The Japanese collaborated study of Fragile X syndrome and its related disorders

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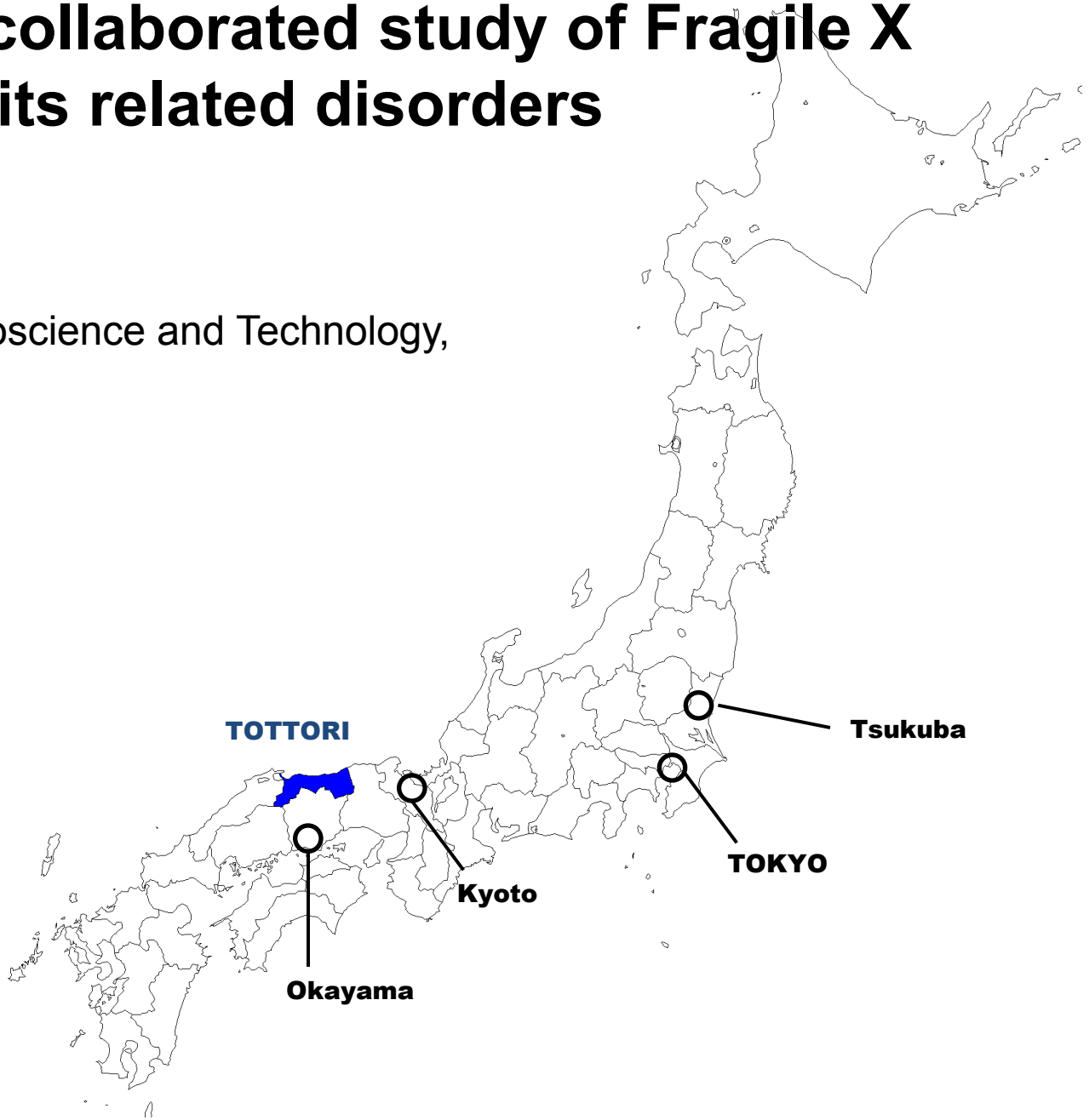


Carrier Screening in Japanese normal population: CGG repeat analysis in *FMR1* gene (Dr. Nanba, 2010)

ELSEVIER

Brain & Development 32 (2010) 110–114

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Fragile X carrier screening and *FMR1* allele distribution in the Japanese population

Susumu Otsuka [a,h], Yumiko Sakamoto [a], Haruhiko Siomi [b], Mituo Itakura [c], Kenji Yamamoto [d], Hideo Matumoto [e], Tsukasa Sasaki [f], Nobumasa Kato [g], Eiji Nanba [a,*]

Table 2
FMR1 allele frequencies in autistic patients and normal controls.

No. of *FMR1* CGG repeats		Autism ($n = 116$ alleles)		Controls ($n = 1161$ alleles)	
		Male ($n = 102$)	Female ($n = 14$)	Male ($n = 513$)	Female ($n = 648$)
6–39	(Normal)	102	14	508 (99%)	647 (99%)
40–54	(Intermediate)	0	0	5 (0.97%)	1 (0.15%)
55–200	(Premutation)	0	0	0	0
⩾200	(Full mutation)	0	0	0	0

Frequency of FXS in Japan

Number of the allele			Full mutation (200＜)	Pre-mutation (55-200)	Inter-mediate
Our study	1,161	Male	0	0	**1：171** 1)
		Female	0	0	**1：324**
Taiwan (Tzeng CC. 2005)	10,046	Male	1：10,046	1：1,674	**1：143** 1)
Spain (Rifé M. 2003)	5,000	Male	1：2,466	1：1,233	**1：449** 3)
		Female	1：8,333	1:411	
Canada (Dombrowski C. 2002)	10,572	Male		1：813	**1：441** 1)
Israel (Hagit TA. 2001)	28,668	Female	1：3,584	**1：113**	**1：179** 2)

