



## King's Research Portal

DOI:

[10.1001/jamadermatol.2016.1187](https://doi.org/10.1001/jamadermatol.2016.1187)

*Document Version*

Publisher's PDF, also known as Version of record

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Lwin, S. M., Hsu, C.-K., McMillan, J. R., Mellerio, J. E., & McGrath, J. A. (2016). Ichthyosis Prematurity Syndrome: From Fetus to Adulthood. *JAMA dermatology*. Advance online publication. <https://doi.org/10.1001/jamadermatol.2016.1187>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

# Letters

## OBSERVATION

### Ichthyosis Prematurity Syndrome: From Fetus to Adulthood

Ichthyosis prematurity syndrome (IPS) is a rare form of autosomal recessive congenital ichthyosis caused by mutations in *SLC27A4* (OMIM: 604194) encoding fatty acid transport protein 4 (FATP4) that affect keratinocyte differentiation and skin barrier formation. It is characterized by prematurity, thick caseous desquamating epidermis, and perinatal respiratory asphyxia. Despite its well-described clinical features and major perinatal mortality risk, IPS is still rarely recognized, and only a few cases have been reported.

**Report of a Case** | The female proband was first diagnosed with IPS as a 22-week-old fetus by amniocentesis and fetal skin biopsy, which was performed because her older brother was born prematurely at 33 weeks' gestation, owing to maternal polyhydramnios, and died at age 12 hours with ichthyosis and pulmonary obstruction. The proband's amniotic fluid contained numerous abnormal corneocytes and debris (Figure 1A). Histologic analysis of her fetal skin revealed hyperkeratosis and acanthosis with follicular plugging (Figure 1B). Transmission electron microscopy demonstrated perinuclear swelling of keratinocytes (Figure 1C) and lipid profiles with curved trilamellar lamellae in the horny layer (Figure 1D). All of these findings are characteristic of IPS.

The proband was also delivered prematurely at 31 weeks' gestation, owing to maternal polyhydramnios. Immediately after birth, she was on a ventilator for 2 days and remained in neonatal intensive care for an extended period because of respiratory asphyxia resulting from aspiration of amniotic fluid debris. At birth, she was erythrodermic with a thick caseous desquamating epidermis and hyperkeratotic scale over the scalp and eyebrows that persisted beyond age 8 weeks (Figure 2A). The vernix caseosa-like scale was shed over several weeks, leaving generalized follicular ichthyosis. Hair, eyes, teeth, mucosa, and nails were all normal. During childhood, follicular ichthyosis and skin hyperpigmentation became more prominent over the flexures (Figure 2B). She also had asthma, allergic rhinitis, and mild eosinophilia (1050/ $\mu$ L; normal range, 100/ $\mu$ L-800/ $\mu$ L) that persisted into adulthood. Serum IgE was not recorded. During adolescence, a 12-month treatment regimen of oral retinoids ( $\leq 1$  mg/kg acitretin) had no clinical benefit. At last follow-up, age 21 years, her skin displayed generalized nonerythrodermic ichthyosis with follicular hyperkeratosis particularly over the flexures with mild hyperpigmentation (Figure 2C).

Both affected younger siblings of the proband shared a similar clinical course, with generalized follicular ichthyosis and atopic manifestations. However, both unrelated parents,

the proband's only child (7-month-old son), and all 3 children from her father's previous marriage were unaffected.

Genomic sequencing of *SLC27A4* on the 3 affected living siblings, including the proband (Figure 2D), and the unaffected parents revealed 2 recessive heterozygous mutations: a missense mutation, c.899A>G, p.Gln300Arg (exon 7); and a nonsense mutation, c.1336C>T, p.Gln446\* (exon 10) (a new variant). Both mutations were found within the highly conserved adenosine monophosphate-binding domain of FATP4 (amino acids 103-536). Immunofluorescence staining for FATP4 (clone ab72724; Abcam) showed almost complete loss of expression in the proband's lesional skin compared with the bright mid and upper epidermal labeling in control skin (Figure 1E).

