SOCIEDAD ARGENTINA DE PEDIATRÍA
Dirección de Congresos y Eventos

Por un niño sano
en un mundo mejor

2° Jornadas Nacionales Conjuntas
de Alergia e Inmunología en Pediatría

11, 12 y 13 de Abril de 2013
Sede:
Ariston Hotel – Córdoba 2554 –Ciudad de Rosario – Provincia de Santa Fe

Mesa Redonda

Síndromes autoinflamatorios

Sábado 13 de abril / 09:45 a 11:15

Diagnósticos moleculares en Argentina

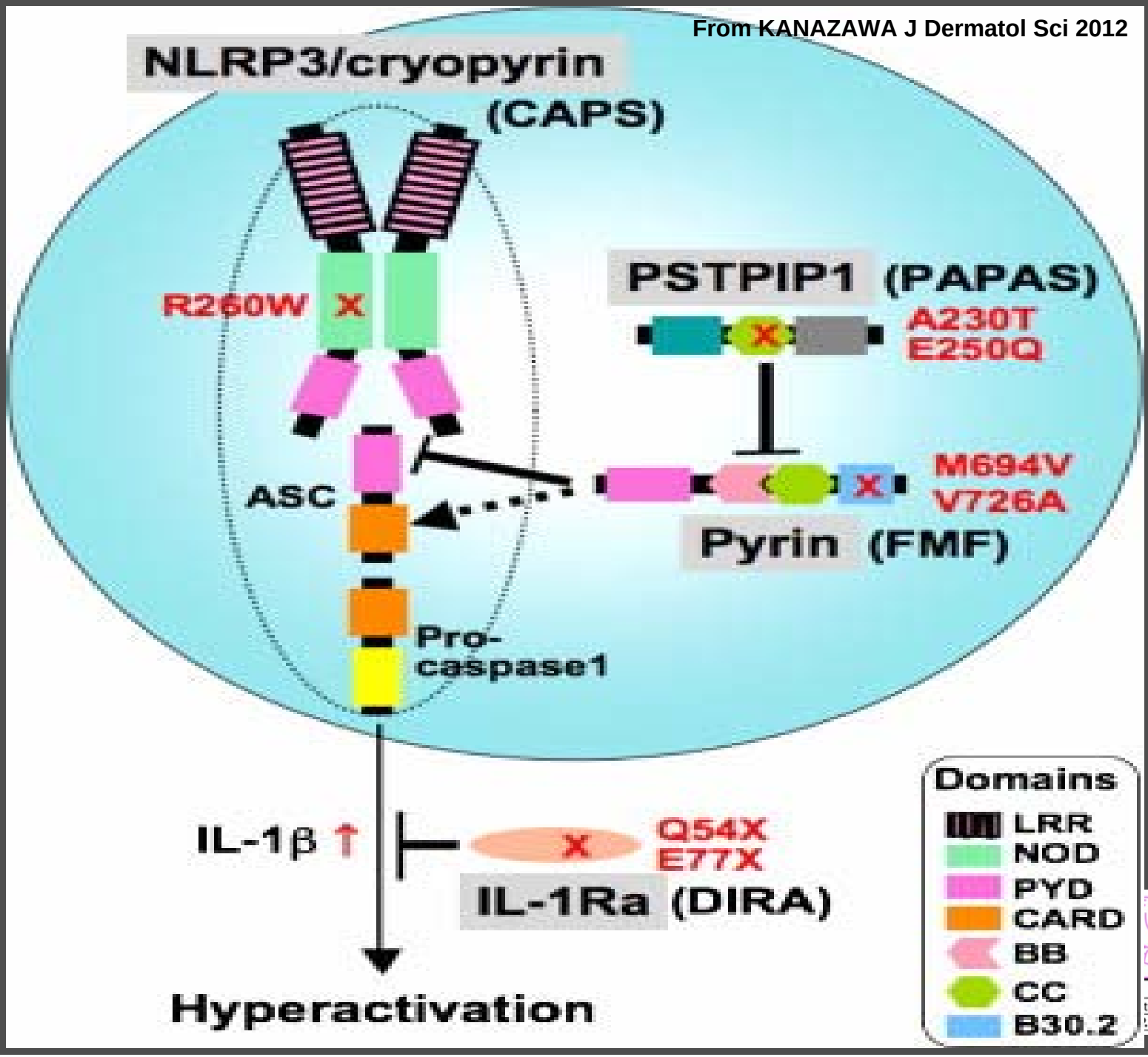
Silvia Danielian

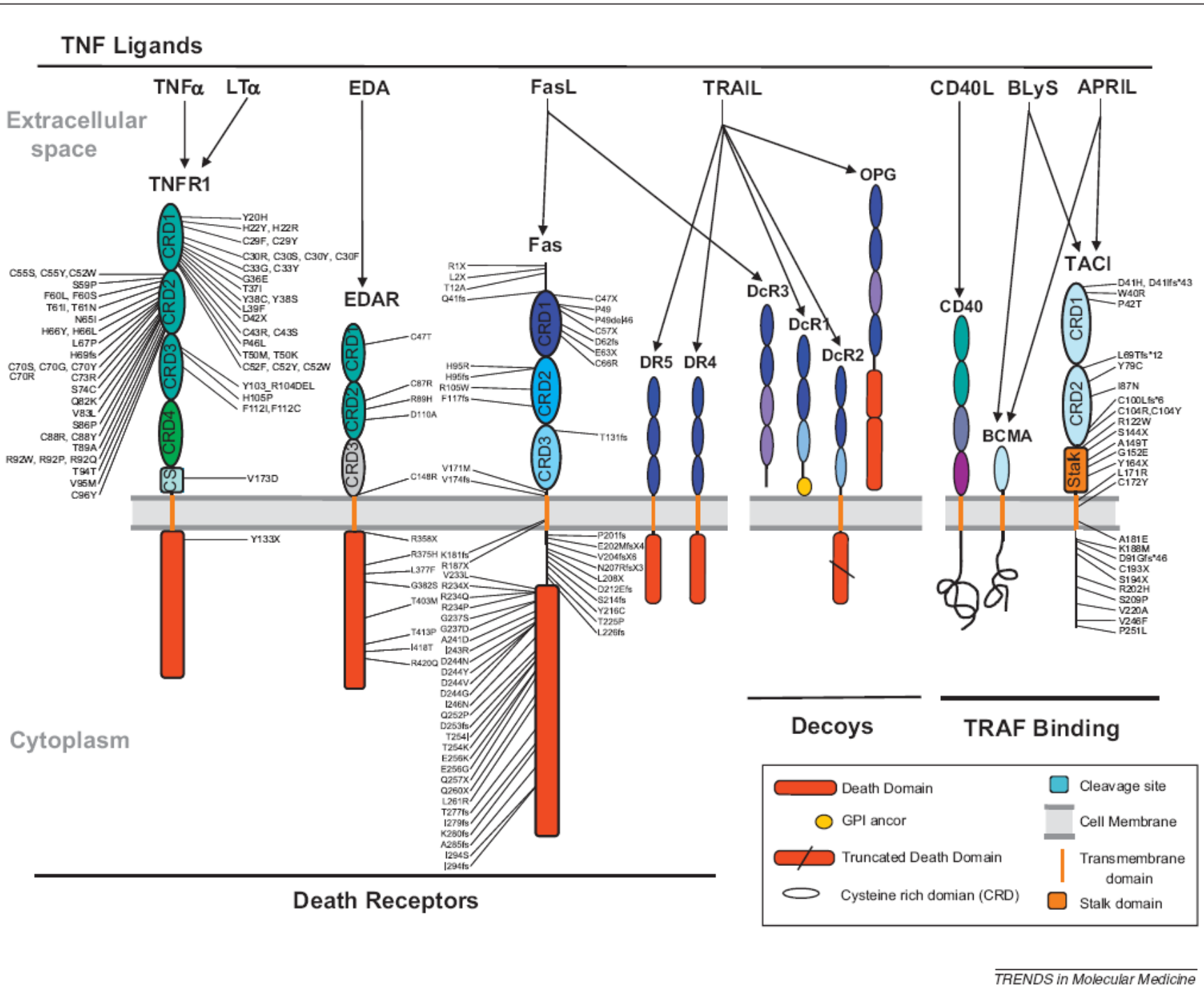
Área Biología Molecular

Servicio de Inmunología y Reumatología

HOSPITAL DE PEDIATRIA
S.A.M.I.C.
"PROF. DR. JUAN P. GARRAHAN"

From KANAZAWA J Dermatol Sci 2012





TRENDS in Molecular Medicine

Diagnosis at molecular level

- Unequivocal diagnosis → **Selection of gene (s) to evaluate**
- Accurate genetic counseling → **AR vs AD**

HOSPITAL DE PEDIATRIA
S.A.M.I.C
"PROF. DR. JUAN P. GARRAHAN"

Ficha para solicitud de estudios moleculares para Fiebres Periódicas Hereditarias (FPH)

