Inmunodeficiencias del receptor para antígeno del linfocito T (TCR)

Jose R. Regueiro
Inmunologia
Facultad de Medicina
Universidad Complutense
28040 Madrid SPAIN
regueiro@med.ucm.es

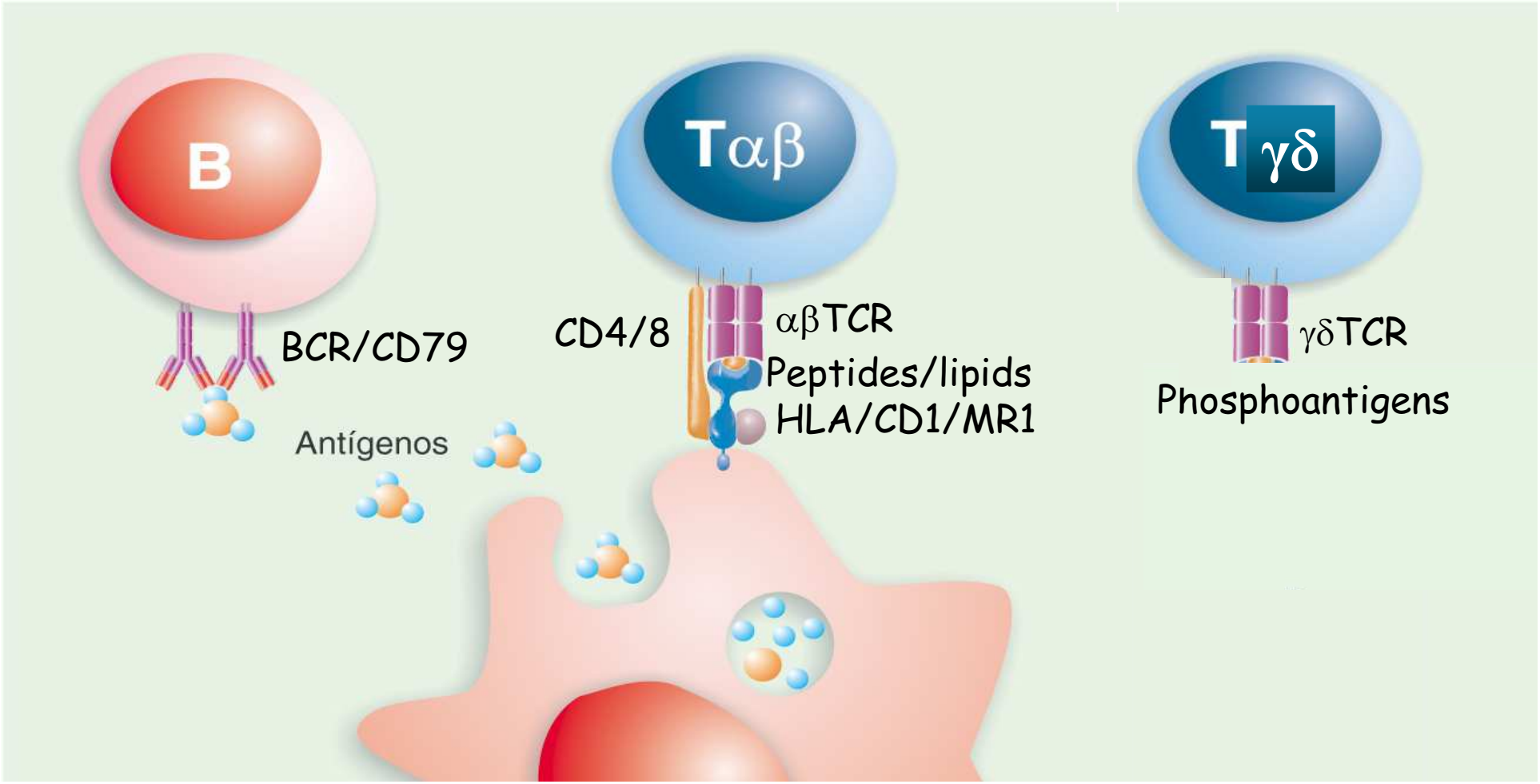
3ras JORNADAS NACIONALES CONJUNTAS DE ALERGIA E INMUNOLOGIA EN PEDIATRIA
Ciudad de Córdoba 19/4/2015, 18:40-19:10. Gracias a Héctor Díaz, Luciano Ianiero, Alejandro y Natalia Lozano, Julio Orellana, Ricardo Saranz

Inmunodeficiencias del TCR

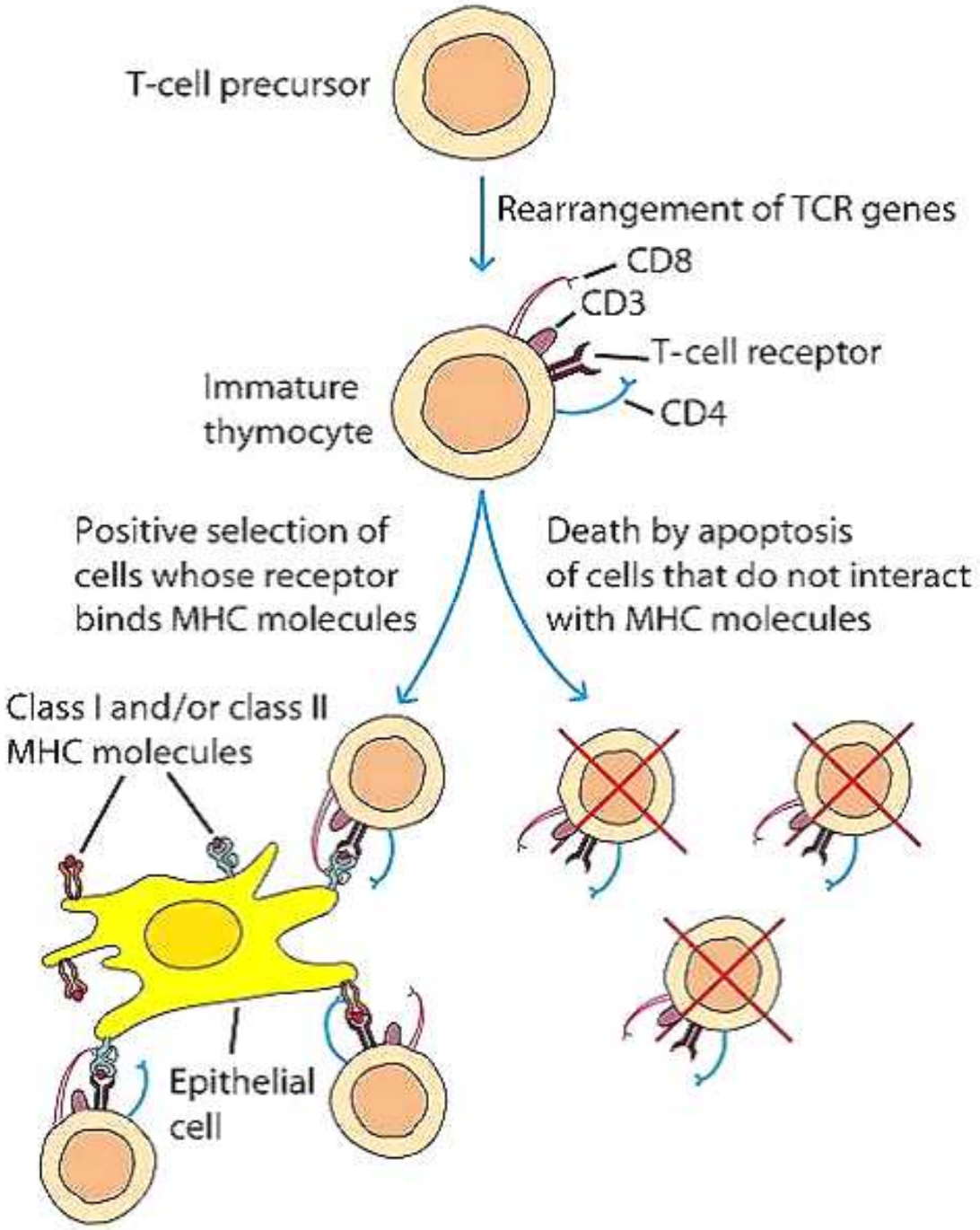
- Isotipos del TCR
- Inmunodeficiencias del TCR
- Diagnóstico
- Tratamiento y pronóstico

