Clinica Chimica Acta 454 (2016) 124–129

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Identification of three mutations in the *MVK* gene in six patients associated with disseminated superficial actinic porokeratosis

Ying Liu [a,1], Jiuxiang Wang [a,1], Yayun Qin [a,1], Changzheng Huang [b], Stephen Archacki [c], Juanjuan Ma [a], Duanzuo Li [d], Mugen Liu [a,*]

[a] Key Laboratory of Molecular Biophysics of Ministry of Education, Department of Genetics and Developmental Biology, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan, Hubei 430074, PR China
[b] Department of Dermatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, PR China
[c] Center for Cardiovascular Genetics, Department of Molecular Cardiology, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, OH 44195, USA
[d] Key Laboratory of Kidney Disease Pathogenesis and Intervention of Hubei Province, Key Discipline of Pharmacy of Hubei Department of Education, Medical College, Hubei Polytechnic University, Huangshi, Hubei 435003, PR China

ARTICLE INFO

Article history:
Received 28 October 2015
Received in revised form 8 January 2016
Accepted 11 January 2016
Available online 12 January 2016

Keywords:
DSAP
MVK
Mutation
Mevalonic pathway

ABSTRACT

Porokeratosis is recognized as a heterogenously inherited epidermal keratinization disorder. Disseminated superficial actinic porokeratosis (DSAP) is considered to be the most common form of porokeratosis and is characterized by multiple, small keratotic lesions on sun-exposed areas of body. *MVK* has been reported to be the main candidate gene associated with DSAP. In this study, six sporadic cases of DSAP were clinically characterized. Direct DNA sequencing analysis of the whole coding regions of *MVK* detected three *MVK* missense mutations, and two were novel for DSAP: c.31C>T (P11S) and c.1004G>A (G335D). The three mutant MVK proteins were less stable than the wild type protein in different degrees. Mutation G335D also resulted in the misfolding of the ATP binding domain. This study extends the mutation spectrum of *MVK*. MVK protein stability and correct folding might be the molecular mechanism causing DASP. A 50% probability of detecting a *MVK* mutation in six DSAP sporadic cases indicated that the *MVK* gene was useful for clinical characterization, genetic counseling and prenatal diagnosis of DSAP.

1. Introduction

Porokeratosis was first described by Mibelli more than a century ago [1]. It is now recognized as heterogenously inherited epidermal keratinization disorder characterized by keratotic lesions surrounded by a slightly raised keratotic ridge [2,3]. Currently there are five subtypes of porokeratosis that are distinguished by size, location and numbers of lesions: disseminated superficial actinic porokeratosis (DSAP), disseminated superficial porokeratosis (DSP), classic porokeratosis of Mibelli (PM), porokeratosis palmaris et plantaris disseminata (PPPD) and linear porokeratosis (LP) [4]. Porokeratosis palmaris et plantaris punctate (PPPP) [3] and another rare type called porokeratosis ptychotropica [5] have also been reported. Among these, DSAP is considered to be the most common form of porokeratosis and is characterized by multiple, small lesions on sun-exposed areas of body such as the face, the V-area of the neck, upper chest, and the distal extremities [1,2,6]. Besides ultraviolet exposure, other risk factors including viral infections and immunosuppression have been shown to be associated with DSAP [3].

The pathogenesis of DSAP has not been fully elucidated. To date, three hypotheses have been proposed: (i) The faulty maturation of keratinocytes rather than an increased rate of proliferation [7]; (ii) early apoptosis and dysregulation of the terminal differentiation of keratinocytes [8]; and (iii) decreased MVK protein kinase activity which has a role in regulating calcium-induced keratinocyte differentiation and protect keratinocytes from apoptosis induced by type A ultraviolet radiation [2].

The genetic basis of DSAP has also been explored. DSAP is considered to be an autosomal dominant epidermal keratinization disorder [2]. Up to now, five chromosome loci (12q23.2–24.1 [9], 12q24.1–24.2 [10], 15q25.1–26.1 [11], 1p31.3–31.1 [12], and 16q24.1–24.3 [13]) have been linked to DSAP. Mutations in genes *SART3* [10], *SSH1* [14,15], *MVK* [2], *SLC17A9* [16], *PMVK*, *MVD* and *FDPS* [17] have been reported to cause DSAP. Although a significant genetic heterogeneity exists in DASP, *MVK* remains the most important causative gene for porokeratosis.

Abbreviations: DSAP, disseminated superficial actinic porokeratosis; MVK, mevalonate kinase; CHX, cycloheximide; PK, porokeratosis; HIDS, hyperimmunoglobulinaemia D and periodic fever syndrome; MKD, mevalonate kinase deficiency; PP, porokeratosis ptychotropica.

* Corresponding author.
E-mail address: lium@hust.edu.cn (M. Liu).

[1] The first three authors are the joint first authors.

http://dx.doi.org/10.1016/j.cca.2016.01.009
0009-8981/

Since Zhang's group had characterized *MVK* as a causative gene of DSAP by exome sequencing [2], more mutations in *MVK* have been reported to be associated with DSAP. Forty-four mutations had been identified in *MVK* gene that were associated with porokeratosis (Table 1). Affected families and sporadic cases sometimes shared the same mutation. Among all these mutations in *MVK* causing porokeratosis, 65.9% were missense mutations. Interestingly, most of the mutations occurred in Exon 10 suggesting it is a "hotspot" and encodes a critical domain.