- **Datos personales**

Apellido y Nombre:

Fecha de nacimiento:

Dirección:

Centro de derivación:

Médico: Correo electrónico:

Diagnóstico presuntivo:

Historia familiar: Si No

Etnia - origen de ancestros:

Familiares con Síndrome Febril Periódico:

☐ Hermanos ☐ Primos

☐ Tíos ☐ Abuelos

- **Datos clínicos:**

Edad de comienzo de síntomas:

Duración del ataque (días):

Intervalo libre (días):

Durante el ataque la fiebre se acompaña de:

Dolor abdominal	SI	NO
Vómitos	SI	NO
Diarrea	SI	NO
Artralgia	SI	NO
Artritis	SI	NO
Rash	SI	NO
Conjuntivitis	SI	NO
Cefaleas	SI	NO
Adenomegalias	SI	NO
Serositis	SI	NO
Faringitis	SI	NO
Mialgias localizadas	SI	NO
Ulceras orales	SI	NO
Otros :		

- **Laboratorio:**

	Durante el episodio	Fuera del episodio
Hemograma		
Eritrosedimentación		
Proteína C reactiva		
IgD		
IgG		
IgM		
IgA		

Tratamiento:

Respuesta al tratamiento:

Estudio que solicita:

Fecha:

Hospital de Pediatría S.A.M.I.C.
"Prof. Dr. Juan P. Garrahan"

Screening for prevalent mutations in all possible genes is not recommended

GENETIC DIAGNOSIS OF AUTOINFLAMMATORY DISEASE

Tick the requested tests [if >2, please justify]

Hereditary recurrent fevers : FMF[1] ☐ MKD[2] ☐ CAPS[3] ☐ TRAPS[4] ☐

[1]Familial Mediterranean fever [2]Mevalonate kinase deficiency [3]SCryopyrin associated periodic syndrome [4]STNF receptor associated periodic syndrome

Other hereditary autoinflammatory disease : ------ ☐ ------- ☐

from Guidelines for the genetic diagnosis of HRF
Shinar et al Ann Rheum Dis 2012

PATIENT
FAMILY NAME
First name
Date of birth - - / - - / - - - -
Gender F M
Date of sampling - - / - - / - - - -

PRE-REQUISITES TO MEET

1. **Prescribing DOCTOR**

FAMILY NAME
First name
Tel
Fax
Email

Complete address

2. ☐ **Informed consent** signed by the patient or her/his guardian: to be joined
3. ☐ **Clinical form** filled in by the prescribing doctor (above-cons)
4. ☐ **Genealogic tree** (to complete next page)
5. ☐ **Number of unexplained inflammatory attacks** : ≥3 yes no ----------
6. ☐ **CRP value during attacks** : ---------- mg/l
7. ☐ **Age at symptoms onset** : ---------- year

Clinical form of the patient

Box the symptoms presented by the patient before the start of the treatment
+++ differentiate No and ND (No determined)

Fever	Yes 38°C	Yes 39°C	Yes 40°C	Yes >40°C
Thorax				
Pain	Yes	No	ND	
Pericarditis	Yes	No	ND	
NeuriSensorial				
Deafness	Yes	No	ND	
Conjonctivitis	Yes	No	ND	
Uveitis	Yes	No	ND	
Papillitis	Yes	No	ND	
Headache	Yes	No	ND	
Meningitis	Yes	No	ND	
Mental retardation	Yes	No	ND	
Squeleton				
Myalgia	Yes	No	ND	
Arthritis	Yes	No	ND	
Arthralgia	Yes	No	ND	
Deforming Arthropathy	Yes	No	ND	

Abdomen			
Pain	Yes	No	ND
Vomiting	Yes	No	ND
Diarrhea	Yes	No	ND
Skin			
Pseudoerysipelas	Yes	No	ND
Urticaria	Yes	No	ND
Buccal Aphtosis	Yes	No	ND
Genital aphtosis	Yes	No	ND
Scrotitis	Yes	No	ND
Kidney			
Proteinuria	Yes	No	ND
Amyloidosis	Yes	No	ND
Other			
Splenomegaly	Yes	No	ND
Hepatomegaly	Yes	No	ND
Adenopathy	Yes	No	ND
Pharyngitis	Yes	No	ND
Growth retardation	Yes	No	ND

Triggering factor	Cold	Heath	Vaccination	Stress	Fatigue	No ND
Attack frequency	< 1/month		1 à 2 /month	> 2/ month		ND
Attack duration	------ hours		------ days			ND
Other sign or disease ------						No ND

