Registry are clearly valuable for drawing inferences and generating hypotheses.

Conclusions

The MPS I Registry is the largest global database of information from MPS I patients and provides a useful tool for expanding knowledge about disease presentation, clinical status, and treatment outcomes. Greater understanding of the symptomatology of the disease can lead to earlier diagnosis and initiation of treatment, which may in turn lead to better patient outcomes. Each of the three MPS I phenotypes, Hurler, Hurler–Scheie, and Scheie, is associated with a characteristic constellation of symptoms and disease course. This analysis of data from almost 1,000 patients facilitates definition of the natural history of MPS I across the phenotypic spectrum, which will hopefully increase awareness of the disease and improve early diagnosis. In addition, results from this investigation will be important in establishing benchmarks for future analyses of treatment interventions.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

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The novel *SLCO2A1* heterozygous missense mutation p.E427K and nonsense mutation p.R603* in a female patient with pachydermoperiostosis with an atypical phenotype

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Dear Editor, Pachydermoperiostosis (PDP), or primary hypertrophic osteoarthropathy (PHO: MIM 167100), is a rare genetic disease affecting the skin and bones. The major diagnostic criteria include finger clubbing, periostosis, pachydermia and cutis verticis gyrata (CVG). Additional symptoms, including sebaceous hyperplasia, hyperhidrosis and arthropathy, have been reported.[1,2]

Uppal *et al.*[3] discovered that a homozygous mutation in *HPGD*, which encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH), causes PHO and PDP. However, PHO and PDP are genetically heterogeneous. Exome analysis of PDP in Japanese, Chinese, Caucasian and other races has revealed homozygous mutations in the solute carrier organic anion transporter family member 2A1 (*SLCO2A1*) gene, which encodes prostaglandin transporter (PGT).[4–8] Increased levels of prostaglandin E2 (PGE2) resulting from defective degradation contribute to the pathogenesis of PHO and PDP. A genetic defect in either *SLCO2A1* or *HPGD* can cause PHO and PDP.

In this study, we describe the first observation of a *SLCO2A1* mutation in a female patient.

A 67-year-old woman was referred for *SLCO2A1* mutation analysis. At the age of 43 years, she developed myelopathy of unknown aetiology. She received rehabilitation therapy without medication. A neurologist had examined her muscle weakness at the T-helper 7 level on the right side following a diagnosis of suspected multiple sclerosis. At the age of 64 years, she had multiple seronegative arthralgias but no serious problems. She was referred to Tohoku Kouseinenkin Hospital because of recurring arthralgia and was treated with methotrexate and prednisone. She responded favourably to the medication with alleviation of the pain and decreased serum levels of C-reactive protein. Physical examination revealed finger clubbing and swelling of the large joints, as seen in Figure 1b,c. No skin manifestations, including facial coarseness or greasiness, and no hyperhidrosis were observed. Marked thickening of the scalp (CVG) was not evident. Radiological examination showed the presence of periostosis of the diaphysis of the tibia and fibula (Fig. 1d). No hydrarthrosis was evident. A diagnosis of possible incomplete type of PDP or PHO was made because of minimal pachydermia. She had no history of peptic ulcers or anaemia. Diagnostic imaging and laboratory data revealed no evidence of secondary PDP. She has a healthy son and daughter.

This study was approved by the ethics committee of the National Centre for Child Health and Development and Keio University School of Medicine. The participants provided written informed consent. All exons of *HPGD* and *SLCO2A1* along with sequences adjacent to the exon–intron borders were amplified, sequenced and screened for mutations.[4] Serum and urinary levels of PGE2 were measured with a commercial enzyme immunoassay kit (Cayman, Cayman Biochemical, Ann Arbor, MI, U.S.A.).[4]

We identified compound heterozygous novel mutations c.1279G>A/p.E427K and c.1807C>T/p.R603* in *SLCO2A1* (Fig. 2). We also detected a heterozygous mutation c.1279G>A in her daughter, but she has not developed any triad of PDP.

