Homology-directed repair (HDR)-defective lung adenocarcinomas in circulating tumor DNA (ctDNA)

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Background

Tumors lacking key homology-directed repair (HDR) regulators such as, BRCA1 or BRCA2 and AT-rich interaction domain 1A (ARID1A), are hypersensitive to PARP inhibitors[1]. Mutations in HDR genes and ARID1A deficiency have been associated with response to PD-1 or PD-L1 blockade[2,3]. ARID1A is one of the genes with the highest mutation rate across several types of tumors[4].

We carried out the Spanish Lung Liquid versus Invasive biopsy Program (SLLIP), a multi-center, non-inferiority observational study designed to demonstrate the non-inferiority of cell-free DNA (cfDNA)-based versus tumor tissue-based genotyping as it pertains to the detection of clinically-actionable biomarkers in treatment naïve, metastatic lung adenocarcinoma. The primary objective was achieved[5].

A secondary aim of the SLIPP study was the discovery of additional drivers and actionable mutations. Here, we report the presence of HDR and ARID1A genes alterations in advanced lung adenocarcinoma patients.

Methods

From August 2016 to June 2017, the plasma DNA genome profile of 185 treatment-naïve advanced lung adenocarcinoma patients was performed with a clinically validated cell-free DNA (cfDNA) assay (Guardant360, Guardant Health, Inc.).

Guardant360 measures single-nucleotide variants, small insertions/deletions (indels), gene rearrangements/fusions, and copy number gain (CNG) across 73 clinically relevant cancer genes. All patient samples were collected and processed in accordance with the Guardant360 clinical blood collection kit instructions as previously described[6].

Determination of deleterious mutation status was based on public databases (ClinVar and BRCA Exchange) and expert curation.

ClinicalTrials.gov identifier, NCT03248089

MUNICH 2018 ESMO congress

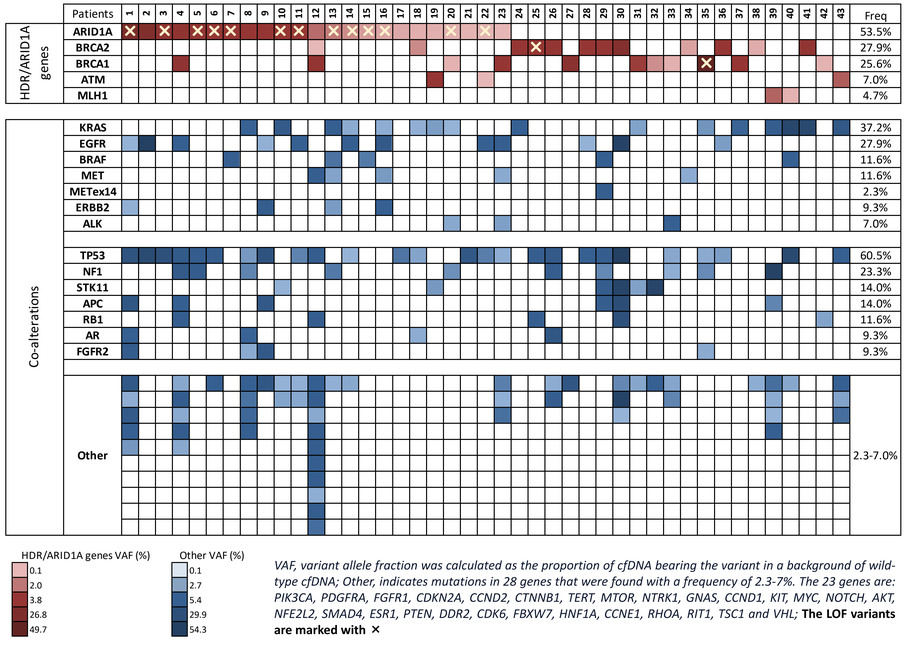
Results

23% (43 of 185) of patients had genomic alterations in HDR (BRCA1, 11; BRCA2, 12; ATM, 3; MLH1, 2) and ARID1A (23) genes.

Approximately 10% of BRCA1, BRCA2, and MLH1 variants were considered deleterious.

57% of the ARID1A variants were verified or likely deleterious on the basis of in silico modeling. Only 17% of ARID1A mutations were classified as synonymous (**Table 1**).

Figure 1. Genetic mutations identified by targeted next-generation sequencing in the plasma of 43 patients with NSCLC harboring HDR and ARID1A mutations.



VAF, variant allele fraction was calculated as the proportion of cfDNA bearing the variant in a background of wild-type cfDNA; Other, indicates mutations in 28 genes that were found with a frequency of 2.3-7%. The 23 genes are: PIK3CA, PDGFRA, FGFR1, CDKN2A, CCND2, CTNNB1, TERT, MTOR, NTRK1, GNAS, CCND1, KIT, MYC, NOTCH, AKT, NFE2L2, SMAD4, ESR1, PTEN, DDR2, CDK6, FBXW7, HNF1A, CCNE1, RHOA, RIT1, TSC1 and VHL; **The LOF variants are marked with ×**

Table 1. Mutations in HDR and ARID1A genes in lung adenocarcinoma patients of the SLIPP study

