GERMLINE IMMUNE GENETICS INFLUENCING CAR T-CELL THERAPY RESPONSE IN PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA

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Introduction

Anti-CD19 CAR-T therapy has shifted the paradigm for patients with relapsed/refractory non-Hodgkin lymphoma (R/R NHL). However, major challenges remain, including early progression, which occurs in approximately 40% of cases. **Developing predictive tools to anticipate progression** would be highly beneficial, and **immune system gene polymorphisms are promising candidates** for this purpose.

Objective

To **identify polymorphisms within immune system genes** and clinical characteristics that allow for the **prediction of early progression** in **aggressive B-cell lymphoma** patients treated with **CAR T cells**.

Methods

The study included **102 samples from patients with aggressive B-cell lymphoma treated with CAR T cells** (axicabtagene ciloleucel and tisagenlecleucel).

Clinical information was collected for all subjects. Samples were sequenced using a custom panel of 6,000 variants on the MiSeq platform (Figure 1).

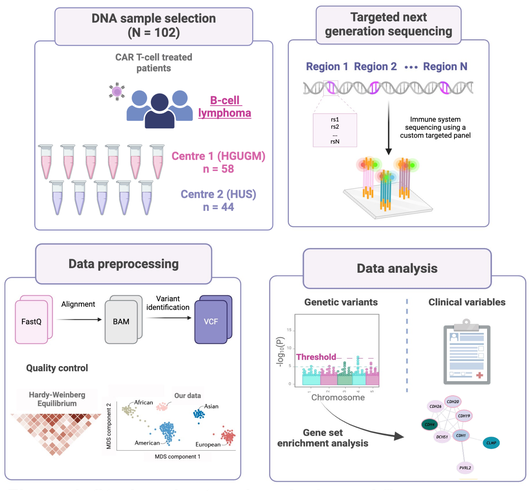


Figure 1. Study cohort and analysis workflow.

Data preprocessing was performed following Genome Analysis Toolkit (GATK) best practices. Quality control and filtering were conducted according to the standards established for population association studies using PLINK and R. Variant annotation was carried out with Variant Effect Predictor (VEP). The association of genetic variants and early progression (defined as progression within the first 3 months) was analyzed using logistic regression. For clinical characteristics, Mann Whitney U and chi-square tests were used for numerical and categorical variables, respectively. Results with a $P<.05$ were considered significant. Finally, enrichment analyses were performed using Cytoscape and stringApp.

References

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Results

Early progression was significantly associated with the absence of prior autologous transplantation and with disease progression occurring before apheresis or infusion (Table 1).

Variable		Total (N = 102)	Non-early progression (n = 51)	Early progression (n = 51)	*P*
Age	Mean (SD)	58.4 (13.9)	59.6 (13.3)	57.1 (14.5)	0.441
Sex	Male	62 (60.8)	28 (54.9)	34 (66.7)	0.311
	Female	40 (39.2)	23 (45.1)	17 (33.3)	
Lymphoma subtype	DLBCL	75 (73.5)	35 (68.6)	40 (78.4)	1
	DHL/THL	8 (7.8)	5 (9.8)	3 (5.9)	1
	PMBCL	7 (6.9)	4 (7.8)	3 (5.9)	1
	TFL	6 (5.9)	4 (7.8)	2 (3.9)	1
	Other	6 (5.9)	3 (5.9)	3 (5.9)	1
ASCT	No	77 (75.5)	32 (62.7)	45 (88.2)	**0.006**
	Yes	25 (24.5)	19 (37.3)	6 (11.8)	
No. previous lines of treatment	3 or more	29 (28.4)	12 (23.5)	17 (33.3)	0.38
Anti-CD19 CAR T-cell product	Axi-cel	60 (58.8)	35 (68.6)	25 (49.0)	0.07
	Tisa-cel	42 (41.2)	16 (31.4)	26 (51.0)	
Bridge therapy	No	17 (16.7)	10 (19.6)	7 (13.7)	0.595
	Yes	85 (83.3)	41 (80.4)	44 (86.3)	
Disease status PA	Non-progressive (PR, CR, SD)	16 (15.7)	13 (25.5)	3 (5.9)	**0.014**
	Progressive	86 (84.3)	38 (74.5)	48 (94.1)	
Disease status PI	Non-progressive (PR, CR, SD)	29 (28.4)	20 (39.2)	9 (17.6)	**0.028**
	Progressive	73 (71.6)	31 (60.8)	42 (82.4)	
CRS	No	12 (11.8)	4 (7.8)	8 (15.7)	0.357
	Yes	90 (88.2)	47 (92.2)	43 (84.3)	
CRS grade	< 1	71 (69.6)	35 (68.6)	36 (70.6)	1
	> 1	31 (30.4)	16 (31.4)	15 (29.4)	
ICANS	No	65 (63.7)	30 (58.8)	35 (68.6)	0.41
	Yes	37 (36.3)	21 (41.2)	16 (31.4)	
ICANS grade	< 1	81 (79.4)	38 (74.5)	43 (84.3)	0.327
	> 1	21 (20.6)	13 (25.5)	8 (15.7)	

Table 1. Patient characteristics associated with early disease progression.

Regarding genetic variants, early progression was associated with 267 variants located in 67 distinct genes. Among them, 16 genes were identified as involved in the dysregulation of the Hippo-Merlin pathway, with these genes harboring the highest number of variants (38%) (Figure 2).

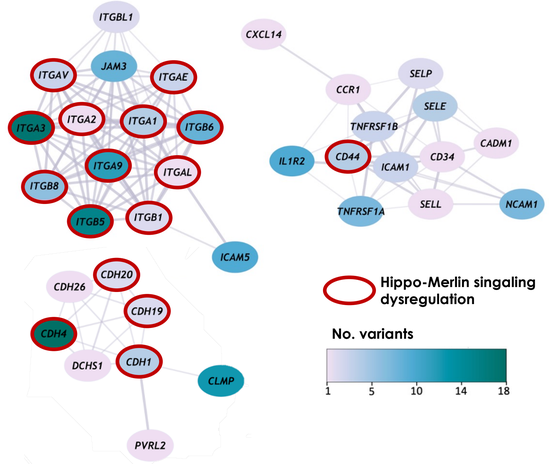


Figure 2. Identified variants map to genes involved in the Hippo-Merlin dysregulation pathway. Shown are protein–protein interaction clusters containing at least one gene from this pathway.

Summary

This study identifies clinical and **germline genetic factors associated with early progression** in aggressive B-cell lymphoma patients treated with CAR T-cell therapy, with nearly **40% of variants linked to the Hippo-Merlin pathway**. Dysregulation of this pathway may contribute to CAR-T **therapy resistance** by promoting the recruitment of tumor-associated macrophages and their polarization into M2 macrophages, creating an **anti-inflammatory microenvironment that hinders immunotherapy efficacy.**

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