In her seventh decade, the patient's atypical history showed minimal impact of pachydermia. Serum PGE2 was not detected and her urinary PGE2 was within normal limits (372 pg mL^{-1}). One of the mutations, c.1279G>A (p.E427K), is included within the region of a previously reported deletion, c.1279_1290del12 (p.E427_P430del).[4] Another mutation, c.1807C>T/p.R603*, is detected close to the C-terminus of PGT, resulting in a shortened predicted protein. The loss of function in truncated PGT is consistent with the presence of the p.R603* mutation in another patient, who had the complete type of PDP (manuscript in preparation).

This patient is the first woman with PDP who had an *SLCO2A1* gene mutation. It is unlikely that the mild phenotype of P1 was due to the missense mutation p.E427K. A recent report on PDP in a Chinese family described a homozygous p.A286Qfs*35 frameshift mutation in a male proband who had PDP.[7] Two of the proband's sisters were also homozygous for p.A286Qfs*35, but at ages 42 years and 47 years, they had neither history nor findings suggestive of PDP.[7] Diggle *et al.*[6] reported that two women in two PDP families were homozygous for pathogenic *SLCO2A1* mutations. One had mild finger clubbing but no musculoskeletal or skin symptoms at 34 years of age. The other was asymptomatic at 19 years of age. Taken together, we propose that PDP resulting from *SLCO2A1* defects is a sex-dependent autosomal recessive disease, and women homozygous for pathogenic *SLCO2A1* mutations may develop late-onset PDP symptoms. The explanation of mild- and low-frequency disease in women remains unclear. Hatano *et al.*[9] suggested that reactivity to prostaglandin was milder in women than in men. Ospina *et al.*[10]

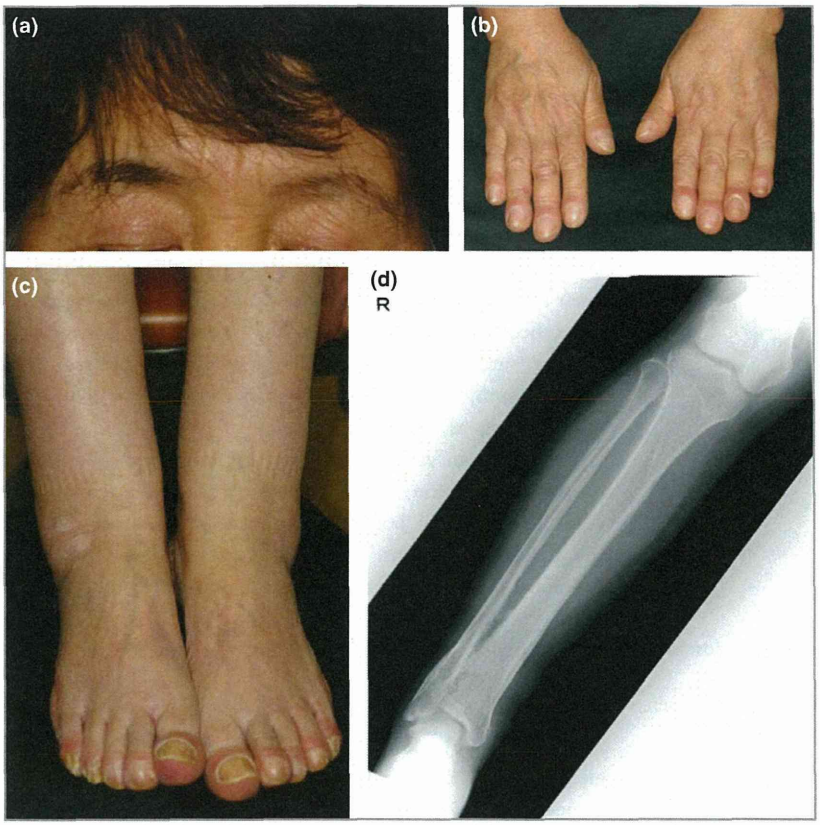

Fig 1. Clinical features including radiograph. (a) The facial appearance of the patient. Furrowing of the forehead and greasiness of facial skin are negligible. (b) Digital clubbing. (c) Clubbing of toes and cylindrical enlargement of the legs. (d) Periosteal hyperostosis of the tibia and fibula.