Molecular analysis of the *MVK* gene is important and useful for diagnosis. Although the MVK gene mutations are highly heterogeneous, studies of individual mutations would help to identify DSAP pathogenesis. In this study, two novel missense mutations for DSAP c.31C>T (P11S) and c.1004G>A (G335D), as well as a previously reported mutation c.1126G>A (G376S) [2] were identified by direct DNA sequencing analysis of the entire coding regions of *MVK* in six DSAP sporadic cases. *MVK* gene mutations were identified in 50% of the DSAP sporadic cases in this study. This indicates that mutation screening in MVK could be a tool in the clinical characterization, genetic counseling and prenatal diagnosis of DSAP [26].

2. Subjects and methods

2.1. Patients

Six sporadic cases with DSAP were identified in the Affiliated Union Hospital of Huazhong University of Science and Technology. The patients underwent a careful physical examination, and the diagnoses were confirmed by histology. Biopsy specimens from DSAP patients were fixed in buffered formalin, embedded in paraffin for routine hematoxylin–eosin sections and evaluated by a dermatopathologist. This study followed the Declaration of Helsinki and was approved by the ethics committee of College of Life Science and Technology, Huazhong University of Science and Technology. Written consents were obtained from all the patients before they participated in the genetic investigation.

2.2. Mutation detection

Venous blood samples were collected, and genomic DNA isolation was performed as Ren et al. [27]. Genomic DNA was quantified by

Table 1
All the mutations identified in *MVK* for porokeratosis to date.

Mutation type	Exon	Nucleotide mutation	Protein alteration	Disease	Cases	References
Missense	2	c.31C>T	p.Pro11Ser	DSAP	Sporadic	This study
	2	c.34G>C	p.Gly12Arg	DSAP	Family	[2,18]
	2	c.74G>T	p.Gly25Val	PK	Family	[17]
	3	c.122T>C	p.Leu41Pro	DSAP	Family	[2]
	3	c.122T>G	p.Leu41Arg	PK	Family	[17]
	3	c.205T>A	p.Ser69Thr	DSAP	Family	[19]
	4	c.235G>A	p.Asp79Asn	PK	Family	[17]
	4	c.235G>T	p.Asp79Tyr	PK	Family	[17]
	5	c.437G>A	p.Ser146Asn	PK	Family	[17]
	5	c.451G>A	p.Val151Met	PK	Family	[17]
	6	c.604G>A	p.Gly202Arg	DSAP/HIDS/PK	Family/sporadic	[2,17,20]
	6	c.605G>A	p.Gly202Glu	PK	Sporadic	[17]
	7	c.643C>G	p.Arg215Gly	DSAP	Family	[21]
	7	c.650A>C	p.His217Pro	PK	Family	[17]
	8	c.710C>A	p.Thr237Asn	PK	Family	[17]
	8	c.764T>C	p.Leu255Pro	DSAP	Family	[2]
	9	c.836T>C	p.Leu279Pro	DSAP	Family	[2]
	9	c.871T>G	p.Tyr291Asp	DSAP	Family	[2]
	10	c.926G>T	p.Gly309Val	DSAP/PK	Family/sporadic	[17,22]
	10	c.935A>G	p.His312Arg	DSAP/PK	Family	[2,17,18]
	10	c.965C>A	p.Thr322Asn	PK	Family	[17]
	10	c.1004G>A	p.Gly335Asp	DSAP/HIDS	Sporadic	This study, [23]
	10	c.1012G>A	p.Gly338Ser	PK	Sporadic	[17]
	10	c.1024A>G	p.Thr342Ala	PK	Family	[17]
	10	c.1028T>C	p.Leu343Pro	DSAP	Family	[4,18]
	11	c.1067C>G	p.Thr356Arg	PK	Sporadic	[17]
	11	c.1093T>A	p.Phe365Ile	PK	Family	[17]
	11	c.1094T>C	p.Phe365Ser	DSAP/PK	Family	[2,17,18]
	11	c.1126G>A	p.Gly376Ser	DSAP/MKD/PK	Family/sporadic	[2,17,23]
Nonsense	3	c.186G>A	p.Trp62*	DSAP	Sporadic	[4,18]
	4	c.254C>G	p.Ser85*	PK	Family	[17]
	10	c.904C>T	p.Gln302*	PK	Family	[17]
Deletion	1–5	c.-1880_527+533del	p.?	PK	Family/sporadic	[17]
	5	c.395del	p.Val132Glufs*27	DSAP/PK	Family/sporadic	[17,18,24]
	5	c.481_482delTG	p.Cys161Argfs*25	DSAP/PK	Sporadic	[2,17]
	7	c.635_637delGAG	p.Gly212del	DSAP	Family	[2,18]
	7	c.671del	p.Leu224*	PK	Sporadic	[17]
	9	c.852dup	p.Ala285Serfs*15	DSAP	Sporadic	[18,24]
	10	c.902del	p.Asn301Thrfs*5	PK	Sporadic	[17]
	11	c.1057delTGGAGGCCACGAAG	p.Val353Alafs*9	DSAP	Sporadic	[18,24]
Insertion	5	c.417_418insC	p.Gly140Argfs*47	DSAP/MKD/PK	Sporadic	[2,17,25]
Start codon	2	c.3G>C	p.Met1?	DSAP	Family	[2]
Splice site	4	c.371+2T>A	p.Glu76Glyfs*9	PP	Family	[17]
	10	c.1039+2T>C	p.Leu348Ilefs*17	DSAP	Family	[2]

PK: porokeratosis.
DSAP: disseminated superficial actinic porokeratosis.
HIDS: hyperimmunoglobulinaemia D and periodic fever syndrome.
MKD: mevalonate kinase deficiency.
PP: porokeratosis ptychotropica.