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Study of a Taiwanese family with oculopharyngeal muscular dystrophy

Hung-Chou Kuo [a,*], Chiung-Mei Chen [a], Guey-Jen Lee-Chen [c], Fen-Ju Hu [c], Chun-Che Chu [a], Chia-Wei Liou [b], Chin-Chang Huang [a,*]

[a] Department of Neurology, Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taipei, Taiwan
[b] Department of Neurology, Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Kaohsiung, Taiwan
[c] Department of Life Science, National Taiwan Normal University, Taipei, Taiwan

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ABSTRACT

Background: Oculopharyngeal muscular dystrophy (OPMD) is a late onset autosomal dominant muscle disorder. OPMD is caused by a short trinucleotide repeat expansion encoding an expanded polyalanine tract in the polyadenylate binding-protein nuclear 1 (*PABPN1*) gene. We identified and characterized a *PABPN1* mutation in a Taiwanese family with OPMD.
Methods: The phenotypic and genotypic characteristics of all subjects were evaluated in a Taiwanese OPMD family. Genetic alterations in the *PABPN1* gene were identified using PCR and DNA sequencing.
Results: Ten subjects with OPMD (6 symptomatic and 4 asymptomatic) within the Taiwanese family carried a novel mutation in the *PABPN1* gene. The normal $(GCG)_6(GCA)_3GCG$ sequence was replaced by $(GCG)_6(GCA)(GCG)_4(GCA)_3GCG$ due to an insertion of $(GCG)_4GCA$ into the normal allele in the Taiwanese OPMD subjects.
Conclusions: In contrast to a single GCG expansion in most of OPMD patients in the literature, an insertion of $(GCG)_4GCA$ in the *PABPN1* gene was found in the Taiwanese OPMD subjects. The identification of this mutation appears to support the molecular mechanism of unequal cross-over of two *PABPN1* alleles.

1. Introduction

Oculopharyngeal muscular dystrophy (OPMD), an adult-onset autosomal dominant genetic disorder, is characterized by slowly progressive ptosis, dysphagia, and dysphonia [1]. This disorder has a worldwide distribution [2], but reported cases are most from Caucasian families, especially French-Canadian trait [3–9]. In Asian population, OPMD patients have only been reported in the Japanese families and sporadic patients in other countries morphologically and genetically [10–16].

Genetic studies revealed a small expansion of a $(GCG)_6$-repeat in the first exon of the polyadenylate (polyA) binding-protein nuclear 1 (*PABPN1*), or also known as polyA binding-protein 2 gene located on chromosome 14q11 [17,18]. The polyalanine expansion mutation may lead to aggregate with tubular filaments within the nuclei of skeletal muscle fibers and is thought to confer a toxic gain-of-function on aberrant PABPN1 protein [1,19–22]. Interestingly, over-expression of normal *PABPN1* gene may reduce the cytotoxicity of aberrant PABPN1 and protect cells against pro-apoptotic events [23].

Herein, we report a Taiwanese family with autosomal dominant OPMD along with genetic analysis of *PABPN1*. To our knowledge, this is the first report of a Taiwanese family with OPMD that also identifies the respective mutation in the *PABPN1* gene.

2. Materials and methods

2.1. Patients

In this study, 10 subjects in three generations of a Taiwanese OPMD family who lived in mid-western Taiwan were studied (Fig. 1). Informed consent was obtained from all subjects who participated in this study. The proband's father (subject I-1) died of suffocation due to difficulty swallowing at the age of 59 years. The proband's mother died at age of ninety. All 10 members of the OPMD family received an electrophysiological examinations, and/or muscle biopsy (Table 1). The protocol was approved by the institutional review board of Chang Gung Memorial Hospital. OPMD was diagnosed according to the criteria reported by Brais et al. [17] including three major criteria 1) positive family history, 2) ptosis or previous surgical correction, and 3) dysphagia. After a detailed neurological examination, 6 of 32 individuals fulfilled the clinical criteria, and were diagnosed as symptomatic. The family pedigree shown is consistent with an autosomal dominant mode of inheritance.

Patient II-3 was a 68 year-old woman, who developed an insidious onset of biocular eyelid dropping and double vision for 6 years and

* Corresponding author. Department of Neurology, Chang Gung Memorial Hospital & Chang Gung University 199, Tung Hwa North Road Taipei, Taiwan. Tel.: +886 3 3281200x8413; fax: +886 3 3287226.
E-mail addresses: kuo0426@adm.cgmh.org.tw (H.-C. Kuo), cch0537@adm.cgmh.org.tw (C.-C. Huang).

