CHAPTER TWO

Human T-cell receptor inborn errors of immunity shed light on the real-life role of γδ vs αβ T lymphocytes

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Abstract

T lymphocytes are critical components of adaptive immunity. They are involved, together with other leucocytes, in defense against pathogens, including viruses, bacteria, fungi and parasites. Mature T cells include two subsets, αβ and γδ, depending on the variable T-cell receptor (TCR) expressed on their surface. αβ T cells, the largest subset in blood, are well characterized in terms of their functions in

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defense against infections. Their central role in protective immunity is dramatically clear in rare human inborn errors of immunity (IEI) causing selective αβ T-cell lymphopenia. Such defects frequently associate to early-onset health-threatening infections and autoimmunity (rather than cancer) and require hematopoietic stem cell transplantation for survival. γδ T-cell function, by contrast, is still not well understood, as we review here. Human IEI affecting several invariant and variable TCR chains (TCRIEI) have been reported, in some cases with a different impact in αβ vs γδ T-cell numbers. By comparing them, we show that clinical severity, as a proxy of importance for survival, associates with the absence of αβ T cells, irrespectively of γδ T-cell numbers. Several species and animal knock-out models which naturally or artificially lack γδ T cells support this contention. Thus, TCRIEI teach us that αβ T cells are crucial for defense against infections, whereas γδ T cells may have a comparatively marginal role in real-life human immunity.

1. Human T-cell receptor (TCR) isotypes

The human TCR is a cell surface protein ensemble expressed by T cells or their precursors with a variable recognition domain and multiple invariant signaling domains. There are three TCR isotypes (Fig. 1): pre-TCRαβ, TCRαβ and TCRγδ. All share two invariant heterodimers called CD3γε and CD3δε and a single invariant homodimer termed ζ or CD247 (Call et al., 2002) and differ in the invariant pre-Tα chain or the variable TCRα and TCRβ for αβ, and TCRγ and TCRδ for γδ T cells.

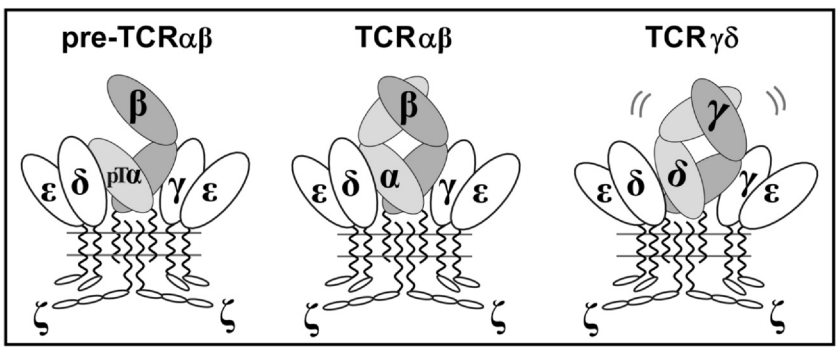

Fig. 1 Human T-cell receptor (TCR) isotypes. Note that extracellular domains of variable chains in the TCRγδ are more flexible than in other isotypes (Gully et al., 2024) and may show clonotype-dependent propensity for dimerization (Hoque et al., 2025), supporting higher diversity of antigen recognition than the HLA-restricted TCRαβ. TCR: T-cell receptor.

2. Real-life role of human αβ vs γδ T cells

2.1 Human αβ T cells are crucial for defense against infections, not tumors

αβ T lymphocytes are adaptive leucocytes involved, as all other immune system cells, in defense against pathogens, including viruses, bacteria, fungi and parasites (Table 1). They are equipped to respond to inflammatory signals caused by them, to detect and eliminate such organisms using their Human Leukocyte Antigen (HLA)-restricted TCR, to signal for help against infection from non-resident leucocytes and for help in tissue repair from many other cells. These functions are deployed while maintaining self-tolerance. αβ T lymphocytes record each infection in the form of memory cells to be better prepared, should it occur again. Inborn errors of immunity (IEI) affecting αβ T lymphocytes show severe lethal infections early in life, rather than cancer, that frequently require hematopoietic stem cell transplantation (HSCT) for survival (Notarangelo et al., 2020). Cancer rate in all IEI is 40-fold higher than in the general population (12 vs 0,3 %, respectively, Fekrvand et al., 2024), but most of the cancer cases affect patients with DNA repair defects. Also, most of the cancers in IEI are hematologic (EBV+ B-cell lymphomas) or gastrointestinal rather than breast, lung, or prostate, which are the most common in the general population. This suggests differential oncogenic mechanisms in IEI, mostly lymphocyte DNA repair or apoptosis defects, and chronic infections (HBV, HPV, EBV), rather than impaired cancer immune surveillance. A recent case report maps a common skin cancer to congenitally impaired αβ T-cell recognition of HPV-infected cells, as it was resolved after TCR signaling restoration by HSCT (Ye et al., 2025).

Table 1 Ligands and biological roles of αβ vs γδ T-cell subsets. BTN: BuTyrophiliN; phAgs: phosphoantigens; pHLA-I/II: peptide-human leukocyte antigen complex class I/II molecule.