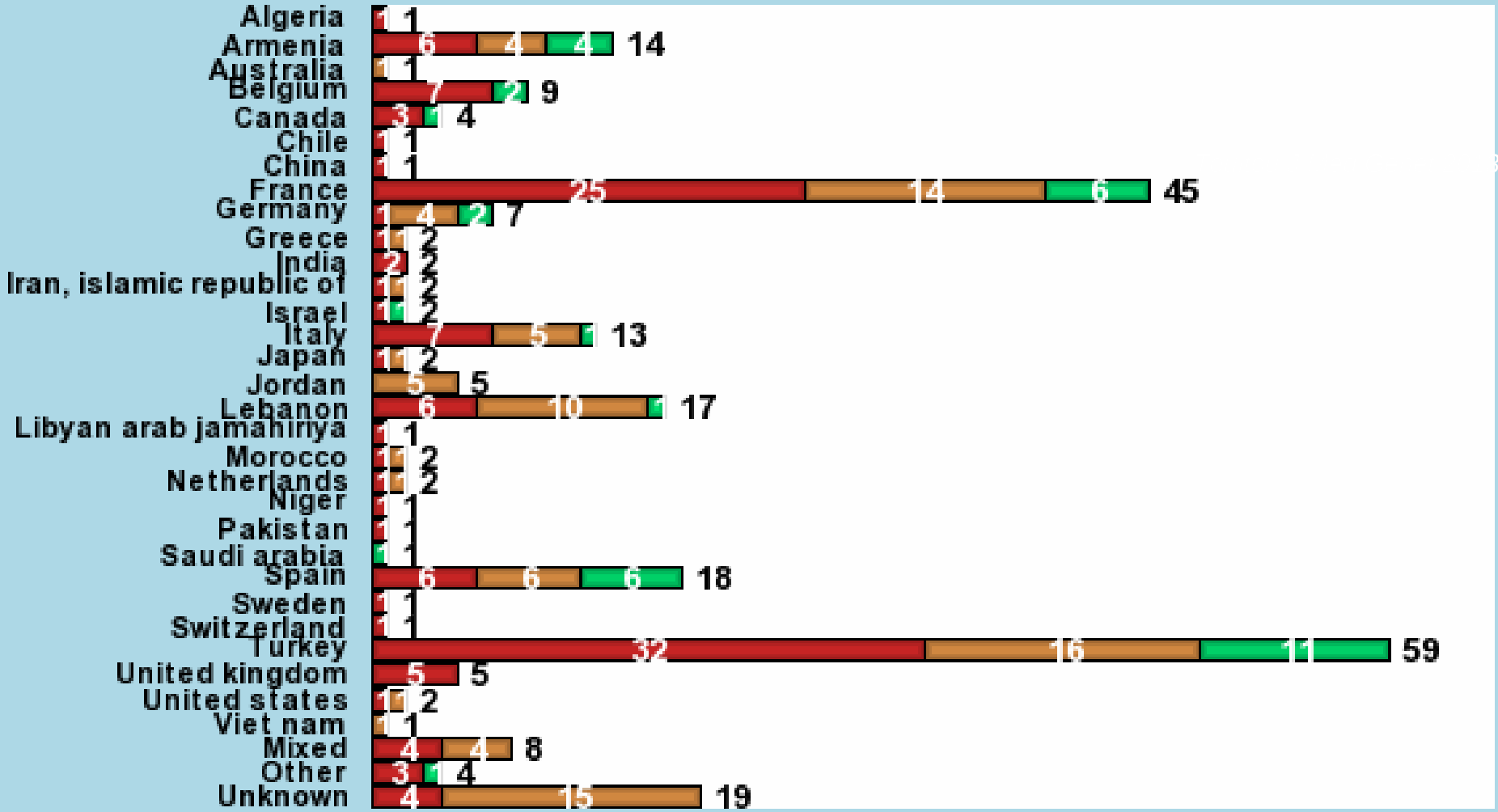
BIOLOGY already realised to fill if known

Mevalonate aciduria during attacks ------ Mevalonate kinase activity ------
Other genes already analysed ------

