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Identification of novel homozygous *SLURP1* mutation in a Javanese family with Mal de Meleda

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Conflict of Interest: None declared.

[a]Both authors contributed equally.

Abstract

Background Mal de Meleda (OMIM# 248300; keratosis palmoplantaris transgrediens) is an autosomal recessive form of palmoplantar keratoderma, clinically characterized by sharp demarcated erythema and hyperkeratosis of the palms and soles that progress with age and extend to the dorsal aspects of the hands and feet. The mal de Meleda is caused by mutations in the *SLURP1* gene that encodes secreted lymphocyte antigen 6/urokinase-type plasminogen receptor-related protein 1 (SLURP1). To date no reported cases from Indonesia. The aims of the study were to describe the typical features of mal de Meleda cases in a Javanese family in Indonesia and identify the mutation in the *ARS B* gene which encodes *SLURP1*.

Patients and Methods In this study, three Javanese patients, siblings from nonconsanguineous nonaffected parents, presented with classical symptoms of mal de Meleda. Genetic analysis screening SLURP1 gene was conducted for the specimens from the patients and other family members.

Results A novel homozygous three-nucleotide deletion in exon 3, i.e. c.271-273TCTdel, was identified in the patients. Subcloning and sequencing revealed both parents (I.2 and I.3) and one of the father's siblings (I.1) carry heterozygous c.271-273TCTdel, while the other father's sibling (I.2), the mother's sister (I.4), and a healthy control matched the ethnicity of the family, showing normal sequence of the entire *SLURP1*.

Conclusion This is the first mal de Meleda case of Javanese ethnicity to be documented, and the unique mutation has not previously been reported. The finding supports the notion that despite the rarity, SLURP1 mutation causing mal de Meleda is ubiquitous.

Introduction

Mal de Meleda (OMIM# 248300; keratosis palmoplantaris transgrediens of Siemens) is an autosomal recessive genodermatoses characterized clinically by erythema and hyperkeratosis of the palms and soles with sharp demarcation that progress with age (progrediens) and extend to the dorsal aspects of the hands and feet (transgrediens).[1,2] The disease was first recognized by Luca Stulli, a Dubrovnik's state physician, in 1826 on the Adriatic island of Meleda.[3] The Mljet disease or mal de Meleda is named after one of the Croatian islands, and it entered the records of world literature under this name in 1897, thanks to the physicians Hovorka and Ehlers, and has retained this name up until the present.[4]

Mal de Meleda has an onset in early infancy and a prevalence of one in 100,000 in the general population.[5] The lesions might be associated with painful fissures, macerations, hyperhydrosis, perioral erythema, prominent knuckle pads, nail abnormalities, malodourous because of microbial superinfection, pseudoainhum, and brachydactyly, as well as congenital

cataracts.[6–11] Histologically, the lesions show hyperkeratosis and acanthosis without epidermolysis in the epidermis, accompanied by perivascular lymphocytic infiltrate in the dermis.[9,12]

The mal de Meleda gene has been mapped to chromosome 8q24.3,[1] with mutations in ARS (component B)-81/s gene (*LY6LS*), also known as *SLURP1*, encoding secreted Ly-6/uPAR related protein 1 (SLURP1).[1,13] Cases of mal de Meleda with *SLURP1* mutations have been reported in Algerian,[1] Bedouin,[14] Chinese,[15] Croatian,[1] Dutch,[16,17] German,[14,16,18] Indian,[19] Indonesian,[20] Italian,[21] Japanese,[6,22] Korean,[23] Kurdish,[2] Libyan,[24] Pakistani,[25] Palestinian,[14] Scottish,[18] Swedish,[26] Taiwanese[27,28] Tunisian,[18,21,29] and Turkish descents.[14,30–33]

To date no cases has been reported from a Javanese family, though the mutation has been reported in Indonesian woman who live in Australia.[20] In this report, we describe a familial case of mal de Meleda with a unique mutation in *SLURP1* gene in a Javanese family, which substantiates that mal de Meleda because of *SLURP1* mutation is ubiquitous and Javanese ethnicity is not spared from the occurrence.

Patients and methods

The study conformed to the ethical guidelines of the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine Universitas Gadjah Mada, Yogyakarta, Indonesia. Patients and all family members provided consent prior to the clinical examination and blood specimen collection for genetic analysis.