Adaptive antigen receptors

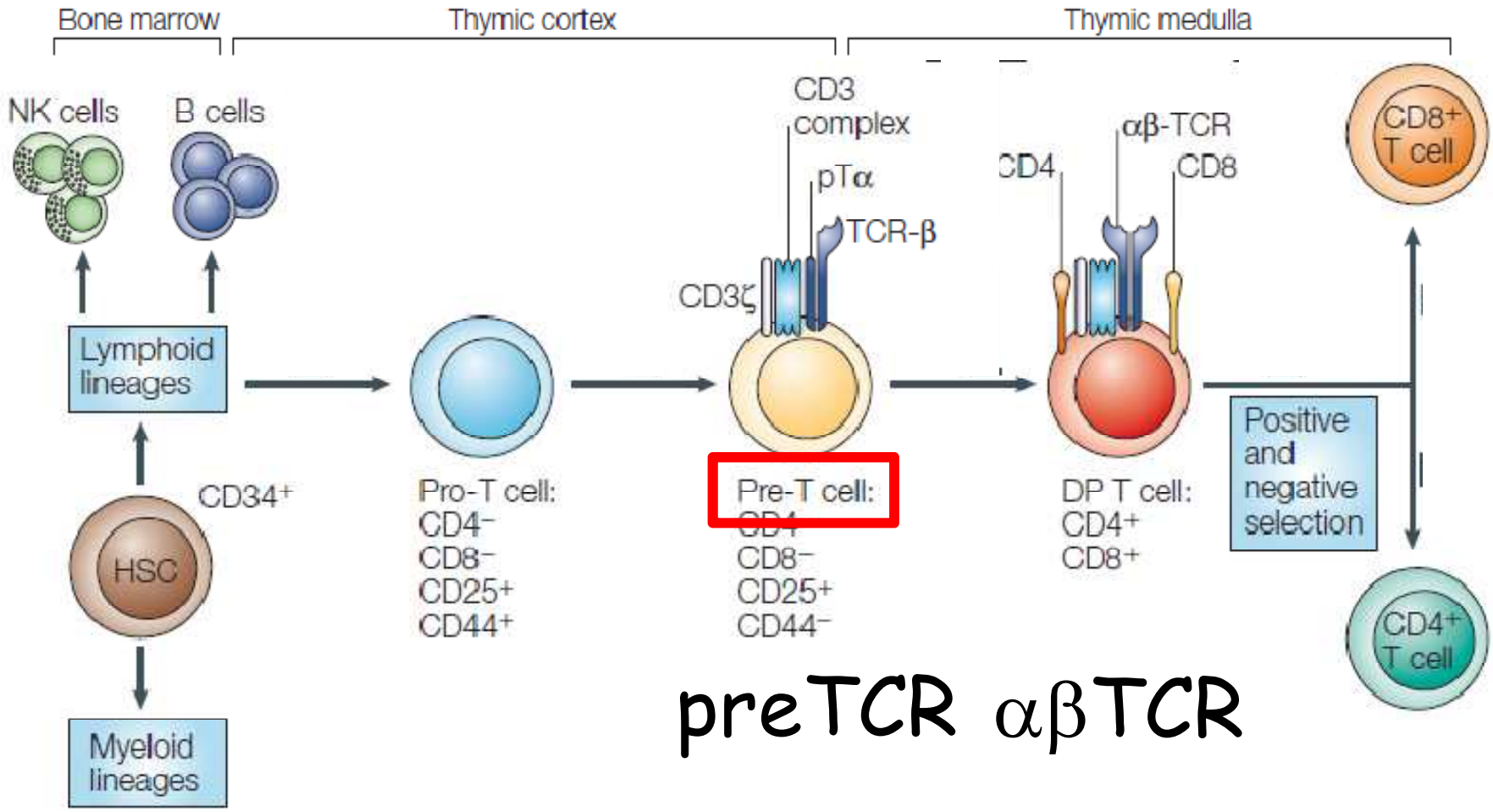
Th1, Th2, Th17, Tc,
Treg, NKT, MAIT



THE TCR IS REQUIRED FIRST FOR SELECTION



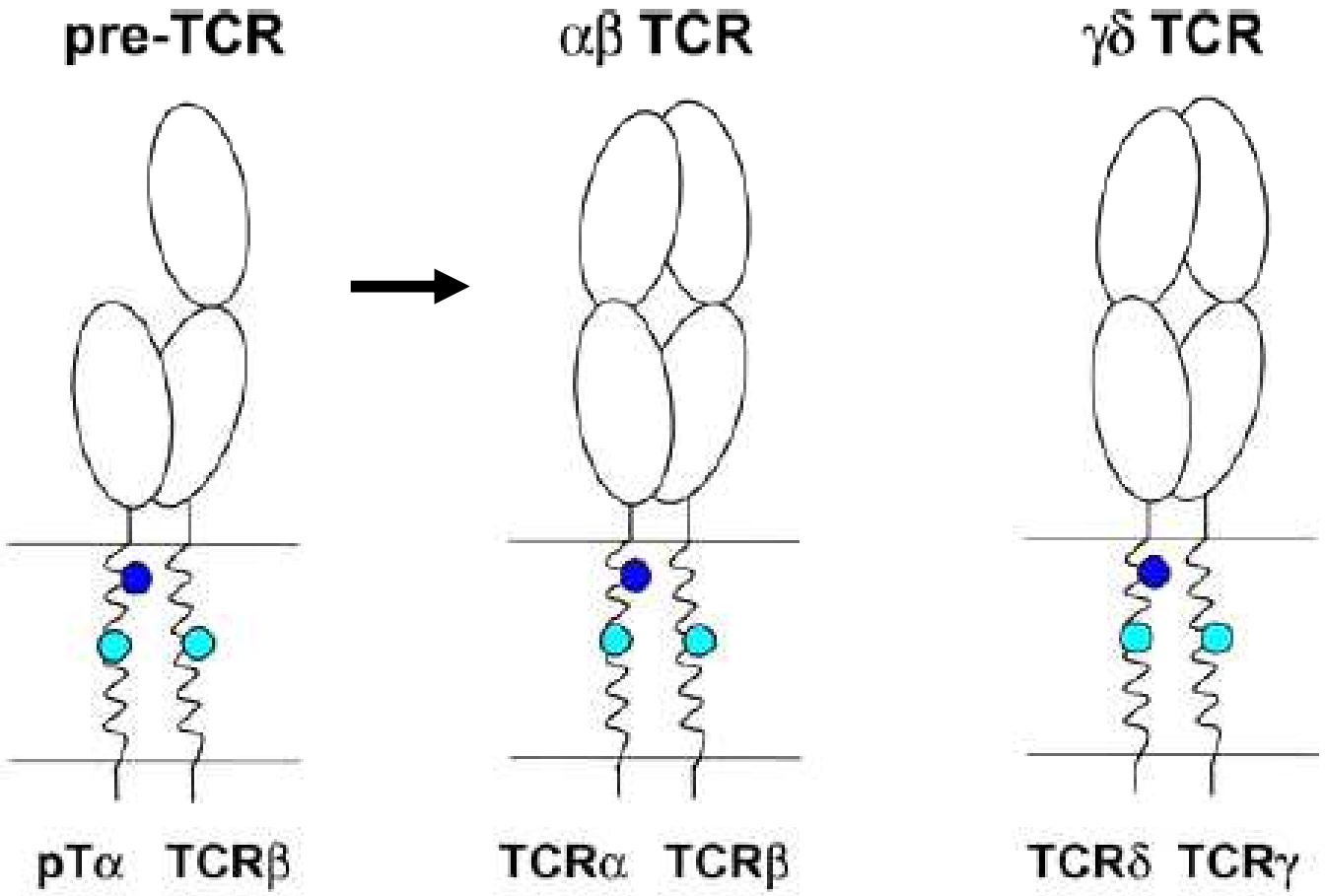
An immature TCR for αβ-to be T cells



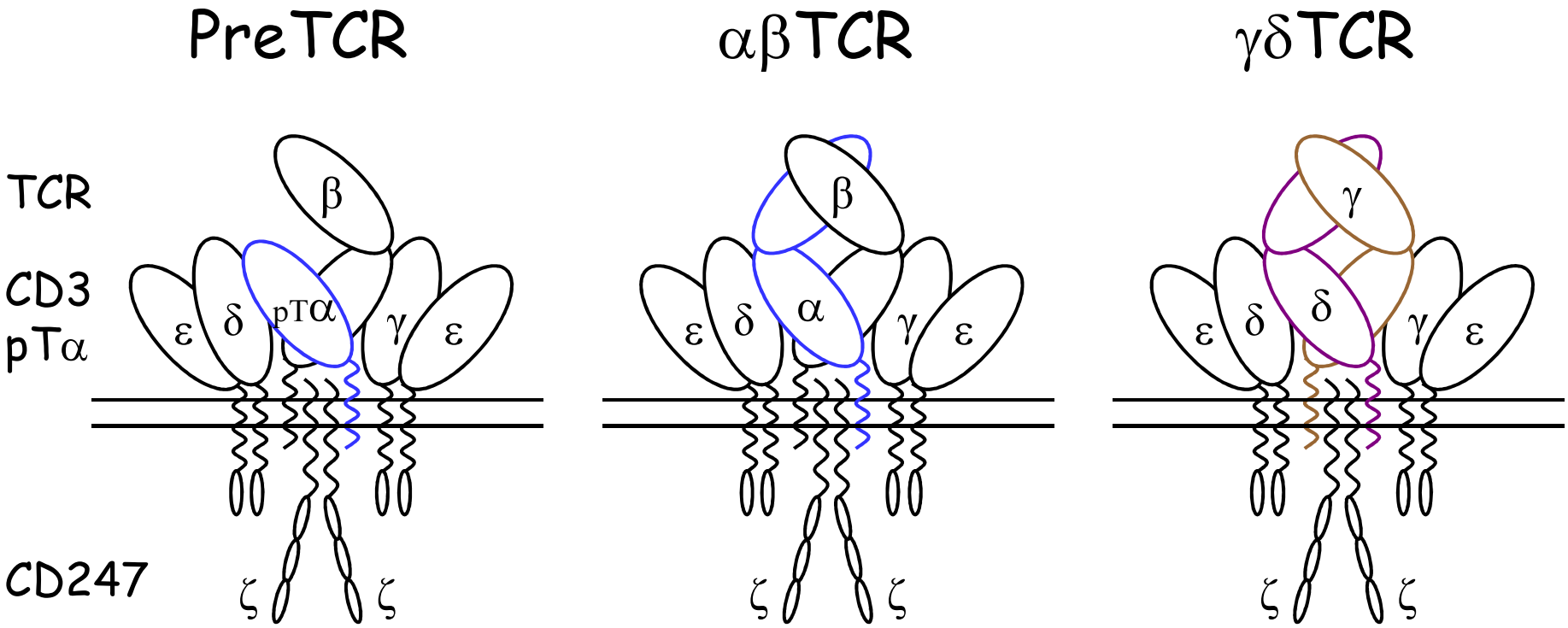
preTCR αβTCR

NRI 2005 Cunningham

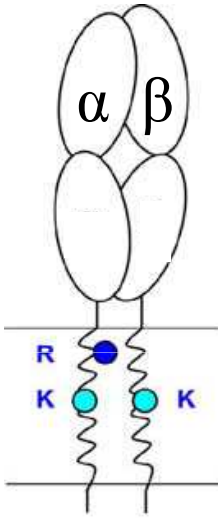
Four variable chains build three different TCR dimers



Each TCR dimer binds to three invariant CD3 and CD247 dimers to build three TCR isotypes

