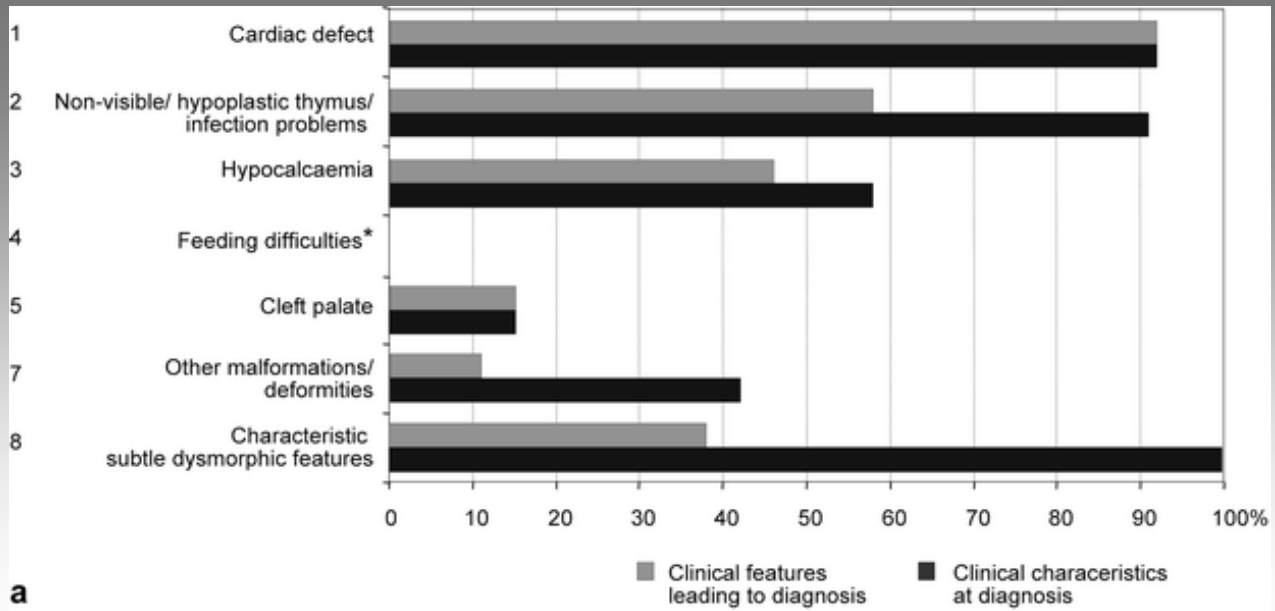
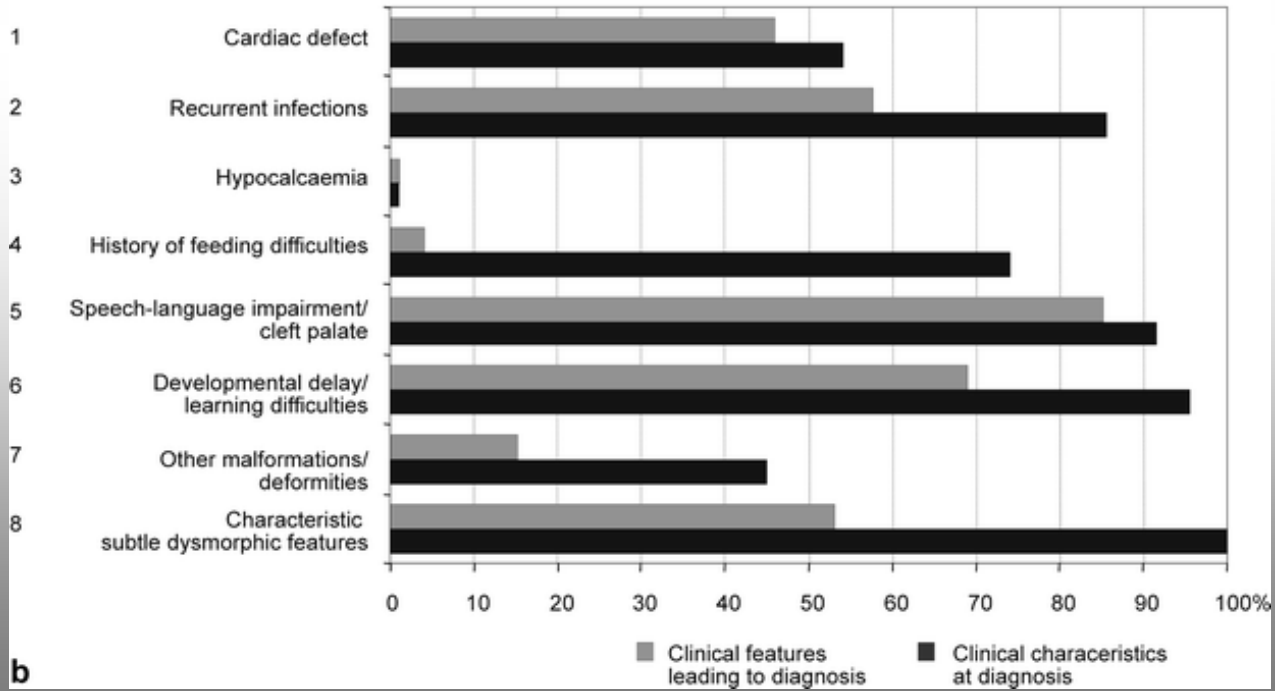
Di George syndrome
22q11.2 deletion syndrome

