Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Munetsugu T, Igawa K, Fujimoto T, Shibama S, Nishizawa A, Yokozeki H.	Cold-induced hyperhidrosis: possible association with hyper-IgE syndrome.	Int J Dermatol.		doi: 10.1111/ijd.13357.	2016 Oct 25.
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杉本 佐江子, 佐田 憲映, 新関 寛徳, 中林 一彦, 岩月 啓氏	**【遺伝子検索を行った皮膚病】 <臨床例>SLCO2A1遺伝子ヘテロ複合型変異が同定された肥厚性皮膚骨膜症.**	**皮膚病診療**	38:	813-816	2016.08
Nakazawa S , Mori T, Niizeki H, Matsuda M, Nakabayashi K, Tokura Y	Complete type of pachydermoperiostosis with a novel mutation c.510G>A of the SLCO2A1 gene.	J Dermatol.		doi: 10.1111/1346-8138.13728.	2016 Dec 27
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Ⅳ．研究成果の刊行物・別刷

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LETTER TO THE EDITOR

Infiltration of mast cells in pachydermia of pachydermoperiostosis

Dear Editor,

Pachydermoperiostosis (PDP; Online Mendelian Inheritance in Man #614441) is a rare hereditary disease characterized by distinctive digital clubbing, periostosis and pachydermia.[1] Patients with PDP harbor homozygous mutations in the solute carrier organic anion transporter family member 2A1 gene (*SLCO2A1*) or the 15-hydroxyprostaglandin dehydrogenase gene (*HPGD*), resulting in elevated prostaglandin E2 (PGE2) levels.[1]