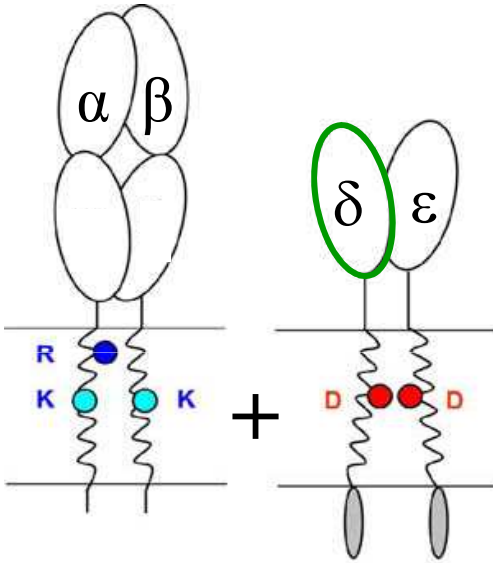


TCR ASSEMBLY



TCRαβ

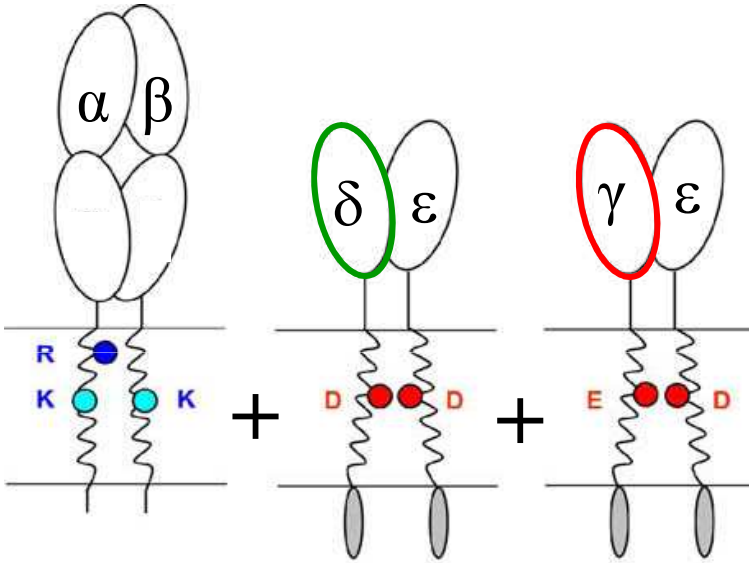
TCR ASSEMBLY



TCRαβ **CD3δε**

CD3δ ≠ TCRδ

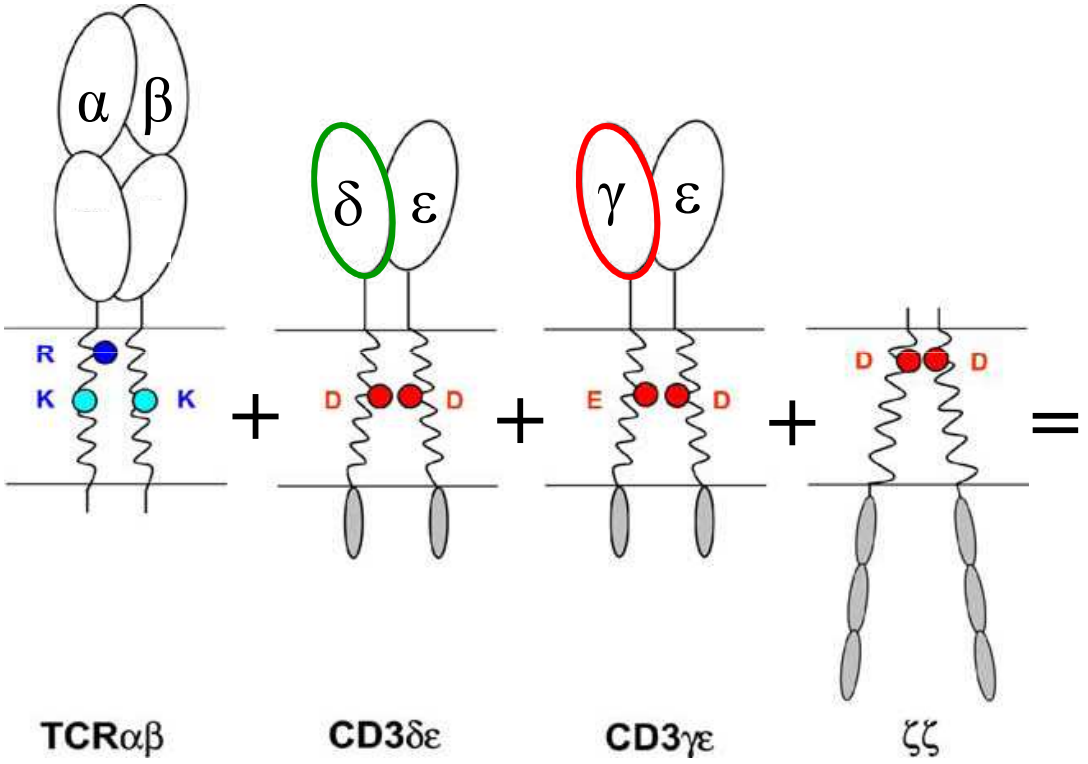
TCR ASSEMBLY



TCRαβ CD3δε CD3γε

CD3γ ≠ γ_c or TCRγ

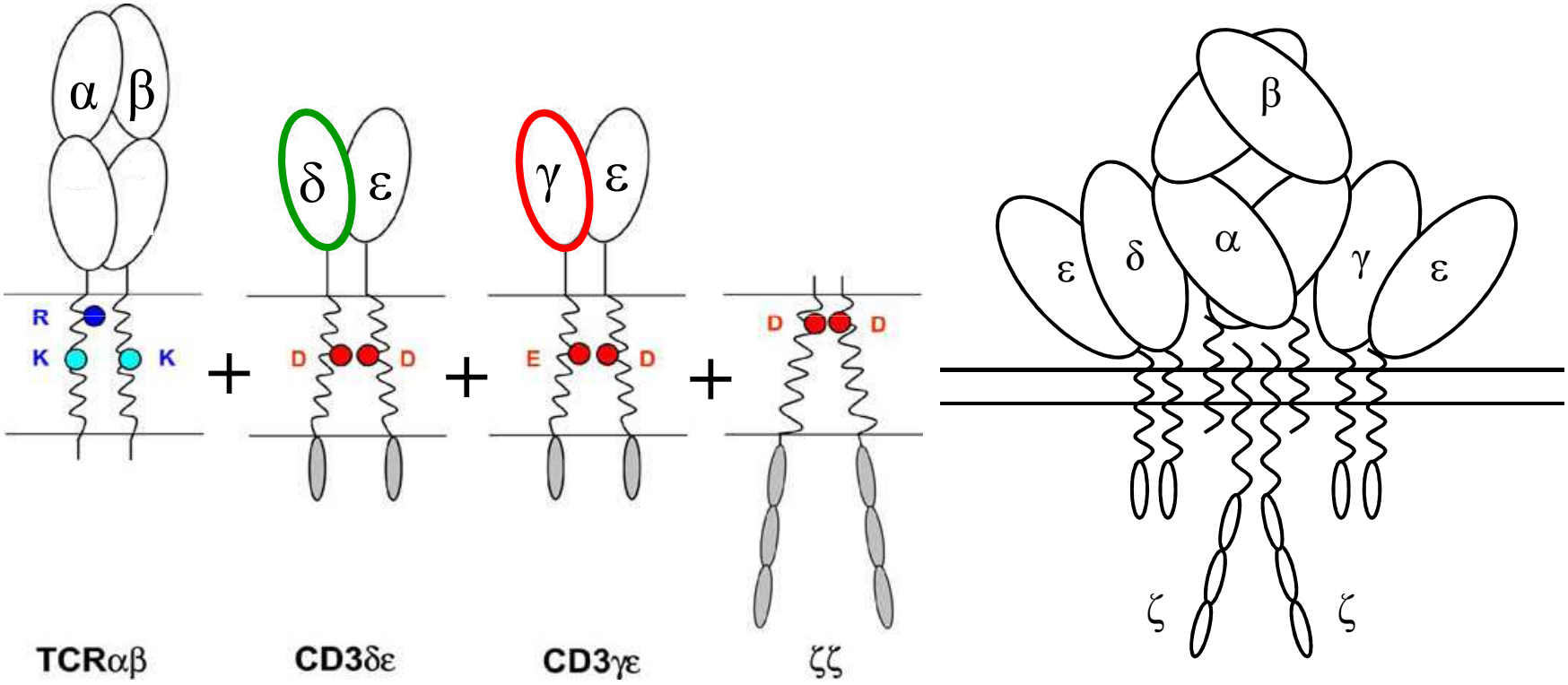
TCR ASSEMBLY



CD247 or TCRζ
Also in NK cells

THE TCR IS A COMPLEX OF 4 DIMERS

αβTCR

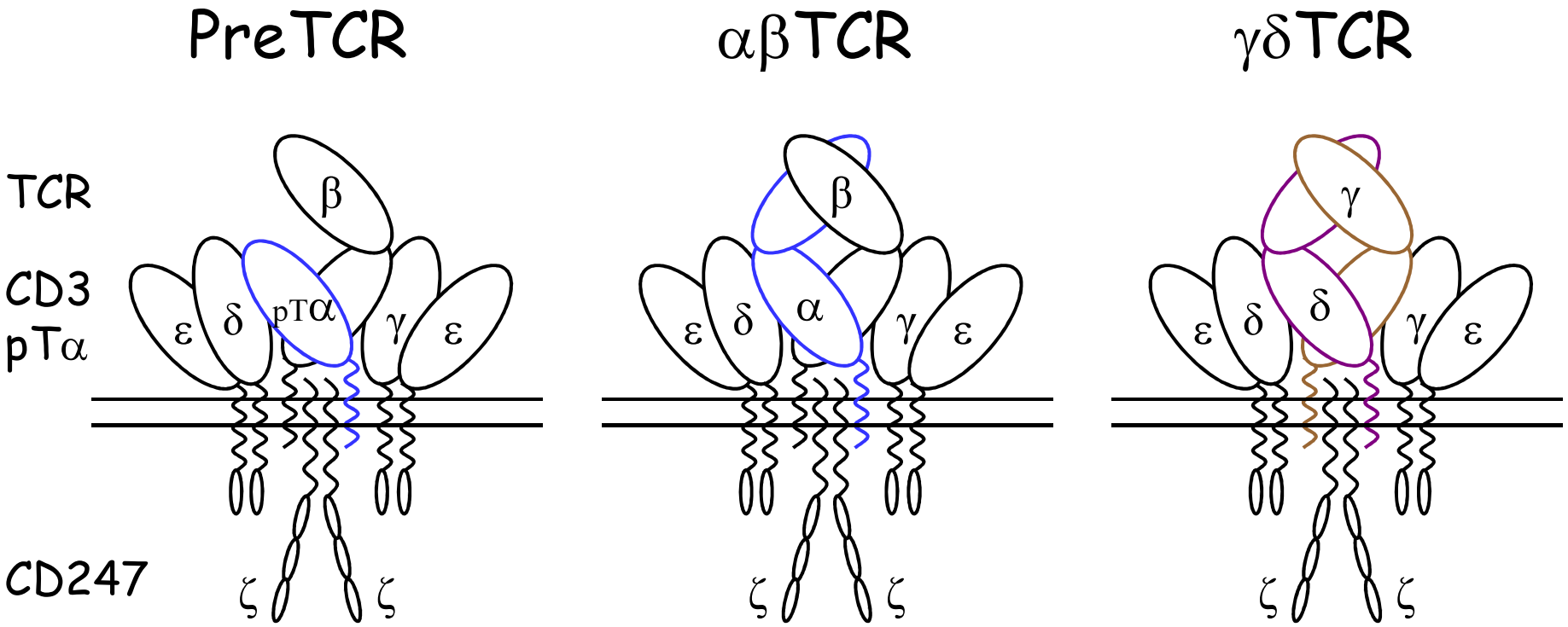


TCR/CD3/CD247

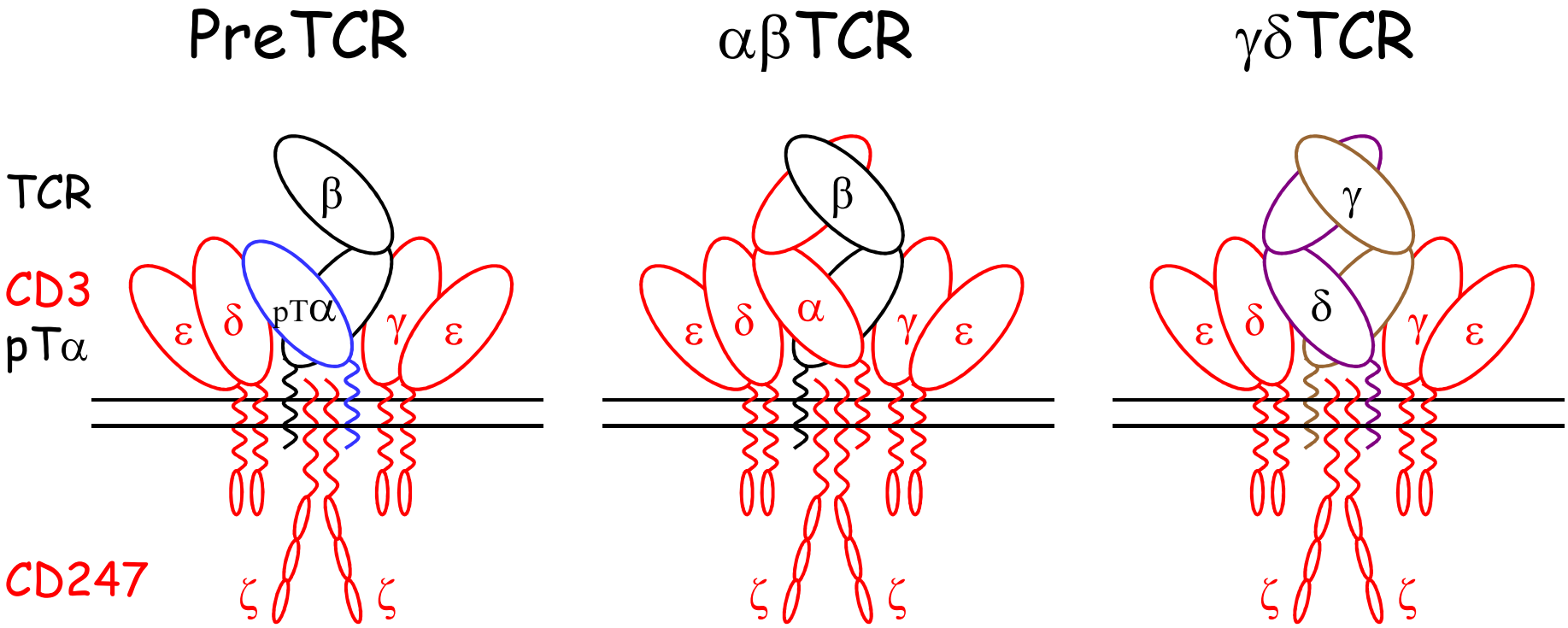
Inmunodeficiencias del TCR

- Isotipos del TCR
- Inmunodeficiencias del TCR
- Diagnóstico
- Tratamiento y pronóstico

Human TCR isotypes

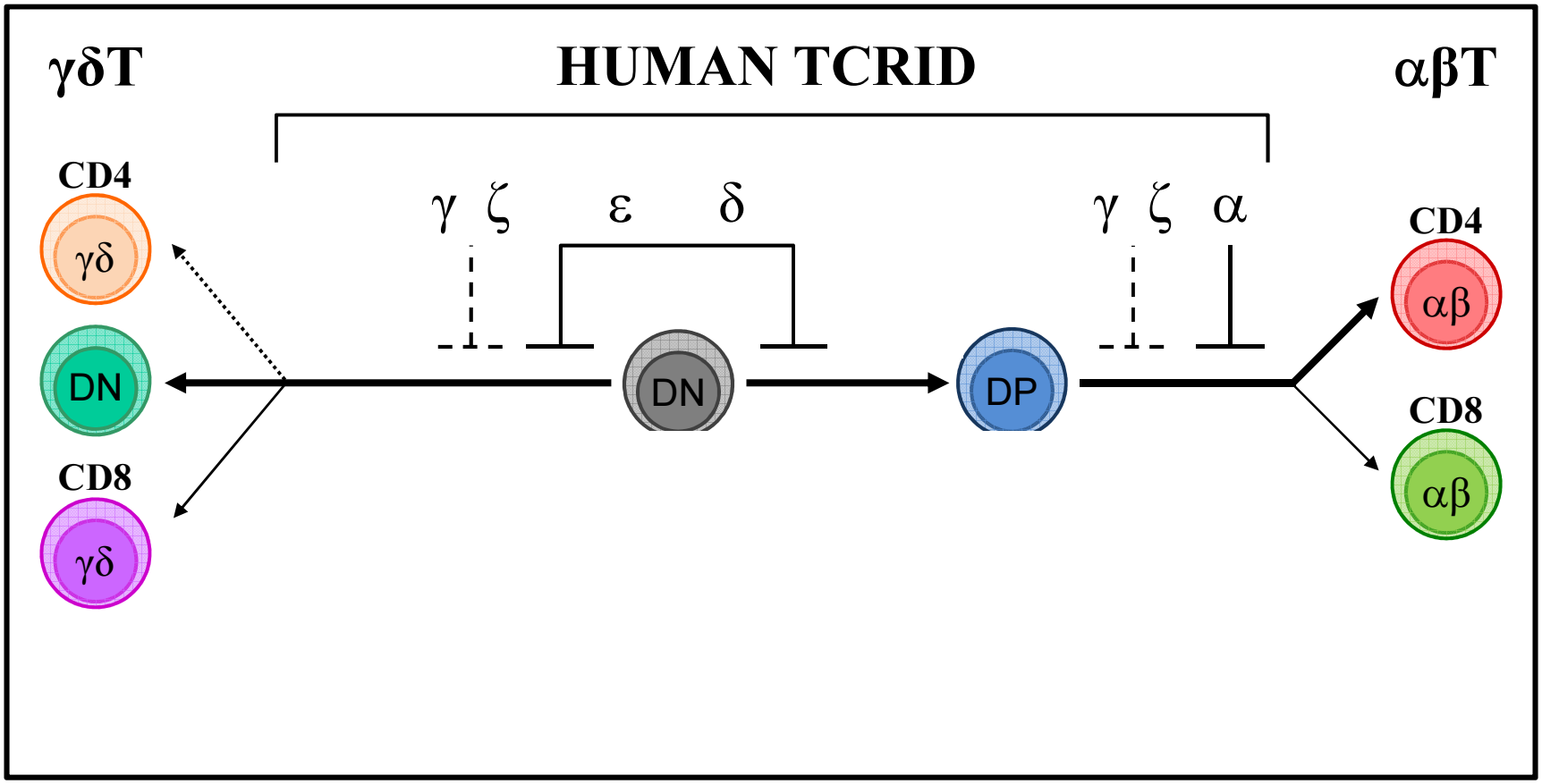


Human TCR immunodeficiencies

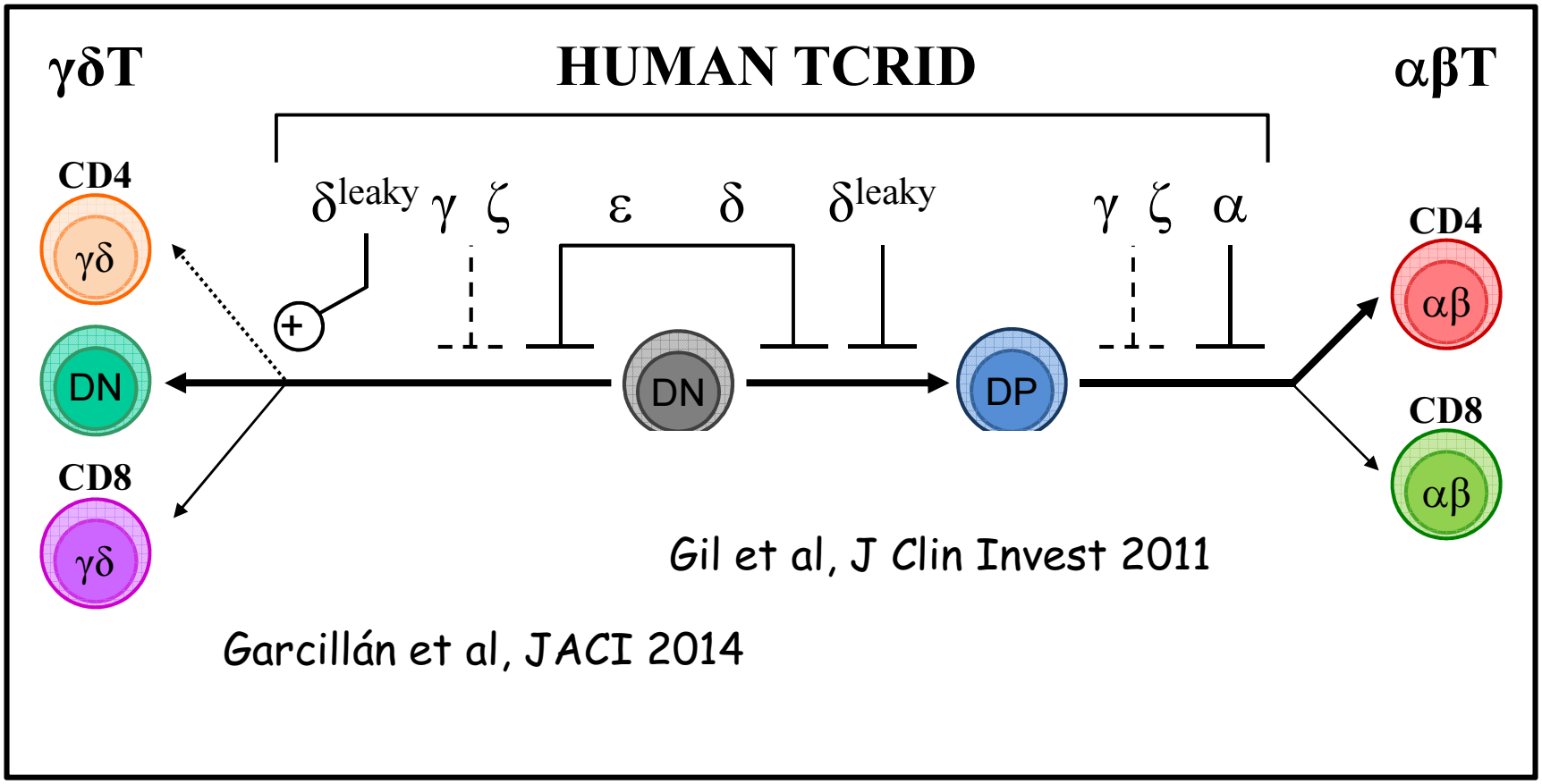


Blocked T cell development?