Patients

Patient 1

A 22-year-old Javanese male (II.1) presented with sharply demarcated hyperkeratotic plaques on the palms and soles since the first 5 months of life that extended onto the upper arms and legs. He also complained of malodor on the palms and soles as well as athlete's foot that recurred intermittently, especially during hot season. Physical examination revealed transgressive hyperkeratosis and erythema of the palms (Fig. 1a) and soles (Fig. 2a), extending to the upper arms

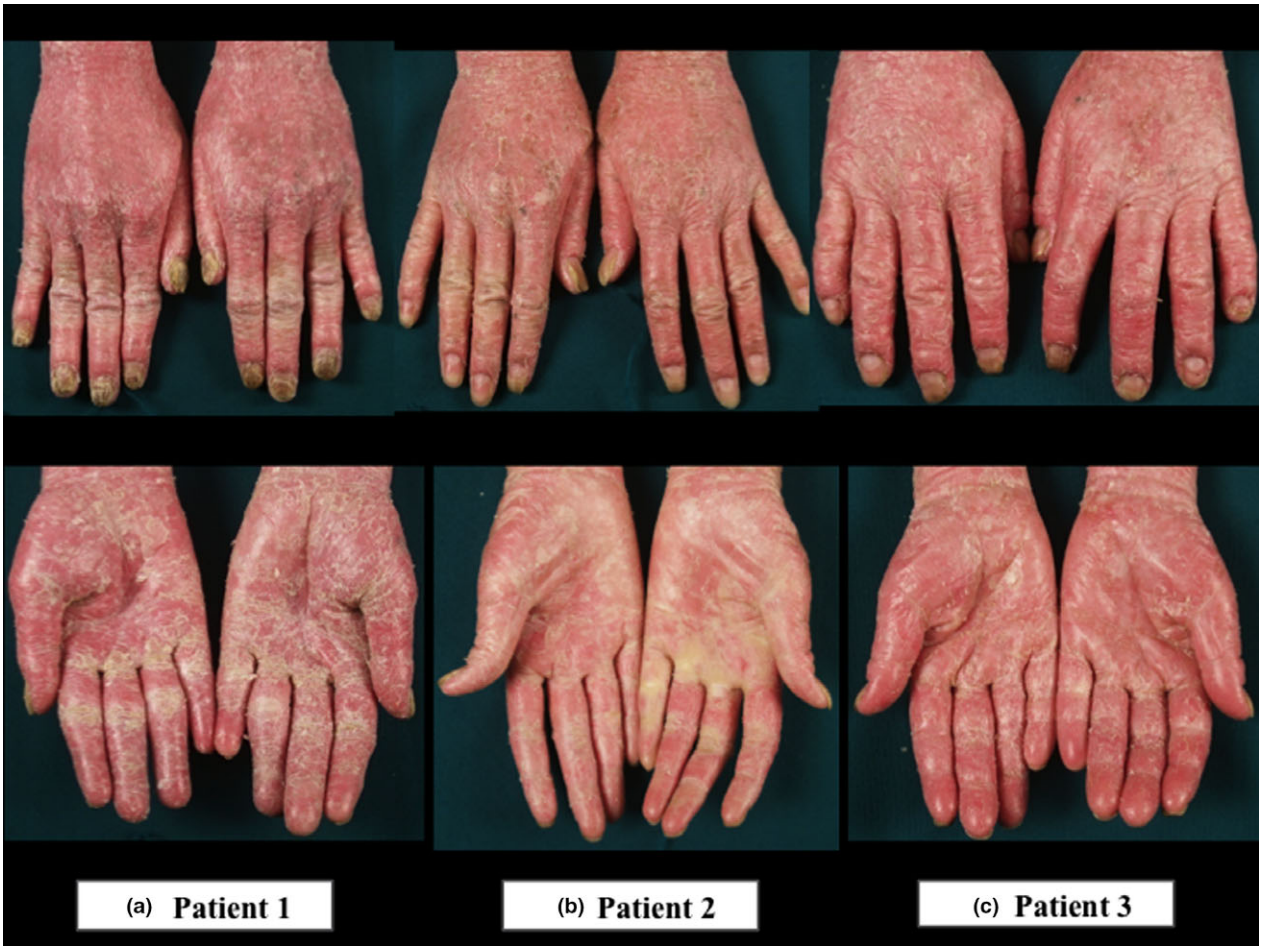

Figure 1 Sharply demarcated hyperkeratosis and erythema of the palms extending to the dorsum of the hands symmetrically (a) Patient 1; (b) Patient 2; (c) Patient 3