TCR	Subset	Normal ligand	Origin	Role	Function
αβ	CD4	Non-self pHLA-II	Exogenous	Cooperation	Defense, repair
	CD8	Non-self pHLA-I	Endogenous	Cytolysis	Defense
γδ	Vδ1	Stress, non-self lipids	Endogenous	Cooperation	Defense, repair
	Vδ2	BTN/non-self phAgs	Endogenous	Cytolysis	Defense

2.2 Human αβ T cells are capable of tumor clearance when modified

While the main biological role of αβ T cells is not to detect and eliminate cancer cells, they are well equipped to do so when they are manipulated in different ways (Waldman et al., 2020), although relapses are frequent (Table 2). In certain instances, αβ T cells eliminate cancer cells by virtue of non-cancer features, such as allogeneic HLA molecules (as in HSCT) or enforced tumor-associated self-antigen recognition by autologous αβ T cells (as with CD19-targeted Chimeric Antigen Receptor or CAR) which are otherwise tolerant to such self-antigens. In other cases, mutation-dependent tumor-specific HLA-restricted peptides termed neoantigens are targeted by blocking natural T-cell self-tolerance using checkpoint inhibitors, a proof that cancer cell tolerance is evolutionarily more important than cancer cell elimination in normal conditions (Ghorani et al., 2023). A similar mechanism (blocking natural T-cell self-tolerance) is likely at play in BCG-induced vesical cancer immunotherapy (Hilligan et al., 2025). Indeed, tolerance must exist to the frequent long-term DNA lesions steadily occurring throughout life in nonmalignant somatic cells from all tissues in normal individuals (Spencer Chapman et al., 2025). Note that with CAR, checkpoint inhibitors or even BCG, off-target Immune Related Adverse Effects (IRAE) are notorious, as expected from a non-tumor-specific iatrogenic breach in systemic self-tolerance (Table 2). Conversely, natural autoimmunity may protect from cancer, suggesting that loss of self-tolerance causing damage to nonmalignant tissues extends to malignant cells sharing target self-molecules (Ghanem et al., 2023).

2.3 Human γδ T cells are involved in, but not crucial for, defense against infections or tumors

γδ T cells are also involved in defense against pathogens, including viruses, bacteria, fungi and parasites. They are believed to have ontogenically earlier roles in immune responses compared with the other two adaptive lymphocytes (αβ T and B cells). Due to their anatomical locations in epithelial barriers (skin and mucosal surfaces), γδ T cells are believed to provide a first line of defense in a tissue-specific fashion, by virtue of both innate and adaptive (TCR) surface receptors (Gray et al., 2024). However, in contrast to αβ T cells, γδ T cells are believed to recognize and respond with their highly flexible variable extracellular domains to a great diversity of pathogen-induced non-peptide changes in self-ligands (cellular stress), rather than to rigid non-self HLA-restricted peptides (Fig. 1 and Table 1).

Table 2 Modifications that allow αβ and γδ T cells to detect tumor ligands and eliminate cancer cells, while off-targeting nonmalignant self-tissues. One-year relapse rates indicate that complete remissions are often short-term. HSCT: Hematopoietic Stem Cell Transplantation; allo-HLA: allogeneic Human Leukocyte Antigens; CAR: Chimeric Antigen Receptor; GvHD: Graft-versus-Host Disease; ID: Immunodeficiency; IRAE: Immune-Related Adverse Events; mAb: Monoclonal Antibody.

TCR	Subset	Modification	Tumor ligand	Off-target ligands (disease)	Relapse
αβ	CD4/8	HSCT	Non-self allo-HLA	Non-malignant cells (GvHD)	65 %
	CD4 > 8	CAR	Self molecules (CD19)	Non-malignant cells (ID)	50 %
	CD8 > 4	Checkpoint mAb	Self pHLA-I (neoAgs)	Self pHLA-I (IRAE)	30 %
γδ	Vδ1/2	CAR	Self molecules (CD19)	Non-malignant cells (ID)?	?
	Vδ1	Checkpoint mAb	Stress?	Non-malignant cells?	?
	Vδ2	Zoledronate	BTN/phAgs	Non-malignant cells?	?

Indeed, γδ T cells can kill infected cells, recruit and activate other leucocytes and tissue cells to promote tissue repair and wound healing in response to danger signals by means of cytokine secretion (Ribot et al., 2021). Mouse and human γδ T cells and TCRγδ are notoriously different (Qu et al., 2022; Siegers et al., 2007), and thus mouse studies poorly predict their role in humans (Kim, 2024). However, TCRγδ composition governs γδ T-cell distribution in both species. In humans, γδ T cells early in life are polyclonal and adaptive (TCR-dependent) in blood and tissues, with repair (Vδ1) and cytolytic (Vδ2) functions. Antigenic exposures later drive their clonal expansion, functional differentiation and tissue homing. In adults, Vδ2 cells predominate in blood, whereas Vδ1 cells are enriched in tissues and express residency profiles (Gray et al., 2024). Inflammation attracts blood Vδ2 cells to distressed tissues, where they can display both cytolytic and antigen-presenting-cell properties. Indeed, Vγ9Vδ2 γδ T cells likely provide early innate defense against microbial phosphoantigen-containing self-cells, whereas Vδ1 γδ T cells expand to provide early adaptive defense against virus-infected self-cells (by HCMV particularly) and tissue repair features (Table 1).