**Discussion** | Recent cases of IPS from Asia suggest that its frequency may be underestimated worldwide.<sup>1,2</sup> The highest incidence of IPS reported has been in Scandinavia, with p.Gln300Arg as a frequent recurrent ancestral mutation<sup>3,4</sup>—the same maternal mutation identified in the present case, although geographically that side of the family resided in Ireland for several generations. It is plausible, therefore, that this mutation (which has not been detected in other Irish cases of IPS)<sup>5</sup> has occurred on a different genetic background. Indeed, a different recurrent mutation in Scandinavia, p.Val477Asp, has also been identified in 2 Irish siblings with IPS.<sup>5</sup>

The clinical characteristics and course of our patient are similar to previously reported features of IPS,<sup>1-6</sup> of which the largest case series examined 17 European families.<sup>6</sup> The present case uniquely describes pathognomonic ultrastructural features in the skin and amniotic fluid from as early as 22-weeks' gestation. When our patient was born, genetic testing was unavailable, and therefore fetal skin biopsy was essential for the diagnosis. Consequently, through genetic counseling, the mother underwent regular antenatal ultrasonography with each subsequent pregnancy, facilitating preemptive management of polyhydramnios and perinatal respiratory asphyxia with excellent postnatal outcomes for all 3 surviving children. Our case highlights the importance of early recognition and diagnosis of IPS with coordinated multidisciplinary care for optimal management.

Su M. Lwin, MRCP, MBBS, BSc (Hons)

Chao-Kai Hsu, MD

James R. McMillan, PhD

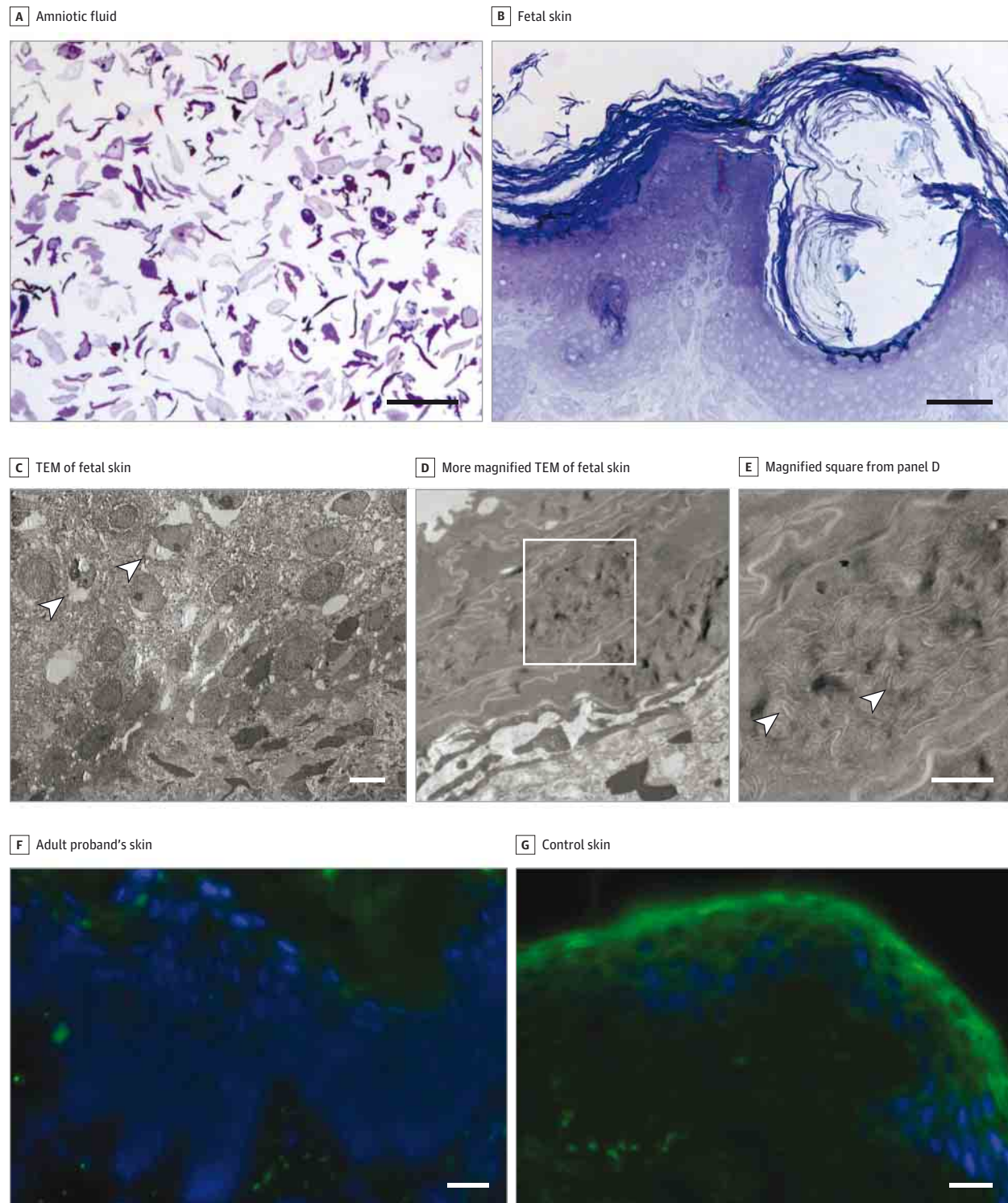
Jemima E. Mellerio, MD, FRCP, MBBS, BSc (Hons)