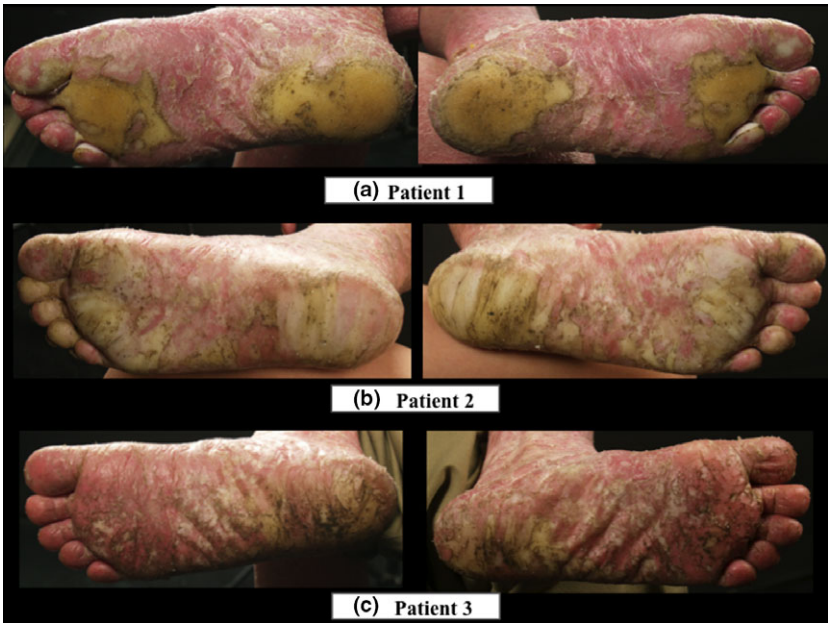

Figure 2 Sharply demarcated hyperkeratosis and erythema of the soles extending to the dorsal aspects of the feet symmetrically (a) Patient 1; (b) Patient 2; (c) Patient 3

Figure 3 The lesion extending to the upper arms (a) Patient 1, symmetrically; (b) Patient 2, lower arms; (c) Patient 3, lower arms

(Fig. 3a) and legs (Fig. 4a) symmetrically, 20-nails dystrophy as well as perioral and nose erythema. He experienced seizures at 1 year old. He has two younger brothers and a sister, two of whom have the same symptoms (II.3, II.4) (Fig. 5).

Patient 2

A 14-year-old girl (II.3) presented with extensive palmoplantar hyperkeratosis which extended onto the dorsal surfaces of the hands and feet since her first 3 months of life. Physical examination revealed hyperkeratosis and erythema of the palms (Fig. 1b) and soles (Fig. 2b) with transgrediens, extending to the lower arms (Fig. 3b) and lower legs (Fig. 4b), as well as nail dystrophy. Similar with her older brother, she experienced seizures at the age of 2 years.

Patient 3

A 12-year-old boy (II.4) presented diffuse erythema and hyperkeratosis of the hands (Fig. 1c) and feet (Fig. 2c) that appeared during the first 2 weeks of life and progressively extended to the dorsal aspect of the lower arms (Fig. 3c) and