2.4 Human γδ T cells are capable of tumor clearance when modified

One of the hypothesized biological roles of γδ T cells is immune surveillance against some tumors, as they can recognize stressed cells independently of HLA molecules (Wiesheu & Coffelt, 2024). However, γδ T-cell contribution to cancer surveillance in humans remains speculative due to a lack of clinical studies linking γδ T-cell dysfunction with increased cancer incidence. Although the biological role of γδ T cells may not include to detect and eliminate cancer cells, they are, like αβ T cells, well equipped to do so when they are manipulated in different ways (Schamel et al., 2024; Table 2). Indeed, γδ T cells expressing CD19-targeted constructs are expectedly capable of such self-antigen recognition (Guerrero-Murillo et al., 2024), although clinical efficacy still favors αβ T cells. Checkpoint inhibitors can unleash dormant/tolerant antitumoral activity by Vδ1 γδ T cells in rare cases (Lien et al., 2024), particularly when αβ T cells are not competent (as in tumors lacking HLA-I) (de Vries et al., 2023). The mechanism remains unclear, likely induced non-peptide changes in self-ligands (cellular stress). Potential advantages of γδ T cells include their poor allogeneic responses (which allow for allogeneic immunotherapy including CAR), their innate recognition of stressed

tumor cells and their tissue homing capabilities. However, the use of γδ T cells for human cancer immunotherapy is still at its infancy, and the clinical results to date are very poor, compared with αβ T cells (Mensurado et al., 2023; Table 2).

3. Human T-cell receptor (TCR) inborn errors of immunity (TCRIEI)

Inborn errors of immunity (IEI), formerly called primary immunodeficiencies (PID), are rare monogenic disorders of the immune system that cause immunodeficiency, but also autoinflammation, autoimmunity, allergy and/or certain cancers (see above, Section 2.1). IEI of TCR components (TCRIEI) are low-prevalence autosomal recessive diseases that result from inherited mutations in genes codifying certain TCR chains (Fig. 2) (Marin et al., 2015).

TCRIEI patients suffer from severe combined ID (SCID) and/or autoimmunity due to peripheral blood T-cell lymphopenia and/or impaired TCR function, and often require HSCT for survival. Carefully studying TCRIEI can thus help to understand the real-life role of T lymphocytes in cancer vs infection surveillance. Human TCRIEI in some cases have a different impact in (estimated) αβ vs γδ T-cell numbers. By comparing their clinical features, we can address the relative impact of each subset in infection vs cancer susceptibility.

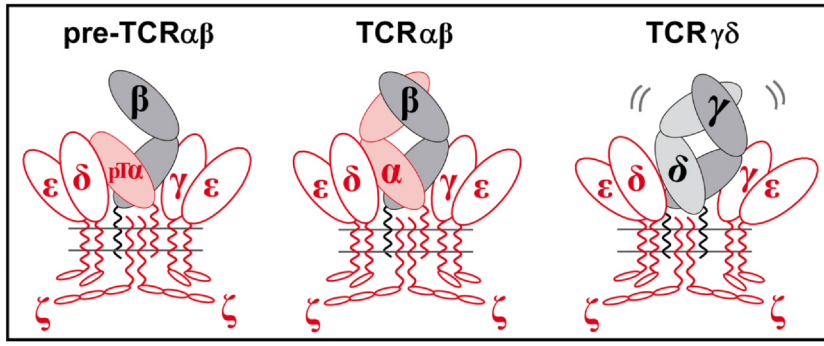

Fig. 2 Reported human T-cell receptor (TCR) inborn errors of immunity (IEI). Red color marks chains of human TCR isotypes where mutations have been reported to cause immunodeficiency and (or) autoimmunity (see Tables 3–5). Note that no mutations have been reported for TCRβ, TCRγ or TCRδ genes yet. TCR: T-cell receptor.

More than 80 TCRIEI patients have been reported to date (Table 3, summarized in Table 4 for non-leaky cases). TCRIEI lacking CD247, CD3δ, or CD3ε show very low or undetectable γδ T cells in peripheral blood, as indicated by cell numbers, whereas TCRIEI lacking TCRα or preTα show normal or even high numbers of γδ T cells. Expectedly, TCRIEI lacking TCRα show selective αβ T cell lymphopenia (Table 3 and Table 4). CD3γ and CD247 TCRIEI show partial defects in T-cell development which allow for selection of some T cells that are poorly functional in the case of CD247 TCRIEI.

These results can be represented in a linear differentiation model from early thymus progenitors to mature peripheral T cells as shown in Fig. 3. Unexpectedly, compared to TCRα TCRIEI, pre-Tα TCRIEI patients show normal to low levels of functional αβ T cells, likely due to increased non-canonical differentiation from early thymic progenitors (ETP).

We analyzed the ClinVar database to address the fact that mutations have been reported in all invariant TCR chains and in the constant region of TCRα, but not of TCRβ or TCRδ. Germline single nucleotide variants (SNV, Table 5) are frequent in the invariant genes (around 30–250/gene), with 7–15 % of them predicted as pathogenic, like in other IEI genes such as *ATM* (16 % pathogenic). In contrast, SNV in the constant region of variable TCR chains are extremely rare or absent (0–2/gene). As both variable and invariant TCR chains are required for T-cell selection and function, we believe such resistance to germline variation in the constant region genes of variable TCR chains may be due to intrinsic mechanisms related to the generation of diversity.