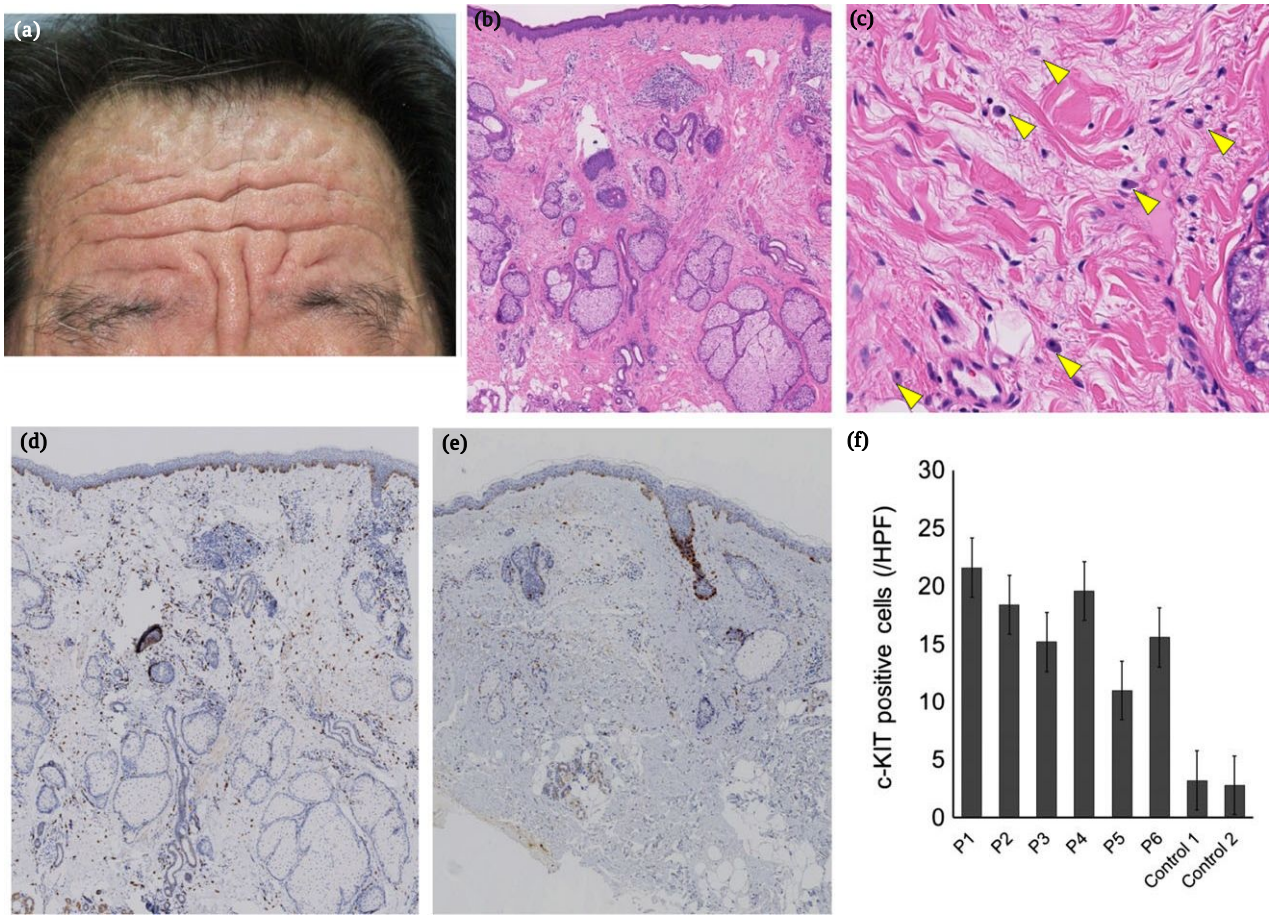

Figure 1. (a) Representative clinical features of the forehead. Moderate pachydermia was noted in the forehead of patient 1. (b) Representative histopathological features of pachydermia (hematoxylin–eosin, original magnification 94). This specimen was obtained from the forehead of patient 1. Dermal edema, fibrosis and sebaceous hyperplasia were noted. (c) High-powered view at 9200. Infiltration of mast cells was noted (yellow arrowheads). (d) Immunohistochemical analysis of pachydermia sample for c-Kit staining (94). The sample was obtained from the forehead of patient 1. Prominent infiltration of c-Kit-positive cells was noted in the dermis. (e) Immunohistochemical analysis of normal forehead skin with c-Kit staining (94). This specimen was obtained from the area surrounding a benign tumor and used as a control. (f) Score of the c-Kit-positive cells in the dermis. Dermal c-Kit-positive cells from five different randomly selected areas in the dermis were counted using a high-powered field (HPF, 9400), and the average of the five sums was calculated. The number of c-Kit-positive cells in the dermis was increased in the pachydermia samples approxi- mately three- to eightfold compared with controls.

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Pachydermia shows the histopathological findings of dermal edema, mucin deposition, elastic fiber loss, dermal fibrosis and sebaceous gland hyperplasia. Previously, we reported that the degree of these findings is correlated with pachydermia severity.[2] Upon further observation, we found that mast cells were notably infiltrated in the dermis of pachydermia samples.

In this study, pachydermia specimens obtained from six patients with PDP were analyzed. Diagnosis was made according to established clinical and radiological criteria.[3] The study was approved by the ethics committee of the National Center for Child Health and Development and Keio University School of Medicine. Participants provided written informed consent.

Patient characteristics are summarized in Table S1. All participants were male (age range, 19–51 years). No participant had a family history of PDP. Samples were obtained from the forehead (Fig. 1a) and stained with hematoxylin–eosin (Figs 1b,c, S1), immunohistochemical staining for c-Kit (Figs 1d,e,S1) and toluidine blue (Fig. S1). The number of infiltrated mast cells was calculated by counting and averaging the number of dermal c-Kit-positive cells or toluidine blue metachromatic staining cells in five randomly selected areas using 9400 magnification (Fig. S2). Two samples of normal skin from the forehead of a healthy individual were used as a control (Figs 1e,S1). The slides were independently interpreted by two investigators (K. T. and A. I.) without any knowledge of the clinical data. Any discrepancies in the findings were reconciled by a third investi- gator (H. N.). The number of dermal c-Kit-positive cells was three- to eightfold higher in pachydermia samples than in con- trols (Fig. 1f). Increased dermal mast cells were also confirmed by toluidine blue staining, as c-Kit-positive cells may include dermal melanocytes (Fig. S2).

