Virology 468-470 (2014) 244–247

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Brief Communication

No association between Birt-Hogg-Dubé syndrome skin fibrofolliculomas and the first 10 described human polyomaviruses or human papillomaviruses

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ARTICLE INFO

Article history:
Received 16 June 2014
Returned to author for revisions
15 July 2014
Accepted 14 August 2014
Available online 6 September 2014

Keywords:
Birt–Hogg–Dubé syndrome
Human papillomavirus
Human polyomavirus
Fibrofolliculomas
Renal cancer
Pneumothorax

ABSTRACT

The rare autosomal dominant condition Birt–Hogg–Dubé syndrome (BHD) is attributed to mutations on chromosome 17 in the folliculin (FLCN) gene, but not always diagnosed due to lack of, or a variety of symptoms such as fibrofolliculomas, lung cystic lesions, spontaneous pneumothorax and renal cancer. We hypothesized that the lack of or variability in symptoms could be due to BHD patients potentially being abnormally susceptible to infections with human papillomavirus (HPV) or human polyomavirus (HPyV), which can be associated with skin lesions or latency in the kidneys. Seven fibrofolliculoma skin lesions, one renal cancer and one lung cyst from nine patients with BHD treated at the Karolinska University Hospital were therefore analyzed for cutaneous and mucosal HPV types and 10 HPyVs by bead based multiplex assays or by PCR. All samples were negative for viral DNA. In conclusion, the data suggest that HPV and HPyVs do not contribute to BHD pathology

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Introduction

Birt–Hogg–Dubé syndrome (BHD) is autosomally dominant and attributed to mutations on chromosome 17p12-q11.2 in the folliculin (FLCN) gene encoding folliculin, a protein involved in the mTOR pathway, but with an essentially unknown function. (Birt et al., 1997; Khoo et al., 2001; Schmidt et al., 2001; Menko et al., 2009). BHD patients may present with benign skin fibrofolliculomas, trichodiscomas and acrochordons often after the age of 20 years, multiple lung cystic lesions, spontaneous pneumothorax and renal cancer (Birt et al., 1997; Schmidt et al., 2001). However, BHD is not always diagnosed, due to a wide clinical variability as well as limited experience among health workers. (Menko et al., 2009). Some patients and families present with only sporadic cystic lung disease, pneumothorax or renal cancer or very few unnoticed fibrofolliculomas, Others may only have inconspicuous fibrofolliculomas, and it has been estimated that up to 25% of FLCN-mutation carriers older than 20 years of age do not display apparent skin lesions (Schmidt et al., 2005; Toro et al., 2008). Facial angiofibromas and multiple small intraoral papules in the mucosal surfaces of the lips, buccal mucosa and gingivae have also occasionally been described in BHD as have other tumor types and second hit mutations have been suggested in renal, but not skin cancers (van Steensel et al., 2007; Menko et al., 2009). The diagnosis of BHD is best performed by the detection of a pathogenic FCLN germ line mutation (Khoo et al., 2001; Schmidt et al., 2001).

BHD may thus solely be a genetic disease, but its variability in the clinical presentation could also reflect upon a special sensitivity to an infectious agent, similar to that of e.g. Epidermodysplasia verruciformis (EV) patients (Orth, 2006; Patel et al., 2010). Patients with EV, have an inactivating mutation on either the EVER1/TMC6 or EVER2/TMC8 genes, also on chromosome 17, and exhibit special

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http://dx.doi.org/10.1016/j.virol.2014.08.011
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sensitivity to infections with certain common cutaneous human papillomavirus (HPV) types (Orth, 2006; Patel et al., 2010). In contrast to the general population, EV patients may upon e.g. HPV type 5 infection develop pityriasis like macules, flat wart-like and cutaneous carcinomas (Orth, 2006).