AGE <2



AGE 2-18



European J Ped Nov 2004

IMMUNOLOGIC FEATURES

Aplasia-Hypoplasia Thymus

↓

Variable immunological defects

(from normal to severe combined immunodeficiency)

20-40% DGS + immunological defects are not associated with conotruncal cardiac defects

IMMUNOLOGICAL CLASSIFICATION

Complete DGS	Partial DGS
- ↓↓↓CD3/CD4/CD8	- ↓ CD3/CD4/CD8
- No T cell response to mitogens	- ↓/N proliferation tests *in vitro*
- ↓↓↓ CD45RA,TREC	- ↓ CD45RA,TREC
- ↓↓↓ *TCRBV*	- ↓ *TCRBV*

DGS with normal T cell subset

PARTIAL DGS

- Frequent
- ↓ T cells/ n/ ↓ proliferation test
- Humoral defects
- Autoimmunity
- variable therapy

Infections in 22q11.2 deletion syndrome

-No symptoms

- Recurrent respiratory infections

-Other infections (rare) (recurrent parotitis , papilloma virus,mastoiditi, osteomielitis)

HUMORAL DEFECTS

Hypo-Hypergammaglobulinemia IgG

↓ **IgA** , ↓ IgM

↓ Subtypes IgG

↓ anticorpi specific antibody response (antipneumococcal, antitetanous, antihaemofilus)

Jawad 2001, Kornfeld 2000, Smith 1998, Jennery 2003, Chinen 2003

FACTORS INFLUENCING INFECTIONS IN DGS

- Immunodeficit/Allergy
- Anatomical Anomalies (ear, larinx, trachea, atresia coane)
- Reflux gastroaesophagus
- Congenital heart disease
- Malnutrition

ORL

DGS e Autoimmunity

Autoimmune manifestation (10%)

- NO CORRELATION T cell values

but

- ↓ T CD4+CD25+ *Sullivan KE*, 2002

→ Play a role in development of autoimmunity

AUTOIMMUNITY

- Autoantibody
- JCA
- Trombocytopenia (Bernard-Soulier)
- Hemolitic anemia
- Tiroiditis
- Raynaud
- Urticaria
- Vitiligo
- Psoriasis
- RA corea
- Cerebellitis?

Jawad 2001, Kornfeld 2000, Smith 1998, Jennery 2003 Chinen 2003

T CELLS IN DGSp

- T CELL VALUES ARE DECREASED COMPARED WITH AGE MATCHED HEALTHY DONORS

BUT

- THEY ARE NOT PREDICTIVE OF INFECTIONS

Sullivan K 2001

Kinetics of the T-cell receptor CD4 and CD8 Vβ repertoire and immune function in DGSp to determine the extent and nature of the immunodeficiency and to correlate it to clinical and immunological findings