Mast cells are filled with secretory granules containing histamine, protease, cytokines, chemokines and proteoglycans.[4] These granules are released into the extracellular environment by a variety of mechanisms such as immunoglobulin E cross-linking, complement activation and neuropeptide stimulation.[4] A recent report showed that PGE2 can directly activate mast cells to secrete histamine, mediating PGE2-induced vascular permeability.[5] Mast cell degranulation may cause not only der- mal edema but also proteoglycan deposition positive for Alcian blue staining; these findings are typically noted in pachyder- mia.[2] However, the mechanisms of increased mast cells are yet to be clarified, including the role of upregulated PGE2. Nevertheless, we speculate that mast cells are closely associ- ated with the pathobiology of PDP. Further analysis is neces- sary to reveal the role of mast cells not only in the skin, but also in the other organs of PDP patients.

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CONFLICT OF INTEREST: None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Figures show the histological features of six pachydermia samples and two normal control samples stained with hematoxylin–eosin staining (original magnification 940), c-KIT (9100) and toluidine blue (9100).

Figure S2. (a) Representative high-powered field (original magnification 9400) microscopic feature of pachydermia sample stained for c-Kit.

Table S1. Summary of the patients analyzed in this study

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LETTER TO THE EDITOR

Complete type of pachydermoperiostosis with a novel mutation c.510G>A of the *SLCO2A1* gene

Dear Editor,

Pachydermoperiostosis (PDP), or primary hypertrophic osteoarthropathy (PHO; Mendelian Inheritance in Man no. 167100), is a rare genetic disease characterized by finger clubbing, periostosis, pachydermia and cutis verticis gyrata (CVG). Additional symptoms include sebaceous hyperplasia, hyperhidrosis and arthropathy. Two genes, *HPGD* and *SLCO2A1*, are known to be related to PDP and PHO.[1–3] There have been several *SLCO2A1* mutations reported. However, the prevalence of complete type of PDP (clinical triad including CVG) remains largely unknown. Here, we report a case of PDP carrying a novel *SLCO2A1* mutation.

A 37-year-old man was referred to us for finger clubbing and pachydermia. He developed these symptoms at the age of 20 years and noticed oily facial skin and palmoplantar hyper- hidrosis at 30 years. On examination, the patient had pachy- dermia (Fig. 1a), CVG (Fig. 1b) and clubbed fingers (Fig. 1c,d). His parents had no abnormalities in appearance. Radiological examination revealed diaphyseal periostosis of the radius, ulna, tibia and fibula (Fig. 1e). No endocrinosis (growth, thyroid, sex- ual and adrenal hormones), tumor lesion or hypokalemia was found by blood examination, urinalysis or computed tomogra- phy. Gastrointestinal endoscopy showed no abnormality. We diagnosed the patient as having the complete type of PDP.