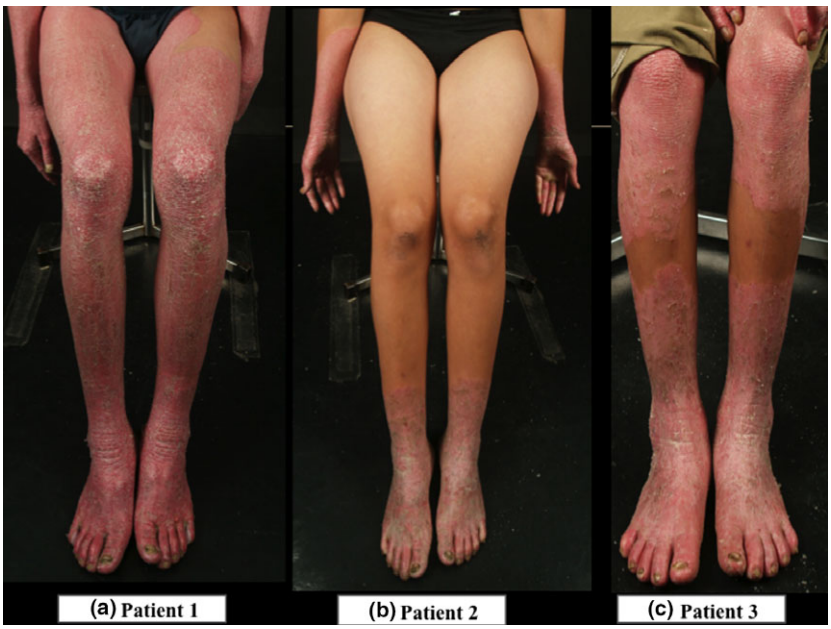

Figure 4 The lesion extending to upper legs (a) Patient 1; (b) Patient 2 symmetrically; (c) Patient 3 to thighs with area of normal skin on the lower legs

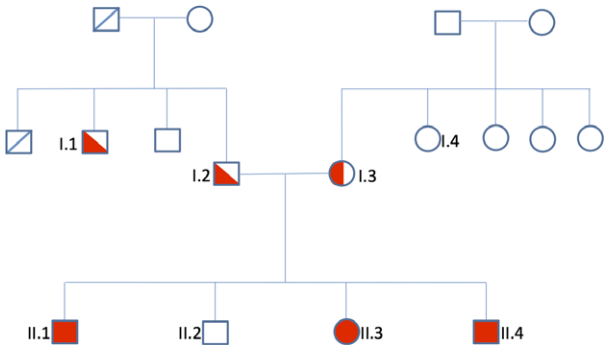

Figure 5 Pedigree of the family

thighs with an area of normal skin on the lower legs symmetrically (Fig. 4c).

All the patients experienced hyperhidrosis localized on the palms and soles. We performed histopathology of all patients.

PCR and sequencing for the *SLURP-1* mutation screening

Genomic DNA was isolated from blood samples by E.Z.N.A Blood DNA Kit (Omega Bio-tek, Norcross, Georgia, USA) according to the manufacturer's protocol. Polymerase chain reaction (PCR) amplification of DNA was performed with specific sets of primers for all three exons of *SLURP1* gene that includes part of the 5′UTR in exon 1, the flanking introns, and the 3′UTR in exon 3. The amplicons were purified using Qiagen Purification Kit (Qiagen GmbH, Hilden, Germany). The purified products were directly sequenced using the Big Dye Terminator Sequencing Kit (Version 3.0 Cycle Sequencing Kit) and analyzed on the ABI 3700 DNA sequencing system (PE Applied Biosystems, Foster City, CA). Sequence comparisons and analysis were performed using Basic Local Alignment Search Tool (BLAST) from the National Centre for Biotechnology Information (NCBI) with *SLURP1* GenBank accession number NG_011494 (NCBI) or 606119 (MIM) as reference.

To validate the mutation, various databases of genetic variation in *SLURP1* were screened for the same mutation found in the affected members of the family in this study.

PCR and subcloning to characterize the nucleotide changes

DNA amplification was done to amplify exon 3 of *SLURP1* using a pair of specific primers located in intron 2 and the 3′UTR in exon 3. PCRs was performed under optimized conditions using GoTaq DNA Polymerase (Promega Corp, Madison, WI, USA) in a DNA Thermal Cycler 480 (Perkin-Elmer, Branchbura, NJ, USA). The amplicons were then cloned into TOPO® XL PCR cloning kit (Invitrogen, Carlsbad, CA, USA) following the protocol provided by the manufacturer. A number of clones were picked randomly, and their sequences were characterized by sequencing using primers to reveal the sequence of each *SLURP1* allele in the region that contained exon 3 and its partial flanking introns. Sequencing was performed using a DNA Sequencing Kit with BigDye Terminators ABI 373 automated DNA Sequencer (Applied Biosystems). The primers used for PCR and sequencing are available upon request.