				ARID1A		ATM		BRCA1		BRCA2		MLH1	
	Age	Gender	Smoking status	Nucleotide; Amino acid	Mutation; PrFS	Nucleotide; Amino acid	Mutation; PrFS	Nucleotide; Amino acid	Mutation; PrFS	Nucleotide; Amino acid	Mutation; PrFS	Nucleotide; Amino acid	Mutation ;PrFS
1	57	Male	Smoker	--; p.Asp1850fs	Frameshift LOF								
2	64	Female	Never smoker	C>T; p.Q479*	Nonsense; LOF								
3	71	Male	Ex-smoker	A>G; p.N218S	Missense; VUS								
4	55	Male	Ex-smoker	G>T; p.S304S	Synonymous; LB			G>A; p.S423F	Missense; VUS				
5	75	Female	Ex-smoker	T>A; L2061*	Nonsense; LOF								
6	71	Male	Smoker	G>T; E2054*	Nonsense; LOF								
7	62	Female	Smoker	--; p.Ser2272fs	Frameshift; LOF								
8	60	Female	Smoker	T>C; p.I2185T	Missense; VUS								
9	48	Male	Smoker	G>C;p.R2164R	Synonymous; LB								
10	64	Female	Ex-smoker	C>T; p.Q1584*	Nonsense; LOF								
11	62	Female	Ex-smoker	--; p.Glu2250fs	Frameshift; LOF								
12	72	Male	Smoker	A>G; p.I1701V	Missense; VUS			A>T; p.N877K	Missense; VUS	G>A; p.E2702K	Missense; VUS		
13	56	Male	Smoker	C>T; p.Q790*	Nonsense; LOF								
14	82	Female	Never smoker	C>T; p.Q1584*	Nonsense; LOF								
15	71	Female	Never smoker	--; p.His203fs	Frameshift; LOF				Missense; VUS				
16	84	Female	Never smoker	C>T; p.Q1212*	Nonsense; LOF								
17	65	Male	Ex-smoker	A>G; p.T852T	Synonymous; LB								
18	57	Male	Smoker	C>A; p.P494T	Missense; VUS					A>T; p.K2075N	Missense; VUS		
19	73	Male	Smoker	G>A; p.A1304T	Missense; VUS	G>A; p.D2708N	Missense; LP						
20	65	Male	Ex-smoker	C>T; p.Q1367*	Nonsense; LOF			C>T; p.E1167K	Missense; VUS				
21	61	Male	Smoker	G>A; p.A257T	Missense VUS								
22	60	Female	Never smoker	C>T; p.Q1584*	Nonsense; LOF	C>A; p.R3008H	Missense; LP						
23	85	Female	Never smoker	A>G; p.S2272S	Synonymous; LB			G>A; p.V154V	Synonymous; LB				
24	76	Female	Ex-smoker							G>T; p.A2897S	Missense; VUS		
25	75	Male	Ex-smoker							C>T; p.Q2024*	Nonsense; LOF		
26	67	Male	Smoker							G>C; p.R2645T	Missense; VUS		
27	63	Male	Ex-smoker					C>A; p.R841L	Missense; VUS				
28	61	Male	Smoker							C>T; p.T1974I	Missense; LB		
29	71	Male	Ex-smoker							G>C; p.K241N	Missense; VUS		
30	63	Male	Smoker							G>A; p.D3042N	Missense; VUS		
31	48	Male	Smoker					C>A; p.L857F	Missense; VUS				
32	68	Male	Smoker					G>A; p.S1383L	Missense; VUS				
33	69	Male	Smoker					G>C; p.V722V	Synonymous; LB				
34	66	Female	Never smoker							A>C; p.V465V	Synonymous; LB		
35	65	Male	Unknown					; p.Ile42fs	Frameshift; LOF				
36	82	Female	Never smoker							C>A; p.S2001Y	Missense; VUS		
37	78	Male	Ex-smoker					C>T; p.E1735K	Missense; VUS				
38	68	Female	Never smoker							G>A; p.V484I	Missense; VUS		
39	73	Male	Ex-smoker									C>T; p.S368L	Missense; VUS
40	80	Male	Ex-smoker									C>T; p.S368L	Missense; VUS
41	57	Male	Smoker							C>T; p.T176I	Missense; VUS		
42	48	Female	Never smoker					G>T; p.P811T	Missense; VUS				
43	82	Male	Smoker			G>A; p.R3008H	Missense; LP						

PrFS, Predicted functional significance; LOF, loss of function (nonsense substitutions, frame shifting indels, and splice sites); VUS variant of uncertain significance or it was not found in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and BRCA Exchange (http://brcaexchange.org/); LP, likely pathogenic based on ClinVar; LB, likely benign based on ClinVar.; Single-letter abbreviations for the amino acid residues are as follows: A, Ala; D, Asp; E, Glu; H, His; I, Ile; L, Leu; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val.

Co-occurring alterations (**Figure 1**):

- The 11 BRCA1 mutant patients had a median number of 3 (range 1-15) co-occurring genetic alterations. Two patients had an EGFR mutation, and 4 patients had KRAS mutations.
- The 12 BRCA2 mutant patients had a median number of 4 (range 1-14) cooccurring genetic alterations. Three patients had EGFR mutations, 1 patient had a MET exon 14 mutation and 3 patients had KRAS mutations.
- All 3 ATM mutant patients had co-occurring EGFR or KRAS alterations.
- The 2 MLH1 mutant patients had co-occurring KRAS alterations.
- The 23 ARID1A mutant patients had a median number of 4 (range 1-15) co-occurring genetic alterations. Nine patients had EGFR mutations and 8 patients had KRAS mutations.

Conclusions

Here we show, through genomic analysis of 185 lung adenocarcinoma cfDNA samples, that HDR and ARID1A mutations are present in 23% of the patients and co-occur with oncogenic drivers.

Legal entity responsible for the study: Medica Scientia Innovation Research-MEDSIR
Funding: Guardant Health Inc.

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