John A. McGrath, MD, FRCP, FMedSci

**Author Affiliations:** St John's Institute of Dermatology, King's College London, Guy's Campus, London, England (Lwin, Hsu, Mellerio, McGrath); Viapath, St Thomas' Hospital, London, England (McMillan).

**Corresponding Author:** John A. McGrath, MD, FRCP, FMedSci, Dermatology Research Laboratories, Floor 9 Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, England (john.mcgrath@kcl.ac.uk).

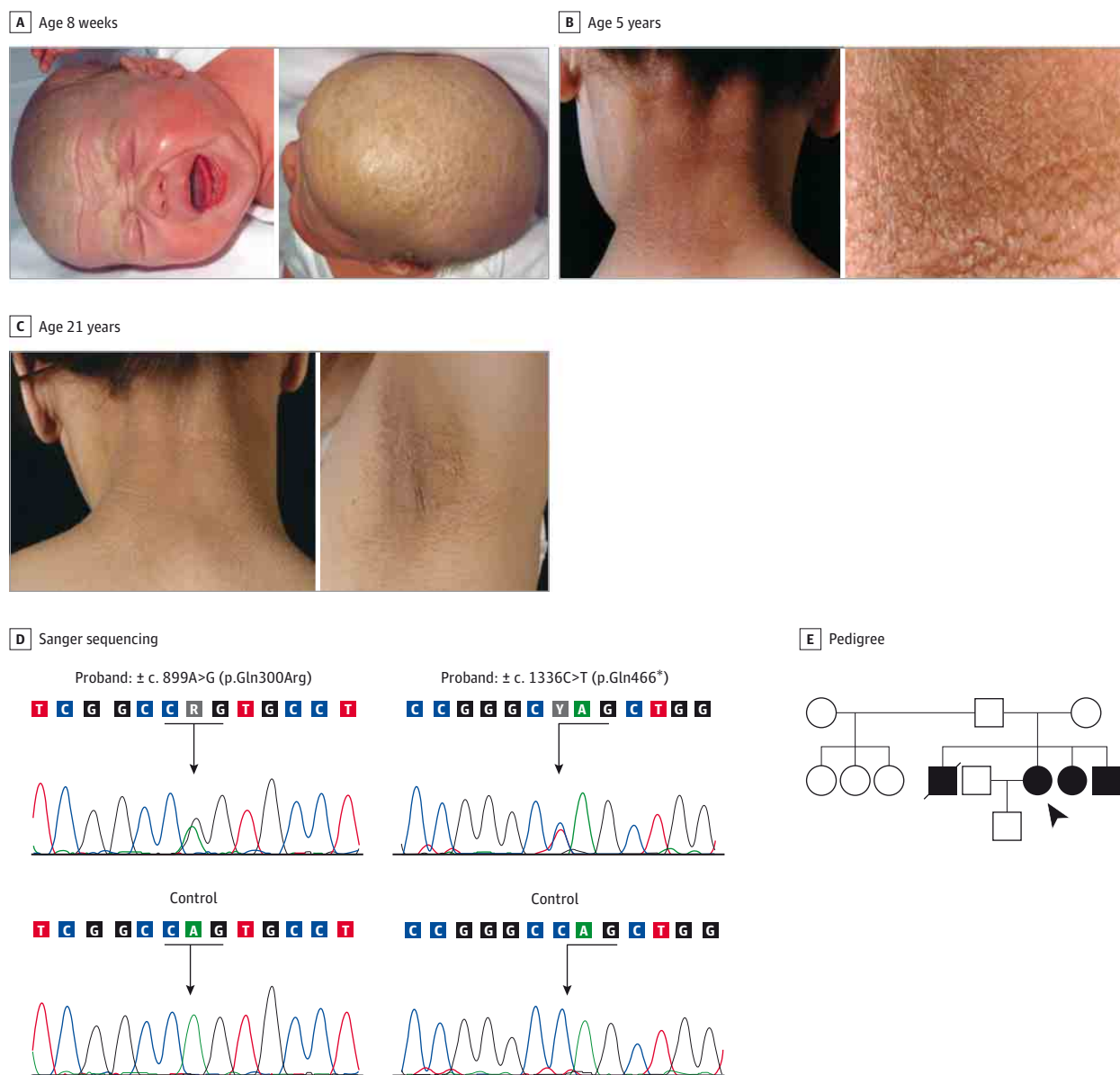
**Figure 1. Diagnosis of Ichthyosis Prematurity Syndrome (IPS) in Proband as a 22-Week-Old Fetus and Molecular Features of Proband's IPS at Age 21 Years**



