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Germline NQO1c.559C>T as a biomarker of genetic susceptibility to Immune Checkpoints Blockade resistance

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Background

- Tobacco is the main risk factor for developing lung cancer. Yet, some heavy smokers do not develop cancer while others do at young ages.
- The study of cancer immunology has led to the surge of immune checkpoint blockade (ICB), which transformed the treatment landscape of cancer pts.
- NQO1 has been associated with extreme phenotypes of high risk for the development of tobacco-induced NSCLC and with poor survival outcomes for xerographs.
- Development of biomarkers for ICB has been mainly focused on tumor-related factors while genetic susceptibility of the host has been poorly explored to date and some evidence suggests that genetic dysregulation may enables immune escape.

Methods

- From June 2016 to January 2023, 326 NSCLC pts from two main University Hospitals of Malaga (Spain) receiving ICB were prospectively enrolled, blood samples were gathered for all patients receiving ICB.
- We selected a representative set of 60 consecutive patients for an exome sequencing in order to characterize the germline contribution to resistance (progression within the first 6 months of treatment).
- DNA was extracted from patient's PBMC fraction and prepared for exome sequencing. The raw sequencing data was processed to remove low-quality reads and aligned to a reference genome using BWA. Base recalibration, germline variant calling and variant filtering was performed through GATK. The remaining variants CRAVAT (Cancer-Related Analysis of Variants Toolkit).
- Survival probabilities were estimated with the Kaplan-Meier method and survival curves were compared using the log-rank test. We explored the lung cancer related genes among our results.

Results

- We found 26 germline variants associated with overall survival (OS) and progression free survival (PFS), and 52 genes variants with response to ICB. Univariant analysis of the 8 most significant genes variants related to the three survival outcomes are shown in table 3. The variants were missense or involved a stop gain/loss.

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*First author declare no conflict of interest.

Results

Table 1. Descriptive analysis of our 60 patients cohort selected for an exome sequencing in PBMC.

Table 1. Description of the sample.				
	Variable	**N**	**%**	**p**
SEX	Mujer	14	0.233	< .001
	Hombre	46	0.767	< .001
HISTOLOGICAL SUBTYPE	No adenocarcinoma	16	0.267	< .001
	Adenocarcinoma	44	0.733	< .001
AGE AT DIAGNOSIS	< 65	31	0.517	0.897
	> 65	28	0.467	0.699
	AN/D	1	0.017	< .001
STAGE AT DIAGNOSIS	I-A	1	0.017	< .001
	II	1	0.017	< .001
	II-A	2	0.033	< .001
	II-B	2	0.033	< .001
	III-A	4	0.067	< .001
	III-B	2	0.033	< .001
	IV	9	0.150	< .001
	IV-A	21	0.350	0.027
	IV-B	14	0.233	< .001
	IV-C	3	0.050	< .001
	AN/D	1	0.017	< .001
ECOG	0	10	0.167	< .001
	1	45	0.750	< .001
	2	2	0.033	< .001
	AN/D	3	0.050	< .001
PDL1	[0,1)	23	0.383	0.092
	[1,49]	20	0.333	0.013
	[50,100)	13	0.217	< .001
	AN/D	4	0.067	< .001
LIPI	0	14	0.233	< .001
	1	37	0.617	0.092
	2	9	0.150	< .001
Note: H, is proportion > 0.5				

Median age at diagnosis was 64 (54-85) years. 76,6% were men. 44/60 (73,3%) were adenocarcinoma, PD-L1 was ≥1% in 55% of patients, 22% showed PD-L≥50%. 78% of patients reported advanced disease at diagnosis. 65% received ICB in combination with chemotherapy.

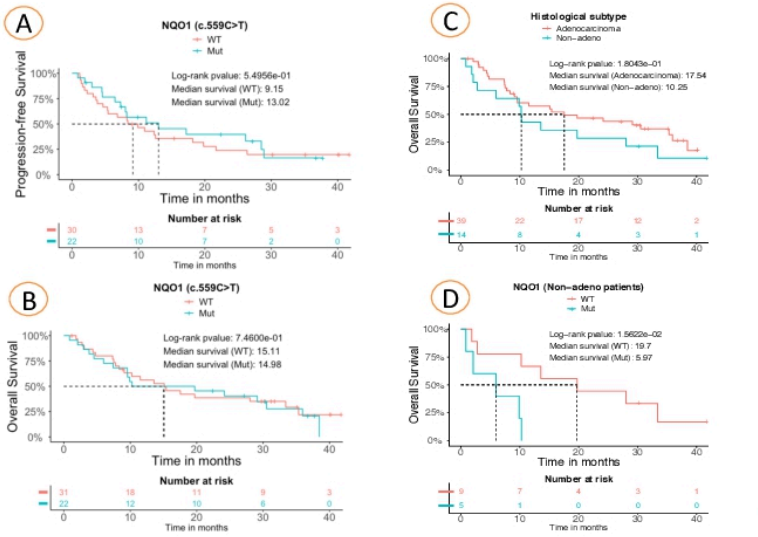

Figure 1. We found NQO1c.559C>T in 46,6% of pts (28/60). The variation was not associated with survival outcomes in the multivariant analysis (p>0.05). Kaplan Meier curve of median PFS and OS for NQO1 c.559C>T genetic variant, comparing mutation (blue line) and wild type (red line) is shown inf figure 1A and 1B respectively. However, we found a poor OS for non-ADC histology (Figure 1D) (19.7m vs 6m for mutated and WT, respectively: p<0.01). Multivariant analysis shown IGFLR1c.565T>C, ZNRF4c.488G>A and RREB1c.4315G>A as independent prognostic factors for OS, the two later for PFS as well. SLC17A3c.298G>A, SAMM50c.329A>G and RREB1c.4315G>A were independent pedictive factors of response at 6 months in the Likelihood Ratio Test (LTR). **Figure 2** show the multivariant analysis for OS (figure 2A) and PFS (figure 2B) of main ICB prognostic factors

Figure 2

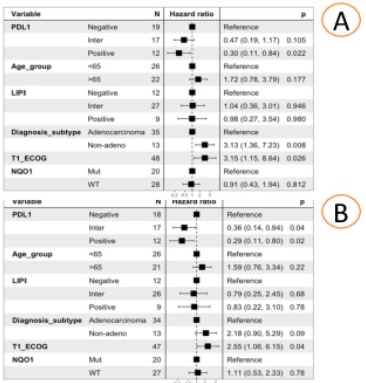

Table 3. Multivariant analysis			OS	PFS	LRT
hugo	v.c	change			
SLC17A3	missense_variant	c.298G>A	0.0536	0.1128	0.0053
MYO18A	missense_variant	c.2873C>T	0.0526	0.0700	0.4021
IGFLR1	missense_variant	c.565T>C	0.0019	0.1568	0.3383
B4GALNT4	missense_variant	c.200C>T	0.0819	0.1680	0.0600
SAMM50	missense_variant	c.329A>G	0.1588	0.4103	0.0180
ZNRF4	missense_variant	c.488G>A	0.0457	0.0130	0.0632
RREB1	missense_variant	c.4315G>A	0.0168	0.0315	0.0196
ARAP1	start_lost	c.3A>G	0.1600	0.1297	0.1831

Table 3: Multivariant analysis of the main gene variations in our sample. We can see in red color those mutations which seem to be statistically significant (p<0.05).

Conclusions

Exome sequencing analysis of germline variants could be a suitable methodology to identify subrogated biomarkers of immune resistance in NSCLC patients. NQO1c.559C>T might help to identify poor prognosis non-ADC pts in the ICB setting.