Results

Clinical data

Physical examination of all affected individuals showed classical findings of mal de Meleda, i.e. transgressive keratoderma from the palms and soles progressively extending to the dorsa of the hands and feet, erythema surrounding the hyperkeratotic lesions, in a "glove-and-socks" distribution. Nail dystrophy with subungual hyperkeratosis were observed in all patients. The histopathologic study of all patients showed marked hyperkeratosis, acanthosis, and normogranulosis, without epidermolysis in the epidermis, accompanied by perivascular lymphocytic infiltrate in the dermis.

The parents did not show any skin symptoms (I.2 and I.3), were otherwise healthy, and were not consanguineous, and there were no other family members affected with the same disease.

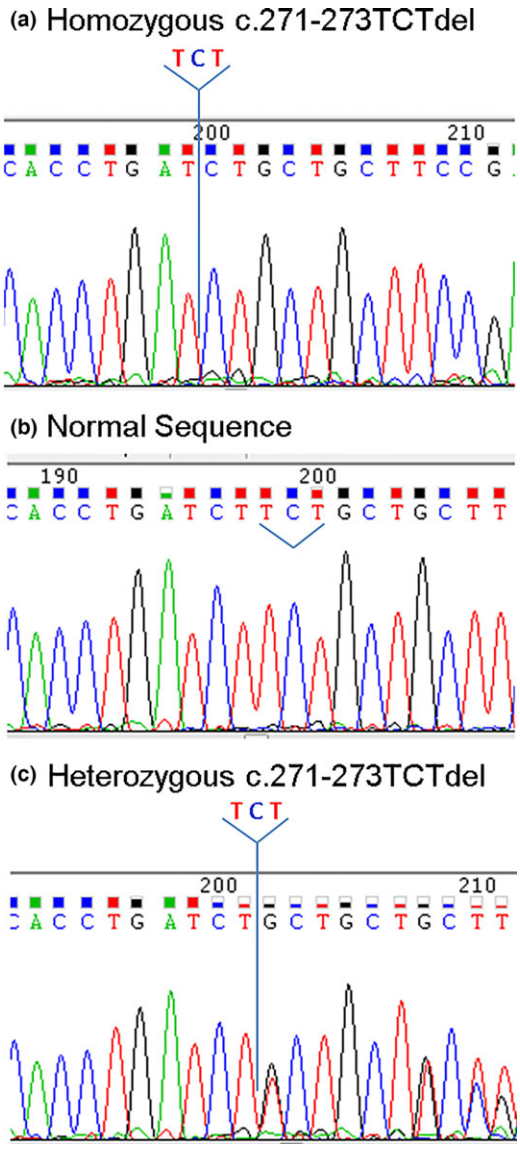

Figure 6 Deletion of c.271-273TCT of *SLURP1* in homozygous form (a) was identified in all affected patients. The same mutation in heterozygous form (c) was identified in both parents and one of the father's brother. Healthy controls and the rest of the patients' family members tested showed normal sequence of SLURP1 (b)

Mutation detection and confirmation

PCR amplification of three *SLURP1* exons for patients' DNA sample yielded amplicons of similar sizes as their unaffected family members as well as healthy controls. Direct sequencing of the amplicons showed that all three affected children (II.1, II.2, and II.4) carry homozygous small three nucleotides deletion in exon 3, i.e. c.271-273TCTdel or p.Ser91del (Fig. 6a). Both parents (I.2 and I.3) and one of the father's siblings (I.1) carry heterozygous c.271-273TCTdel (Fig. 6c) that was verified by subcloning. The other father's sibling (I.2), the mother's sister (I.4), and a healthy control matched the ethnicity of the family showed normal sequence of the entire *SLURP1* (Fig. 6b).

Discussion

Mal de Meleda was initially known as a unique form of palmoplantar keratoderma found among populations on the Croatian isle of Mljet with the first to be documented in the 19th century.[4]

The genetic basis responsible for mal de Meleda, i.e. mutations in *SLURP1*, was identified by Fischer *et al.* in 2001.[1] To date, mal de Meleda has been found to affect 19 ethnic populations, spreading in 21 countries, and associated with at least 20 mutations in *SLURP1* (Tables 1 and 2). Majority of the cases are homozygous mutations with very few patients carrying compound heterozygous mutation. This in accordance with the rarity of the disease indicating the spread of the disease is still clustered within founder mutations.