A, Amniotic fluid contains numerous abnormal corneocytes and debris (Richardson stain, scale bar = 25  $\mu$ m). B, Fetal skin biopsy from the chest wall reveals hyperkeratosis and acanthosis with follicular plugging (Richardson stain, scale bar = 50  $\mu$ m). C, Transmission electron microscopy (TEM) of fetal skin shows perinuclear swelling in several keratinocytes (black arrows; scale bar = 10  $\mu$ m); D and E, Higher magnification TEM images reveal lipid profiles with curved

trilamellar lamellae in the stratum corneum (white arrows; scale bar = 0.5  $\mu$ m). F and G, in adult skin, immunofluorescence staining for FATP4 (fatty acid transport protein 4) shows barely detectable labeling in the proband (F; sampled from right axilla at age 21 years) compared with bright staining within the upper epidermis in normal control adult skin (G) (scale bars = 25  $\mu$ m).

Figure 2. Clinical Photographs, Pedigree, and Mutation Analysis of the Proband With Ichthyosis Prematurity Syndrome



A, At age 8 weeks, there is thick hyperkeratotic desquamating epidermis affecting the scalp and eyebrows. B, At age 5 years, there is hyperkeratotic cobbled skin with mild hyperpigmentation on the back of the neck. C, At age 21 years, there is generalized nonerythrodermic ichthyosis affecting the body and limbs with flexural hyperpigmented follicular hyperkeratosis; D, Sanger sequencing of *SLC27A4* reveals 2 recessive heterozygous mutations: (1) a

single-nucleotide transition, c.899A>G, in exon 7 resulting in an amino acid substitution, p.Gln300Arg; and (2) a single-nucleotide transition, c.1336C>T, in exon 10 leading to a premature termination codon, p.Gln466\*. E, The family pedigree in keeping with autosomal recessive inheritance (proband is indicated with an arrow; affected siblings, black symbols; black square with slash, older brother who died of ichthyosis prematurity syndrome).

**Published Online:** May 25, 2016. doi:10.1001/jamadermatol.2016.1187.

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** This study was supported in part by the Department of Health via the UK National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre award to Guy's and St Thomas' National Health Service (NHS) Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust.

**Role of the Funder/Sponsor:** The funding institutions had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Additional Contributions:** We thank the patient for granting permission to publish this information. We also thank Lu Liu, PhD, Viapath, St Thomas' Hospital, London, England, and Rashida Pramanik, BSc (Hons), St John's Institute of Dermatology, King's College London (Guy's Campus), London, England, for technical support; and Debra E. Lomas, MA MB BChir, MRCP, Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, England, for administrative and material support. None received any compensation for their contributions.

1. Tsuge I, Morishita M, Kato T, et al. Identification of novel *FATP4* mutations in a Japanese patient with ichthyosis prematurity syndrome. *Hum Genome Var*. 2015;2:15003. doi:10.1038/hgv.2015.3.

2. George R, Santhanam S, Samuel R, et al. Ichthyosis prematurity syndrome caused by a novel missense mutation in FATP4 gene-a case report from India. *Clin Case Rep*. 2015;4(1):87-89.
3. Klar J, Schweiger M, Zimmerman R, et al. Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome. *Am J Hum Genet*. 2009;85(2):248-253.
4. Sobol M, Dahl N, Klar J. FATP4 missense and nonsense mutations cause similar features in ichthyosis prematurity syndrome. *BMC Res Notes*. 2011;4:90.
5. Kiely C, Devaney D, Fischer J, Lenane P, Irvine AD. Ichthyosis prematurity syndrome: a case report and review of known mutations. *Pediatr Dermatol*. 2014;31(4):517-518.
6. Khnykin D, Rønnevig J, Johnsson M, et al. Ichthyosis prematurity syndrome: clinical evaluation of 17 families with a rare disorder of lipid metabolism. *J Am Acad Dermatol*. 2012;66(4):606-616.