 104/100,** respectively‡ [1,4–6]

BIMZELX was well tolerated, the most frequently reported adverse reactions were: upper respiratory tract infections and oral candidiasis. Other common reported adverse reactions include tinea infections, ear infections, herpes simplex infections, oropharyngeal candidiasis, gastroenteritis, folliculitis, headache, rash, dermatitis, eczema, acne, injection site reactions, fatigue, and vulvovaginal mycotic infection (including vulvovaginal candidiasis).[4]

This promotional material has been created and funded by UCB Pharma Ltd and is intended for healthcare professionals in the UK.

BIMZELX is indicated for the treatment of: moderate to severe plaque PsO in adults who are candidates for systemic therapy; active PsA, alone or in combination with methotrexate, in adults who have had an inadequate response, or who have been intolerant, to one or more DMARDs; active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI, in adults who have responded inadequately, or are intolerant, to NSAIDs; active AS in adults who have responded inadequately or are intolerant to conventional therapy; and active moderate to severe HS (acne inversa) in adults with an inadequate response to conventional systemic HS therapy.[4]

Prescribing information for United Kingdom click here.
Please refer to the SmPC for further information.

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.mhra.gov.uk for the UK. Adverse events should also be reported to UCB Pharma Ltd at UCBCares.UK@UCB.com or 0800 2793177 for UK.

These data are from different clinical trials and cannot be directly compared.

Co-primary endpoints PASI 90 and IGA 0/1 at Week 16 were met.**Secondary endpoints. †N= mNRI, missing data were imputed with mNRI (patients with missing data following treatment discontinuation due to lack of efficacy or a TRAE were counted as non-responders; multiple imputation methodology was used for other missing data). ‡43.9% (n=189/431), and 43.4% (n=116/267) of biologic-naïve and TNFi-IR PsA patients achieved the primary endpoint of ACR 50 at Week 16 in BE OPTIMAL and BE COMPLETE, respectively (vs 10.0% [n=28/281] and 6.8% [n=9/133] placebo, p<0.0001); 54.5% (n=235/431) and 51.7% (n=138/267) maintained it at Week 52 (NRI).[4–6]

ACR 50, ≥50% response in the American College of Rheumatology criteria; **AS**, ankylosing spondylitis; **CRP**, C-reactive protein; **DMARD**, disease-modifying antirheumatic drug; **HS**, hidradenitis suppurativa; **IGA**, Investigator's Global Assessment; **(m)NRI**, (modified) non-responder imputation; **MRI**, magnetic resonance imaging; **nr-axSpA**, non-radiographic axial spondyloarthritis; **NSAID**, non-steroidal anti-inflammatory drug; **PASI 75/90/100**, ≥75/90/100% improvement from baseline in Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsD**, psoriatic disease; **PsO**, psoriasis; **TNFi-IR**, tumour necrosis factor-α inhibitor – inadequate responder; **TRAE**, treatment-related adverse event.

References: 1. Gordon KB, et al. Lancet. 2021;397(10273):475–486. 2. Blauvelt. 2025. AAD Presentation 62275. 3. Mease PJ, et al. Rheumatol Ther. 2024;11(5):1363–1382. 4. BIMZELX SmPC. 5. Ritchlin CT, et al. Ann Rheum Dis. 2023;82(11):1404–1414. 6. Coates LC, et al. RMD Open. 2024;10(1):e003855. 7. Strober B, et al. AAD 2024;oral presentation.

Inspired by patients. Driven by science.

GB-BK-2500315 | July 2025

Bimzelx®▼ (bimekizumab)