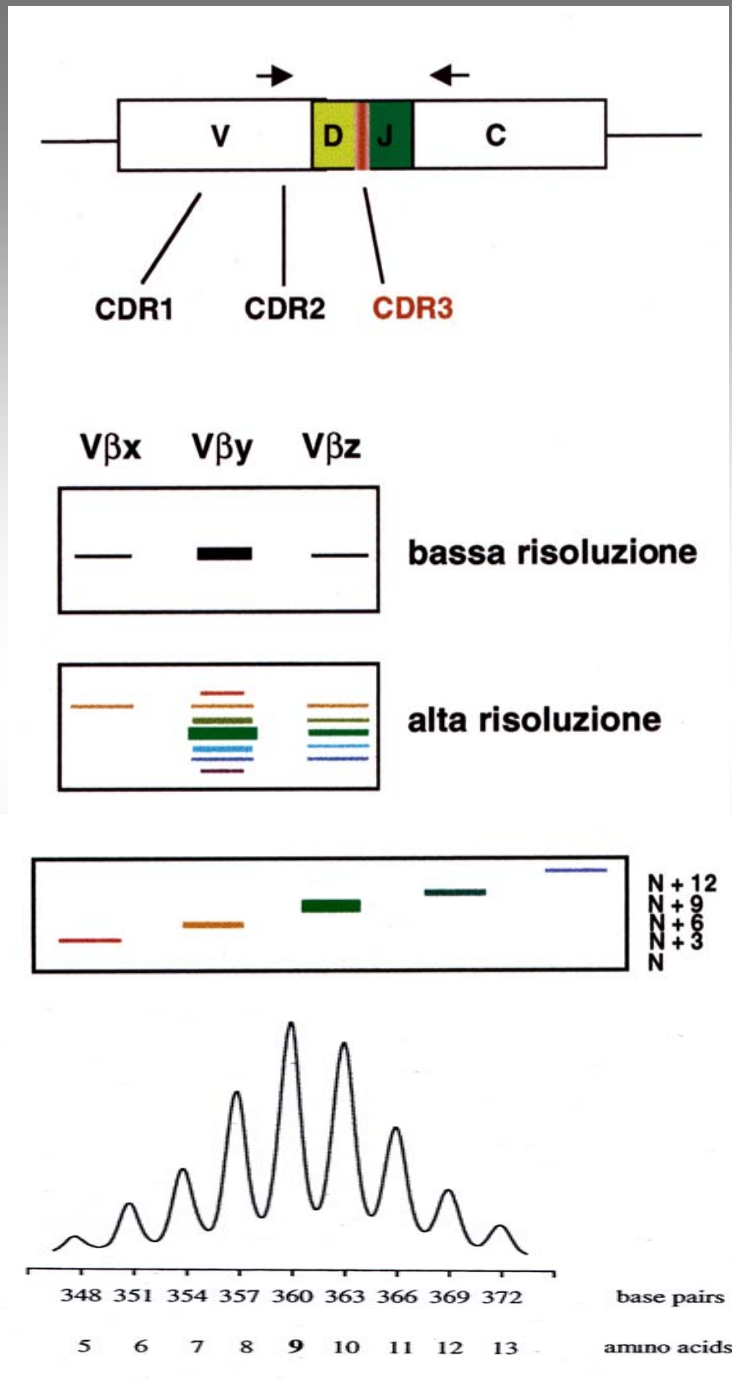
Humoral compartment by analyzing antibody response in vivo and by immunophenotyping B cell subsets in peripheral blood

Patient.	Sex	F.U.	CHD	Facies	Hypocal	Thymus	FISH	Infections	Treatment
1	M	65mo	IAA, AVSD	+	-	Hypoplasia	+	Recurrent Pneumonia, URI, Candidosis,	Antibiotic phrophylaxis
2	M	51mo	TA	+	+	Absent	+	Recurrent OM,URI	Antibiotic phrophylaxis IVIG
3	M	37mo	IAA, AVSD	+	+	Absent	+	Recurrent OM, URI	Antibiotic phrophylaxis IVIG
4	M	44mo	ASD,PS	+	+	Absent	+	None	None
5	M	33mo	ASD	+	+	Absent	+	Pneumonia, Recurrent OM, URI,	Antibiotic phrophylaxis
6	F	14mo	VSD	+	+	Normal	+	None	None
7	M	24mo	PA, VSD	+	+	Absent	+	URI	None
8	F	25mo	PA, VSD	+	-	Hypoplasia	+	Septicaemia, Recurrent Pneumonia, URI,	Antibiotic phrophylaxis
9	M	6mo	IAA, VSD	+	-	Absent	+	None	None
10	M	78mo	Absent	+	-	Normal	+	URI	None
11	F	29mo	AVSD	+	-	Absent	+	None	None
12	M	29mo	VSD	+	+	Hypoplasia	+	None	None
13	M	41mo	TA	+	+	Hypoplasia	+	None	None