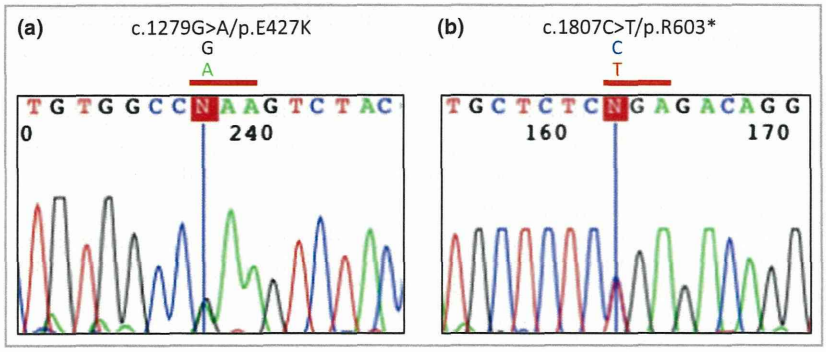

Fig 2. Two novel mutations in *SLCO2A1* were identified by the Sanger method. CodonCode Aligner (CodonCode Corporation, Centerville, MA, U.S.A.) was used to assemble sequences and detect mutations. (a) One nonsynonymous mutation: c.1279G>A/p.E427K (P1). (b) The premature stop codon mutation: c.1807C>T/p.R603*.

reported that oestrogen suppressed interleukin-1β-mediated induction of the COX-2 pathway in rat cerebral blood vessels. These data imply that a decreased level of oestrogen plays a role in the sex-dependent pathogenesis. Further analyses will clarify this issue.

In conclusion, we have described the first female case of PDP with compound heterozygous *SLCO2A1* mutations. Her atypical history shows minimal pachydermia impact.

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Conflicts of interest: None declared.

Urticaria-like neutrophilic dermatosis in association with IgA gammopathy: a new entity

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Dear Editor, IgA gammopathy and multiple myeloma have been associated with multiple neutrophilic dermatoses including subcorneal pustular dermatosis,[1–4] erythema elevatum diutinum,[5] urticarial vasculitis,[6] Sweet syndrome[7] and pyoderma gangrenosum.[8] We report an unusual urticaria-like neutrophilic dermatosis as the presenting sign of IgA myeloma. An 84-year-old woman with cardiomyopathy, atrial fibrillation, rectal cancer in remission, and hypertension was admitted for syncope. She reported bone pain and an intermittent rash over the preceding months. Laboratory studies were notable for normocytic anaemia, normal white blood cell count, negative serologies for HTLV-1, RPR, hepatitis and HIV, widespread osteolytic lesions on skeletal survey, elevated serum IgA (1080 mg dL^{-1}, normal: 70–350), decreased serum IgG (599 mg dL^{-1}, normal: 700–1700) and IgM (< 6·5 mg dL^{-1}, normal: 50–300) and a monoclonal IgA kappa on serum protein electrophoresis consistent with plasma cell dyscrasia and confirmed with bone marrow biopsy, demonstrating 15% atypical plasma cells.

The patient had noticed a mildly pruritic rash on the back and legs for the preceding 2 months; individual lesions lasted 3–4 days. On examination, she had annular and round erythematous plaques, some with central clearing, on the back, buttocks and proximal extremities, as well as pink-brown patches, corresponding to resolved lesions (Fig. 1). Several lesions were marked in pen and noted to persist for a minimum of 3 days.

Skin biopsy demonstrated a moderate superficial interstitial infiltrate of predominantly neutrophils with some nuclear deb-

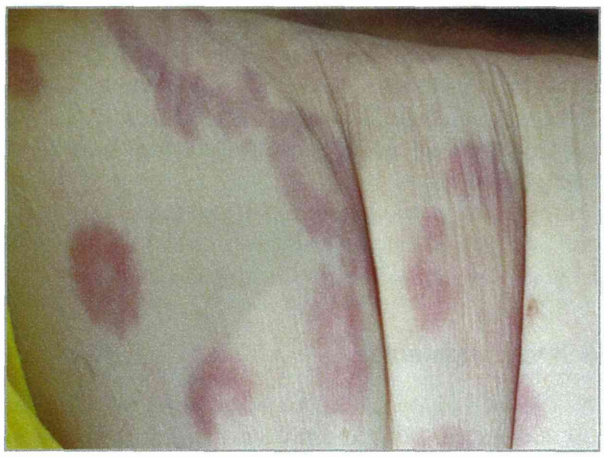

Fig 1. Clinical image showing lesions.