3.1 TCRIEI teach us that αβ T cells are critical to sustain normal immune responses

Human TCRIEI lacking most blood αβ T cells (such as CD3δ, CD3ε or TCRα TCRIEI, Table 3) suffer from severe immunodeficiency characterized by life-threatening infections by viruses, bacteria, fungi or parasites very early in life (<3 years of age in most cases, Fig. 4) that abundant γδ T cells cannot prevent in the case of TCRα TCRIEI. Only replacing αβ T cells by HSCT is curative, thus they are clearly non-redundant. Autoimmune features are relatively rare because all types of T-cell-dependent functions and dysfunctions are absent. When some (dysfunctional) αβ T cells are present (as in TCRα, pre-Tα, CD3γ or CD247 TCRIEI), they tend to lose self-tolerance, and autoimmunity disorders ensue. When close to normal numbers of functional αβ T cells are present (as in CD3γ or pre-Tα TCRIEI),

Table 3 Summary of TCRIEI patients reported, grouped by mutated gene and ordered by higher (*TRAC, PTCRA*) to lower (*CD3D, CD3E*) mean γδ T-cell numbers. Pale blue and orange boxes highlight values below or above age-matched normal ranges, respectively. Age-matched normal ranges are from Schatorjé et al., 2011. TCRIEI T cells may show impaired surface anti-CD3, -TCRαβ or -TCRγδ antibody binding (Garcillán et al., 2015), which may underestimate such subsets. Thus, highest CD3+ T-cell numbers were also estimated as total lymphocytes – B – NK cells (*Total lymph – B – NK*), and highest αβ T-cell numbers as either $CD4^+$ + $CD8^+$ (*CD4+ CD8*) lymphocytes or as *T* – TCRγδ$^+$ cells (*T – TCRγδ*), where highest T cell numbers were estimated as $CD3^+$ or as Total lymph – B – NK, whichever was larger (estimation columns are marked in yellow). ID: patient identification; NML: nonmalignant lymphoproliferation; GLILD: granulomatous lymphocytic interstitial lung disease; TP: Tinea Pedis; TB: tuberculosis; HPV: human papilloma virus; EBV: Epstein-Barr virus; HHV6: human herpesvirus 6; *C. alb.*: *C. albicans*; CMV: cytomegalovirus; HSV: Herpes simplex virus; Sequence variations in ***italics***: reported as leaky, thus associated with milder clinical features.

