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A case of lamellar ichthyosis with a novel *TGM1* mutation and Parkinson's disease

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Short title: A case of lamellar ichthyosis with Parkinson's disease
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The transglutaminase 1 (TGM1) gene is known to be a major causative gene of autosomal recessive congenital ichthyoses (ARCI): lamellar ichthyosis (LI), congenital ichthyosiform erythroderma, self-healing/self-improving collodion baby and bathing suit ichthyosis (BSI) [1,2]. Additionally, Israeli *et al.* discovered a mutation in epidermal lipase N (*LIPN*) that causes a late-onset form of ARCI [3]. To date, 12 genes responsible for ARCI have been identified: *TGM1*, *ALOX12B*, *ALOXE3*, *ABCA12*, *CYP4F22*, *NIPAL4*, *SDR9C7*, *LIPN*, *CERS3*, *PNPLA1*, *ST14* and *CASP14* [4-6]. Parkinson's disease (PD) is a debilitating neurodegenerative disorder and 5-10% of all patients suffer from a monogenic form of PD [7]. The Movement Disorders Genetic Mutation Database summarizes clinical information on PD patients with causative mutations in *SNCA*, *VPS35*, *Parkin*, *DJ-1* and *PINK1*. Our report outlines a unique case of PD with genetically diagnosed ARCI.

The proband is a 66-year-old Japanese woman, the first daughter born to non-related parents. She presented with generalized ichthyosis soon after birth. No family history of skin disorders was reported. Examination revealed severe, large brown scales on the scalp, trunk and extremities (Fig. 1a, b). Severe hypotrichosis had progressed since the age of 50 years. Moreover, she had axial symptoms (freezing of gait and pulsion symptoms) and had been diagnosed with PD from the age of 64 years. Oral levodopa and

carbidopa were effective treatments for these movement disorders. A skin biopsy specimen revealed marked compact hyperkeratosis (Fig. 1d).

Following informed consent, genomic DNA from the proband was used for whole-exome sequencing (WES) [8]. In the patient, two heterozygous *TGM1* mutations were identified: the previously reported missense mutation c.1570G>A (p.Gly524Ser) and the novel frameshift mutation c.1510_1511delTA (p.Tyr504Leufs*6), which were verified by Sanger sequencing. Because the two mutations were close in distance, we determined they were present in *trans* by WES (Fig. 1e) [9]. p.Gly524Ser was present in the patient's daughter and p.Tyr504Leufs*6 was demonstrated in her sister (Fig. 1c). Moreover, the patient had a previously unreported heterozygous missense variant in *LIPN* (c.602C>T: p.Pro201Leu). The pathogenicity of this variant was estimated by the SIFT (damaging) and the PolyPhen-2 (probably damaging) programs. Next, we conducted immunohistochemical analysis with an anti-TGM1 antibody (sc-25786; Santa Cruz Biotechnology, Santa Cruz, CA) on a lesional skin sample from the patient. Figure 1f shows reduced expression of TGM1 in the patient' skin compared with the control skin (Fig. 1g).

Severe phenotypes of ARCI are caused more frequently by truncating mutations than missense mutations of *TGM1* [6]. A compound heterozygous mutation p.Gly524Ser

and p.Arg315Cys was previously reported to show collodion baby and BSI (a relatively mild type of ARCI) later from childhood [10]. We hypothesized that the difference between p.Tyr504Leufs*6 and p.Arg315Cys may determine whether the phenotype is LI or BSI. Additionally, she was heterozygous for the previously unreported variant of *LIPN*. Progressive alopecia due to severe hyperkeratosis had appeared from the age of 50 years. A heterozygous *LIPN* variant may be considered as a modifying factor for ARCI patients with *TGM1* mutations, although we cannot exclude the possibility that the *LIPN* variant had no effect on the phenotype in the heterozygous state. Thus, WES has given additional benefits, such as the identification of potential genetic modifications. Furthermore, to confirm the *cis*/*trans* allelic condition previously, it was necessary to perform TA cloning even if the two mutations were near each other. We successfully identified the bi-allelic condition of the two mutations directly from WES.

The present proband had PD as well as LI. We did not identify potentially pathogenic mutations of any genes implicated in PD in the exome data. The relationships between *TGM1* mutations and PD are unknown, although some mRNA and protein expression of TGM1 in nervous tissue, including the brain, has been confirmed (GeneCards, http://www.genecards.org/). To date, no PD has been reported in ARCI cases. Therefore, we hypothesized that the complication of PD in the present case was probably

coincidental with LI.

In conclusion, this is the first reported case of LI complicated with PD. This report suggests potential insights regarding genetic modifications in determining ARCI phenotypes, and it enriches the database of mutational analysis.