＊The range of CGG repeats ： 1) 45-54、2) 50-54、3) 52-55

Background/starting point of present study

1. Frequency of FXS in Japan in male is about 1/10,000

2. Lower frequencies of FXS in Japan seem to be due to poor diagnostic systems/guideline or other secondary reasons

3. The first FXTAS patient was found in Japan (Internal Med. 2010)

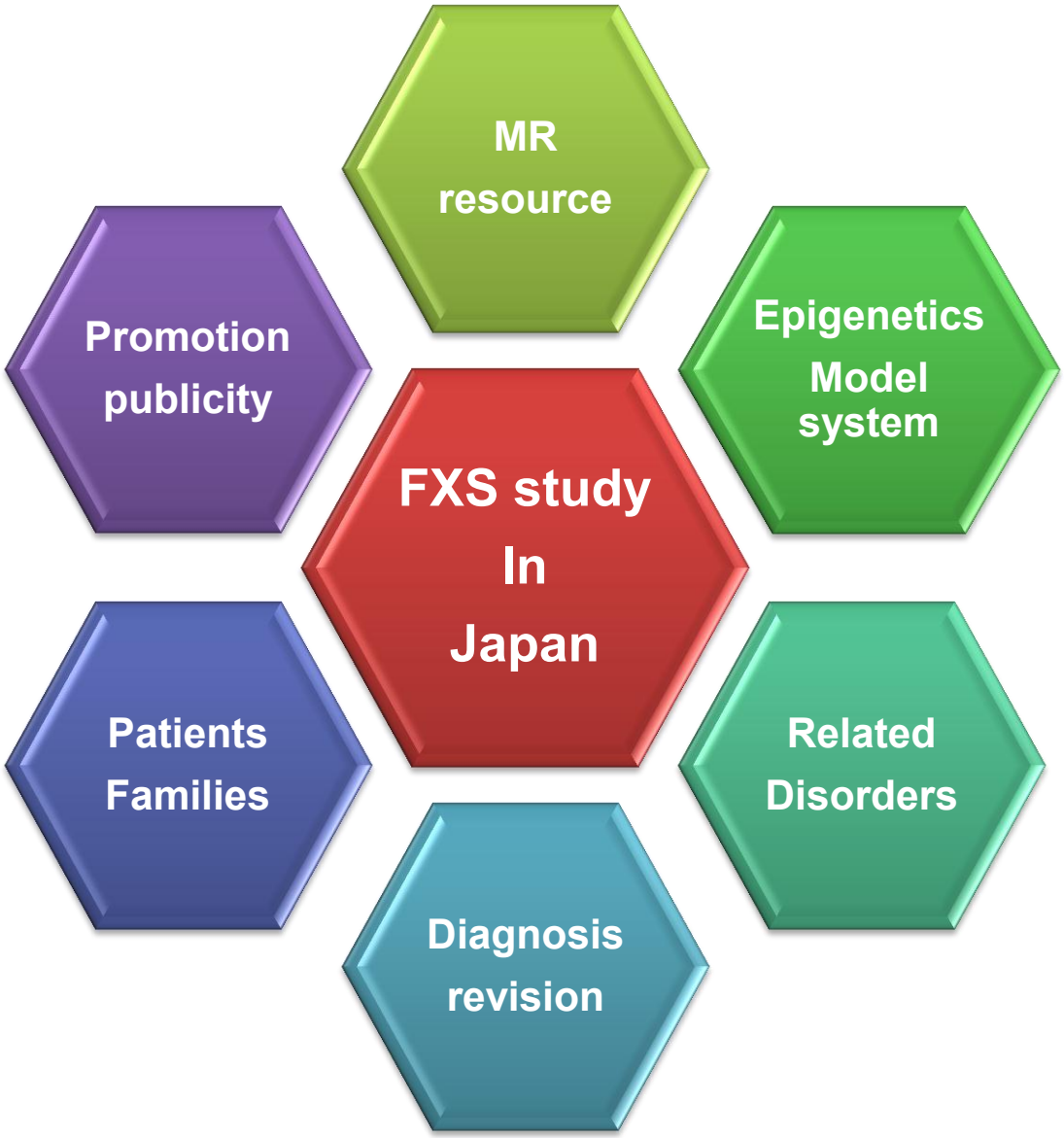
These evidences prompted us to promote or spread…

The knowledge about FXS and related disorders to public health, medicals, and related committees

The Study about FXS and related disorders toward development of diagnosis starategy, pharmaco-therapy, or treatments in future

The Systematic approach toward improving any kinds of situation / limitation / inaccesibilities related to FXS and related disorders in Japan

“The study of diagnosis and treatment for Fragile X syndrome and related disorders in Japan”



Members

This research was supported by Ministry of Health Labor and Welfare
(Research on intractable diseases) from 2009 to 2011

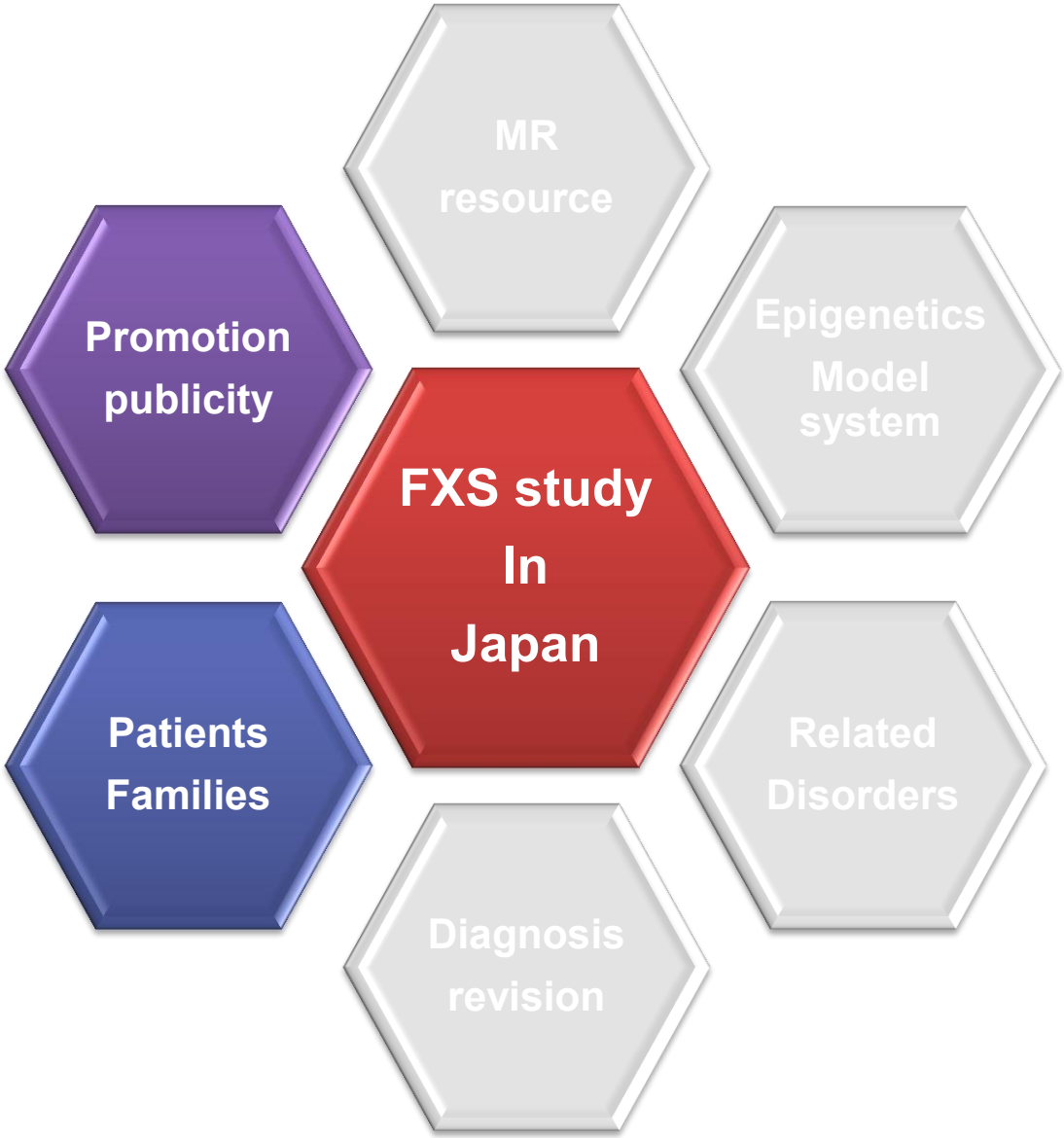
- Eiji Nanba (Tottori Univ.)
- Tadao Arinami (Tsukuba Univ.) epigenetic regulation and FXS in elders
- Hideo Sugie (Jichi Medical Univ.) pharmacotherapy and its guideline
- Yu-ichi Goto (National Center of Neurology and Psychiatry)
- Tsukasa Sasaki (Tokyo Univ.)
- Kousaku Ohno (Tottori Univ.)
- Kenji Nakashima (Tottori University)
- Bunpei Ishizuka (St. Marianna Univ.)
- Tohru Matsuura (Okayama Univ.)