Yes: CD3δ, CD3ε, TCRα
No: CD3γ, CD247 (ζ)



Partial defects emerging due to leaky mutations



Inmunodeficiencias del TCR

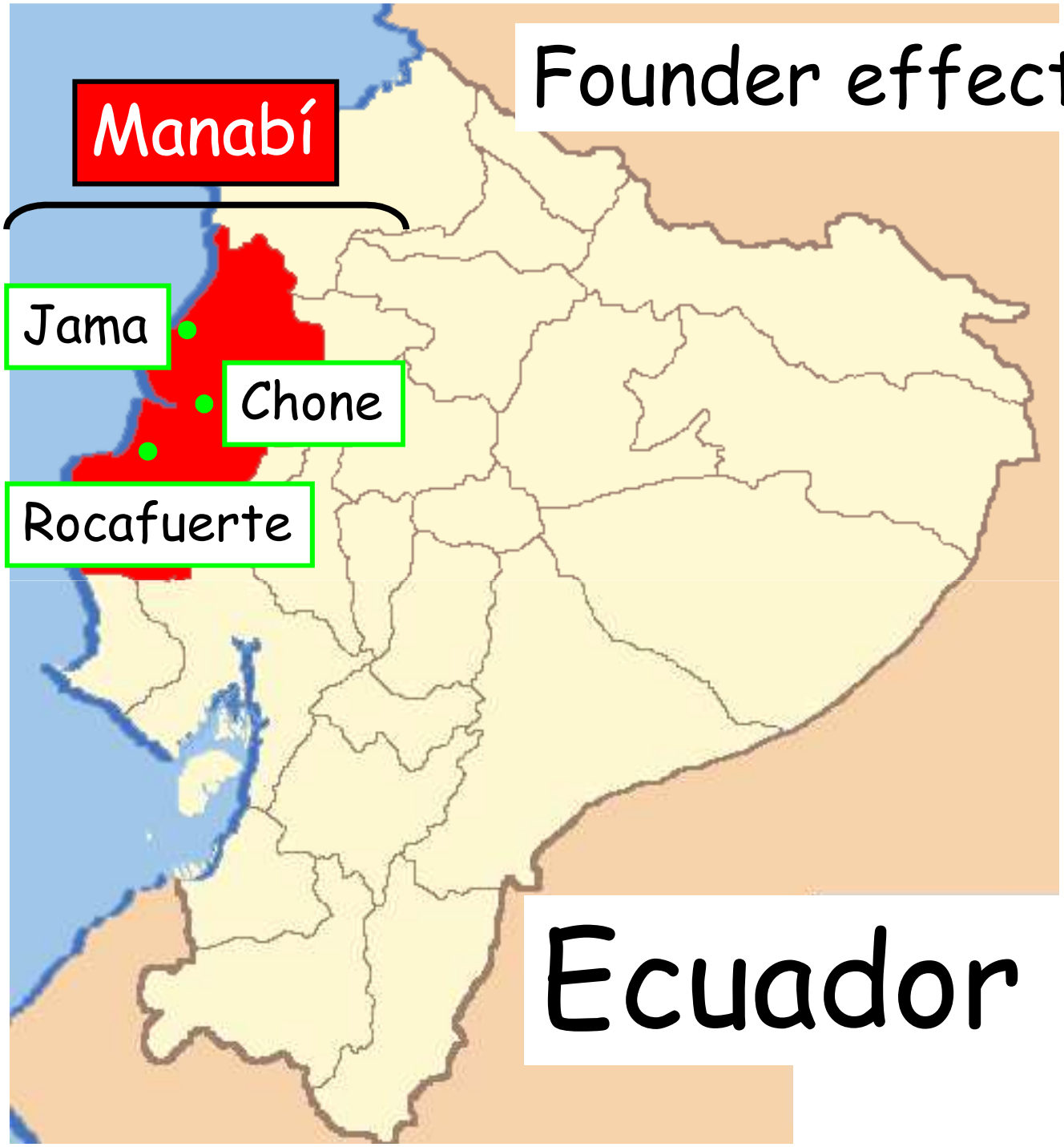
- Isotipos del TCR
- Inmunodeficiencias del TCR
- Diagnóstico: clínico
- Tratamiento y pronóstico

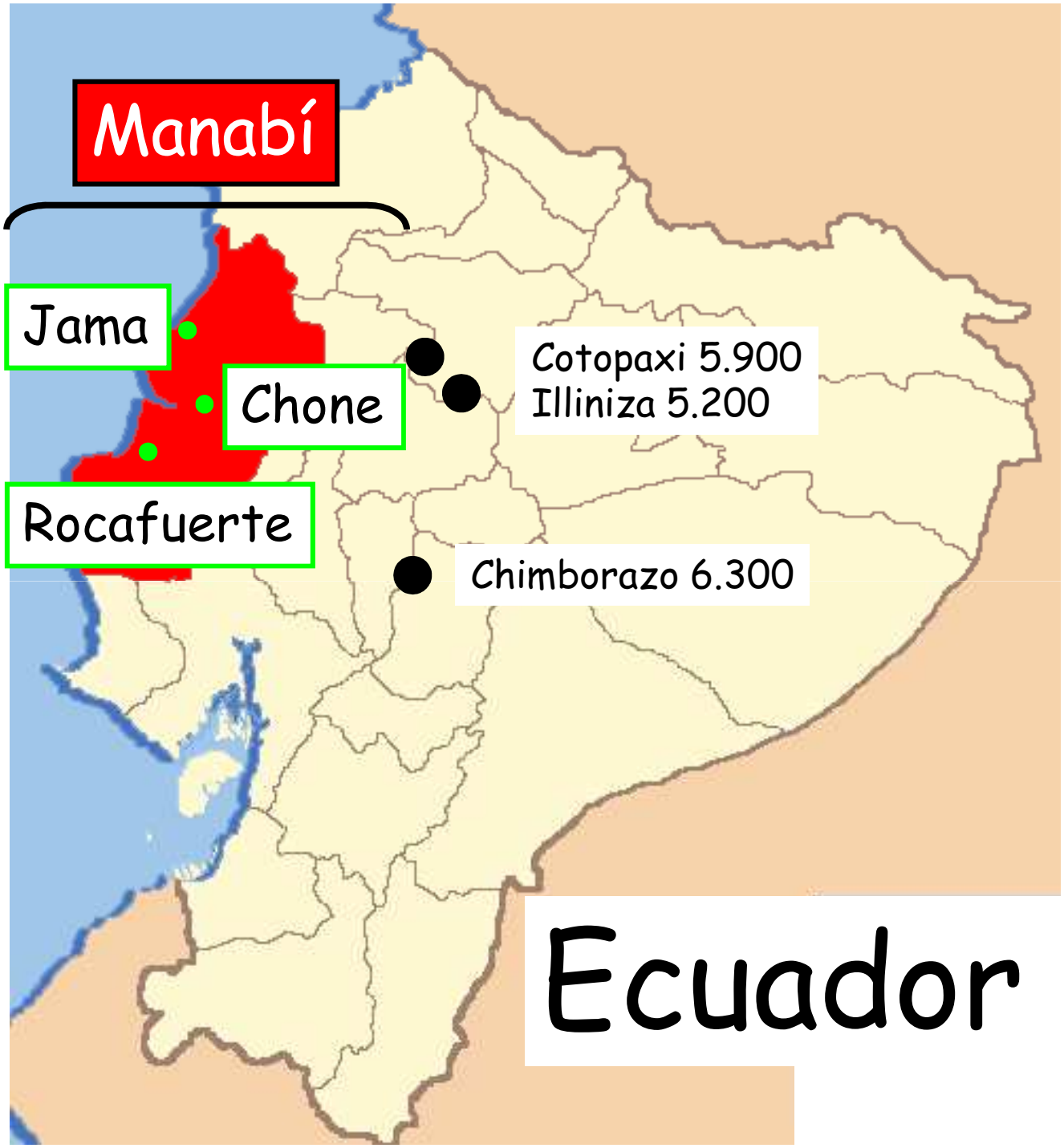
TCRID are mostly rare (<1%) Severe Combined Immuno Deficiency

Prevalence TCR ID 1/5.000.000

SCID = respiratory infections, diarrhea, failure to grow, 6% of PID

%	n	SCID
28.1	1.370	Other SCID
12.4	607	γc
7.2	352	Rag
7.1	344	DiGeorge
6.5	319	Omenn
6.4	310	ADA
6.3	309	MHC-II
5.8	285	CD40L
3.3	162	Jak3
2.7	134	Artemis
2.7	130	IL-7Rα
2.3	111	Dock 8
2.1	102	Cartilage hh
1.5	74	Zap70
0.8	41	CD40
0.8	40	PNP
0,8	39	CD3, CD247
100,0	4.876	JMF survey

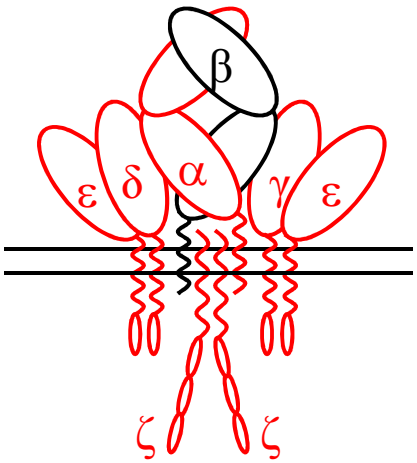

Founder effects
Manabí
Jama
Chone
Rocafuerte
Ecuador


Manabí
Jama
Chone
Rocafuerte
Cotopaxi 5.900
Illiniza 5.200
Chimborazo 6.300
Ecuador

CD3δ and CD3γ TCRID are the most frequent

Protein	Gene	Chr.	OMIM	Complete	Partial	TOTAL
CD3γ	*CD3G*	11	186740	10		**10**
CD3δ	*CD3D*	11	186790	16	3	**19**
CD3ε	*CD3E*	11	186830	4	1	**5**
CD247	*CD247*	1	186780	3		**3**
TCRα	*TRAC*	14	186880	2		**2**
			TOTAL	**35**	**4**	**39**

αβTCR



Deficiency	CD3δ																		
Family	1					2	3	4			5		6	7			8	9	10
Ethnic background	Mennonites (Canada, USA, Germany)										France			Japan			Ecuador		
Patient/sex	1F	2M	3M	4F	5M	6F	7M	8F	9M	10F	11F	12F	13M	14F	15M	16M	17M	18M	19F
Consanguineous	Yes					Yes	Yes	Yes			Yes		Yes	Yes			No	No	No
Mutation	c.202C>T										c.279C>A			c.275-2A>G			c.27415G>A		
Predicted effect (leaky)[7]	Truncation										Truncation			Skip3			*Skip2*		
Diagnosis at (m)[1]	0	2	2	9	0	0	0	10	13	0	3	0	2	3	0	0	14	4	10
% CD3$^+$ cells[2]	0.3	0.1	0.6	2	0	0	1	0	27	1	<1	<1	0	1.7	0.2	0	14	30	2
HSCT[3] at (m, y)[1]	MB4m	No	No	MB16m	MB4m	IDB1m	HP6m	HP12m	HB14m	HB2m	No	H	H	HP4m	MIC1m	MC1m	IDP23m	HP8m	No
Cause of death[4]	AW	ADV	CMV	AW	AW	AW	GvHD	HHV6	CMV	AW	CMV	Asp	EBV	CMV	AW	AW	AW	CMV	A

Deficiency	CD3γ										CD3ε					ζ/CD247			TCRα	
Family	1		2	3		4				5	1	2			3	1	2	3	1	2
Ethnic background	Turkey			Spain		Turkey					France				Germany	Caribbean	Hawaii	Turkey	Pakistan	
Patient/sex	1M	2M	3M	4M	5M	6F	7F	8F	9M	10F	1M	2F	3M	4F	5F	1M	2F	3F	1F	2M
Consanguineous	Yes		Yes	No		No		Yes			No	Yes			No	NR[5]	No	Yes	Yes	Yes
Mutation	c.205A>T			c.1A>G & c.IVS2-1G>C		c.IVS2-1G>C		c.IVS2-1G>C			c.IVS7+2T>C & c.230G>A	c.128_129del			c.IVS2+1 G>C	c.207C	c.411insC	c.2T>C	c.*1G>A	
Predicted effect (*leaky*)[7]	Truncation			Trunc, Het		Truncation		Truncation			*Skip7, Tr, Het*	Truncation			Skip 2	Trunc	Insertion	Trunc	Skip3	
Diagnosis at (m)[1]	3	7	48	12	48	12	240	84	132	14	48	5	1	0	2	4	10	2	15	6
% CD3$^+$ cells[2,6]	37	27	30	10	18	40	45	33	32	45	63	NR[5]	NR	<1	100[8]	21	64	60	21	50
HSCT[3] at (m,y)[1]	No	ID	No	No	No	No	No	No	No	No	No	No	No	H	H7m	H30m	H>12m	H18m	IDB6y	IDB7y
Cause of death[4]	Sepsis	Pneum	AW	Pneum	AW	AW	AW	AW	AW	AW	AW	Pneum	CMV	ADV	AW	AW	AW	A	AW	AW

1- m (months); y (years).