F.U. follow up;CHD, Congenital heart disease; Hypocal, hypocalcemia; F, female; M, male; Facies, dysmorphic facies; VSD, ventricular septal defect; AVSD,Atrioventricular septal defect; IAA,interrupted aortic arch; PA, pulmonary atresia; PS, pulmonic stenosis;TA,truncus arteriosus;IVIG, intravenous immunoglobulin, OM, otitis media;URI, upper respiratory tract infection.

Pt. Age	CD3 (mm/^{3})	CD4 (mm/^{3})	CD45RA /CD4 (mm/^{3})	CD45R0 /CD4 (mm/^{3})	CD8 (mm/^{3})	CD45RA / CD8 (mm/^{3})	CD45R0 /CD8 (mm/^{3})	CD19 (mm^3)	CD16 (mm/^{3})	IgG (Mg/dl)	IgA (Mg/dl)	IgM (Mg/dl)	IgG subclass (Mg/dl)	Isohem	Sp Ab	LTM
1(74)	643↓	392↓	165↓	227	141↓	70↓	70	486	423	1200	202	86	Low IgG3	Low	Low HIB	N
2(46)	992↓	702↓	665	327	315↓	227↓	85↓	1006	251	1250	<5,9↓	33	N	N	N	N
3(68)	2151	1261	706	542	853	640	298	983	445	923	145	28↓	N	N	Low HIB	N
4(57)	2440	1680	n.d.	n.d.	720	n.d.	n.d.	480	680	835	128	62	N	N	N	N
5(38)	787↓	427↓	217↓	210	202↓	317↓	85	1125	225	939	68	137	N	Low	Low PCP; Tet	N
6(12)	5115	2923	2307	643	1624	893	893↑	1299	1461↑	437	26	58	n.d.	n.d.	N	N
7(31)	1025↓	634↓	431	202	268↓	179↓	88	561	854↑	947	75	50	N	N	N	N
8(40)	1625	1161	697	464	387↓	271	116	541	310	859	147	254	n.d.	N	Low PCP	N
9(6)	1007↓	758↓	553↓	205	213↓	192↓	21↓	677	592	662	55	65	n.d.	n.d.	n.d.	N
10(84)	909↓	476↓	333	143	298↓	229	68	387	141	1190	100	50	N	N	N	N
11(30)	818↓	471↓	306	165	298↓	238↓	60↓	1066	545	689	38	30↓	N	Low	Low PCP	N
12(30)	1811	1180	826	354	665	552	113	1083	435	1600	91	96	N	n.d.	N	N
13(42)	1834	1167	n.d.	n.d.	375↓	n.d.	n.d.	792	1417↑	827	229	61	N	N	n.d.	N

Pt: Patients; Age: months; FU: follow up;↓,↑:based on aged- matched controls; N:normal; n.d.:not done; Sp Ab:specific antibody response; Isohem: Isohaemaglutinin titre; LTM:lymphocyte proliferation to mitogens.