LOCUS	Sequence variation	ID	T-cell number (cells/mm3)									Age of (years old)			Malignancies	Recurrent infections			Immune-mediated or-dependent diseases	Reference
			Age at testing (months or years)	Total			αβ				γδ					Respiratory	Gastrointestinal	Opportunistic		
				CD3	Total lymph - B - NK	Age-matched normal range	TCRαβ+	CD4+ CD8	T - TCRγδ+	Age-matched normal range	TCRγδ+	Age-matched normal range	Onset	HSCT	Exitus						
TRAC	c.192_205del	P1	4m	1,314	1,320	1,400-11,920	0	-	72	1,200-12,000	1,248	38-890	<1	2			Yes	Yes	CMV		
	c.361C>T	P2	3y	244	293	850-4,300	0	244	144	600-4,300	100	27-960	<1		3		Yes	Yes			Materna et al., 2025
		P3											<1		<1		Yes				
		P4											<1		<1		Yes				
	c.347C>G	P5	1m	189	-	1,900-8,400	Data not available				Data not available		<1						Data not available		Garkaby et al., 2022
	c.*1G>A	P6	9y	1,335	2,631	770-4,000	36	1,207	1,398	600-3,700	1,253	27-960	<1		11		Yes		HPV		Rawat et al., 2021
		P7	8y	581	-	770-4,000	10	599	39	600-3,700	542	27-960	<1		8		Yes		HPV		
		P8	1y	1,017	1,165	2,400-8,300	13	514	167	2,000-8,000	998	70-630	<1			B lymphoma	Yes		EBV		
		P9	3y	2,356	2,777	850-4,300	-	2,204	893	600-4,300	1,884	27-960	1	6			Yes	Yes	EBV, HHV6	Vitiligo, alopecia areata	Morgan et al., 2011
		P10	2y	696	864	850-4,300	-	655	595	600-4,300	399	27-960	<1	7			Yes	Yes		Eczema, anemia	
PTCRA	c.58G>C, Δex1-3	P11	7y	758	-	770-4,000	-	-	500	600-3,700	252	27-960	<1						TP		
		P12	4y	1,050	-	850-4,300	-	-	800	600-4,300	250	27-960	<1				Yes				
	c.446G>A	P13	31y	0	-	780-3,000	-	-	0	600-3,300	0	25-200	<20				Yes			NML, thrombocytopenia, gastrointestinal	Materna et al., 2024
	c.296_290del	P14	19y	1,700	-	780-3,000	-	-	1,420	600-3,300	280	25-200	15		24		Yes				
		P15	12y	1,750	-	850-3,200	-	-	850	700-2,800	800	39-540	13							Hypothyroidism	
		P16	8y	1,050	-	770-4,000	-	-	600	600-3,700	450	27-960	8								
	c.446G>A; c.429del	P17	66y	0	-	780-3,000	-	-	0	600-3,300	0	25-200	25			B lymphoma	Yes			Hypothyroidism	
		P18	60y	1,220	-	780-3,000	-	-	1,150	600-3,300	100	25-200	60#								
	c.427+A	P19	2y	1,000	-	700-8,800	-	-	700	600-8,500	300	41-640	<3				Yes				
	c.58+5G>A	P20	2y	2,500	-	700-8,800	-	-	1,500	600-8,500	1,000	41-640	<3				Yes				
CD3G	c.393_391delTGinsCT	P21	1y	336	432	2,400-8,300	0	336	240	2,000-8,000	192	70-630	1	1			Yes	Yes	C. alb.		Sonmez et al., 2025
	c.213del/A	P22	3y	413	-	770-4,000	-	374	-	600-3,700	Data not available		4				Yes			Thyroiditis, anemia, thrombocytopenia	Lin et al. 2024
		P23	15y	1,189	-	850-3,200	-	1,092	-	700-2,800	Data not available		15				Yes		TB		Lee et al., 2019
	c.18del/C	P24	3y								Data not available										Platt et al., 2021
	c.1A>G	P25	1y	2,018	2,567	2,400-8,300	-	1,766	-	2,000-8,000	Data not available		<1	3	4		Yes	Yes	EBV	Diarrhea, anemia, GLILD	Delmonte et al., 2021
	c.80-1G.C	P26	15y	630	-	780-3,000	-	560	-	600-3,300	Data not available		15				Yes			Hypothyroidism	Rowe et al., 2018
		P27	8y	2,600	-	770-4,000	-	2,522	-	600-3,700	Data not available		5							Hypothyroidism	
		P28	15y	380	-	850-3,200	-	326	-	700-2,800	Data not available		1				Yes			Hypothyroidism, anemia, ALPS	
		P29	22y	1,200	-	780-3,000	-	1,070	-	600-3,300	Data not available		10							Thyroiditis	
	c.IVS2-1G>C	P30	7y	900	-	770-4,000	140	760	672	600-3,700	28	38-890	<1	10			Yes			Vitiligo, thyroiditis	Goldurk et al., 2014
		P31	11y	630	-	850-3,200	126	560	588	700-2,800	42	39-540	<3				Yes			Thyroiditis	
		P32	1y	2,800	-	2,400-8,300	189	2,522	2,611	2,000-8,000	189	70-630	1							Thyroiditis	
		P33	12y	380	-	850-3,200	10	326	293	700-2,800	87	39-540	1				Yes			Anemia, thyroiditis, thrombocytopenia, hepatitis	
		P34	20y	1,200	-	780-3,000	0	1,070	1,142	600-3,300	58	25-200	<20							Anemia, thyroiditis	
		P35	1y	391	446	850-3,200	8	337	410	700-2,800	28	39-540	1							Anemia, thyroiditis	Tokgoz et al., 2013
		P36	20y	1,218	1,583	780-3,000	44	1,082	1,515	600-3,300	68	25-200	<20							Anemia, thyroiditis	
	c.IVS2-1G>C; c.1A>G	P37	3y	-	2,617	850-4,300	764	-	-	600-4,300	Data not available		<1		3		Yes			Diarrhea, anemia	Amasz-Villena et al., 1992, Recio et al., 2007
		P38	24y	-	866	780-3,000	630	-	980	600-3,300	8	25-200	1				Yes			Diarrhea, vitiligo, atopic eczema, hypothyroidism	
	c.205A>T	P39	1y	1,296	-	2,400-8,300	-	2,246	-	2,000-8,000	Data not available		1				Yes			Psoriasis	Sonmez et al., 2025
		P40	4y	-	1,372	850-4,300	1,079	-	1,336	600-4,300	36	27-960	<1				Yes				Recio et al., 2007
		P41	4y	632	-	850-4,300	-	864	-	600-4,300	Data not available		<1		2		Yes			Diarrhea	Sanal et al., 1996
CD247	c.62C>T	P42	2y	103	2,526	700-8,800	-	2,167	-	600-8,500	Data not available		2		2		Yes			Thrombocytopenia	Seita et al., 2021
	c.27+C	P43	11m	1,320	1,905	2,400-8,300	-	-	1,899	2,000-8,000	7	70-630	1	2	3		Yes		CMV	Hemophagocytic lymphohistiocytosis	Merin et al. 2017
	c.411insC	P44	10m	2,705	-	2,400-8,300	16	-	2,689	2,000-8,000	16	70-630	<1	1			Yes	Yes	CMV	Thrombocytopenia	Roberts et al., 2007
	c.20T>C	P45	10m	264	348	2,400-8,300	-	264	-	2,000-8,000	Data not available		<1	2			Yes	Yes	HSV, C. alb.	Erythroderma	Rinus-Laucat et al., 2006
CD3D	c.158C>A	P46	5m	17	57	1,400-11,500	Data not available										Yes				Vignesh et al., 2021
	c.56-1G>T	P47	1y	0	950	2,400-8,300	-	0	-	2,000-8,000	Data not available		1	1			Yes		C. alb.	patogenic	Sonmez et al., 2025
	c.247G>T	P48	0m				Data not available														Platt et al., 2021
		P49	1y				Data not available												Data not available		McAuley et al., 2023
	c.202C>T	P50					Data not available														Quinn et al., 2022
		P51					Data not available														
		P52	6m	38	1,000	1,400-11,500	-	25	-	1,200-12,000	Data not available		<1		<1		Yes			Diarrhea, eczema, hemophagocytic lymphohistiocytosis	Ahalamah et al., 2015
	c. IVS2-2A>G	P53	6m	1,610	1,607	1,400-11,500	Data not available										Yes		C. alb.		Vignesh et al., 2021
		P54	3m	Data not available									<1	<1	<1		Yes		CMV		Takada et al., 2005
		P55	0m	Data not available									<1	<1			Yes				
	c.279C>A	P56	5m	-	-	2,200-9,200	Data not available						<1		<1			Yes	CMV		de Saint Basile et al., 2004
		P57	0	30	31	1,900-8,400	-	47	-	2,200-8,300	Data not available		<1	<1	<1		Yes		Aspergillus		
		P58	5m	0	-	2,200-9,200	-	58	-	2,200-8,300	Data not available		<1	<1	<1		Yes	Yes	EBV, C. alb.		
		P59	0m	11	122	1,900-8,400	-	17	-	2,200-8,300	Data not available		<0	<0	<0				Data not available		
	c.202C>T	P60	0m	90	173	1,900-8,400	-	46	-	2,200-8,300	Data not available		<0	<0	<0				Data not available		
		P61	0m	3	-	1,900-8,400	0	3		1,600-8,600	0	12-100	<1	<1							Dadi et al. 2003
		P62	2m	7	-	1,900-8,400	-	0	-	2,200-8,300	0	12-100	<1		<1		Yes		Adenovirus		
		P63	2m	6	-	2,200-9,200	-	0	6	2,200-8,300	0	56-510	<1		<1		Yes	Yes	CMV		
	c.IVS2+5G>A	P64	13m	400	-	2,400-8,300	270	-	275	2,000-8,000	125	70-630	1	2			Yes			Atopic dermatitis	Gil et al., 2011, Garcillan et al., 2014
		P65	6m	787	-	1,400-11,500	647	-	677	1,200-12,000	110	30-890	<1	<1	<1		Yes	Yes	CMV		
	c.288T>A	P66	6m	0	144	1,400-11,500	Data not available										Yes	Yes			Vignesh et al., 2021
	c.352+1G>A	P67	7m	6	0	1,400-11,500	Data not available										Yes				
	c.567+42_567+73del	P68	5m	106	4,770	2,200-9,200	212	212	4,770	2,200-8,300	0	56-510	<1	<1	<1				CMV, C. alb.	Hepatitis	Sonmez et al., 2025
	c.176G>A	P69	4m	12	60	2,200-9,200	-	13	-	2,200-8,300	Data not available		<1	<1					C. alb., HPV		Erman et al., 2020
	c.10A-1G>A	P70	0m	Data not available																	Platt et al., 2021
CD3E	c.173del/T	P71	2m	260	396	1,900-8,400	206	468	156	1,600-8,600	130	12-100	<1	<1			Yes		C. alb		Sonmez et al., 2025
		P72	0m	Data not available																	Platt et al., 2021
		P73	1m	Data not available																	
		P74	1m	Data not available																	
		P75	1y	Data not available																	
	c.467T>C	P76	5m	0	-	2,200-9,200	-	0	-	2,200-8,300	Data not available		<1		<1		Yes		CMV		Fintina et al., 2017
		P77	2m	0	-	2,200-9,200	-	0	-	2,200-8,300	Data not available		<1	<1			Yes	Yes	CMV, C. alb.		
		P78	3m	19	704	2,200-9,200	-	0	-	2,200-8,300	Data not available		<1		<1		Yes				Seita et al., 2021
	c.IVS2+1G>C	P79	2m	4,400	-	1,900-8,400	Data not available						<1	<1				Yes			Fuehrer et al., 2014
	c.128_129del	P80					Data not available						<1		<1		Yes	Yes	C. alb.		de Saint Basile et al., 2004
		P81	1m	0	450	1,900-8,400	-	31	-	1,600-8,600	Data not available		<1	<1	<1				Adenovirus		
	c.IVS7+27>C	P82					Data not available						5						Data not available		Soudais et al., 1993