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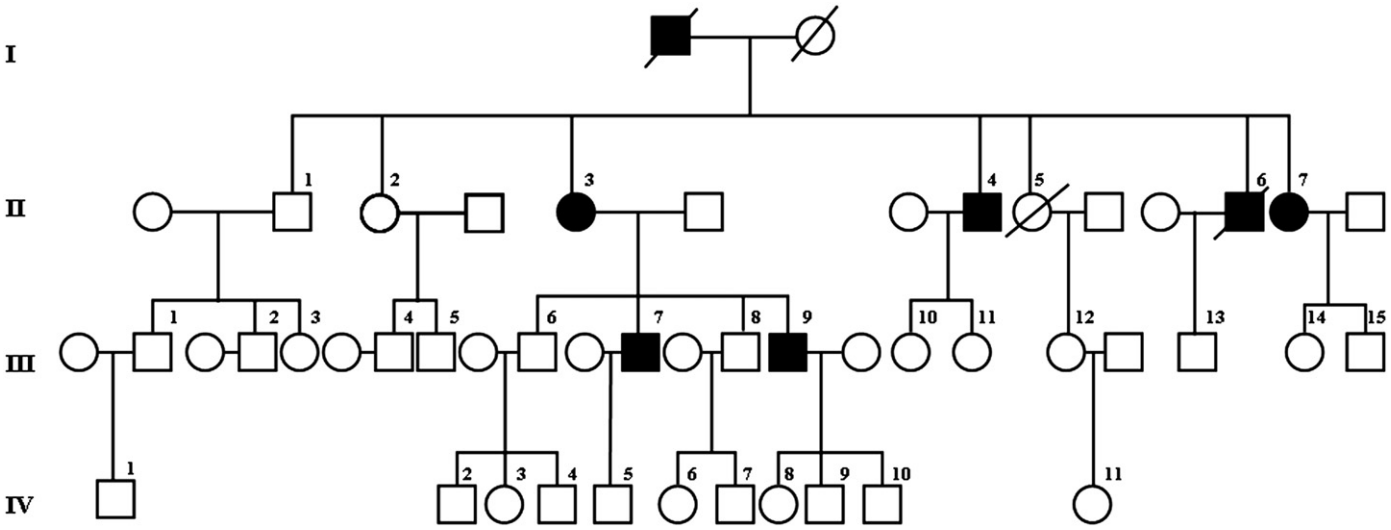

Fig. 1. Pedigree of the OPMD family. Filled symbols indicate symptomatic and open symbols indicate asymptomatic at presentation.

difficulty swallowing in her mid-forties. Neurological examination showed bilateral ptosis with mild to moderate limitation of eyeball movement, and moderate dysphagia and dysarthria. Two of her sons, patient III-7 (a 47 year-old man) and patient III-9 (a 42 year-old man) also experienced bulbar symptoms, mild bilateral ptosis and limitation of eye movement.

Patient II-4, a 67 year-old man, had suffered from speech and swallowing disturbance for more than 15 years. He had received surgical correction for bilateral ptosis at the age of 50 years, but recurrent eyelid dropping and double vision were noted. Neurological examinations showed moderate dysphagia and mild to moderate ophthalmoparesis, and ptosis in both eyes. No limb weakness was noticed. Laboratory tests revealed mild elevation of serum creatine kinase concentration (280 U/L, reference: 15–130 U/L). His 2 daughters (subjects III-10 and III-11) were normal on neurological examination.

Patient II-6, a 62 year-old man, developed slow progression of gait disturbance including climbing upstairs since 5 years ago and slurred speech and easy chocking for 2–3 years. Mild ptosis in both eyes was noted at the age of 42 years. Neurological examination demonstrated dysphagia, dysarthria, ptosis and mild weakness in the shoulder and pelvic girdle muscles. Tendon reflexes were absent in the low extremities. He died of lung cancer at the age of 63 years. His son (subject III-13), a 34 year-old man, did not have specific complaints, but it was observed that the swallowing time for cold water was prolonged.

Patient II-7, a 62 year-old woman with a history of undergoing eyelid operation 15 years ago, had difficulty swallowing for 3 years. She complained of frequent chocking while swallowing powder in her mid-thirty. On examination, ptosis and ophthalmoparesis were mild and bulbar palsy was moderate. Her daughter (subject III-14, a 40 year-old woman) and son (subject III-15) were normal on neurological examination.

Subjects II-1, and II-2 as well as their descendants were all healthy. Subject II-5 died of gastric cancer, but her daughter was normal on examination. The symptomatic subjects of the OPMD family are shown in the Fig. 1 and Table 1.

2.2. Swallowing test

All individuals of the OPMD family were requested to drink three times of 250 mL cold water (20–25 °C), with an interval of 30 min between the two tests. The time to swallow 250 mL of water was recorded. A normal reference was determined by calculating the

Table 1
Clinical data of a Taiwanese family with oculopharyngeal muscular dystrophy

Probands	II-3	II-4	II-6	II-7	III-7	III-9	III-13	III-14	IV-8	IV-10
Age (years)	68	67	62	61	47	42	34	40	18	16
Sex	F	M	M	F	M	M	M	F	F	M
Age of onset (years)	45	<50	42	35	44	40	-	-	-	-
Clinical manifestations										
Initial symptom	Dysphagia	Dysphagia or ptosis	Ptosis	Dysphagia	Dysphagia	Dysphagia, Dysphonia	-	-	-	-
Ptosis	+	+*	+ +	+*	+	+	-	-	-	-
Dysphagia to solid food	+ +	+ +	+ +	+ +	+	+	-	-	-	-
Time to swallow 250 ml of cold water	49. 25**	25.48**	58.90**	66.30**	5.04	12.13	13.68**	5.82	13.07	10.43
Dysphonia	+ +	+ +	+ +	+ +	-	+	-	-	-	-
Proximal limb weakness	-	-	+	-	-	-	-	-	-	-
Nasal regurgitation	+	+	+	+	-	+	-	-	-	-
Limitation of EOM	−2	−2	−3	−1	−1	−1	0	0	0	0
Gait disturbance	-	-	+	-	-	-	-	-	-	-
CK, ref: 20-180 IU/L	70	280	NA	93	90	148	140	NA	NA	NA
EKG	Normal	Normal	Normal	SB	Normal	SB	Normal	NA	NA	NA
NCV/EMG	Normal	Myopathic/neurogenic	Myopathic	Normal	Normal	Normal	Normal	NA	NA	NA

EOM, eye movement and 0 to −4 represent no to full limitation; CK, serum creatine kinase; EKG, electrocardiogram; NCV/EMG, nerve conduction study and electromyogram; F, female; M, male; *, surgical correction; **, prolonged swallowing time and reference (mean ± 2 SD) was 3.81–13.33 seconds; -, absent; +, mild impairment; + +, moderate impairment; NA, not available; SB, sinus bradycardia.