Likely culprits in BHD could be different HPV types or human polyomaviruses (HPyVs) with several new HPyVs detected since 2007, with some (e.g. MCV, HPyV6,7 and TSV) preferentially found in skin, while others (e.g. BKV and JCV) are potentially latent in the kidney (Feng et al., 2008; Schowalter et al., 2010; van der Meijden et al., 2010; Dalianis and Hirsch, 2013; Ehlers and Wieland, 2013). Furthermore, murine polyomavirus (MPyV), another member of the polyomavirus (PyV) family often infects the skin, the kidneys and the lung and can potentially induce many types of tumors (Berke and Dalianis, 1993; Berke and Dalianis, 2000; Ramqvist and Dalianis, 2009). For this purpose we examined fibrofolliculoma skin lesions of seven patients with BHD, in addition to one lung cyst and one kidney biopsy from two other BHD patients for the presence of 10 HPyVs and for at least 44 HPVs including many occurring in the skin.

Results

In total nine biopsies from patients with BHD, (seven histopathology verified skin fibrofolliculomas, a renal cancer and a lung biopsy including a cyst lesion) were included in this study. Patients demographics and clinical features related to BHD are summarized in Table 1. DNA was extracted from all the samples tested for the presence of the 10 most recent human polyomaviruses (HPyVs) and SV40 and LPyV. In addition, all samples were also tested for 44 HPV types, with the seven cutaneous samples tested for additional cutaneous HPV-types. All samples were negative for all analyzed viral DNA, with the exception of one fibrofolliculoma skin sample, which was very weakly positive for WUPyV and MCPyV, with signals <0.1 viral genome per cell (Table 1).

Discussion

Here, seven skin lesion biopsies, one renal cancer biopsy and one lung biopsy including typical lesions from nine patients with BHD, were tested for the presence of HPV and HPyV DNA. All nine samples were negative for the 44 HPVs and the 10 HPyVs included in the analysis, with the exception of one skin sample, which was very weakly positive (<0.1 copy/cell) for WUPyV and MCV. The data thus suggest that none of the tested HPVs or HPyVs contributed to BHD pathology.

Since BHD is an autosomal dominant condition with mutations in the FLCN gene responsible for various symptoms associated with the disease, this may not have been unexpected (Khoo et al., 2001; Schmidt et al., 2001; Menko et al., 2009). However, our results do not exclude the possibility that other infectious agents or additional mutations may still be involved in the development of BHD. There is a possibility that variants of one or several of the PyV included in the assay have been present in the BHD samples but not detected due to mismatch in the primer sequences. However, since the assay includes two target regions (in ST and VP1) for each virus as well as being run with an annealing temperature allowing for at least one mismatch per primers, this is less likely.

With modern technologies, many new, hitherto unknown, infectious agents have been detected, demonstrating how much we still lack in our knowledge of such agents and in the diseases that they may be associated with (Allander et al., 2005a,b, 2007; Dalianis and Garcea, 2009; Dalianis and Hirsch, 2013; Ehlers and Wieland, 2013; Foulongne et al., 2012; Hellwig and Gold, 2011; Johne et al., 2009: Marra et al. 2003). Obvious examples include the detection of e.g. the 10 new HPyVs, where two MCV and TSV have been associated with previously known rare diseases, i.e. Merkel Cell Carcinoma in the elderly and Trichodyspasia spinulosa in immunosuppressed transplanted individuals (Feng et al., 2008; van der Meijden et al., 2010). Another example is the development of progressive multifocal leukoencephalopathy in multiple sclerosis patients after the introduction of treatment with natalizumab (Hellwig and Gold, 2011). Nevertheless, there are numerous studies that fail to identify associations between infectious agents and diseases, or skin conditions potentially caused by infectious. HPyVs and HPVs have e.g. not been confirmed in e.g. none sun-exposed melanomas or keratoacanthoma, nor in this study (Dahlgren et al., 2005; Giraud et al., 2008b; Wieland et al., 2012; Ramqvist et al., 2014), However, MCV sequences have been reported in nonmelanoma skin cancer of immunosuppressed patients (Kassem et al., 2009).

In conclusion, our results indicate that the presently tested 10 HPyVs and the tested cutaneous and mucosal HPV types do not play a major role in the pathology of BHD. However, this does still not exclude the presence of variants of the above viruses, other viruses, or other infectious agents. The search for associations between diseases and infectious agents should still continue and could among this group of patients be complemented by e.g. genome wide sequencing.

