Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency and Expanded Newborn Screening in Japan

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MCAD deficiency

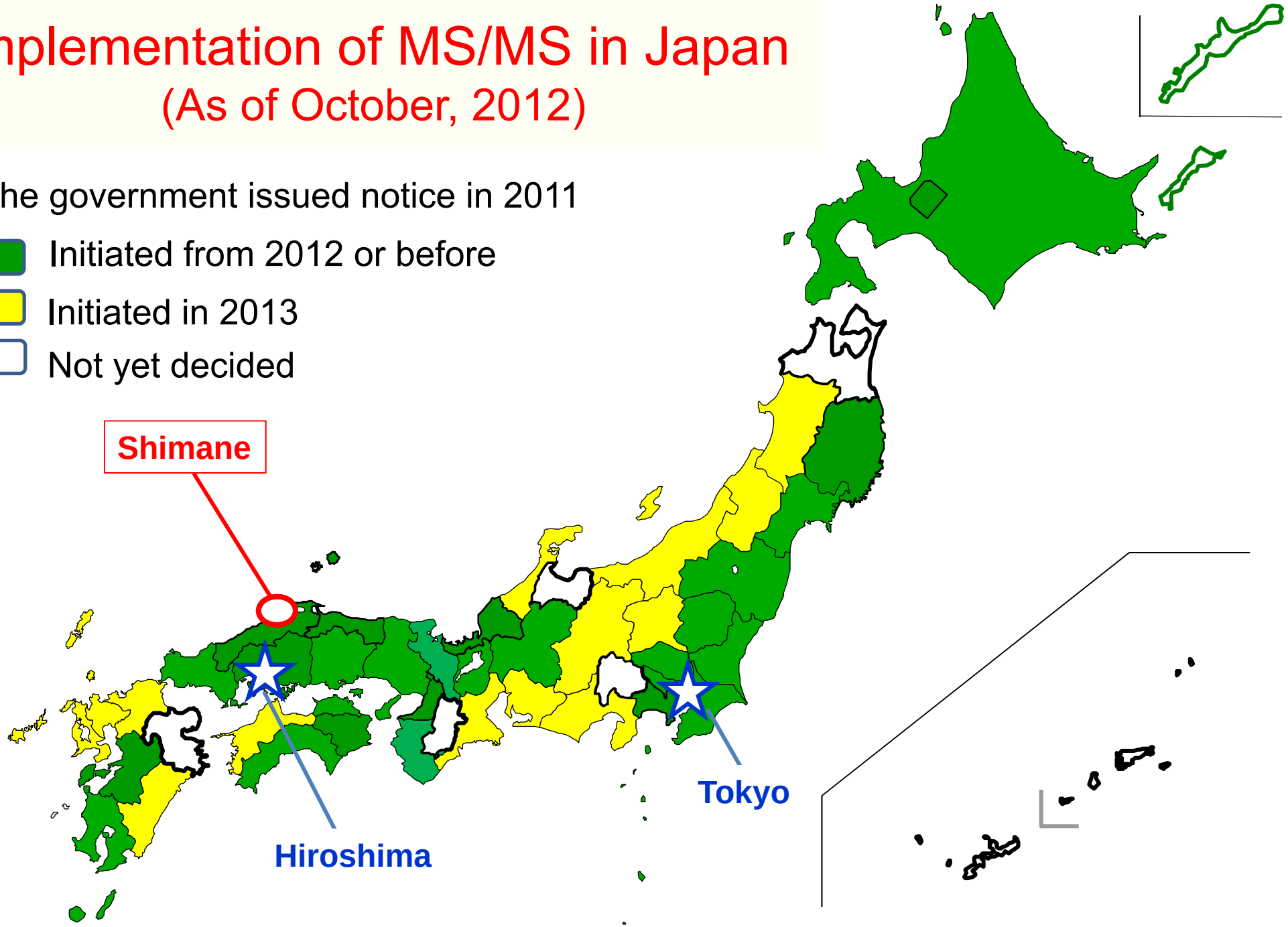
Medium-chain acyl-CoA dehydrogenase deficiency