Researchers (MD)
For
Related disorder

POI, PD,
ASD, FXTAS,
SCA(10&36)

The global survey by the questionnaires (Dr. Tsukasa Sasaki)

Global survey by
questionary investigation
Targeted to specialists



Outline of the global survey in this study

The targets:

1. **1,022 doctors** with special board with child neurology (SBCN)

2. **1,831 doctors** belong to the Japanese Society for Child and Adolescent Psychiatry (JSCAP), working on PDD* subjects

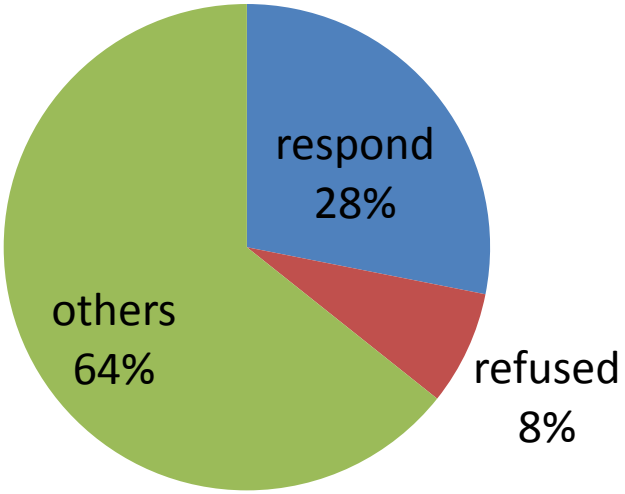
3. **620 doctors** belong to the Japanese Society of Pediatric Psychiatry and Neurology (JSPPN), working on PDD* subjects

4. The public health nurses (PHN) in **653 institutions** in Japan, taking care of infants and young children

***PDD:** Pervasive Developmental Disorders

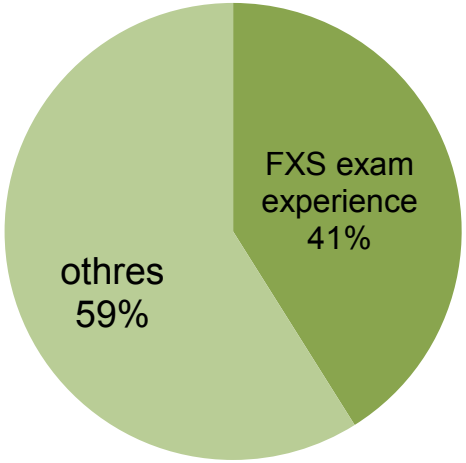
SBCN response to questionary

13 patients were found

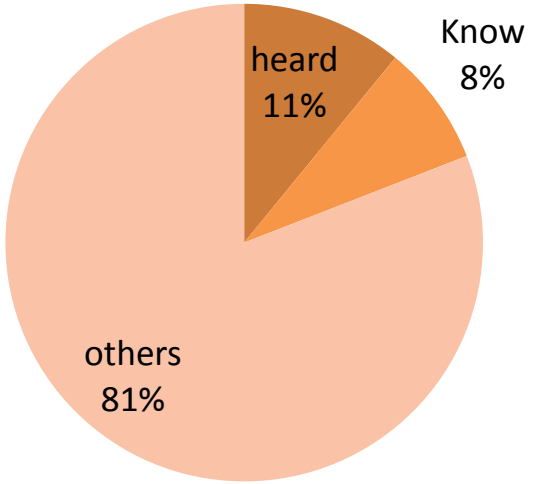


JSPPN FXS exam experience

(Responds: 43.5%)

