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Ataxic form of autosomal recessive PEX10-related peroxisome biogenesis disorders with a novel compound heterozygous gene mutation and characteristic clinical phenotype

Toru Yamashita [a], Jun Mitsui [b], Nobuyuki Shimozawa [c], Shigeo Takashima [c], Hiroshi Umemura [d], Kota Sato [a], Mami Takemoto [a], Nozomi Hishikawa [a], Yasuyuki Ohta [a], Takashi Matsukawa [b], Hiroyuki Ishiura [b], Jun Yoshimura [e], Koichiro Doi [e], Shinichi Morishita [e], Shoji Tsuji [b], Koji Abe [a,*]

[a] Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikatacho, Okayama 700-8558, Japan.
[b] Department of Neurology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan.
[c] Division of Genomic Research, Life Science Research Center, Gifu University, Gifu 501-1193, Japan.
[d] Department of Dermatology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikatacho, Okayama 700-8558, Japan.
[e] Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo 113-8655, Japan.

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ABSTRACT

Peroxisome biogenesis factor 10 (PEX10) is involved in the import of peroxisomal matrix proteins, and the mutation of this gene causes 3 subtypes of peroxisome biogenesis disorders, namely Zellweger syndrome (severe), neonatal adrenoleukodystrophy (moderate) and an ataxic form (mild). Here, we report 3 siblings of the ataxic form with cerebellar ataxia, mild mental retardation, and 3 additional characteristic features: mydriasis, hyperreflexia and involuntary head movement. All 3 siblings are compound heterozygous for a previously reported mutation, c.2T>C (p.M1T), and a novel mutation, c.920G>A, causing a missense change (p.C307Y) located in the RING finger domain of *PEX10*. The present cases suggest that these *PEX10* mutations involve not only cerebellar but also more multiple nervous systems including pupillary autonomic, pyramidal and extrapyramidal systems.

1. Introduction

The peroxisome biogenesis factor 10 (PEX10) protein, which is localized at the peroxisomal membrane, is involved in the import of peroxisomal matrix proteins, and the mutation of this gene can cause the Zellweger syndrome, neonatal adrenoleukodystrophy and an ataxic form of peroxisome biogenesis disorders. These 3 subtypes were currently considered to be included in a spectrum of disease, Zellweger spectrum disorder [1,2]. Three previous papers reported that 6 patients with PEX10-related peroxisomal disorders presented cerebellar ataxia with or without motor neuropathy [3–5]. Here we report 3 siblings of the ataxic form with a characteristic clinical phenotype and carrying a compound heterozygous mutation of *PEX10*, a previously reported point mutation c.2T>C (p.M1T) and another novel point mutation c.920G>A (p.C307Y).

2. Case reports

The parents of the 3 patients were healthy. There was no parental consanguinity. All 3 patients showed strongly similar clinical characteristics.

Patient II-1 is 29 years old (yo), and is the elder sister of patients II-2 and II-3 (Fig. 1). She was born by natural delivery at full term, and early development was normal. When she was 7 yo, she became aware of a gait disturbance and ran slowly. The gait disturbance progressed slowly, showing mild dysarthria within 2 years. When she visited our hospital at the age of 19 yo, she showed mild mental retardation. A neurological examination revealed that she showed bilateral mydriasis (rt. 7.0 mm, lt. 7.5 mm, light reflex; prompt, Fig. 1b) and evident cerebellar ataxia with impaired smooth pursuit, truncal ataxia, dysarthria and limb ataxia (SARA score = 15.0). She also showed hyperreflexia in all extremities without a pathological reflex. Her sensory system was intact, and there were no signs of oculomotor apraxia (OMA) or pes cavus. Motor

Abbreviations: AFP, alpha fetoprotein; BWA, Burrows Wheeler Aligner; DHA, docosahexaenoic acid; dma, dimethyl acetal; FIQ, full scale intelligence; indels, insertions and deletions; MRI, magnetic resonance imaging; OMA, oculomotor apraxia; PA, phytanic acid; PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; PEX10, peroxisome biogenesis factor 10; PIQ, performance IQ; PMP, peroxisomal membrane protein; SARA, scale for the assessment and rating of ataxia; SNVs, single-nucleotide variants; TM, transmembrane; VIQ, verbal IQ; WAIS-R, Wechsler adult intelligence scale revised; yo, years old.

* Corresponding author.
E-mail address: abekabek@cc.okayama-u.ac.jp (K. Abe).