2- At diagnosis. Normal values 60-85%, includes dull and bright CD3$^+$ cells.

3- First hematopoietic stem cell transplantation from related (matched = ID, haploidentical = H) or unrelated (matched = M, mismatched = MI) don
or cord blood (C).

4- AW (Alive and Well);A (Alive); ADV,CMV,EBV,HHV (viral infection); Pneum (Pneumonia); Asp (Aspergillus); GvHD (Graft vs Host Disease)

5- NR (Not reported)

6- For TCRa defects mostly TCRgd+ T cells, few TCRab^{low} T cells

7- Leaky refers to wild type protein levels. Skip7 (exon 7 skipping), Tr/Trunc (protein truncation), Het (compound heterozygote)

8- T cells from maternal origin

LymphoSign Journal
The journal of inherited immune disorders

Differential clinical and immunological consequences of complete TCRID

	%			Months at		No tx	
n	Surv	T ly	Chain	Diag	Tx	mo †	Surv
4	25	2	CD3ε	2	7	4	0/2
16	44	3	CD3δ	3	6	3	0/3
3	67	48	CD247	5	20	-	-
2	100	36	TCRα	11	78	-	-
10	70	32	CD3γ	60	15	20	7/9

Differential clinical and immunological consequences of complete TCRID

	%			Months at		No tx	
n	Surv	T ly	Chain	Diag	Tx	mo †	Surv
4	25	2	CD3ε	2	7	4	0/2
16	44	3	CD3δ	3	6	3	0/3
3	67	48	CD247	5	20	-	-
2	100	36	TCRα^a	11	78	-	-
10	70	32	CD3γ^a	60	15	20	7/9

The CD3γ exception: healthy or SCID ± autoimmunity (a)

CD3γ deficiency can be lethal

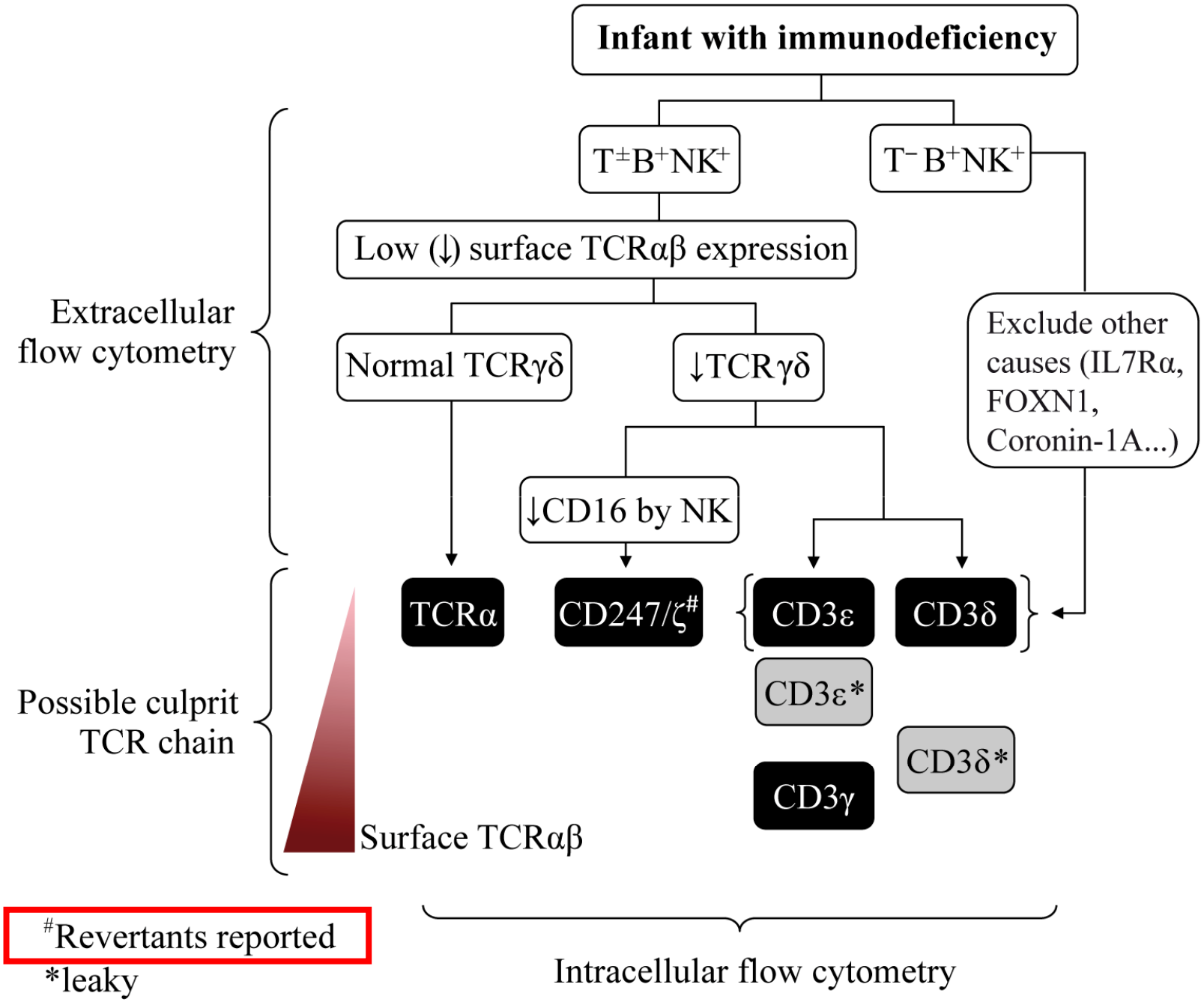
I Tezcan

Partial defects* emerging

	%			Months at		No tx	
n	Surv	T ly	Chain	Diag	Tx	mo †	Surv
4	25	2	CD3ε	2	7	4	0/2
16	44	3	CD3δ	3	6	3	0/3
3	67	15	CD3δ*	9	15	16	0/2
3	67	48	CD247	5	20	-	-
2	100	36	TCRα	11	78	-	-
10	70	32	CD3γ	60	15	20	7/9
1	100	63	CD3ε*	48	-	-	-

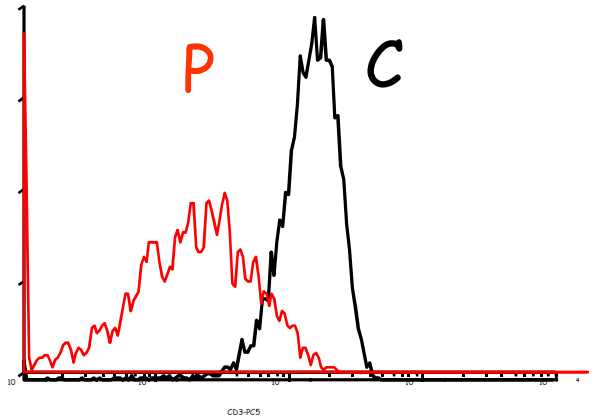
Inmunodeficiencias del TCR

- Isotipos del TCR
- Inmunodeficiencias del TCR
- Diagnóstico: proteínas
- Tratamiento y pronóstico

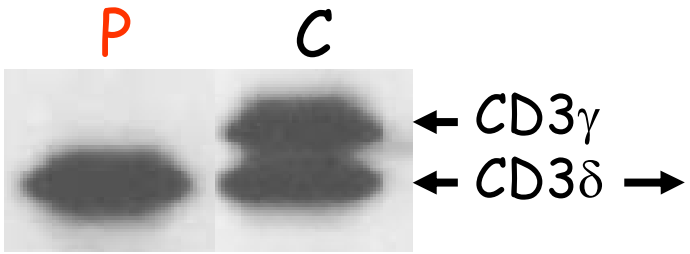

Infant with immunodeficiency
T±B+NK+
T− B+NK+
Low (↓) surface TCRαβ expression
Normal TCRγδ
↓TCRγδ
Exclude other causes (IL7Rα, FOXN1, Coronin-1A...)
↓CD16 by NK
TCRα
CD247/ζ#
CD3ε
CD3δ
CD3ε*
CD3δ*
CD3γ
Surface TCRαβ
Extracellular flow cytometry
Possible culprit TCR chain
#Revertants reported
*leaky
Intracellular flow cytometry

Selective surface TCR expression defect

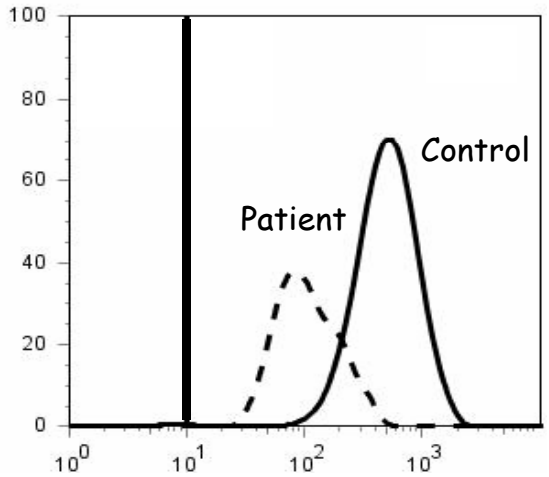
CD3γ (p.K69X)



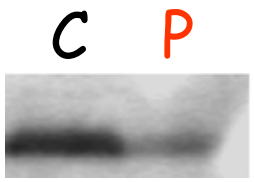
CD3 (UCHT1)



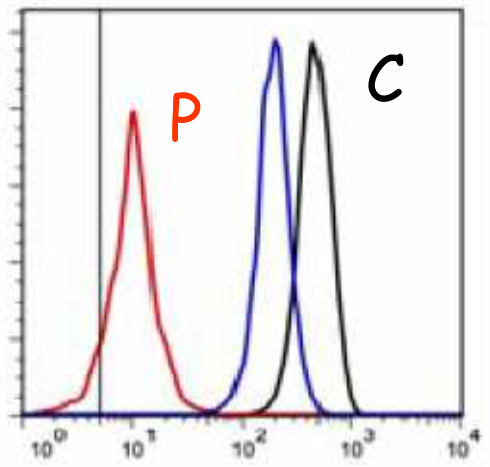
CD3δ* (p.EX2del)

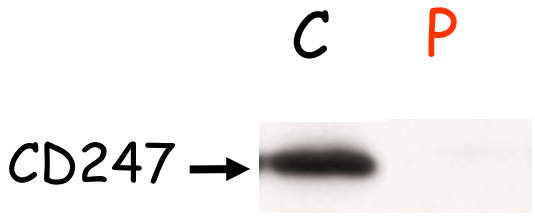


CD3 (SK7)