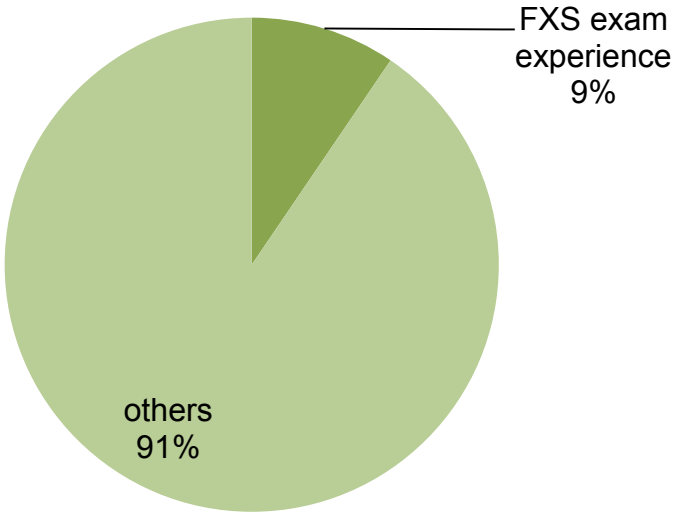


PHN Knowledge about FXS

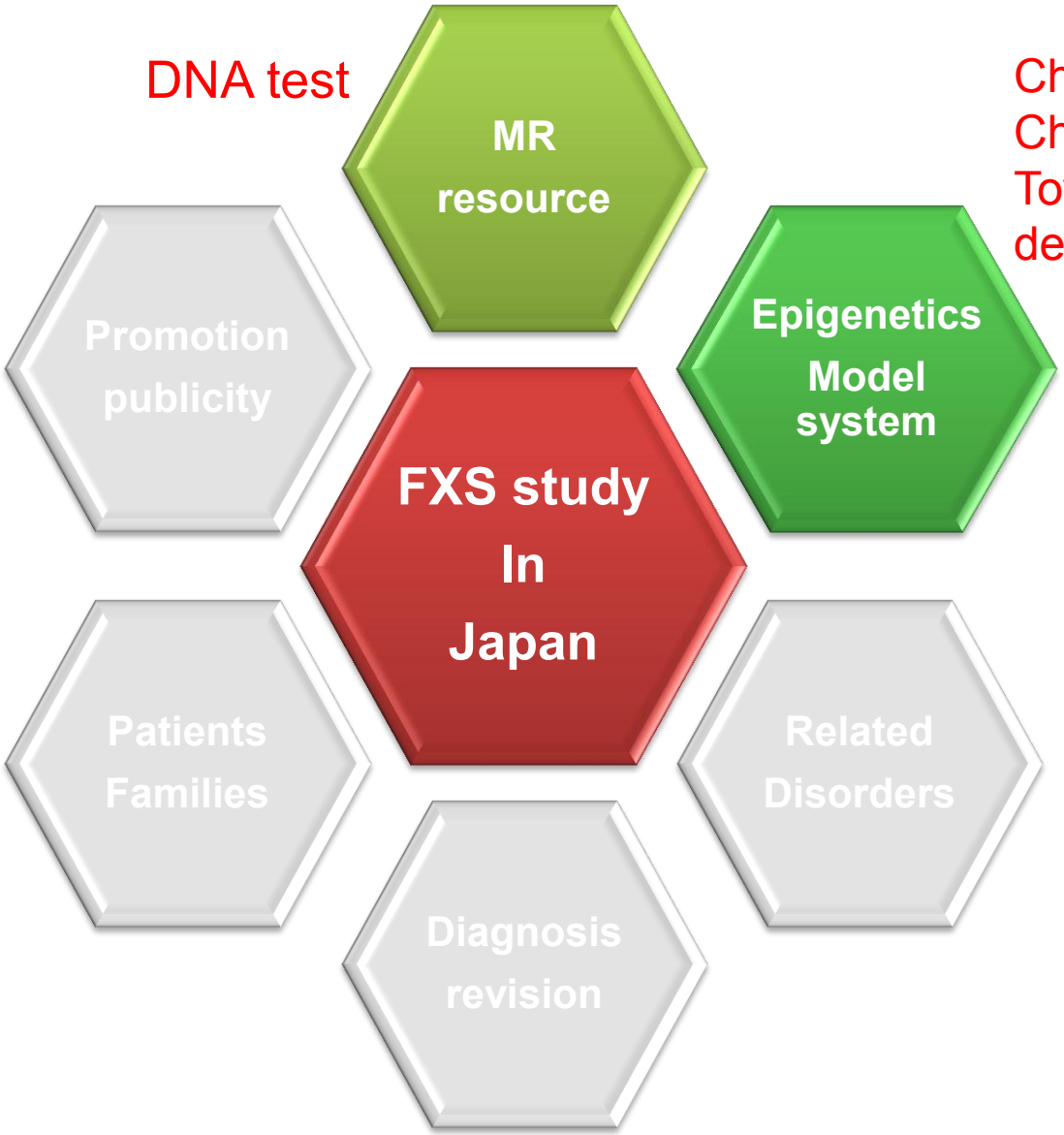


JSCAP FXS exam experience

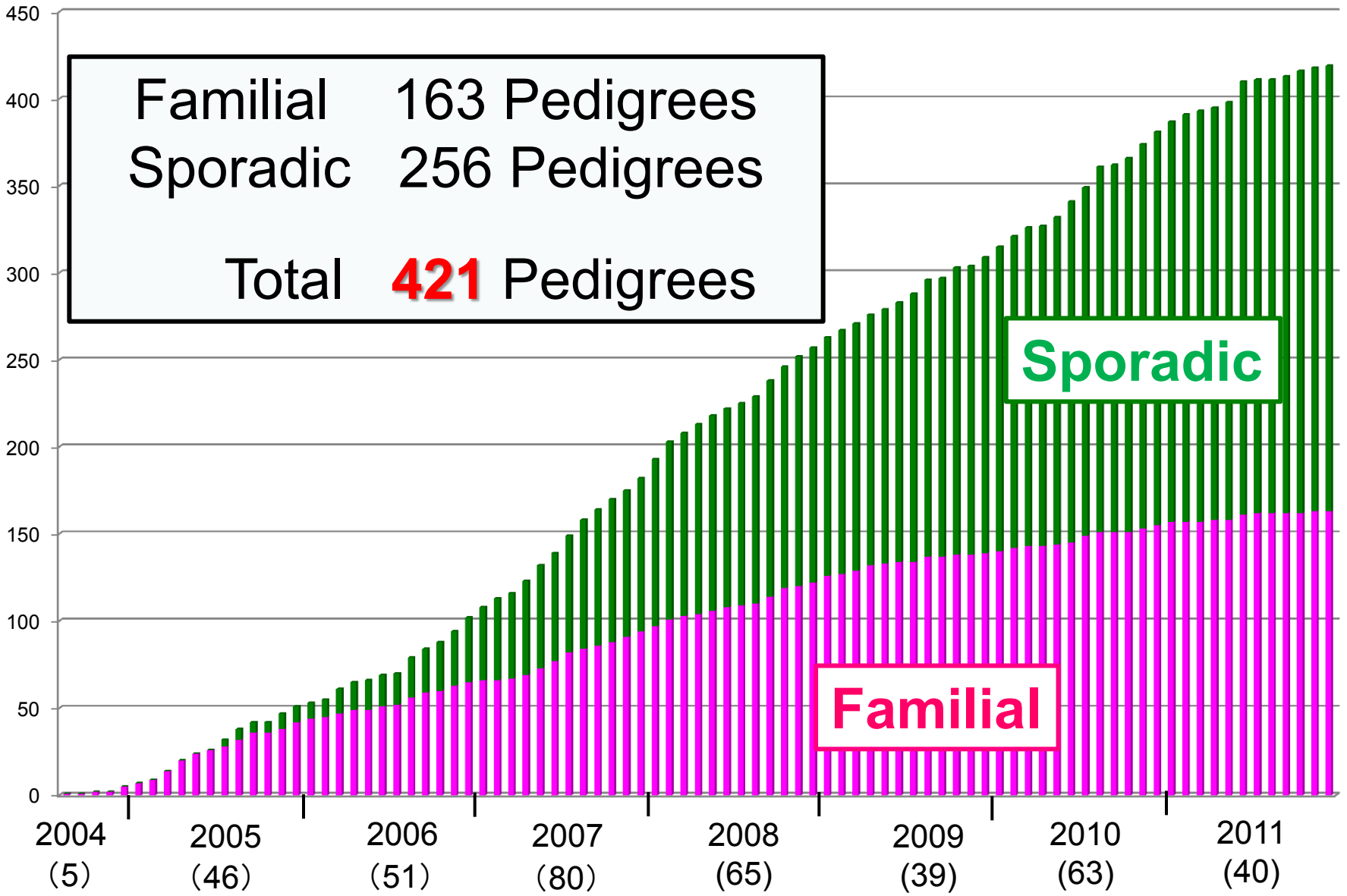
(Responds: 26.9%)