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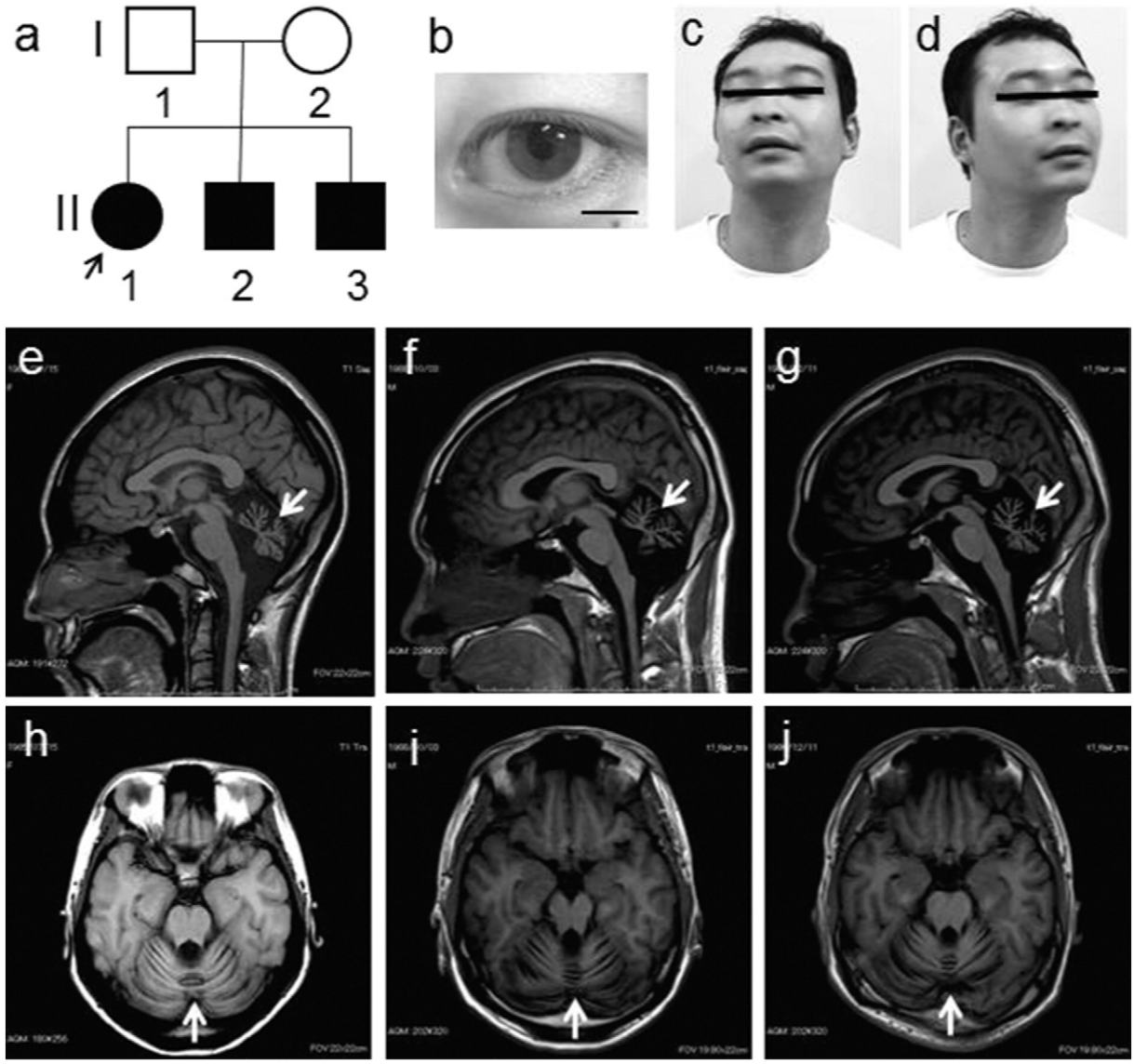

Fig. 1. (a) Family tree of the patients. (b) Photograph of mydriasis (lt. 7.5 mm) in case II-1 (scale bar = 10 mm). (c, d) Photographs showing involuntary head movement (2–3 Hz) of case II-3. (e–j) Magnetic resonance images (MRI) showing vermis dominant cerebellar atrophy (arrows) of patients II-1, 2, and 3.

and sensory nerve conduction studies showed normal amplitudes and conduction velocities. Serum analysis showed hypocholesterolemia (119 mg/dl, normal 130–220 mg/dl), but normal albumin (4.3 g/dl, normal 3.9–4.9 g/dl). Very long-chain fatty acids (VLCFAs), plasmalogen (C16:0 hexadecanal dimethyl acetal) and phytanic acid (PA) in serum from the patient were measured, using GC/MS, as described by Takemoto et al. [6]. The serum C26:0/C22:0 ratio (0.037), PA value (0.111 μg/μL of serum) and PA/C16:0 ratio (0.0060) had increased, but the C25:0/C22:0, C24:0/C22:0, C16:0 dma/C16:0 and DHA/C16:0 ratios were within a normal range (Table 1). Analysis for trinucleotide repeat expansions in *ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A* and *ATN1* were normal. Magnetic resonance imaging (MRI) demonstrated severe cerebellar atrophy (vermis dominant), without atrophy of the corpus callosum or the brain stem (Fig. 1e & h, arrows).

Patient II-2 is a 27 yo elder brother (Fig. 1). He was born by natural delivery at full term, and early development was normal. He was

Table 1
Peroxisomal-related test results (pre-treatment → after diet treatment).

Serum	Case II-1	Case II-2	Case II-3	normal range
C26:0, μg/μL of serum	0.021 → 0.013	0.026 → 0.016	0.016 → 0.015	0.017 ± 0.010
C26:0/C22:0	0.037 → 0.024	0.050 → 0.017	0.032 → 0.018	0.012 ± 0.005
C25:0/C22:0	0.027 → 0.022	0.022 → 0.018	0.023 → 0.017	0.024 ± 0.006
C24:0/C22:0	0.90 → 0.95	0.94 → 0.84	0.95 → 0.87	1.05 ± 0.16
Phytanic acid, μg/μL of serum	0.111 → 0.031	0.033 → 0.008	0.033 → 0.015	0.030 ± 0.029
Phytanic acid/C16:0	0.0060 → 0.0016	0.0012 → 0.0002	0.0013 → 0.0005	0.0009 ± 0.0008
C16:0 dma/C16:0	0.029 → 0.032	0.027 → 0.023	0.028 → 0.024	0.015 − 0.037
DHA/C16:0	0.18 → 0.16	0.16 → 0.15	0.19 → 0.15	0.15 − 0.33

dma, dimethyl acetal; DHA, docosahexaenoic acid.