Material and methods

Patients

Between 2012 and 2014, 7 fibrofolliculoma skin biopsies, 1 renal cancer biopsy and 1 lung biopsy were collected from 9 patients aged 28–75 years of age with BHD at the Karolinska University

Table 1
Some characteristics of the BHD patients and their lesions.

Patient code	Gender[a]	Age[b]	Family relations	Pneumo-thorax	Biopsy	HPV and HPyV status
BHD-1	M	48		>3	Renal cancer	0
BHD-2	M	65	Father of BHD-5 and BHDS-6 twin sisters	3	Folliculoma	0
BHD-3	M	75		30	Folliculoma	WUPyV(3)[c] MCV(9)[c]
BHD-4	M	45		>10	Folliculoma	0
BHD-5	F	28	Daughter of BHD-2. Twin sister of BHD-6	1	Folliculoma	0
BHD-6	F	28	Daughter of BHD-2. Twin BHDS-5	0	Folliculoma	0
BHD-7	F	48		0	Folliculoma	0
BHD-8	M	68	Father of BHD-9	0[d]	Folliculoma	0
BHD-9	F	45	Daughter of BHD-8	1	Lung cystic lesion	0

[a] M=male, F= female.
[b] Years.
[c] Chronic obstructive lung disease.
[d] MFI values corresponding to signals <0.1 copy/cell.

Hospital. Most patients presented with only skin manifestations, but one patient presented with multiple renal cancers and recurring pneumothorax episodes, while another patient aged 45 years, had a cystic lesion in the lung. Some of the patients' characteristics obtained from the patients records are shown in Table 1. The study was performed according to ethical permission 2012/83-31/2 obtained from the Stockholm Regional Ethical Committee at Karolinska Institutet.

DNA extraction

DNA extraction was performed from fresh frozen skin biopsies, obtained after rinsing of the skin with saline and local anesthesia, using the QIAmp DNA micro kit (Qiagen, Hilden, Germany) protocol with minor modifications. Biopsy pieces were mixed with 180 μl Buffer ATL, 20 μl Proteinase K and incubated overnight at 56 °C. 200 μl Buffer AL and 200 μl 99% ethanol was then added to the lysate followed by incubation at room temperature (RT) for 5 min. Lysate was transferred to QIAmp minElute Columns and centrifuge for 1 min 8000 rpm. 500 μl Buffer AW1 was added to the spin columns and centrifuged. This was repeated with 500 μl Buffer AW2, and then centrifuged 8000 rpm for 3 min. The spin columns were transferred to clean 2 ml eppendorf tubes and DNA was eluted with 50 μl Buffer AE. DNA was stored at −20 °C. The renal cancer biopsy was also fresh frozen and DNA extracted as described above. The lung biopsy was formalin fixed and paraffin embedded. Two 5 μm thick sections and one blank counterpart were cut and placed in two 1.5 ml Eppendorf tubes. DNA was prepared using Roche High-Pure RNA paraffin kit (Roche Diagnostics) according to the manufacturer's instructions, but with exclusion of the DNase treatment.

PCR-amplification of PyV and β-globin DNA

For detection of 12 different PyVs a newly-developed PCR assay, was used (Gustafsson et al., 2013). This assay simultaneously targets the small T-antigen (ST) and viral protein 1 (VP1) region of 10 human PyV; BKPyV, JCPyV, KIPyV, WUPyV, MCV, TSV, MWPyV (HPyV10) HPyV6, 7, 9 and two primate PyVs; SV40 and LPyV, together with β-globin. The primers and assay have previously been described in detail, (Gustafsson et al., 2013). The β-globin primers were prolonged as described in Ramqvist et al. (2014). Details of all included primers and probes can be requested from the corresponding author. As described in Gustafsson et al. (2013) the assay has a sensitivity of <5 genomes for each target, with exception of a couple of targets, where the sensitivity was <50 genomes. In addition, the sensitivity of the assay was also validated with control viral DNA mixed with 50 ng human cellular DNA before the PCR. Briefly, the PCR was performed in a 25 μl reaction mix containing 0.2 μM of each primer and Multiplex PCR Master Mix (Qiagen). A denaturation step of 15 min at 94 °C was followed by 40 cycles of 20 s at 94 °C, 90 s at 50 °C and 80 s at 71 °C. The PCR was terminated with a 4 min incubation at 71 °C. The PCR was performed on 10 or 50 ng sample DNA with a corresponding sample volume for blank samples, prepared together with the BHD samples. As a positive general evaluation of the PCR reaction, cellular DNA from the Siha cell line was included in each assay in an amount corresponding to 5, 50 and 500 cell genomes. As positive HPyV controls, BKV and JCV positive urine samples were included in the analysis.