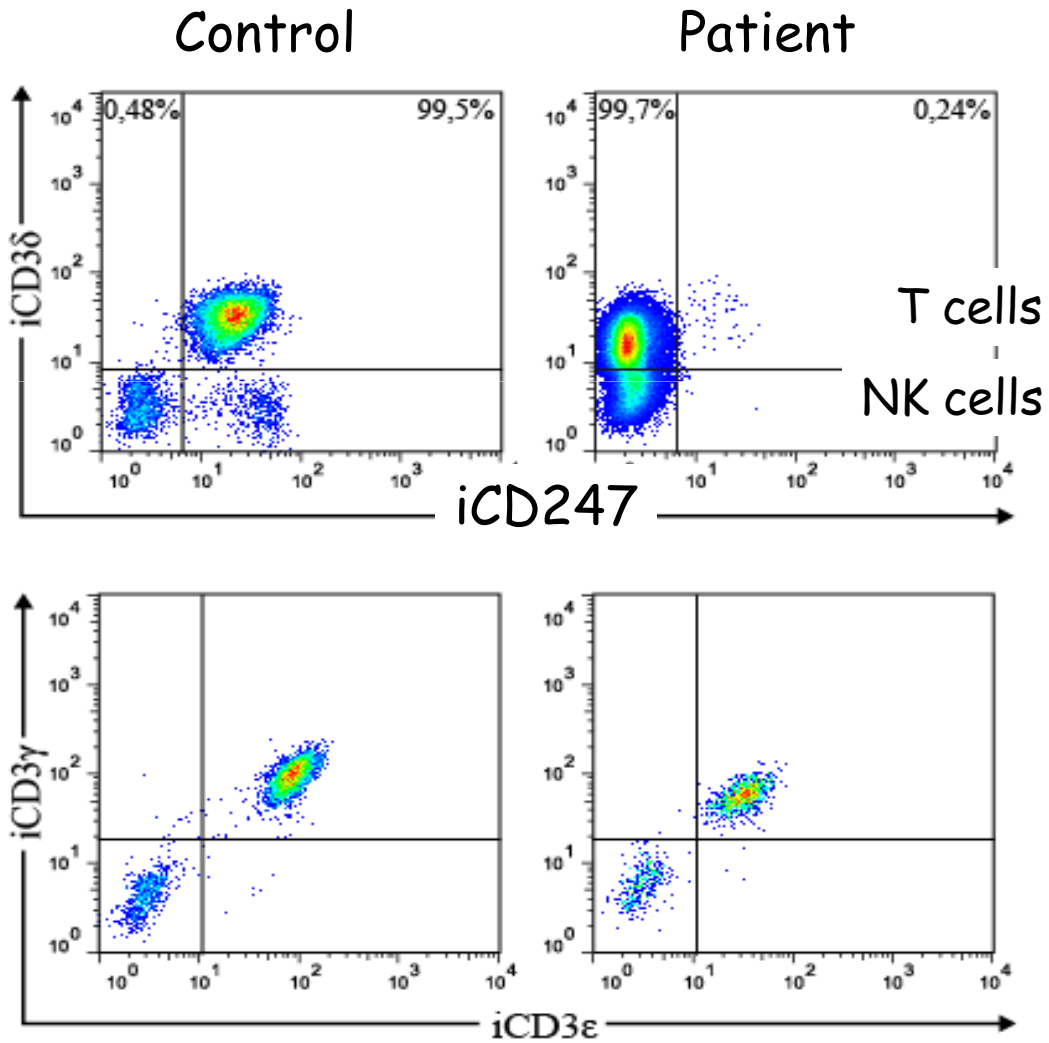


CD247 (p.M1T)

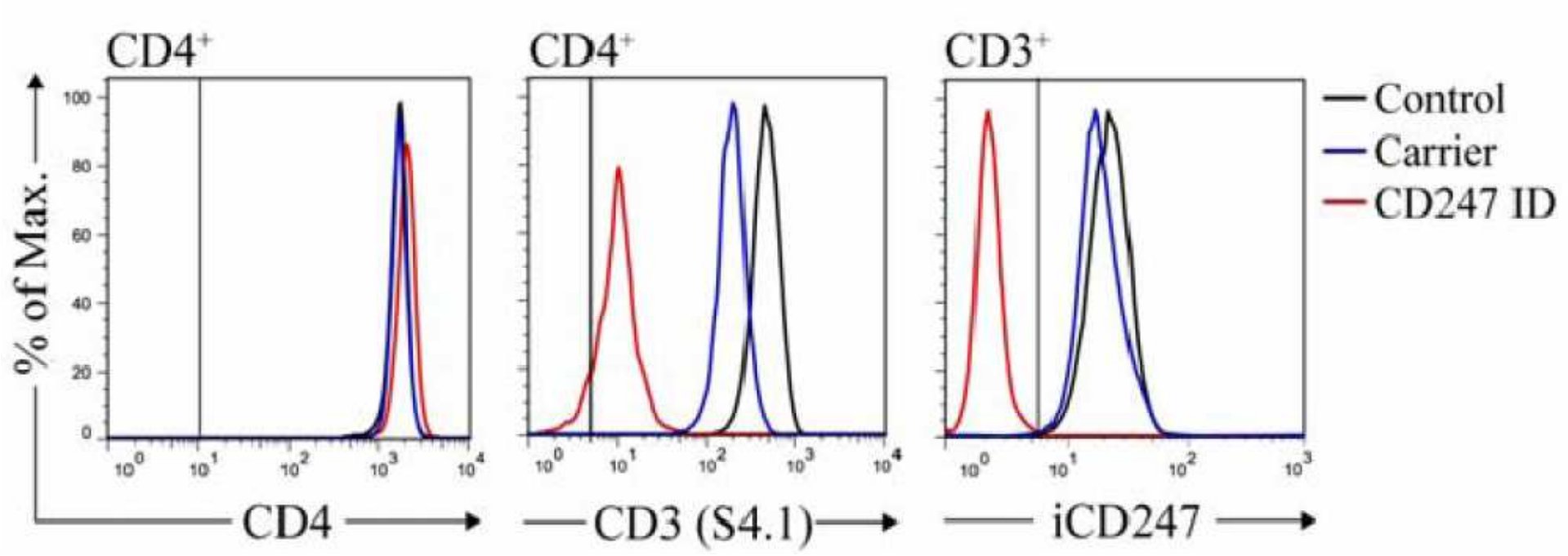




Chain-specific intracellular stainings help



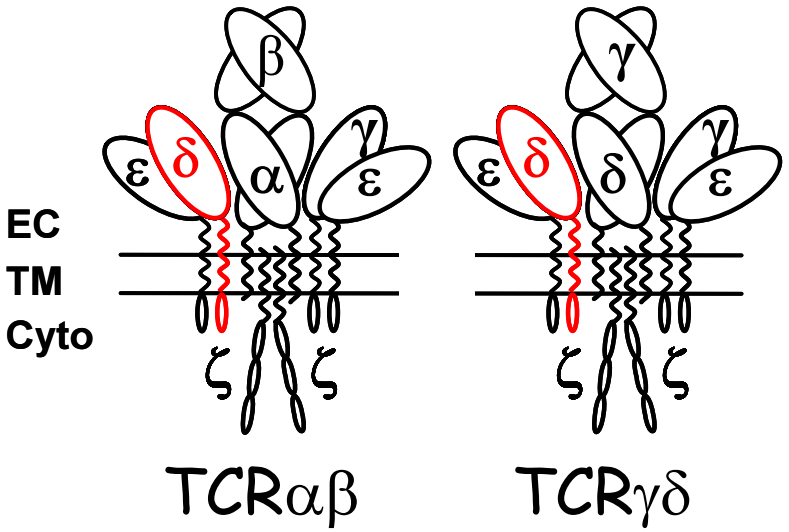
Carriers may have a partial surface TCR expression defect



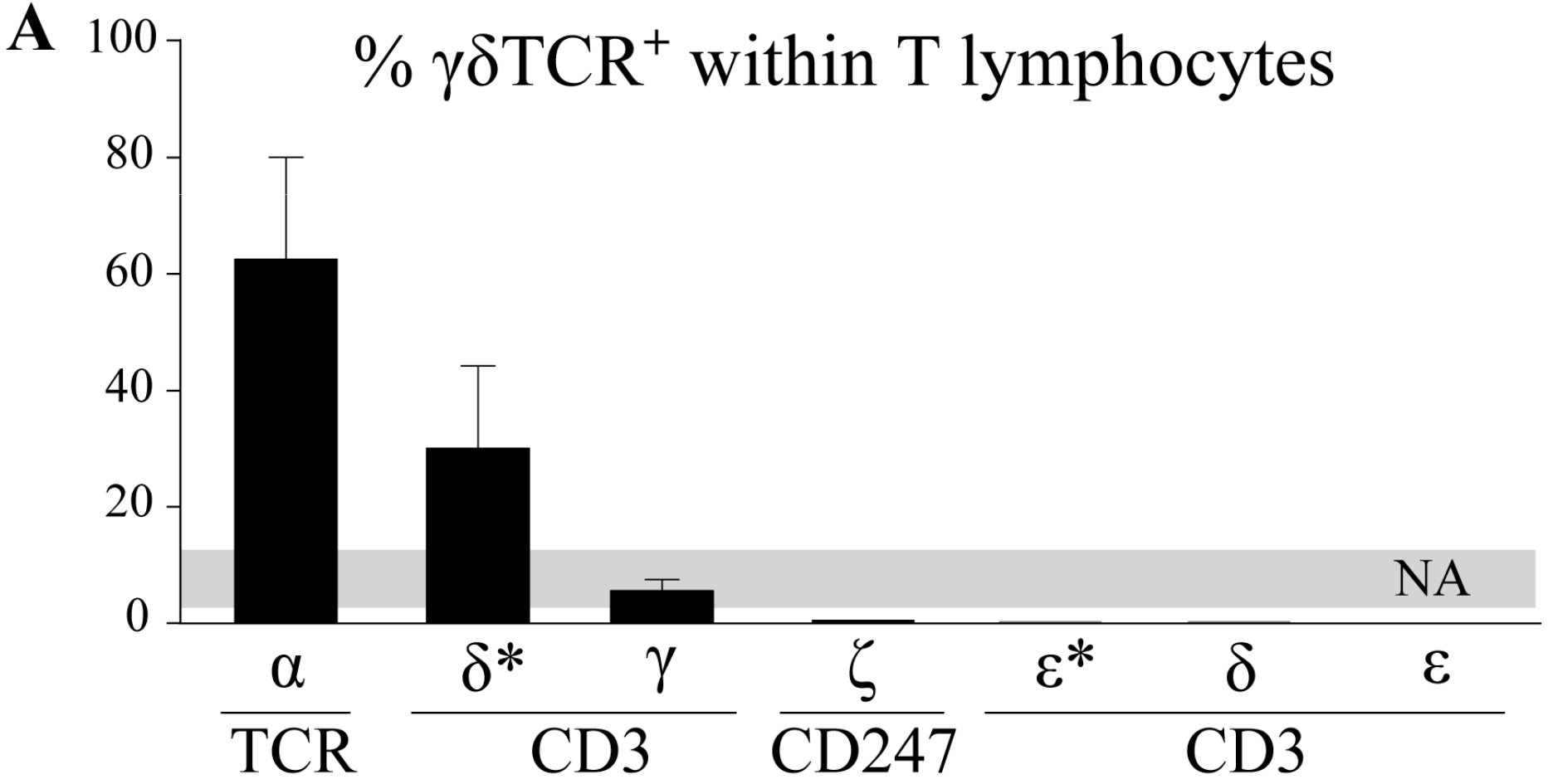
Take-home message: study γδ T cells

TCR complex deficiencies				Number of patients		
Protein	Gene	Chr.	OMIM	Complete	Partial	TOTAL
CD3γ	*CD3G*	11	186740	10		**10**
CD3δ	*CD3D*	11	186790	16	3	**19**
CD3ε	*CD3E*	11	186830	4	1	**5**
CD247	*CD247*	1	186780	3		**3**
TCRα	*TRAC*	14	186880	2		**2**
			TOTAL	**35**	**4**	**39**

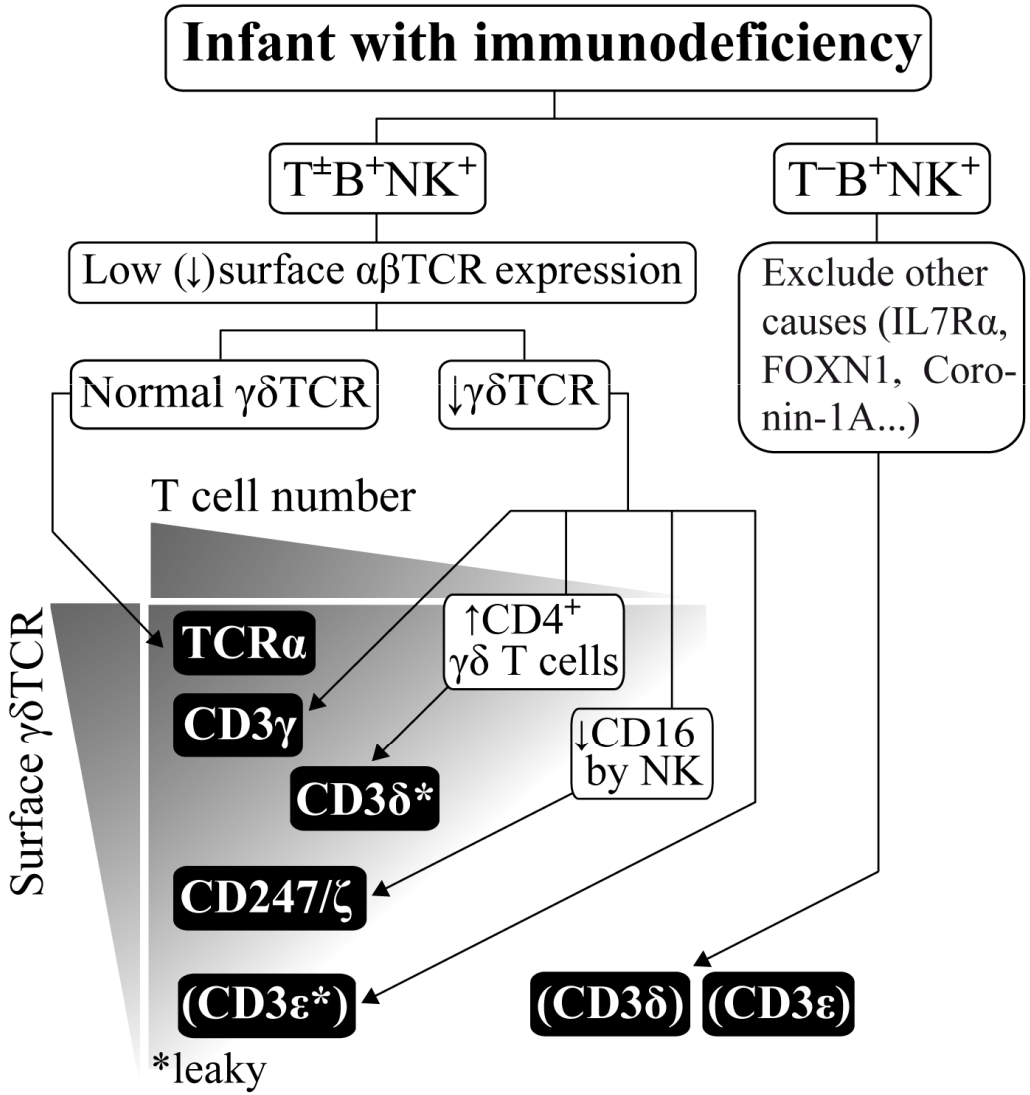
T cell phenotype	
Complete	Partial
Tαβ±Tγδ±	
Tαβ-Tγδ-	Tαβ-Tγδ+
Tαβ-Tγδ-	Tαβ+Tγδ+
Tαβ±Tγδ±	Tαβ+Tγδ+
Tαβ-Tγδ+	