Incidence	1: 10,000 (Caucasian, a common mutation, 985A>G)	
Acute symptoms triggered by long fasting	Vomiting, lethargy, acute encephalopathy Sudden death	
Laboratory test (acute)	Hypoglycemia, hyperammonemia	
Biochemical Markers (mass spectrometry)	MS/MS (blood AC)	C8, C6, C10, C8/C10
	GC/MS (urinary OA)	Hexanoylglycine (HG) Suberylglycine (SG) Dicarboxylic acids
Prognosis	As many as 35% have no episodes lifelong The 1st attack occurs before 3 to 4 years 25% of children suddenly die during the 1st attack	

Implementation of MS/MS in Japan
(As of October, 2012)

The government issued notice in 2011

- Initiated from 2012 or before
- Initiated in 2013
- Not yet decided



Results of Pilot MS/MS Screening in Japan

（1997～2012）

	Disease	Number	Incidence
	AMINO ACIDEMIA	72	**1 : 27 K**
●	PKU	37	★ 1: 53 K
●	MSUD	1	1: 1,950 K
●	HCY	3	1: 650 K
●	Citrulinemia type I	6	1: 330 K
●	Argininosuccinic A	2	1: 980 K
○	Citrin def	23	1: 80 K
	ORGANIC ACIDEMIA	86	**1 : 23 K**
●	MMA	18	★ 1: 110 K
●	PROP	43	★ 1: 45 K
●	IVA	3	1: 650 K
●	MCD	3	1: 650 K
●	MCC def	13	1: 150 K
●	HMGL def	—	—
●	GA1	7	1: 280 K
○	b-ketothiolase def	—	—
	FATTY ACID DISORDER	57	**1 : 34 K**
●	CPT1 def	5	1: 390 K
●	VLCAD def	12	1: 160 K
●	MCAD def	18	★ 1: 110 K
●	TFP def	2	1: 980 K
○	CPT2 def	7	1: 280 K
○	CACT def	—	—
○	GA2	6	1: 330 K
○	CUD (PCD)	7	1: 280 K
△	SCHAD def	1	1: 1,950 K
	Number of cases	215	1: 9,000
	Neonates screened	1,949,987	

● Core target 16 diseases
○ Secondary 6 diseases

Results of MS/MS Screening in Japan

(1997～2012) ～FATTY ACID DISORDER～

Disease	Number	Incidence
FATTY ACID DISORDER	57	**1 : 34 K**
MCAD deficiency	18	1: 110 K
VLCAD deficiency	12	1: 160 K
CPT2 deficiency	7	1: 280 K
CUD (PCD)	7	1: 280 K
GA2	6	1: 330 K
CPT1 deficiency	5	1: 390 K
TFP deficiency	2	1: 980 K
CACT deficiency	—	—
SCHAD deficiency	1	1: 1,950 K

※Letters colored in blue: not primary targets

Biochemical Clinical, and Molecular findings
MCAD Deficiency in Japanese

	Case	Age at onset	Age at diagosis	NBS	MS/MS C8 (<0.3)	GC/MS (PRA, %) HG (-)	GC/MS (PRA, %) SG (-)
SYMPTOMATIC	1	8m	8m	—	5.97	11.1	44.5
	2	1y0m	1yom	—	4.52	n.a	n.a
	3 *a	1y0m	8y10m	—	1.57	45.4	29.6
	4	1y1m	1y1m	—	7.00	14.7	112.2
	5	1y3m	1y3m	—	n.a	n.a	n.a
	6 *b	1y4m	1y4m	—	3.33	9.9	15.3
	7	1y7m	1y7m	—	4.12	6.1	6.4
	8 *a	1y8m	1y8m	—	4.75	69.3	1.2
	9	2y2m	2y2m	—	1.71	n.a	n.a
NON-SYMPTOMATIC	10	—	5d	+	5.92	12.9	14.8
	11	—	5d	+	5.37	6.33	39.88
	12	—	5d	+	4.82	15.3	3.8
	13	—	5d	+	4.04	n.a	n.a
	14	—	5d	+	2.78	11.5	5.9
	15	—	5d	+	2.59	3.08	3.20
	16	—	5d	+	2.58	(-)	1.50
	17	—	5d	+	0.49	9.7	(-)
	18 *b	—	5y5m	—	1.37	n.a	n.a
Hetero	19	—	5d	+	0.44	(-)	(-)
	20	—	4m	—	0.51	(-)	(-)