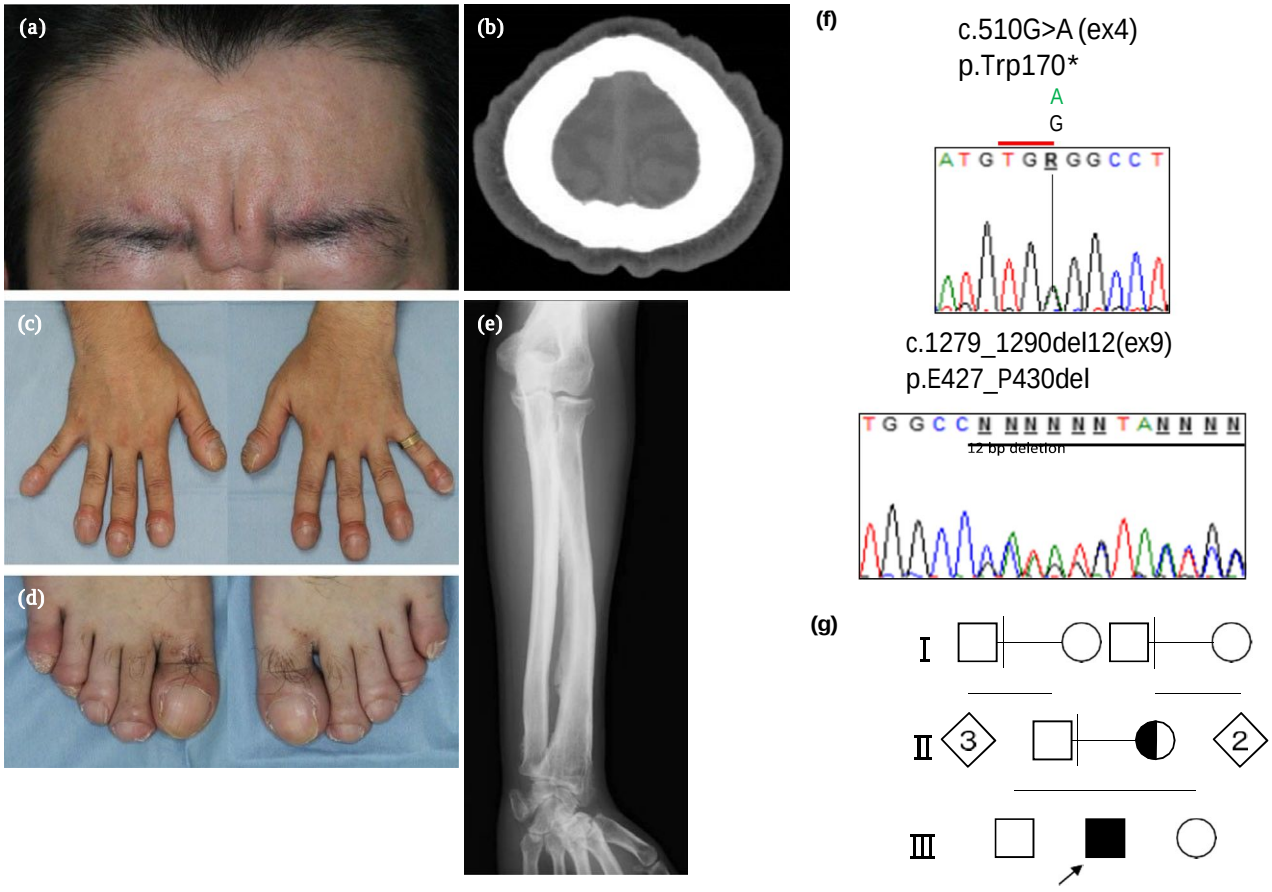

Figure 1. Clinical findings. (a) Pachydermia on the forehead. (b) Computed tomography of cutis verticis gyrate. (c,d) Digital clubbing. (e) Periostosis of the diaphysis in the radius and ulna. (f) A chromatogram demonstrated the mutations in a family of solute carrier organic anion transporters, member 2A1 (*SLCO2A1*) gene. (g) Pedigree of the family.

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We screened the patient for *SLCO2A1* and *HPGD* muta- tions, and identified compound heterozygous mutations at c.510G>A and c.1279_1290del12 in the *SLCO2A1* gene (Fig. 1f). A heterozygous c.510G>A mutation in exon 4 of the *SLCO2A1* gene was novel. This mutation introduces a stop codon at position 170 (p.Trp170*) and has not been identified until our finding. The proband's mother was heterozygous for c.510G>A (Fig. 1g).

SLCO2A1 encodes prostaglandin (PG) transporter, and homozygous mutations in *SLCO2A1* cause PHO/PDP. The resultant PG transporter deficiency leads to a high tissue level of PGE2, which contributes to the pathogenesis of PHO/PDP.[1,2] Zhang *et al.*[1] reported that the urinary levels of PGE2 in PHO patients with *SLCO2A1* mutation are significantly higher than those in controls. In this case, the PGE2 level in urine was 83 ng/mmol creatinine (normal, <50).

Eight *SLCO2A1* mutations: c.310G>A (p.G104*), c.421G>T (p.E141*), c.765C>T (p.R252*), c.940+1G>A (p.R288Gfs*7), c.1040C>T (p.T347I), c.1279_1290del12 (p.E427_P430del), c.1668G>C (p.Q556H) and c.1807C>T (p.R603*) have been thus far confirmed in Japanese PDP patients.[4] However, correlation between the severity of pachydermia and *SLCO2A1* mutational status needs to be confirmed with a greater number of cases.[5]

Here, we first reported a novel mutation c.510G>A of the *SLCO2A1* gene in the complete type of PDP. Our case suggests the genotype–phenotype correlation in *SLCO2A1* as well as the reported cases.

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CONFLICT OF INTEREST: None declared.

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