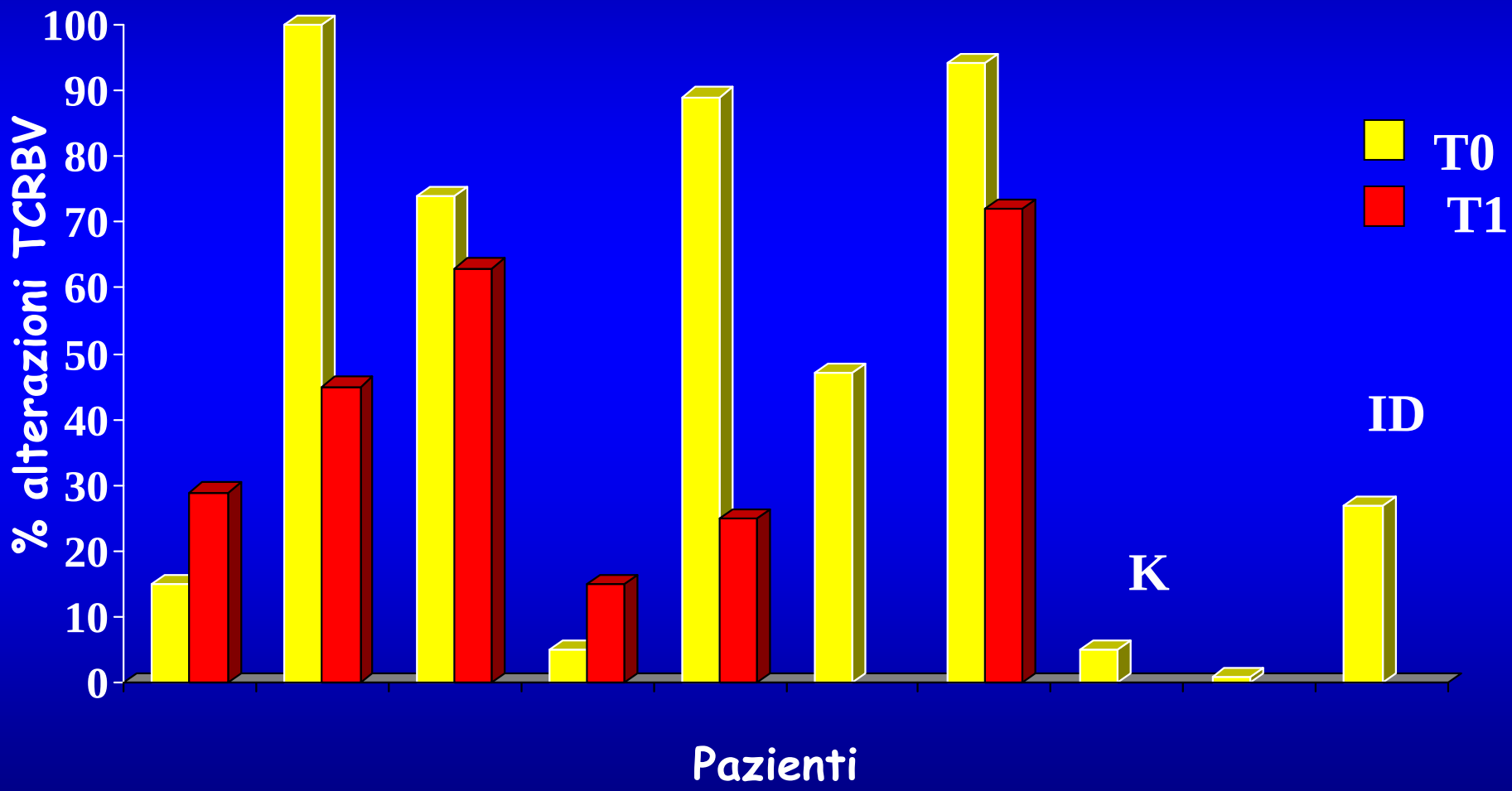


SPECTRATYPING

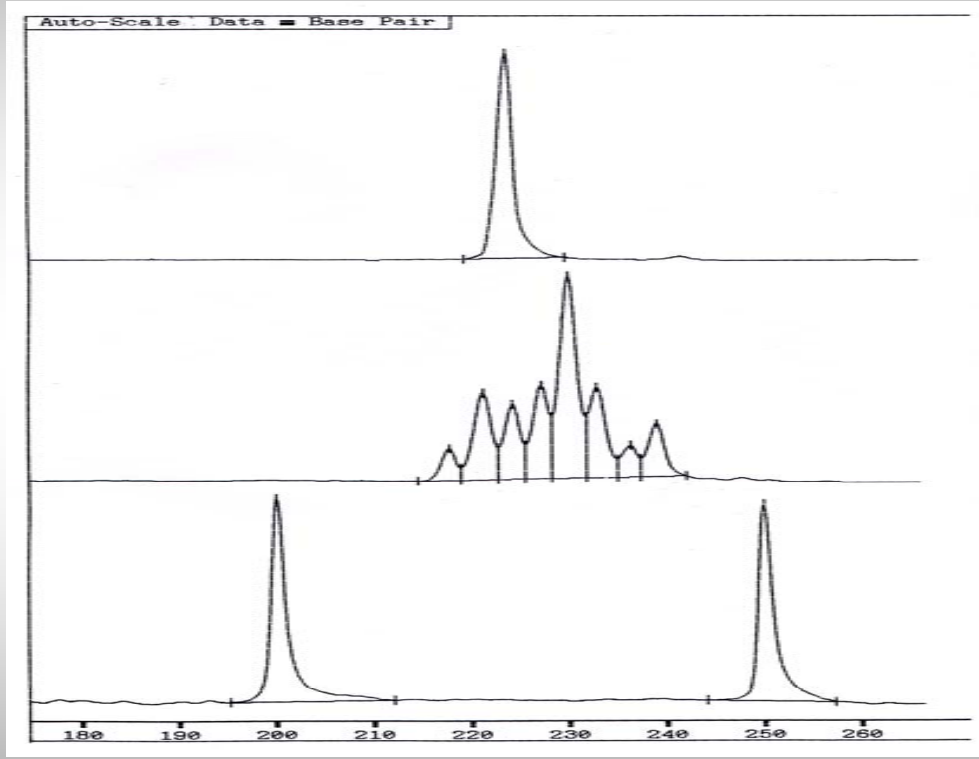
Amplification of TCRBV family by detection of different segment of CDR3

TCRBV DISTRIBUTION IN pDGS (CD4 SUBSET)

TCRBV DISTRIBUTION IN pDGS (CD8 SUBSET)



Kinetics of TCRBV 13.2 (p2)



T=0
6 months of age

T1

TCR repertoire in 22q11.2 deletion syndrome

- ↑ alterations of TCR repertoire in CD8 subset in 22q11.2 deletion syndrome patients compared to age-matched healthy controls (Sullivan 2004, Pierdominici 2003) (p=0,022)
- Improvement TCR repertoire distribution during follow-up
- ↑ alterations of TCR repertoire in CD8 subset in DGSp with recurrent infections (trend p>0.08)

- ↓ TREC values
- These preliminary data suggest that TCR repertoire alteration reflect altered T cell development (CD8 >CD4)

Kinetics of the T-cell receptor CD4 and CD8 Vβ repertoire and immune function in DGSp to determine the extent and nature of the immunodeficiency and to correlate it to clinical and immunological findings

Humoral compartment by analyzing antibody response in vivo and by immunophenotyping B cell subsets in peripheral blood