γδ T cell numbers are informative



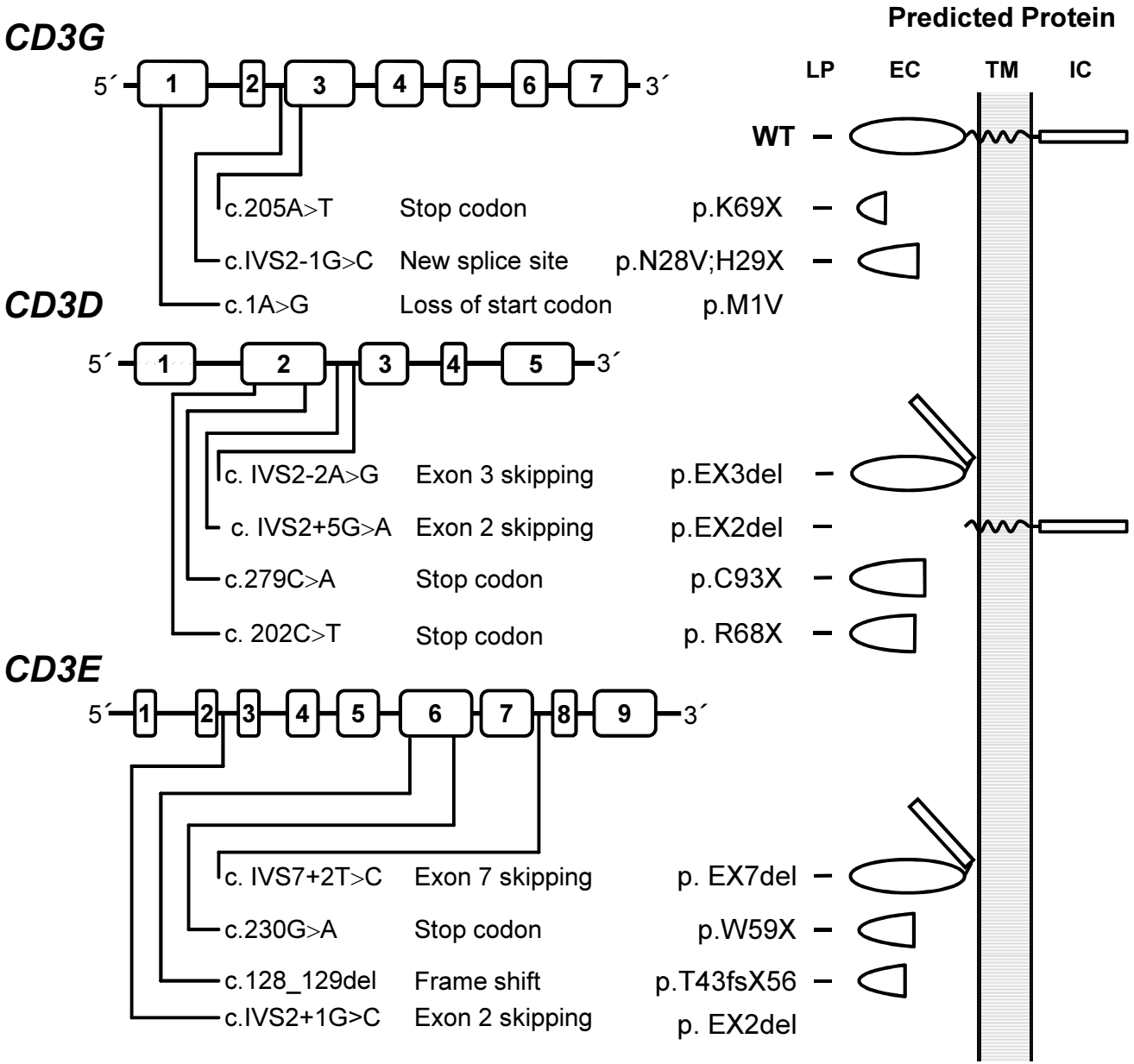
γδ T cells are informative



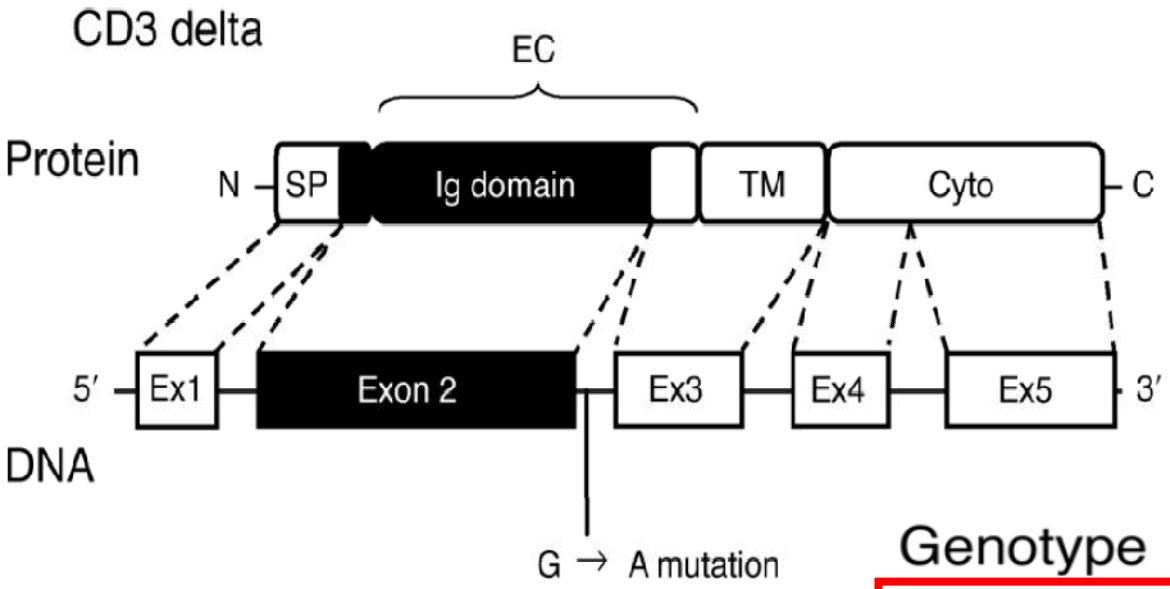
Inmunodeficiencias del TCR

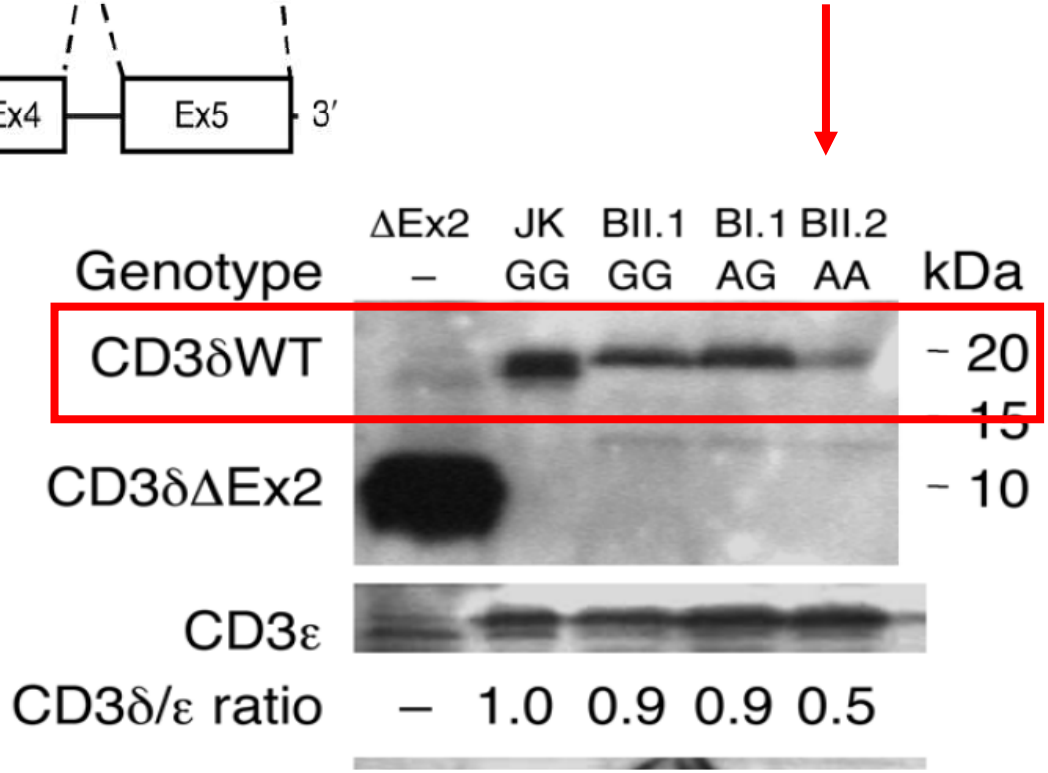
- Isotipos del TCR
- Inmunodeficiencias del TCR
- Diagnóstico: genes
- Tratamiento y pronóstico