Table 4 Summary of reported TCRIEI patients' features, ordered by γδ T-cell numbers. n: patients reported; HSTC: Hematopoietic stem cell transplantation; NHL: non-Hodgkin's B-cell lymphoma.

		T-cell numbers								
Chain	**Nº patients reported**	**αβ**	**γδ**	**Diagnosis at (years old)**	**Clinical course**	**HSCT or exitus**	**Infections**	**Autoimmunity**	**Cancer (%)**	**Type**
TCRα	6	Low/very low	High/normal	1−9	Severe	Frequent	Very frequent	Frequent	Rare (17)	NHL
pTα	10	Normal/ low	Normal/high	2−66	Mild	Very rare	Frequent	Frequent	Rare (10)	NHL
CD3γ	21	Normal/ low	Normal/low	1−24	Mild	Rare	Very frequent	Very frequent	No	
CD247	4	Normal/ low	Low/very low	1−2	Severe	Very frequent	Very frequent	Very frequent	No	
CD3δ	20	Very low	Low/very low	<1	Severe	Very frequent	Very frequent	Rare	No	
CD3ε	17	Very low	Low/very low	<1	Severe	Very frequent	Very frequent	Rare	No	

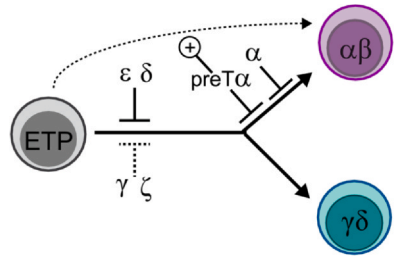

Fig. 3 TCRIEI cause complete (solid T`s) or partial (dashed T) impairments of human αβ and/or γδ T-cell development. Isolated Greek letters stand for CD3, ζ (CD247), or TCRα TCRIEI. + indicates non-canonical biased differentiation (Materna et al., 2024). ETP: Early Thymic Progenitor.

vary late onsets are common (up to 24 or 66 years, respectively, Fig. 4), the clinical course is milder or even asymptomatic (Materna et al., 2024), and HSCT is not required normally for survival. But when close to normal numbers of non-functional αβ T cells are present (as in CD247 TCRIEI), age of onset and clinical course resemble those of TCRIEI with no blood αβ T cells, and HSCT is again required for survival. Taken together, these results show that clinical severity measured as exitus or HSCT in TCRIEI associates with the absence of functional αβ T cells, irrespectively of γδ T-cell numbers.