MR resource was screened for FMR mutation (Dr. Yuichi Goto)

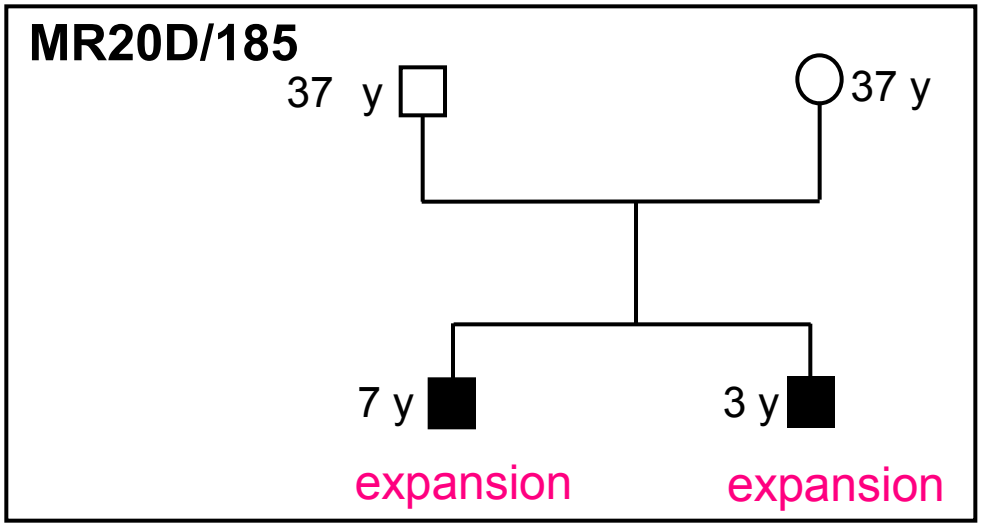


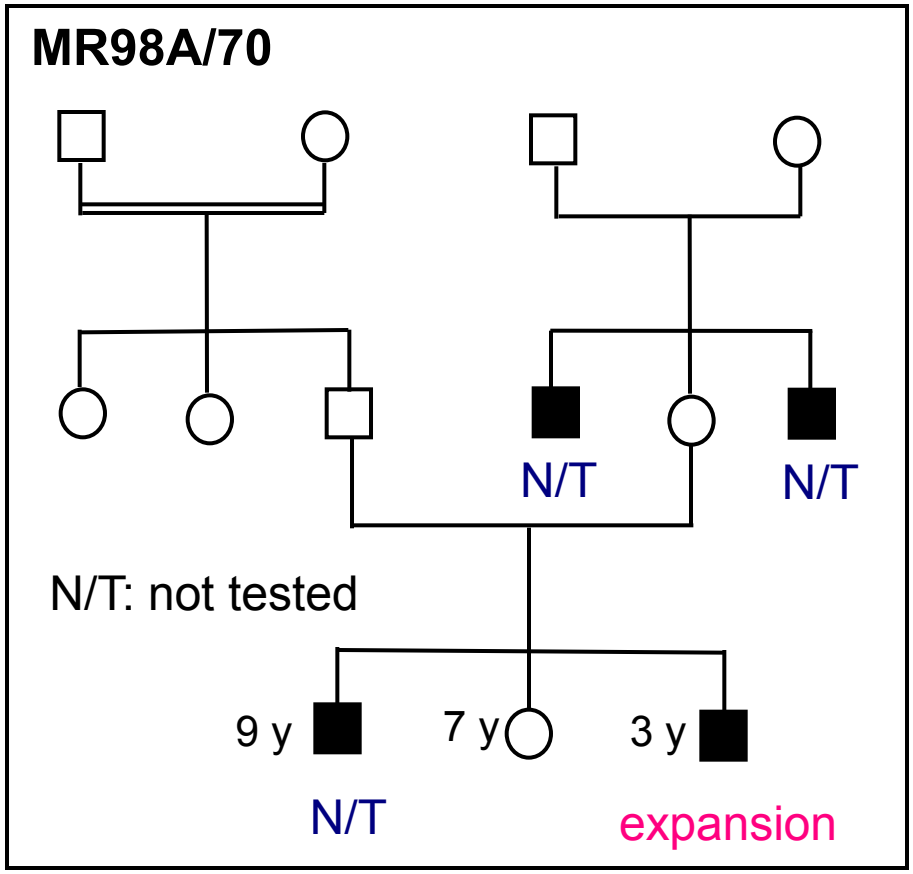
Registration of MR patients in NCNP As of 31 Dec, 2011