Here, we report cases of mal de Meleda in a family of six with three affected children. All three showed classical symptoms of transgrediens and progrediens keratoderma starting from the palms and soles.

The novel mutation reported here added up the list of the SLURP1 mutation known to yield mal de Meleda to be at least 20. The most recurrent mutation is c.82delT (p.Cys28fs32X) that has arisen in 23 kindred from six ethnic groups in six countries surrounding the Mediterranean Sea. The second most recurrent mutation is c.43T>C (p.Trp15Arg) that occurred in 17 kindred from four ethnic groups in four European countries. c.256G>A (p.Gly86Arg) is third in the number of kindred affected, nine, whereby two being large kindred, but most prolific to be found in six ethnic groups spreading in seven countries from the USA and middle east to the far east and Australia (Table 2).

The c.271-273TCTdel (p.Ser91del) was identified in a family of Javanese ethnicity from a certain area in Central Java with no knowledge of their consanguinity status. This is the first

Table 1 The list of ethnic groups and *SLURP1* mutations that have been identified to be associated with mal de Meleda

Patient's ethnics	Patient's location	Mutation	Allele	No of kind-red	Reference
Algerian	Algeria	c.82delT (p.Cys28fs32X)	Homozygous	9	1
		c.178+1G>A	Homozygous	3	
Bedouin	UEA	c.1A>C (p.Met1Leu)	Homozygous	1	14
Chinese	PRC	c.256G>A (p.Gly86Arg)	Homozygous	2	15
	Taiwan	c.256G>A (p.Gly86Arg)	Homozygous	2	27,28
Croatian	Croatia	c.82delT (p.Cys28fs32X)	Homozygous	4	1
		c.286C>T (p.Arg96X)	Homozygous	3	
Dutch	Netherlands	c.43T>C (p.Trp15Arg)	Homozygous	3	16
		c.43T>C (p.Trp15Arg)	Heterozygous	1	17
		c.212G>C (p.Arg71Pro)			
German	Germany	c.43T>C (p.Trp15Arg)	Homozygous	3	14,16,18
Indian	India	c.58+5G>T	Homozygous	1	19
Indonesian (Ethnic unspecified)	Australia	c.256G>A (p.Gly86Arg)	Homozygous	1	20
Italian	Italy	c.82delT (p.Cys28fs32X)	Not known	Not known	21
Japanese	Japan	c.58+1G>C	Homozygous	1	6
		c.211C>T (p.Arg71>Cys)	Homozygous	1	22
Javanese	Indonesia	c.271-273TCTdel (p.Ser91del)	Homozygous	1	This report
Korean	Korea	c.256G>A (p.Gly86Arg)	Heterozygous	1	23
		c.286C>T (p.Arg96X)			
Kurdish	Turkey	c.82delT (p.Cys28fs32X)	Homozygous	1	2
Libyan	Libya	c.256G>A (p.Gly86Arg)	Homozygous	1	24
Pakistani	USA	c.58+1G>A	Homozygous	1 big	25
		c.256G>A (p.Gly86Arg)	Homozygous	1 big	
		c.286C>T (p.Arg96X)	Homozygous	1 big	
Scottish	Scotland	c.43T>C (p.Trp15Arg)	Heterozygous	1	18
		c.82delT (p.Cys28fs32X)			
Swedish	Sweden	c.43T>C (p.Trp15Arg)	Homozygous	8	26
		c.43T>C (p.Trp15Arg)	Heterozygous	1	
		c.280T>A (p.Cys94Ser)			
Tunisian	Tunisia	c.82delT (p.Cys28fs32X)	Homozygous	7	18,21,29
		c.229T>C (p.Cys77Ala)	Homozygous	2	29
		c.296G>A (p.Cys99Tyr)	Homozygous	4 (1 being a big kindred)	18,21,29
Turkish	Turkey	c.129C>A (p.C43X)	Homozygous	1	30
		c.256G>C (p.Gly86Arg)	Homozygous	1	14
		c.286C>T (p.Arg96X)	Homozygous	1	2
		c.293T>C (p.Leu98Pro)	Homozygous	1	32
	Austria	c.244C>T (p.Pro82Ser)	Homozygous	1	33

report of mal de Meleda in a certain Javanese family. Recently Taylor *et al.*[20] reported mal de Meleda case with c.256G>A (p.Gly86Arg) in an Indonesian family that lives in Australia. Although it was mentioned that both parents of the patients lived in Jakarta, their ethnicity was not clear. There are more than 300 ethnic groups in Indonesia,[34] whereby 95% of those are of native Indonesian ancestry.[35] Although most of mal de Meleda cases come from consanguineous families, the two Indonesian mal de Meleda families both are not known to be consanguineous. The fact that the patients from both families carry homozygous mutations highlights the presence of the mutations' carriers in their respective communities.