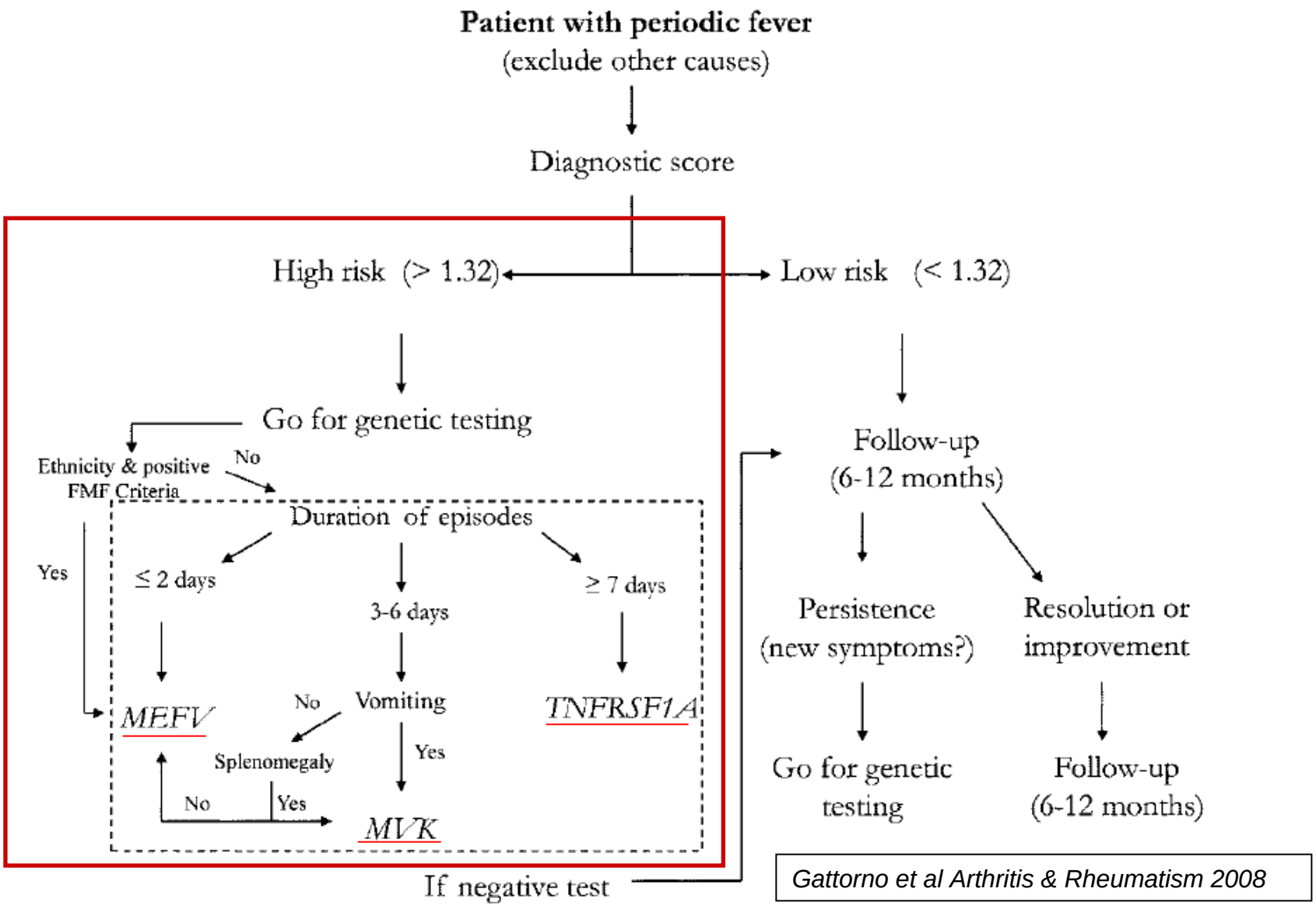
TREATMENT	Dose	Age at start	Effect (N none, P partial, T total)				
Colchicine	----/d	------	N	P	T	No	ND
Corticoïdes	----/d	------	N	P	T	No	ND
Other ------	----/d	------	N	P	T	No	ND