*a-a, *b-b
Siblings

n.a
No data Available

NBS
Newborn mass screening

Japanese MCAD deficiency Clinical onset, outcome and genotype (Shimane Univ. 2012)

	Case	Age at onset	Age at diagnosis	Hypo glycemia	Hyper ammonemia	Genotype Allele 1	Genotype Allele 2	Outcome
Symptomatic	1	8m	8m	(n.a)	(+)	c.449-452del	c.157C>T	Develop. delay
	2	1y	1y	(+)	(-)	IVS4+1G>A	c.422 A>T	Sudden death
	3 *a	1y	8y 10m	(+)	(-)	c.449-452del	c.449-452del	Develop. delay
	4	1y 1m	1y 1m	(+)	(+)	del. ex 11-12	del. ex 11-12	Develop. delay
	5	1y 3m	1y 3m	(n.a)	(-)	del. ex 11-12	del. ex 11-12	Develop. delay
	6 *b	1y 4m	1y 4m	(+)	(-)	c.449-452del	c.449-452del	Develop. delay
	7	1y 7m	1y 7m	(+)	(+)	c.275C>T	c.157C>T	Develop. delay
	8 *a	1y 8m	1y 8m	(+)	(+)	c.449-452del	c.449-452del	Sudden death
	9	2y 2m	2y 2m	(+)	(-)	c.449-452del	c.449-452del	normal
NON-Symptomatic	10	—	5d	(-)	(-)	c.1085G>A	c.843A>T	normal
	11	—	5d	(-)	(-)	c.449-452del	c.154A>G	normal
	12	—	5d	(-)	(-)	IVS3+2T>C	c.843 A>T	normal
	13	—	5d	(-)	(-)	c.449-452del	c.212 G>A	normal
	14	—	5d	(-)	(-)	c.449-452del	c.134 A>G	normal
	15	—	5d	(-)	(-)	c.1085G>A	c.1184A>G	normal
	16	—	5d	(-)	(-)	c.449-452del	IVS3+5G>A	normal
	17	—	5d	(-)	(-)	c.449-452del	c.820 A>C	normal
	18 *b	—	5y 5m	(-)	(-)	c.449-452del	c.449-452del	normal
Carrier	19	—	5d	(-)	(-)	c.845C>T	n.d	normal
	20	—	4m	(-)	(-)	c.843A>T	n.d	normal

a-a, b-b: sibling cases (n.a) data, not available

Mutations in Japanese patients with MCAD deficiency

N	Japanese Mutation	Allele	%
1	c.449-452del	16	44.4
2	del. ex11-12	4	11.1
3	c.157C>T (R28C)	2	5.6
4	c.843A>T (R256S)	2	5.6
5	c.1085G>A (G337E)	2	5.6
6	c.134 A>G (Q20R)	1	2.8
7	c.212 G>A (G46D)	1	2.8
8	c.275C>T (P67L)	1	2.8
9	c.422 A>T (Q116L)	1	2.8
10	c.820A>C (M249V)	1	2.8
11	c.1184A>G (K395R)	1	2.8
12	IVS3+5G>A	1	2.8
13	IVS3+2T>C	1	2.8
14	IVS4+1G>A	1	2.8
	Total	36	100