Acknowledgments

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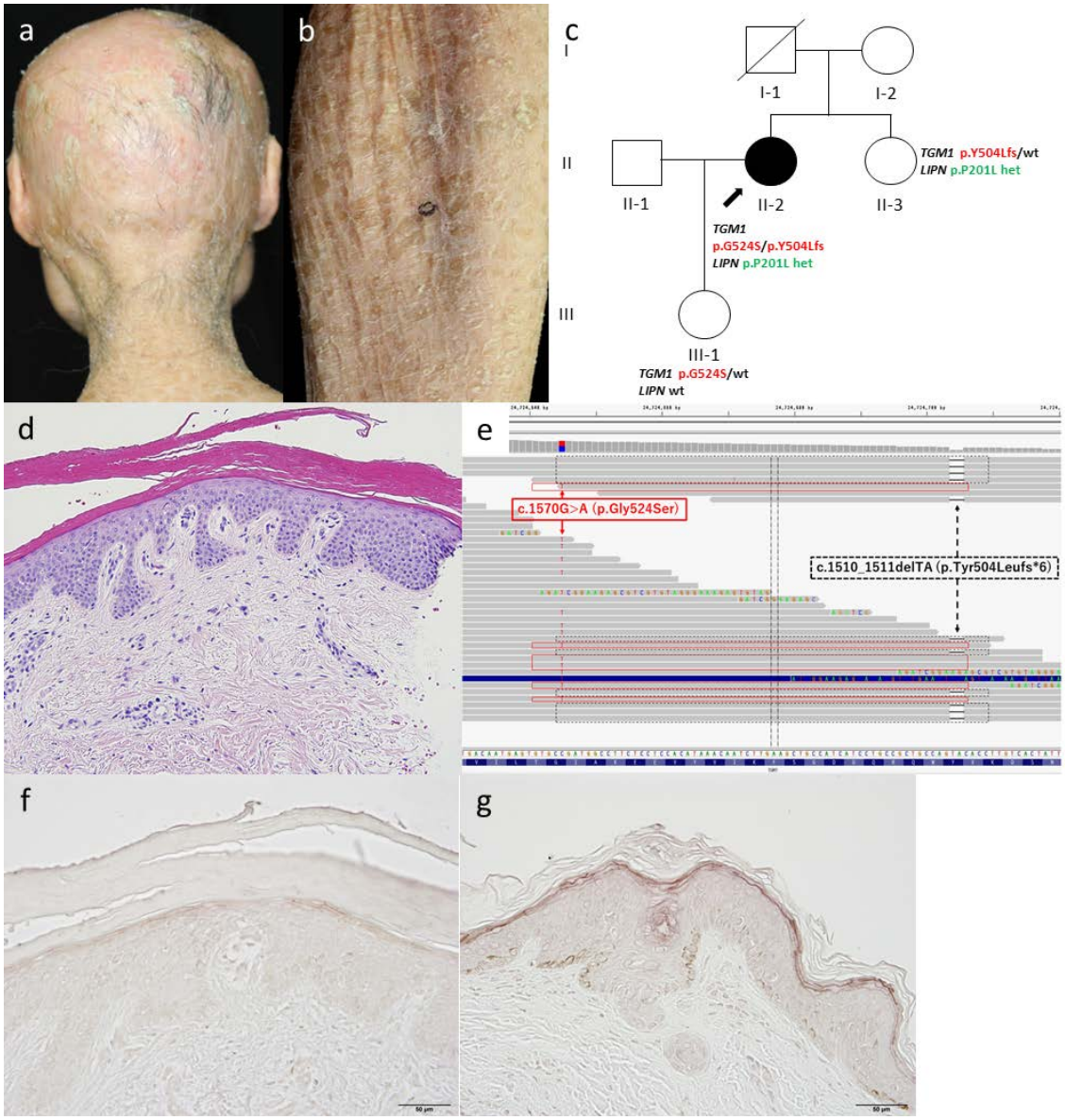
Figure legends

Figure 1. Clinicopathological features of the proband with LI

(a) The patient shows almost total baldness and brown scales on the scalp. (b) Large, brown, thickened scales are seen on the right forearm. (c) Pedigree of the family, showing genotypes for the mutations in *TGM1* and *LIPN*. wt: wild type, het: heterozygote. (d) Haematoxylin-eosin staining from the right forearm shows marked compact hyperkeratosis with normal granular layers and mild acanthosis. x400. (e) The igv software reveals that each *TGM1* mutation is located in *trans*. red: c.1570G>A (p.Gly524Ser), black dot: c.1510_1511delTA (p.Tyr504Leufs*6). (f, g) Immunohistochemistry of the lesional skin with an anti-TGM1 antibody (produced against amino acid residues 731-817 at the C-terminus of human TGase1); the staining intensity is reduced in the patient's skin (f) compared with the control skin (g). Scale bars = 50 μm.


a
b
c
I
II
III
I-1
I-2
II-1
II-2
II-3
III-1
TGM1 p.Y504Lfs/wt
LIPN p.P201L het
TGM1
p.G524S/p.Y504Lfs
LIPN p.P201L het
TGM1 p.G524S/wt
LIPN wt
d
e
c.1570G>A (p.Gly524Ser)
c.1510_1511delTA (p.Tyr504Leufs*6)
f
g