N sequence variants per country

From Infevers website - 2013-03-27



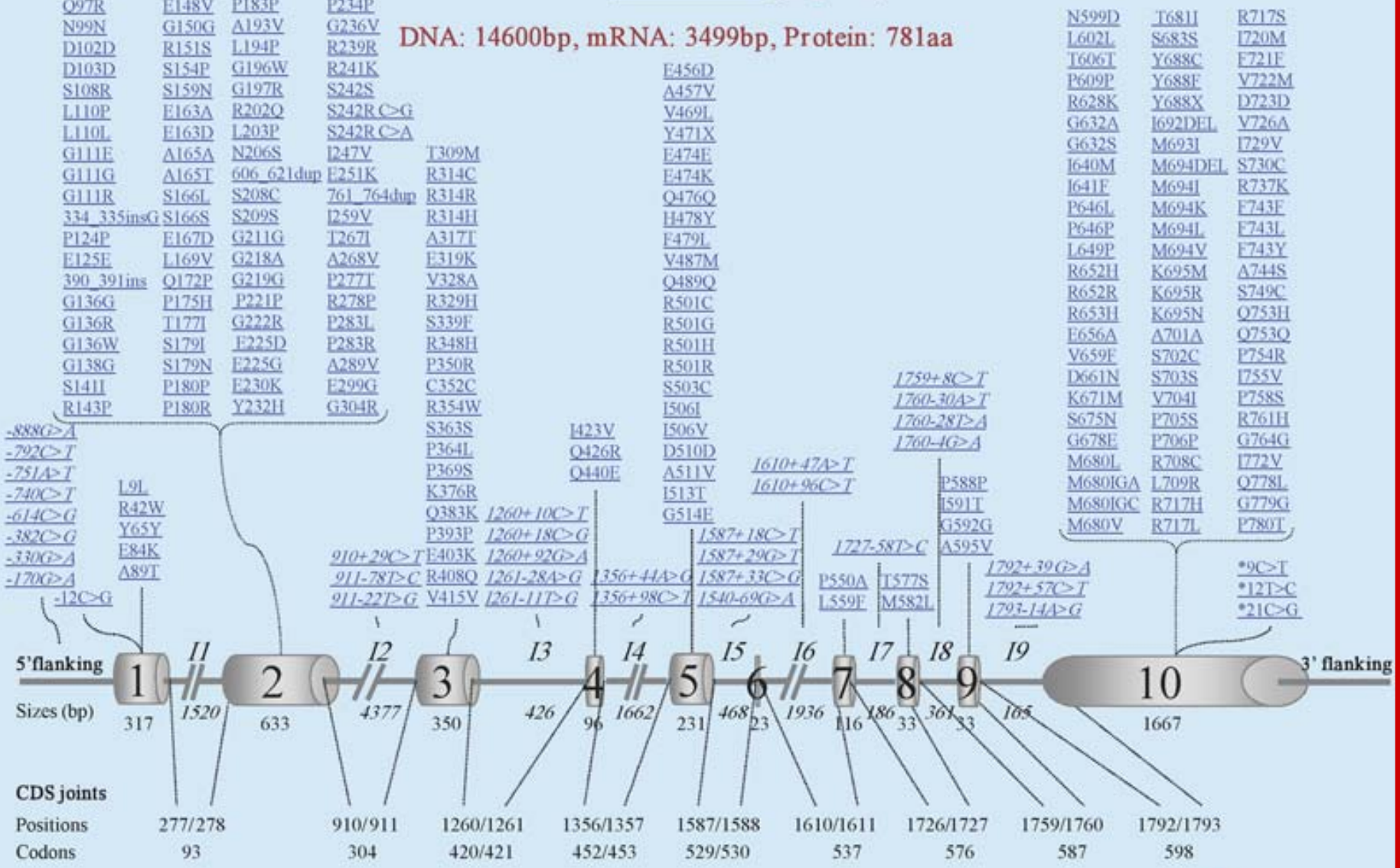
Diagnostic score for molecular studies



Gattorno et al Arthritis & Rheumatism 2008

MEFV NM_000243.2 (16p13.3)

DNA: 14600bp, mRNA: 3499bp, Protein: 781aa



This graph shows the variant usual name (i.e. as first published).
Please refer to the variant detail by clicking on its name for possible edited nomenclature.

March 19, 2013
N Sequence variants: 253

Screening for the set of the most common mutations and detection of a single mutation appears to be sufficient in the presence of clinical symptoms for the diagnosis of FMF. *from Booty et al Arthritis Rheum 2009 60:1851-1861.*

Table 1 Genes responsible for monogenic autoinflammatory diseases and their corresponding mode of transmission, disease names and key symptoms