Note that cancer in such TCRIEI patients is rarely a cause of death (Haas, 2018, Table 4), indicating that pathogen rather than cancer immunosurveillance is the real-life biological role of αβ T cells. Indeed, for the larger group of IEI, the most likely cause of their increased risk of lymphoma is impaired DNA repair or poor response to viruses, whereas they show a lower risk of the most frequent cancers (breast, lung, colon) compared to the general population. Thus, cancer is not caused by immunodeficiency. Rather, it is a genetic disorder causing growth dysregulation in self-cells, which in most cases goes unnoticed by adaptive immunity or, in other cases, induces self-tolerance (see 2.1 and 2.2 above).

3.2 TCRIEI teach us that γδ T cells alone are unable to sustain normal immune responses

Humans selectively lacking γδ T cells have not been reported to date. However, there are patients who have been found to have absent γδ T cells due to loss-of-function mutations in nuclear factor kappa B inhibitor kinase subunit beta (*NFKBIKB*) or gain-of-function mutations in nuclear factor kappa B inhibitor alpha (*NFKBIA*), but these conditions are a broader and

Table 5 Summary of germline single nucleotide variants (SNV) registered for the indicated genes in the NIH ClinVar database (a freely accessible, public archive of reports of the relationships among human variations and phenotypes hosted by the National Center for Biotechnology Information (NCBI) and funded by intramural National Institutes of Health (NIH) funding, https://www.ncbi.nlm.nih.gov/clinvar/), ordered by total number. *TRAC* (Garkaby et al., 2022) and *CD3E*, *CD3D* and *CD3G* (Sonmez et al., 2025; Vignesh et al., 2020) SNV, not listed in ClinVar, were also included.

Protein			CD3ε	CD3δ	CD247	CD3γ	pTα	TCRα	TCRγ	TCRβ			TCRδ
Gene			***CD3E***	***CD3D***	***CD247***	***CD3G***	***PTCRA***	***TRAC***	***TRGC1***	***TRGC2***	***TRBC1***	***TRBC2***	***TRDC***
Chromosome			11	11	1	11	6	14	7	7	7	7	14
Exons			9	6	8	7	4	4	3	4	4	4	4
Germline SNV	**Total number**		290	225	197	168	30	2	2	1	0	0	0
	%	**Bening**	60	50	55	37	10	0	0	100	0	0	0
		Uncertain	29	38	35	45	83	0	100	0	0	0	0
		Pathogenic	11	13	11	18	7	100	0	0	0	0	0

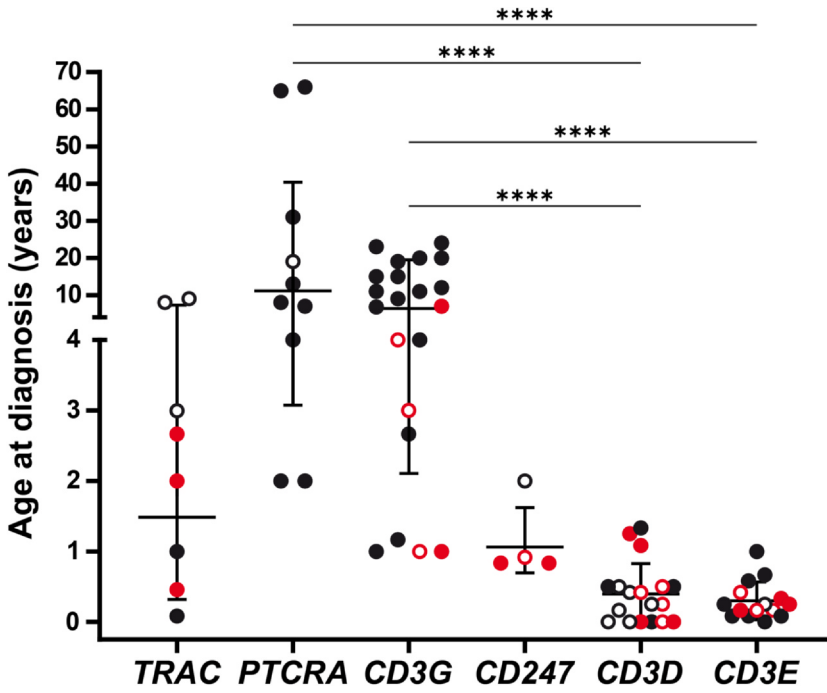

Fig. 4 Age at diagnosis (years) for reported TCRIEI patients ordered by higher to lower numbers of γδ T cells. Red dots denote patients who have undergone hematopoietic stem cell transplantation (HSCT) and empty dots indicate exitus. One-way Anova Kruskal-Wallis test was performed, (**** = $p < 0.0001$).

more complex immunodeficiency syndrome, rather than TCRIEI (Sagar and Ehl, 2025). This may indicate that such cells are critical, or, alternatively, dispensable for survival. Humans selectively lacking normal αβ T cells are extremely rare (TCRα deficiency, Tables 3 and 4) but offer the chance to evaluate the isolated role of γδ T cells in patient survival. The data show that, compared to αβ, γδ T cells are unable to sustain normal immune responses, as patients are diagnosed very early (1–9 years, Fig. 4) and require HSCT for survival. Of note, age at diagnosis in TCRα deficiency is slightly higher than in CD247, CD3δ, or CD3ε deficiencies (Fig. 4), which could be due to compensatory functions by the high numbers of normal γδ T cells or by the low numbers of dysfunctional αβ T cells observed only in TCRα deficiency. A recent report has shown that complete, rather than leaky, TCRα deficiency is a SCID, thus supporting the non-redundant role of αβ T cells and the lack of compensatory functions by γδ T cells in such cases (Materna et al., 2025). Rare cases of leaky CD3δ deficiency with normal numbers of γδ