B CD27+

B natural effector CD27+ IgM+ IgD+

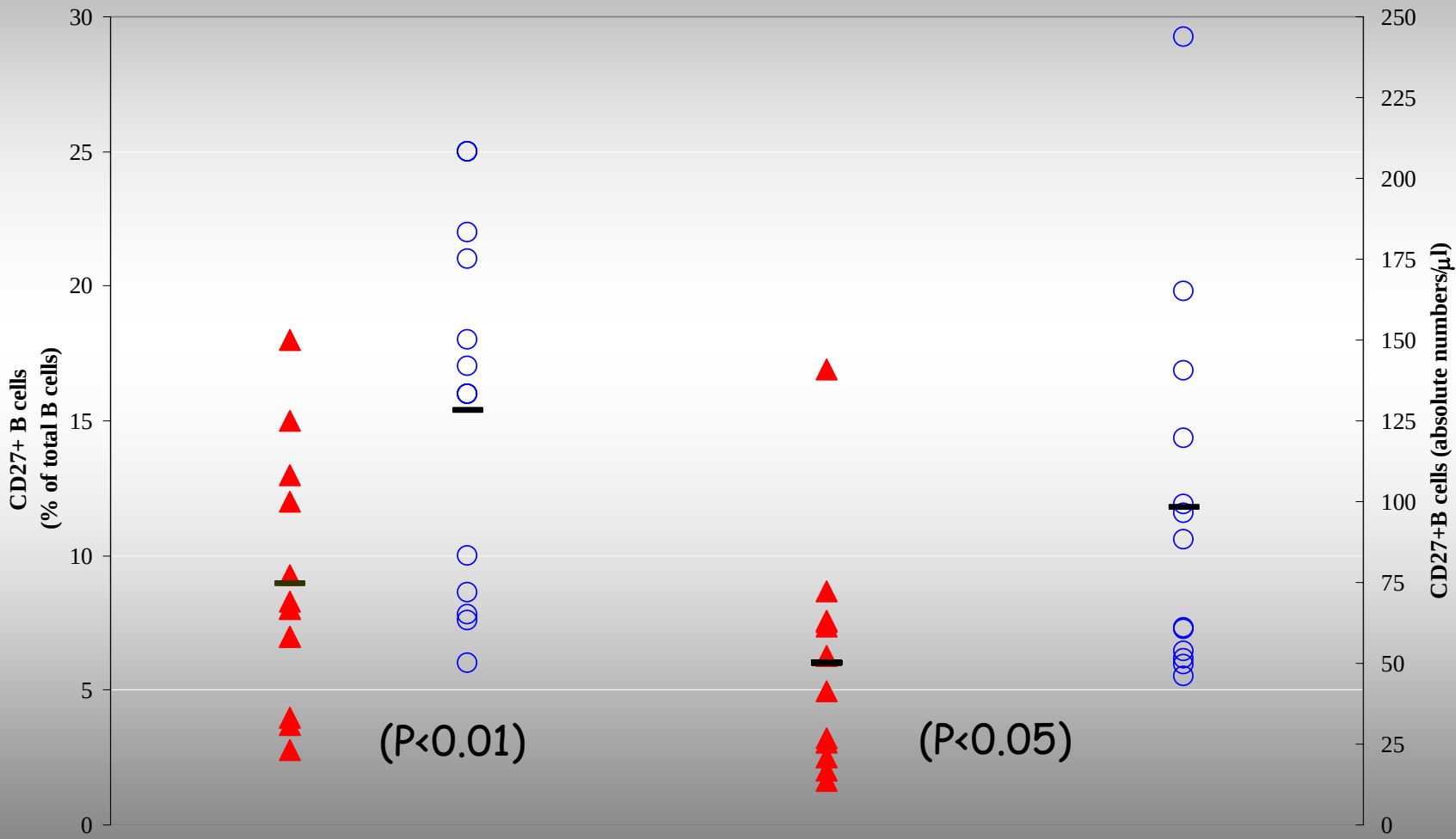
- *Primary response*
- Polisaccharide antigens (pneumococcal)