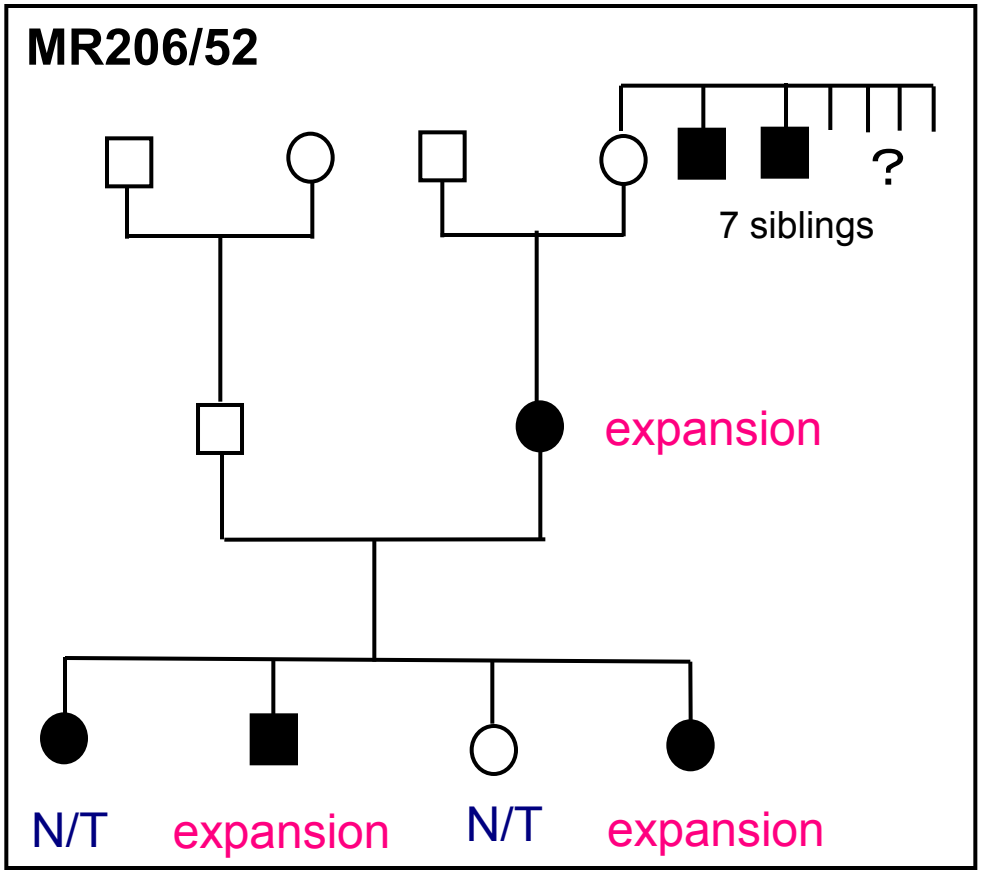


Three Pedigrees with FMR1 full-Mutation in NCNP repository

Total	3 / 295 (1.01 %)
Familial	3 / 136 (2.20 %)
Sporadic	0 / 159 (0.00 %)