Gene name	Transmission	Disease names			Key symptoms
		Historical	Clinical	Physiological	
*CARD14**	Dominant		PRP		Follicular papules, scaly red-orange patches, palmoplantar hyperkeratosis
IL10	Recessive		IBD		Early-onset severe enterocolitis
IL10RA	Recessive		IBD		Early-onset severe enterocolitis
IL10RB	Recessive		IBD		Early-onset severe enterocolitis
IL1RN	Recessive			DIRA	Sterile multifocal osteomyelitis, periostitis, pustular psoriasis
IL36RN	Recessive			DITRA	Psoriasis-associated pustular phenotypes
LPIN2	Recessive	Majeeds syndrome	CRMO (subtype of)		Multifocal osteomyelitis, dyserythropoietic anaemia, neutrophilic dermatosis
MEFV	Recessive	Mamou and Cattan	FMF (periodic fever)		Recurrent fever, peritonitis, arthralgia, erythema
	Dominant†		FMF		Recurrent fever, peritonitis, arthralgia, erythema
MVK	Recessive	Dutch-type fever	HIDS	MKD, mild	Recurrent fever, vomiting, diarrhoea, arthralgias, skin signs, lymphadenopathy

from Touitou I J Med Genet 2013

MEFV sequence variants in Argentina

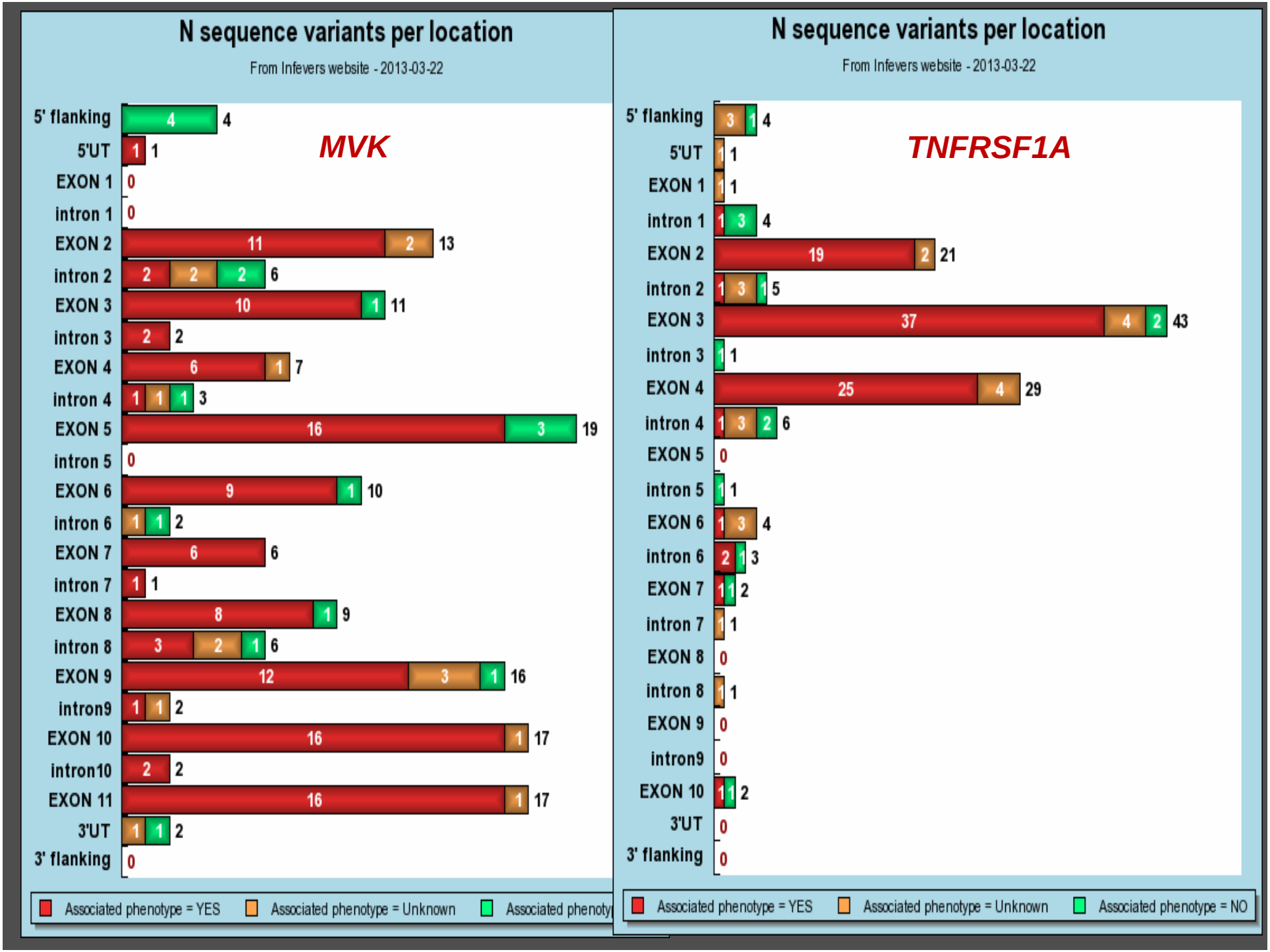
Gen estudiado	N° sin mutación (%)	N° con mutación (%)
MEFV sólo	30 (35)	15 (68)
MEFV + otro	35 (41)	5 (23)
MEFV + 2 genes	20 (24)	2 (9)
Total	85 (100)	22 (100)