B CD27+ IgM-IgD- able to switch

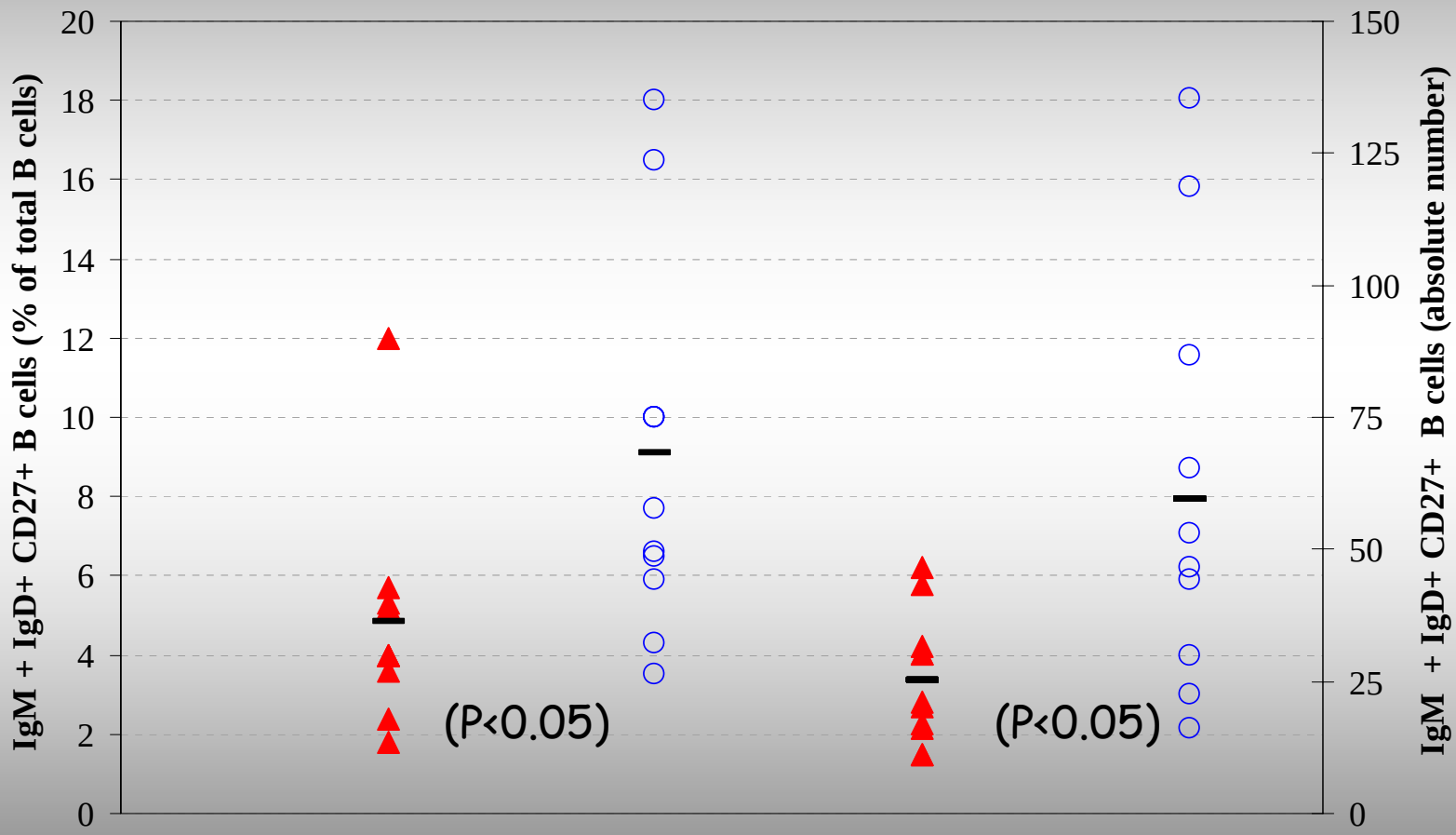
- Rapid activation
- Class switch
- Higher antibody affinity
- *somatic permutation*