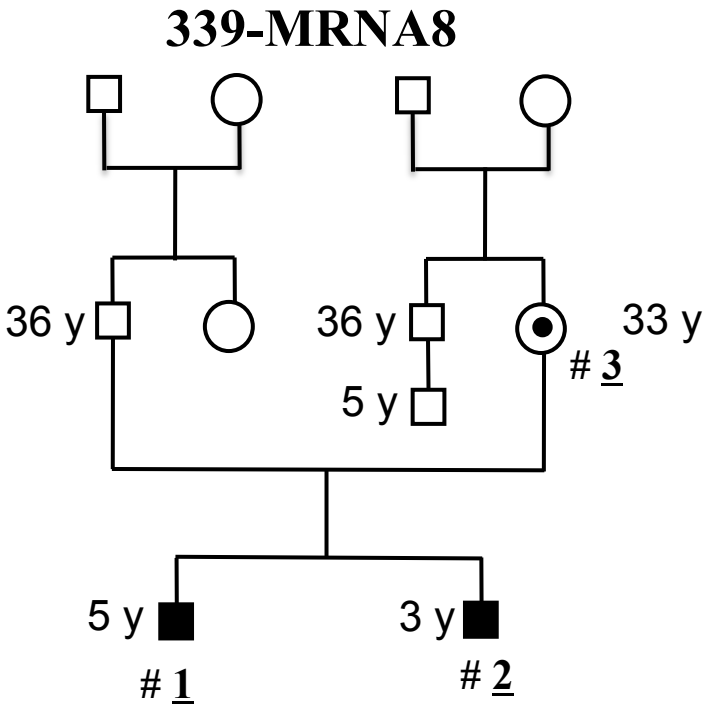


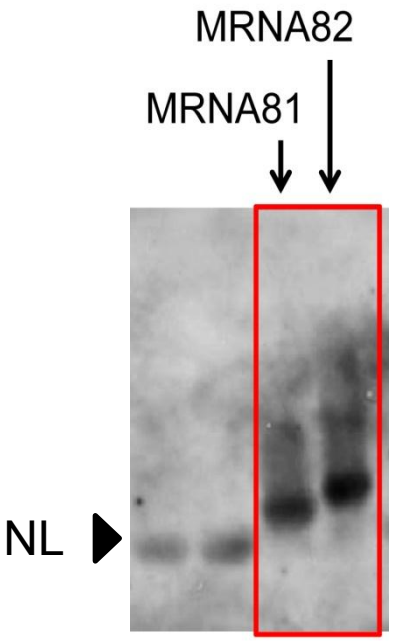


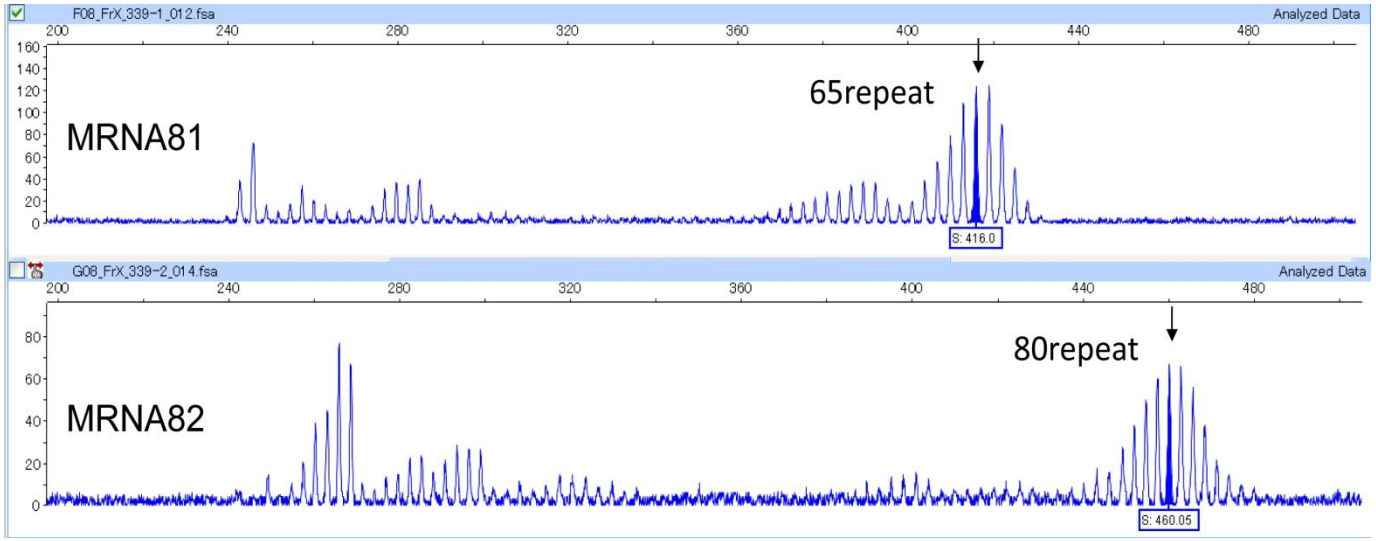


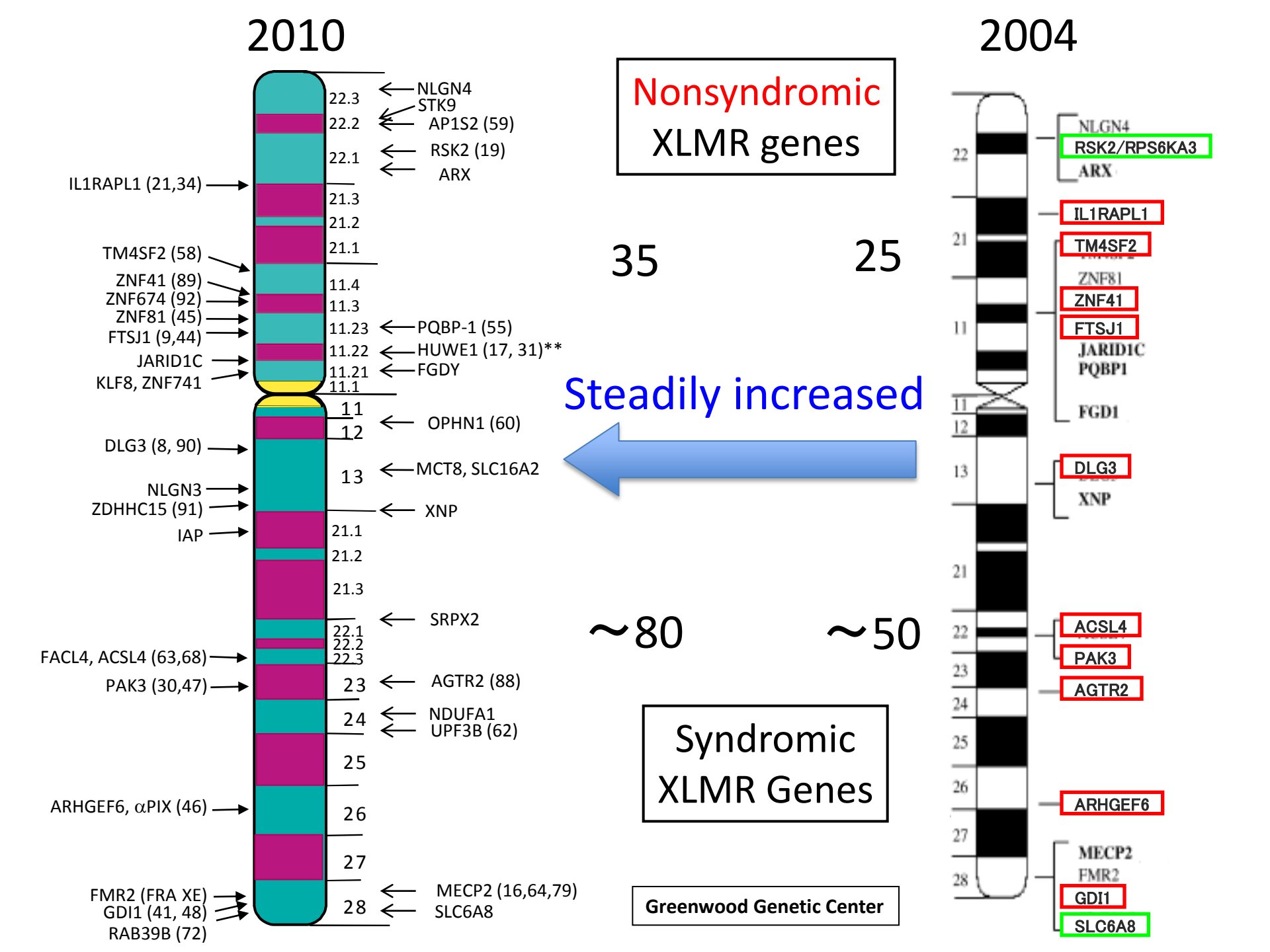
A Family of *FMR1* Premutation/intermediate

Total	3 / 400 (0.75 %)
Familial	3 / 158 (1.90 %)
Sporadic	0 / 242 (0.00 %)








2010
2004
Nonsyndromic
XLMR genes
35
25
Steadily increased
~80
~50
Syndromic
XLMR Genes
Greenwood Genetic Center
NLGN4
STK9
AP1S2 (59)
RSK2 (19)
ARX
IL1RAPL1 (21,34)
TM4SF2 (58)
ZNF41 (89)
ZNF674 (92)
ZNF81 (45)
FTSJ1 (9,44)
JARID1C
KLF8, ZNF741
PQBP-1 (55)
HUWE1 (17, 31)**
FGDY
OPHN1 (60)
DLG3 (8, 90)
MCT8, SLC16A2
NLGN3
ZDHHC15 (91)
XNP
IAP
SRPX2
FACL4, ACSL4 (63,68)
PAK3 (30,47)
AGTR2 (88)
NDUFA1
UPF3B (62)
ARHGEF6, αPIX (46)
FMR2 (FRA XE)
GDI1 (41, 48)
RAB39B (72)
MECP2 (16,64,79)
SLC6A8
RSK2/RPS6KA3
ARX
IL1RAPL1
TM4SF2
ZNF81
ZNF41
FTSJ1
JARID1C
PQBP1
FGD1
DLG3
XNP
ACSL4
PAK3
AGTR2
ARHGEF6
MECP2
FMR2
GDI1
SLC6A8

Newly reported XLMR genes from 2005 to 2010

JARID1C	*PCDH19*	*NDUFA1*	*ZNF674*
ZDHHC15	*SLC9A6*	*NXF5*	*BRWD3*
FANCB	*MBTPS2*	*PRPS1*	*CUL4B*
HCCS	*NSDHL*	*RPL10*	*PORCN*
AP1S2	*RAB39B*	*UPF3B*	*GRIA3*
SMC1A/SMC1L1	*IQSEC2*	*ZDHHC9*	*ZNF711*
SRPX2	*SYP*	*HUWE1*	*MED12*
UBE2A			

Total 13 genes were selected for additional screening On XLMR male patients in the repositories

Results of additional 13 XLMR gene tests

Gene Symbol	mRNA (bp)	exon	Results	
Synapse-related			Group 1 (%)	Group 2 (%)
SYP	**2449**	**6**	**2/53 (3.8)**	**0/131(0)**
GRIA3	**5195**	**16**	0/53	
RAB39B	**3499**	**2**	0/53	
ZDHHC15	**1782**	**11**	0/53	
Transcription factors				
ZNF674	**2689**	**6**	**0/43**	
ZNF711	**4182**	**7**	**0/53**	
JARID1C	**6097**	**26**	**2/53 (3.8)**	**1/113 (0.08)**
BRWD3	**6097**	**41**	**Not done**	
Ubiquitin-related				
HUWE1	**14734**	**81**	**Not done**	
CUL4B	**5365**	**22**	**0/53**	
Others				
RPL10	**2335**	**6**	**1/53 (1.9)**	**0/113(0)**
ZDHHC9	**2949**	**10**	**0/53**	
SRPX2	**2206**	**11**	**0/53**	