T cells in an αβ T-cell-deficient background showed similar clinical features (Gil et al., 2011, P64 and P65 in Table 3). Unexpectedly, humans with pre-Tα deficiency, predicted to be TCRα deficiency phenocopies, showed a very mild clinical course and late diagnosis (2–66 years), likely because they show in peripheral tissues diverse functional memory αβ T cells that were rescued through a pre-Tα-independent developmental pathway (Fig. 3). These TCRIEI show that αβ, but not γδ T cells, are critical for survival to infections in humans, since only αβ T-cell-deficient, but not -sufficient, patients require HSCT for survival, irrespectively of the presence of γδ T cells.

In summary, the biological role of γδ T cells in humans is still unclear, but as judged by available TCRIEI cases, they seem to be early but generally redundant sentinels for epithelial barrier surveillance against pathogens by means of both innate and adaptive TCR-mediated recognition of non-HLA proteins present in infected cells.

4. γδ, but not αβ, T cells are absent in certain species with T lymphocytes and are dispensable in all tested KO animals

There is a great diversity of γδ T-cell presence in different taxonomic groups. Studies in Cyclostomes (jaw-less fish) have proved that in addition to the VCRA+ and VCRB+ lymphocytes (analogues of T and B cells, respectively) they have a third lineage, VCRC+ lymphocytes, which are also T-cell-like. These findings suggest that functional specialization of distinct T-cell-like lineages was an ancient feature of primordial immune systems (Hirano et al., 2013). In tetrapods the landscape becomes more complex and diverse. On one hand, there are the traditional TCRγδ in all Gnathostomes; NAR (New Antigen Receptor)-TCR in cartilaginous fish; the TCRδ with VHδ domain in amphibians, birds and platypus and even the TCRδ-related TCRμ in marsupials and monotremes (Parra et al., 2012). On the other hand, Squamata, but not Archosaurs reptiles, naturally lack γδ T cells altogether due to genomic deletions (Morrissey et al., 2022), although potential αε T cells may have compensated their loss (Sampson et al., 2024). Squamata is the largest order of reptiles, including geckos, lizards, iguanas, and snakes, whereas Archosaurs includes turtles, crocodiles, and birds. Lastly, a family of teleost fish (*Gobiesocidae*) also lack the γδ T-cell lineage (Table 6). These interesting reports suggest that the γδ T-cell

Table 6 Relevant animal KO models or species with selective engineered or natural γδ or αβ T-cell deficiency, respectively. Major phenotypes, housing requirements and selected immune features are indicated. Igs: immunoglobulins; Abs: Antibodies; IEL: intraepithelial lymphocytes.

		T cell numbers				Other immune features		
Species	**KO**	**αβ**	**γδ**	**Phenotype**	**Housing**	**Adaptive**	**Innate**	**References**
Chicken	*Trcb*	Absent	Normal	Severe	Pathogen-free	Low Igs and B cells. Granulomas	High monocytes, spleen/intestinal inflammation	von Heyl et al. (2023)
	Trcg	Normal	Absent	Mild	Pathogen-free	None reported	None reported	
Pig	*Tcrd*	Normal	Absent	Mild	Standard	Low Abs after vaccination	None reported	Petersen et al. (2021)
Mouse		Normal	Absent	Mild	Standard	Low Igs	None reported	Jameson et al. (2002)
	Trac or *Trbc*	Absent	Normal	Severe	Pathogen-free	Low Igs and celular responses	High IEL and intestinal inflammation	Mombaerts et al. (1992) and Mombaerts et al. (1993)
Squamates	None	Normal	Absent	None	Standard	None	None	Morrissey et al. (2022)
Gobiesocidae	None	Normal	Absent	None	Standard	None	None	Mirete-Bachiller et al. (2021)

lineage is an evolutionary branch of immunity which can remain or not depending on the species, with no apparent consequences for adaptation.

In the absence of reports of humans with selective deficiency of γδ T cells, available animal Knock-Out (KO) models may offer interesting insights into the real-life functional roles of these cells as compared to αβ T cells in species where γδ T cells are normally present. A caveat must be raised: human and animal immunity show large differences (Mestas & Hughes, 2004). Published data indicate that severe phenotypes (intestinal inflammation) map to αβ, but not γδ, KO chicken and mice (Table 6). Also, αβ KO animals require pathogen-free housing. In sharp contrast, KO chicken, mice and pigs with no γδ T cells all share a very mild phenotype, and at least mice and pigs (chicken were not tested) can be grown in standard housing facilities. In these studies, αβ T cells or innate lymphoid cells seem to undertake most γδ T cell roles (Sandrock et al., 2018), so we believe this can be the case in humans too.

Taken together, evolution and animal KO models suggest that if humans selectively lacking γδ T cells exist, they may show no salient clinical features and thus would not be analyzed for immunodeficiency.

5. Conclusions

Clinical severity in human TCRIEI associates with the absence of αβ T cells, irrespectively of γδ T-cell numbers. Thus, TCRIEI teach us that αβ T cells are crucial for defense against infections, whereas γδ T cells may have a comparatively marginal role in real-life human immunology. Several species and animal knock-out models which naturally or artificially lack γδ T cells support this contention.

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