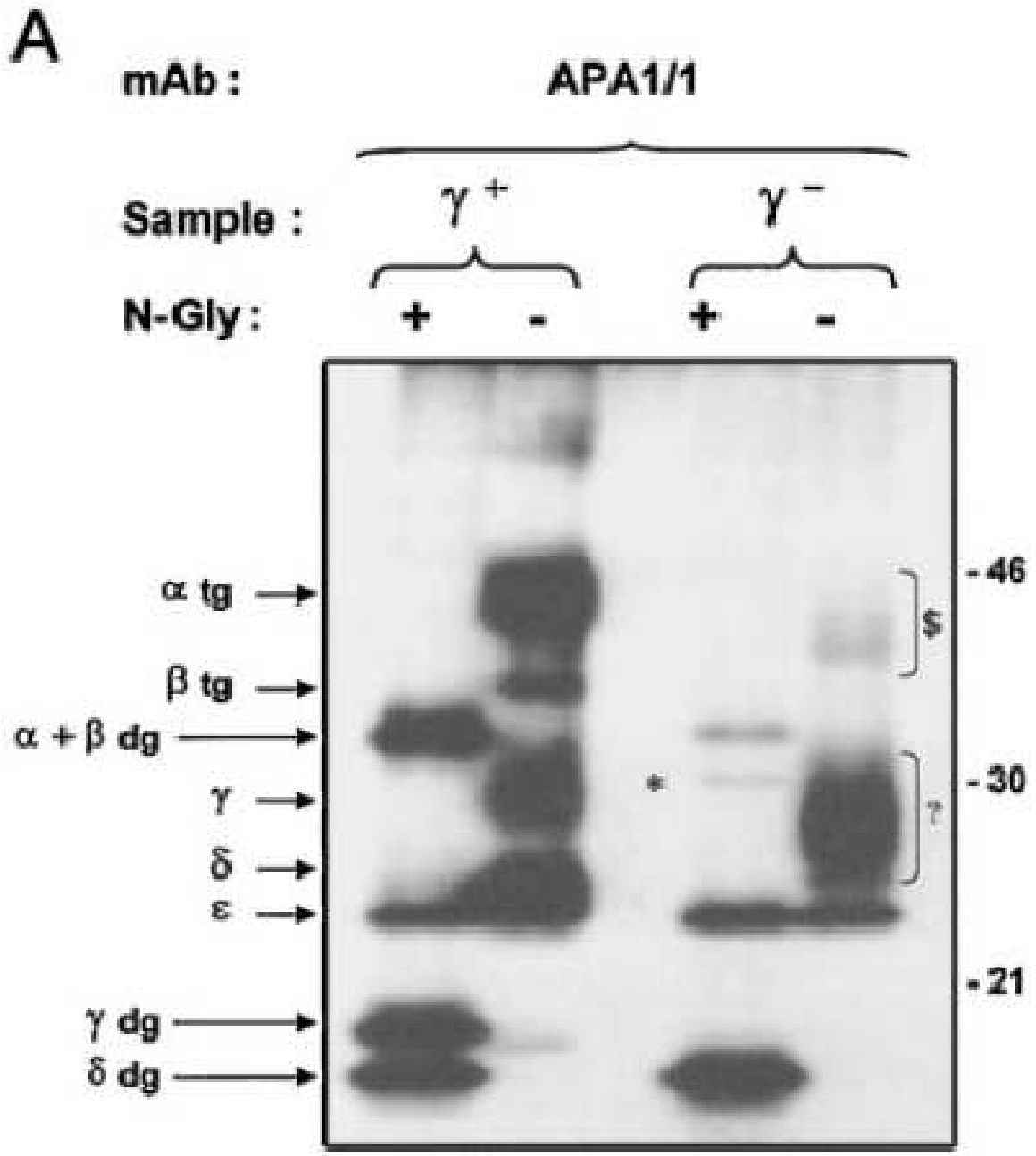
LOF mutations: truncated, unstable



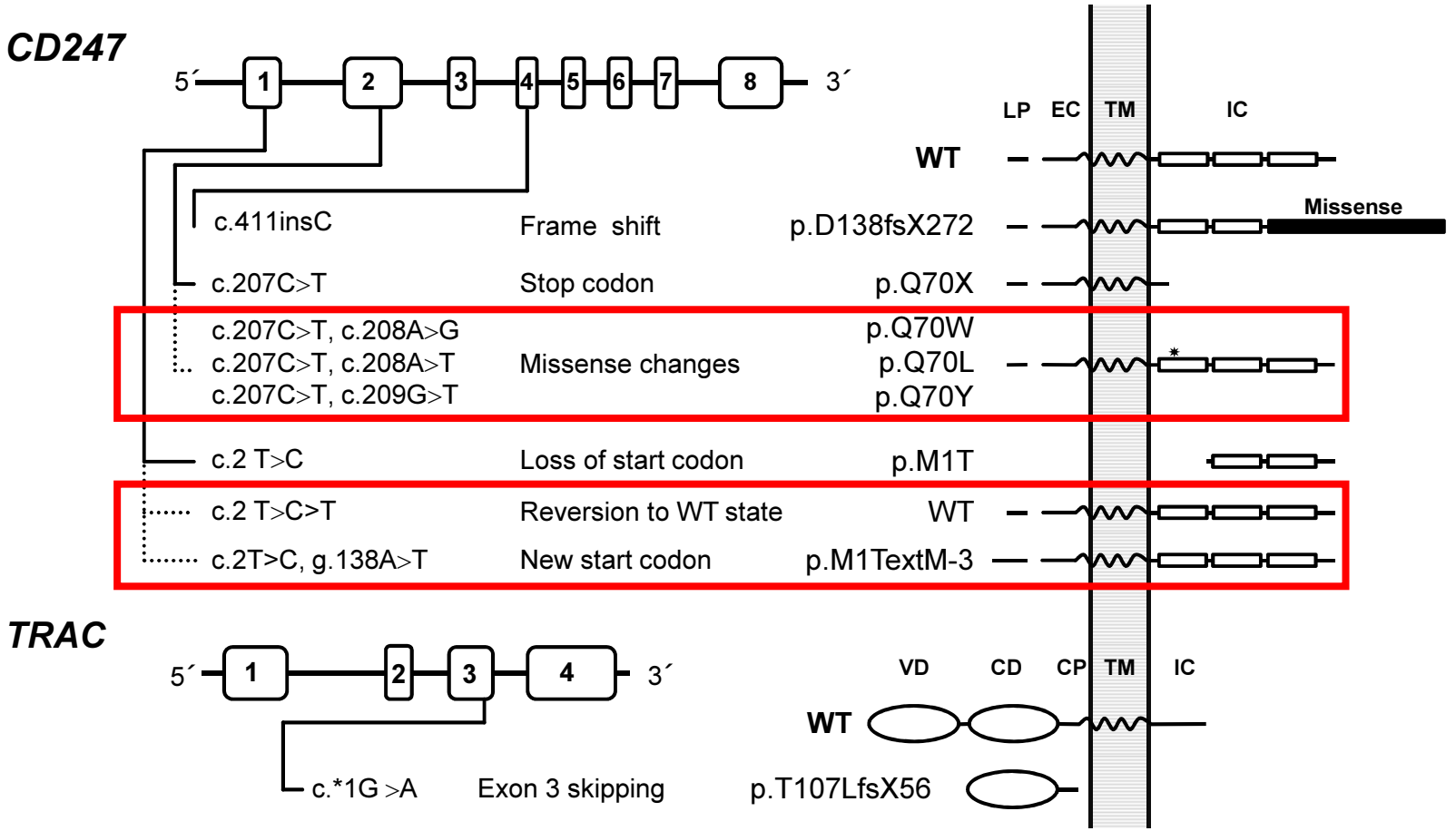
Partial defects due to leaky splice site mutation



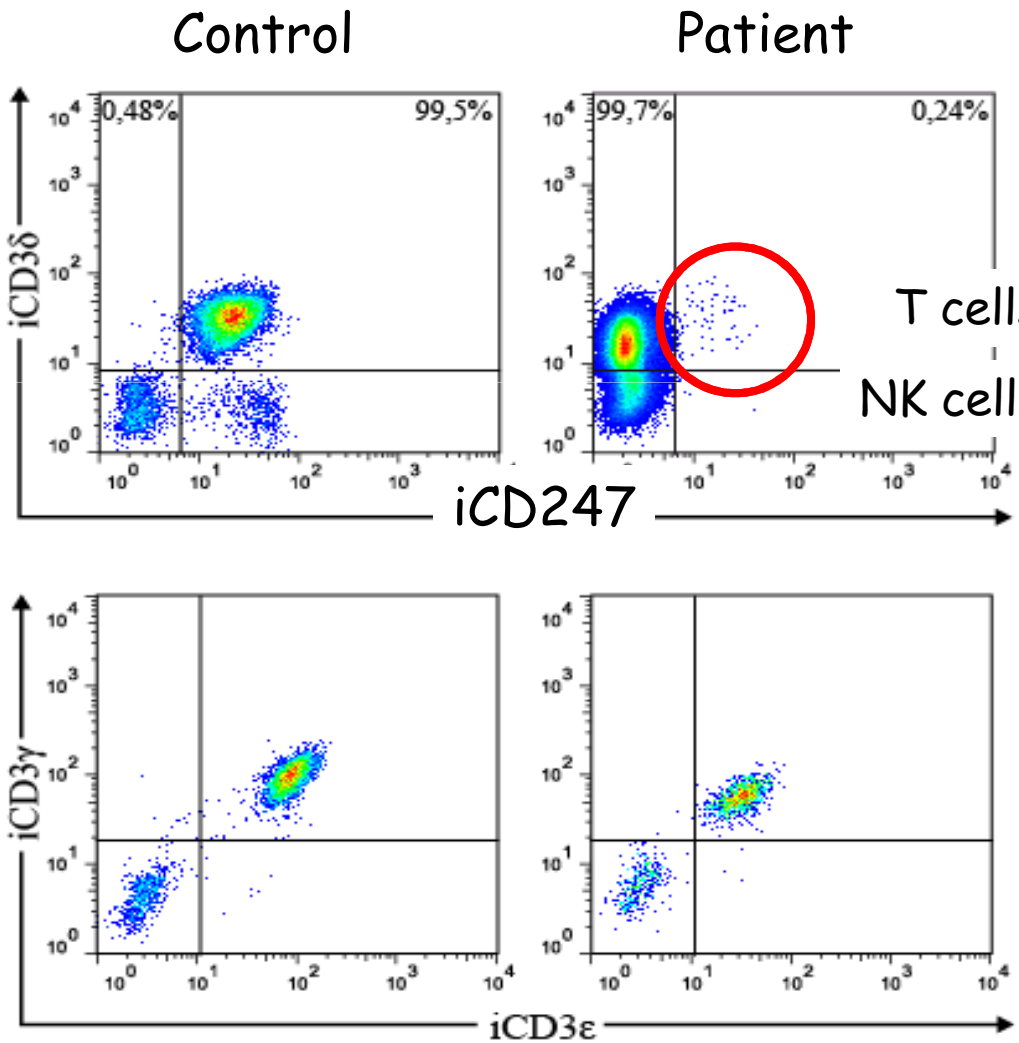



A
mAb :
APA1/1
Sample :
γ +
γ −
N-Gly :
+
-
+
-
α tg
β tg
α + β dg
γ
δ
ε
γ dg
δ dg
- 46
- 30
- 21
$
?
*

Reversions only in CD247 TCRID



TCR expression revertants



T cells (some revertants)

NK cells (no revertants)

Diagnosis

Definitive: Pathogenic mutations in a TCR complex gene (*CD3G, CD3D, CD3E, CD247 or TRAC* to date)

Probable: male/female patient with surface TCR expression defect and selective peripheral blood T lymphocytopenia (T— or T±B+NK+)

Spectrum of disease: from SCID (common) to healthy (rare, overlooked?). Complete CD3ε or δ defects are T—B+NK+, complete CD3γ or CD247 defects and partial defects are T±B+NK+, including Tαβ—Tγδ+ B+NK+. TCR expression revertants due to somatic mutations found only in CD247 deficiency

Differential diagnosis: with T—B+NK+ or T±B+NK+ patients such as IL7Rα, FOXN1, Coronin-1A, Zap70, MHC class I or II, PNP, ADA or DiGeorge defects

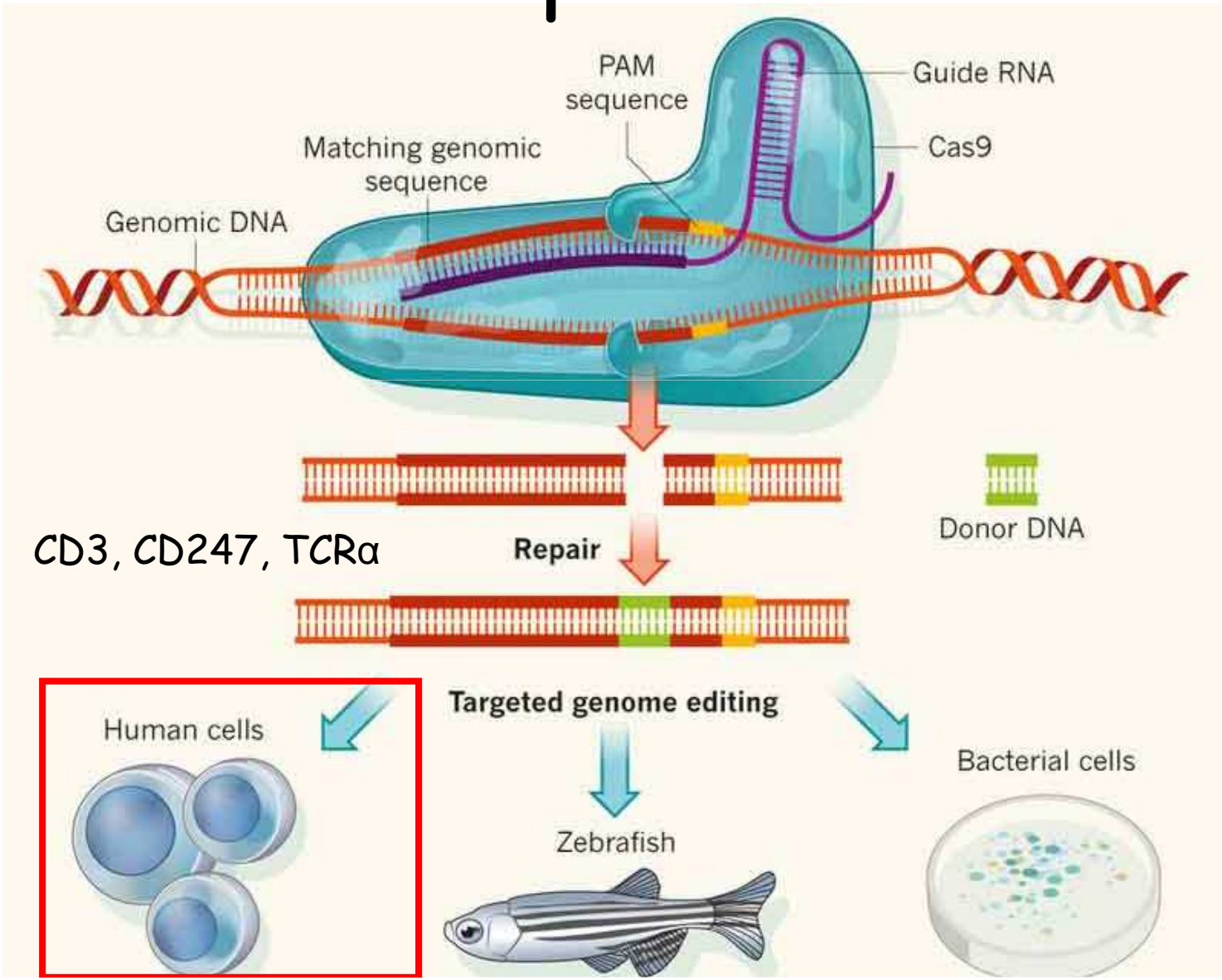
Inmunodeficiencias del TCR

- Isotipos del TCR
- Inmunodeficiencias del TCR
- Diagnóstico
- Tratamiento y pronóstico

Treatment and prognosis

- Hematopoietic stem cell transplantation, the sooner the better, even in mild cases
- Prognosis:
  - CD3δ, CD3ε, partial CD3δ : early lethal SCID unless transplanted
  - CD3γ, CD247, TCRα: late lethal SCID unless tx
  - CD3γ, partial CD3ε: survival beyond 20y
- Gene therapy?

¿Recombinación homóloga? Crispr/Cas9



CD3, CD247, TCRα

CONCLUSIONS

- TCRID are very rare
- CD3ε or δ ID cause $T^{-}B^{+}NK^{+}$ SCID
- CD3γ, CD247 or TCRα ID can be milder
- Keep an eye for partial TCRID
- Early diagnosis and HSCT are critical
- Either no T cells or, if present, selective TCR expression defect
- Intracellular chain-specific studies and γδ T cell analysis help
- ¿Need advice? regueiro@med.ucm.es

Gracias a

MADRID (UCM)
María J. Recio
Edgar Fdez. Malavé
Beatriz Garcillán
Miguel Muñoz Ruiz
Anaïs Jiménez
Ana V Marín

SPAIN
Juana Gil
Luis Allende
E López-Granados
MA. Moreno-Pelayo
Balbino Alarcón
Hugh Reyburn
Oscar de la Calle

ECUADOR
Richard Cedeño

TURQUIA
Cigdem Aydogmus
Aydan Ikinciogullari
Ozden Sanal
Sara S. Kiliç

ALEMANIA
Wolfgang Schamel

JAPON
Hidethoshi Takada

CANADA
Chaim Roifman


TREE
NATIONAL GEOGRAPHIC