Historia Familiar	N° sin mutación	N° con mutación
POSITIVA	10*	9
NEGATIVA	66	11**
NS/NC	9	2
Total	85	22

* 7 historia compatible con AD

** 4 tienen ascendencia con alta prevalencia FMF (judíos y armenios).

Hospital de Pediatría S.A.M.I.C.
"Prof. Dr. Juan P. Garrahan"


N sequence variants per location
From Infevers website - 2013-03-22
MVK
5' flanking 4 4
5'UT 1 1
EXON 1 0
intron 1 0
EXON 2 11 2 13
intron 2 2 2 2 6
EXON 3 10 1 11
intron 3 2 2
EXON 4 6 1 7
intron 4 1 1 1 3
EXON 5 16 3 19
intron 5 0
EXON 6 9 1 10
intron 6 1 1 2
EXON 7 6 6
intron 7 1 1
EXON 8 8 1 9
intron 8 3 2 1 6
EXON 9 12 3 1 16
intron9 1 1 2
EXON 10 16 1 17
intron10 2 2
EXON 11 16 1 17
3'UT 1 1 2
3' flanking 0
Associated phenotype = YES
Associated phenotype = Unknown
Associated phenoty
N sequence variants per location
From Infevers website - 2013-03-22
TNFRSF1A
5' flanking 3 1 4
5'UT 1 1
EXON 1 1 1
intron 1 1 3 4
EXON 2 19 2 21
intron 2 1 3 1 5
EXON 3 37 4 2 43
intron 3 1 1
EXON 4 25 4 29
intron 4 1 3 2 6
EXON 5 0
intron 5 1 1
EXON 6 1 3 4
intron 6 2 1 3
EXON 7 1 1 2
intron 7 1 1
EXON 8 0
intron 8 1 1
EXON 9 0
intron9 0
EXON 10 1 1 2
3'UT 0
3' flanking 0
Associated phenotype = YES
Associated phenotype = Unknown
Associated phenotype = NO

Guidelines for the genetic diagnosis of HRF

from Y Shinar, L Obici, I Aksentijevich, B Bennetts, F Austrup, I Ceccherini, J M Costa, A De Leener, M Gattorno, U Kania, I Kone-Paut, S Lezer, A Livneh, I Moix, R Nishikomori, S Ozen, L Phylactou, L Risom, D Rowczenio, T Sarkisian, M E van Gijn, M Witsch-Baumgartner, M Morris, H M Hoffman, I Touitou
Ann Rheum Dis 2012;71:1599–1605.

	Exons										
Gene	1	2	3	4	5	6	7	8	9	10	11
MEFV		X	X		X					X	
		p.E148Q, ***p.E167D***, ***p.T267I***, *p.R202Q*	p.P369S, *p.R408Q*		p.F479L				p.I591T	**p.M680I**, **p.M694V**, **p.M694I**, **p.V726A**, ***p.A744S***, ***p.R761H***, ***p.I692del***, p.K695R	
MVK		X	X	X	X	X	X	X	X	X	X
		p.H20P	*p.S52N*						**p.I268T**, **p.S272F**		**p.V377I**
TNFRSF1A		X	X	X							
		p.C59R (C30R), **p.C62Y (C33Y)**	**p.D71del (D42del)**, **p.T79M (T50M)**, **p.C81Y (C52Y)**, **p.C84Y (C55Y)**, **p.C102W (C73W)**, p.P75L (P46L)	p.R121Q (R92Q)							

Hospital de Pediatría S.A.M.I.C.
"Prof. Dr. Juan P. Garrahan"

HOSPITAL DE PEDIATRIA
S.A.M.I.C.
"PROF. DR. JUAN P. GARRAHAN"

HOSPITAL DE NIÑOS
RICARDO GUTIÉRREZ

Hospital Pedro
de Elizalde

FUNDACIÓN
HOSPITAL DE NIÑOS
Víctor J. Vilela

Hospital de Niños SOR MARÍA LUDOVICA

Molecular Studies

Verónica Goris
Emma Prieto

Physicians

Matías Oleastro
Mariana Villa
Ricardo Russo
María Martha Katsikas