Detection of PyV amplicons by a multiplex bead based assay

For the analysis of PyV amplicons, a bead-based multiplex assay on a Magpix instrument (Luminex, Houston, TX, US) was used as described previously (Gustafsson et al., 2013). 5 μl of the PCR reaction was incubated for 30 min at 46 °C in a shaker set at 500 rpm, in a buffer consisting of 0.15 M tetramethylammonium chloride, 12 mM Tris, 10 mM EDTA and 2.5 g/l sarkosyl with a pH of 8.0, together with a bead-mix consisting of 1000 beads of each of the 25 different bead types, coupled with probes for ST or VP1, for each of the 12 different PyVs and for β-globin. After washing the beads were incubated for 30 min at room temperature with streptavidin R-phycoerythrin conjugate (Life Technologies, CA, USA) diluted 1:300 in 2.0 M tetramethylammonium chloride, 75 mM Tris, 6 mM EDTA and 1.5 g/l sarkosyl, with a pH of 8.0. The output from the analysis on the MagPix instrument was given as median fluorescent index (MFI). A MFI value over 2 × background+20 was considered as a positive value. All samples with a MFI value for β-globin >30 and were considered to have DNA of enough quality for the analysis. All samples were evaluated in at least two assays.

Analysis of DNA from mucosal and cutaneous HPV-types

Analysis for the presence of 27 different mucosal HPV types (HPV6, 11, 16, 18, 26, 30, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82) was also performed by PCR followed by evaluation by a multiplex bead based assay on a MagPix instrument as described previously (Nordfors et al., 2014). For the PCR reaction 10 or 50 ng sample DNA was added in a 25 μl reaction mix of which 5 μl was evaluated in the MagPix analysis. As a positive control both for viral and cellular DNA, cellular DNA corresponding to 5, 50 and 500 cell genomes from the HPV16 positive Siha cell line was included in each assay. To examine for possible presence of cutaneous HPV DNA a PCR based on the CPI/IIG primer set (Tieben et al., 1993) was run as described previously, with SiHa also here included as a positive control (Mellin et al., 2002). In addition to identify several mucosal HPV types, these primers also detect cutaneous HPV types 1–5, 7–8, 10, 12, 14, 19–22, 24–25, and 36. Thus in combination, the two utilized assays had the capacity to test for 44 HPV types. In addition, the seven fibrofolliculoma skin samples were also analyzed with another broad range HPV PCR with the primers FAP59/64 detecting up to 240 skin HPV-types (Forslund et al., 1999, 2007; Chouhy et al., 2013). As a positive control a mixture of two DNA-extractions of clinical samples, diluted x 1000, with cutaneous HPV57 and HPV28 was used. As a negative control 50 ng of human DNA (Sigma-Aldrich D0711) in TE-buffer (10 mM Tris–HCl, 0.1 mM EDTA, pH 8.0) was used.

Acknowledgments

We are grateful to Ola Forslund who was helpful with the FAP59/FAP64 analysis. This work was supported by: The Swedish Cancer Foundation (120417), The Swedish Medical Research Council (K2011-56X-15282-07-6), The Stockholm Cancer Society (131202), Henning and Ida Perssons Research Foundation, Karolinska Institutet, the Stockholm City Council, Swedish Cancer and Allergy Foundation (150144), and the Stockholm County ALF (20120007/20130078).

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