2 Pedigrees (5 Patients)

2 / 184 (0.9%)

3 Pedigrees (5 Patients)

3 / 168 (1.8%)

1 Pedigree (2 Patients)

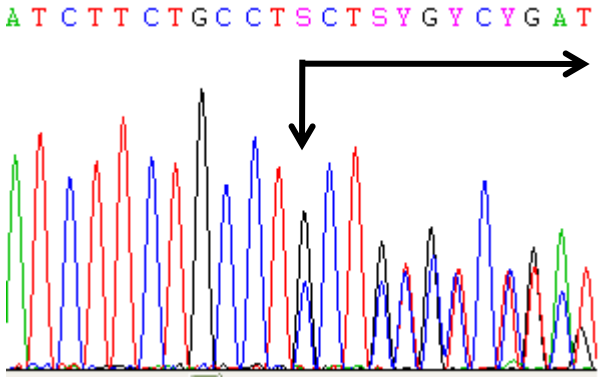
1 / 166 (0.6%)

p.354fs*72

JARID1C (Jumonji, A/T-rich interactive domain 1C)

13-59	76-184	326-374	501-617	707-760	1187-1250
JmjN	Arid/Brigth	PHD Zinc finger	JmjC	C5HC2 Zinc finger	PHD Zinc finger

wt /7bp deletion



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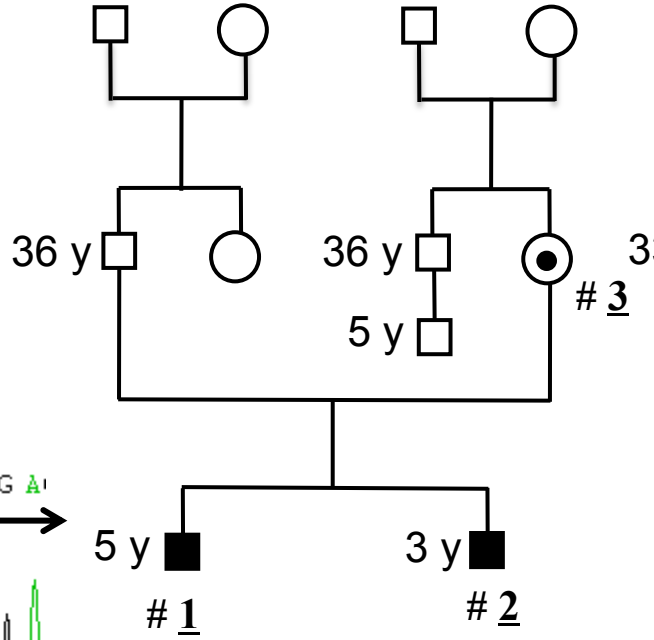
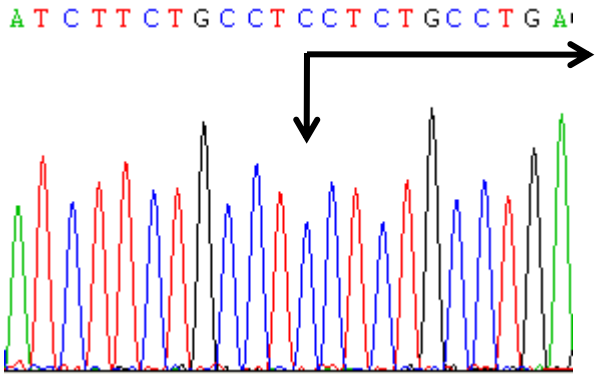
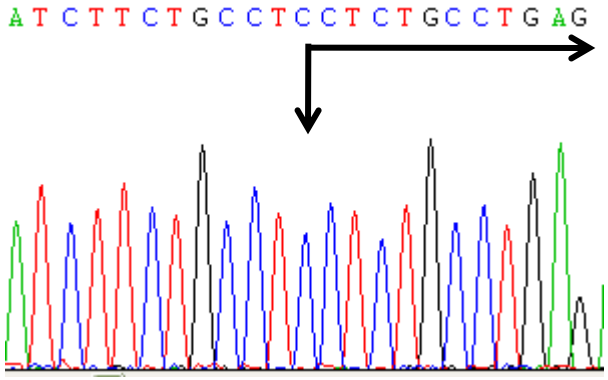


7bp deletion



#1

7bp deletion



#2

339-MRNA8

summary

1. Very low frequencies of FXS in Japan was suggested: not only genetically, but also due to ‘systems’ related to FXS?

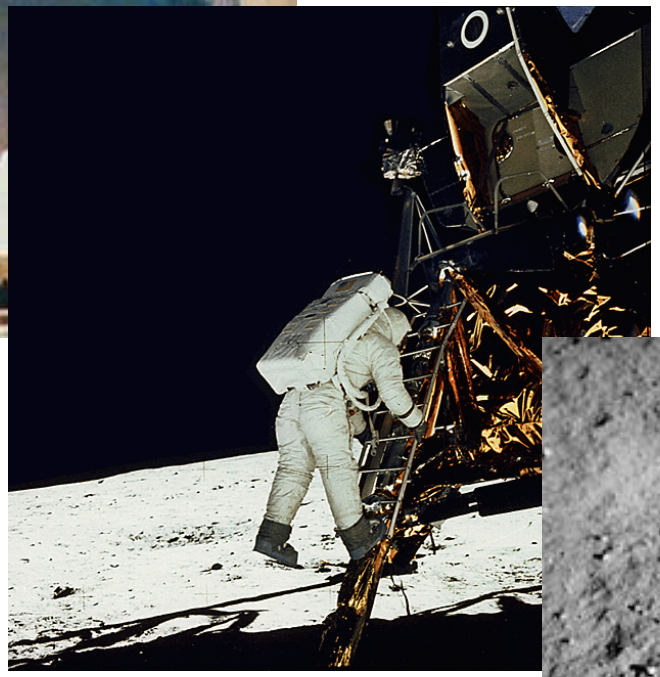
2. Teaching about FXS to medical people is important agenda.

3. MR resource is good gateway to find FXS or its associated patients in Japan

4. Basic research is in progress to develop therapeutics based on epigenetic manner to treat FXS patients in future

Finally, 42 patients with fragile X syndrome were found in this study

To find more patients, to be more cooperative, and to raise FXS publicity more, are key challenges in Japanese FXS study



Japanese FXS study has just started, just made one step….