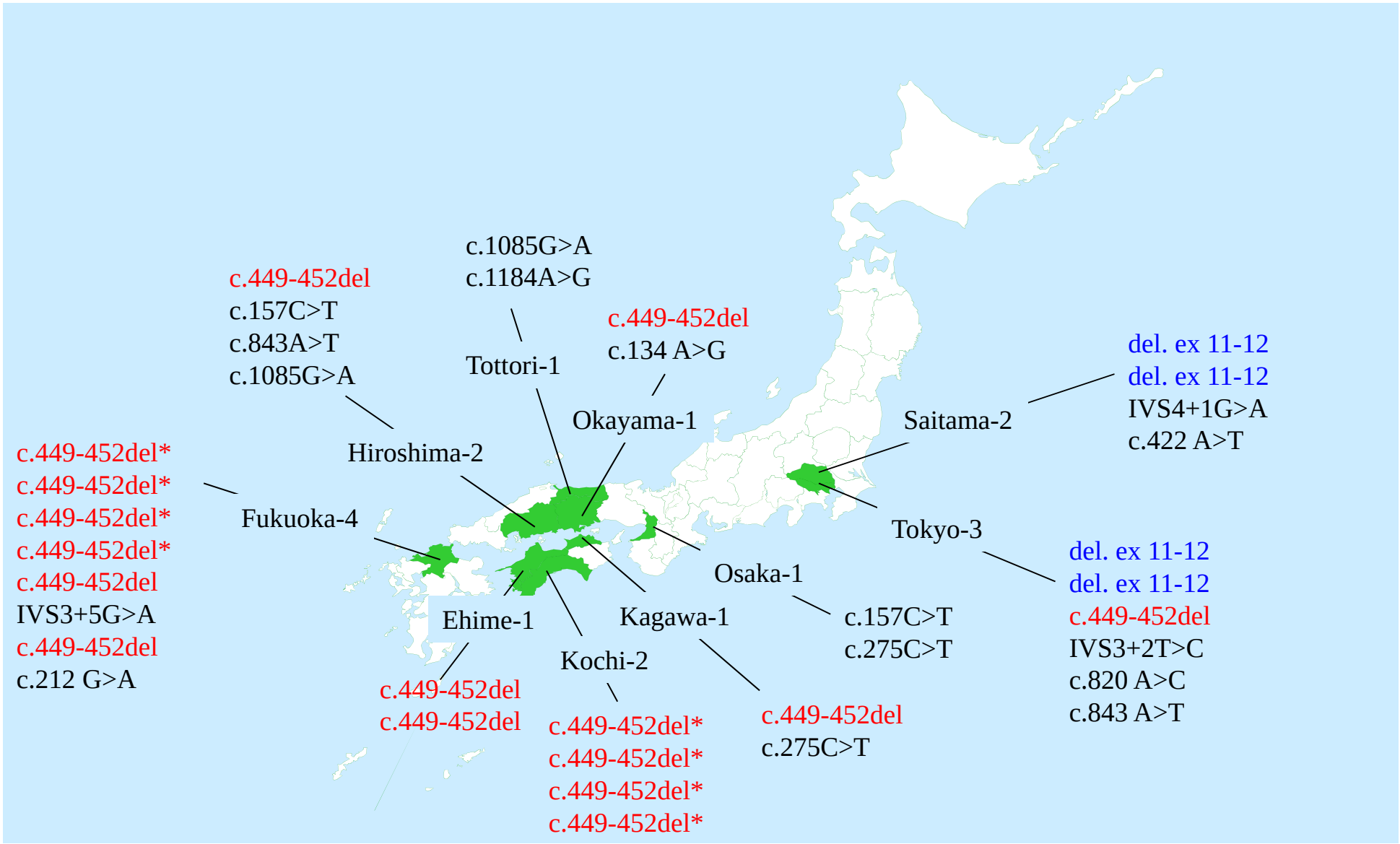
Blue: novel mutations

Korean Patients	Genotype	
	Allele 1	Allele 2
1[a]	c.449-452del	c.461T>G (L129W)
2[b]	c.449-453del	c.843A>T (R256S)
3[b]	c.449-454del	c.1189T>A (Y372N)

a, Ensenauer R et al. Genet Med. 2005
b, Woo HI et al. Korean J Lab Med. 2011

Caucasian common mutation
c.985A>G (covering 90%) :
None! in Japanese

Patient with MCAD deficiency in Japan



Summary & Conclusions

1. The incidence of MCAD deficiency in Japanese is:
   1 in 110 thousands (Caucasian, 1 in 10 thousands).

2. About 45% of Japanese patients have a common mutation,
   c.449-452delCTGA.

3. The genetic background between Japanese and Korean cases is likely similar, but quite different from Caucasians.

4. Correlation between the clinical course and genotype in MCAD deficiency is unlikely.

5. Prognosis of the symptomatic cases were poor!!
   Pre-symptomatic detection of MCAD deficiency is essential to prevent affected children from impairments or sudden death.

Thank you!

Shimane,
JAPAN