The rarity of the case whereby majority of patients carry homozygous mutations indicates that the spreading of mal de Meleda still limited within each founder mutation and *de-novo* mutation is rare.

In conclusion, this report highlights the ubiquitous occurrence of mal de Meleda. Javanese, the biggest ethnic group in Indonesia, is not spared from this genetic disease. The severity and debilitating symptoms of the disease warrants genetic counseling especially for members from families and extended families with affected individuals.

Acknowledgments

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Table 2 The list of *SLURP1* mutations that have been identified to be associated with mal de Meleda

Mutation	Patient's ethnics	Patient's location	No of kindred	Allele	Reference
c.1A>C (p.Met1Leu)	Emirates Bedouin	United Arab Emirates	1	Homozygous	14
c.43T>C (p.Trp15Arg)	Dutch	Netherlands	3	Homozygous	16
			1	Heterozygous	17
	German	Germany	3	Homozygous	14,16,18
	Scottish	Scottish	1	Heterozygous	18
	Swedish	Sweden	8	Homozygous	26
			1	Heterozygous	
c.58+1G>A	Pakistani	USA	1 big	Homozygous	25
c.58+1G>C	Japanese	Japan	1	Homozygous	6
c.58+5G>T	Indian	India	1	Homozygous	19
c.82delT (p.Cys28fs32X)	Algerian	Algeria	9	Homozygous	1
	Croatian	Croatia	4	Homozygous	1
	Kurdish	Turkey	1	Homozygous	2
	Scottish	Scottish	1	Heterozygous	18
	Tunisian	Tunisia	7	Homozygous	18,21,29
	Italian	Italy	Not known	Not known	21
c.129C>A (p.Cys43X)	Turkish	Turkey	1	Homozygous	30
c.178+1G>A	Algerian	Algeria	3	Homozygous	1
c.211C>T (p.Arg71>Cys)	Japanese	Japan	1	Homozygous	22
c.212G>A (p.Arg71His)	Unspecified	France	1	Homozygous	36
c.212G>C (p.Arg71Pro)	Dutch	Netherlands	1	Heterozygous	17
c.229T>C (p.Cys77Ala)	Tunisian	Tunisia	2	Homozygous	29
c.244C>T (p.Pro82Ser)	Turkish	Austria	1	Homozygous	33
c.256G>C (p.Gly86Arg)	Turkish	Turkey	1	Homozygous	14
c.256G>A (p.Gly86Arg)	Chinese	Taiwan	2	Homozygous	27,28
		PRC	2	Homozygous	15
	Indonesian (Ethnic unspecified	Australia	1	Homozygous	20
	Korean	Korea	1	Heterozygous	23
	Libyan	Libya	1	Homozygous	24
	Palestinian	Palestine	1 big	Homozygous	14
	Pakistani	USA	1 big	Homozygous	25
c.271-273TCTdel (p.Ser91del)	Indonesian (Javanese)	Indonesia	1 (3)	Homozygous	This report
c.280T>A (p.Cys94Ser)	Swedish	Sweden	1	Heterozygous	26
c.286C>T (p.Arg96X)	Croatian	Croatia	3	Homozygous	1
	Korean	Korea	1	Heterozygous	23
	Pakistani	USA	1 big	Homozygous	25
	Turkish	Turkey	1	Homozygous	2
c.293T>C (p.Leu98Pro)	Turkish	Turkey	1	Homozygous	32
c.296G>A (p.Cys99Tyr)	Tunisian	Tunisia	4 (1 being a big kindred)	Homozygous	18,21,29

specimen for genetic analysis. We thank Dr. Antonius Wibowo for referring the patients to our hospital.

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