B CD27+ are decreased in CVID, HIV , SCID-transplanted

CD27+ B CELLS in 22q11.2 DS



CD27+ IgM+IgD+ B CELLS in 22q11.2 DS



CD27+ B CELLS in 22q11.2 DS

- ↓ CD27+ IgM+ IgD+ in 22q11.2 DS compared to age-matched controls ($p<0.05$)

- Decreased values of CD27 IgM+IgD+ could increased the risk of recurrent infections in these patients

A COMPLETE EVALUATION OF IMMUNE FUNCTION INCLUDING IgD+ IgM+ CD27+ SUBSET AND HUMORAL COMPARTMENT SHOULD BE CONSIDERED

IMMUNOLOGICAL EVALUATIONS

- **T CELL PHENOTYPE**
- Proliferation Test in vitro
- *spectratyping*

T

- **IgG, IgA, IgM (subtypes)**
- **Specific antibody response**
- **autoantibody**
- *B cell maturation?*

B

CONCLUSION I

- Variability of immunological alterations and of their clinical expression does not allow easily to make a standard protocol of diagnosis and therapy in DGS

- Further study in a larger number of patients could contribute to select which immunological parameters influence the development of infections and autoimmune diseases

CONCLUSION II

Because of the wide clinical spectrum an optimal care of these patients is best provided by a multidisciplinary team of experts in a
Long-term follow-up

Natural history of 22q11.2 DS

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AGE< 1 Year	2-6 years	6 -18 years
Cardiac defect	Cardiac defect	Cardiac defect
A-Hypoplasia thymus Immunodeficiency Recurrent infections	Recurrent infections (> otitis) Immunodeficiency	Recurrent infections Autoimmunity Immunodeficiency
hypocalcemia	hypoparatiroidism	hypoparatiroidism
Feeding difficulties	Feeding difficulties	
Cleft palate	Speech language impairment	Speech language impairment
	Developmental delay Behavioural delay	Behavioural delay Learning difficulties
Others malformations	Others malformations	Others malformations /scoliosis
Dysmorphic features	Dysmorphic features	Dysmorphic features

VACCINATION

Regular schedule

it is recommended :

- anti-HIB
- antipneumococcal

Immunological evaluation before measle vaccination
FIRST YEAR OF LIFE

THERAPY

- Clinical course
- ATB
- Immunoglobulins iv