Molecular and Immune Landscape of *FH*-mutated Cancers

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BACKGROUND

- Fumarate Hydratase (FH) encodes an essential enzyme in the TCA cycle
- Inactivating germline mutations in FH lead to hereditary leiomyomatosis and renal cell cancer syndrome with risk of development of certain cancers
- Sporadic FH mutations have been described in different cancers but implications of somatic mutations on cancer outcomes and survival are not well described
- Here, we characterize the molecular landscape of FH-mutant cancers

METHODS

- Tumors analyzed using NGS (NextSeq, 592 genes; NovaSeq, WES), IHC, and WTS (NovaSeq)(Caris Life Sciences, Phoenix, AZ)
- PD-L1 tested by 22c3, 28-8 (Agilent) and SP-142 (Spring Biosciences) IHC (≥1%). MSI tested by FA, IHC, and NGS
- TMB measured by totaling somatic mutations per tumor (TMB-h ≥ 10 mutations/MB)
- Real-world OS was extracted from insurance claims data and calculated from tissue collection/first treatment to last contact using K-M survival curves for molecularly defined cohorts
- Statistical significance was determined using chi-square and Wilcoxon rank-sum test, adjusted for multiple comparisons (q<0.05)

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RESULTS

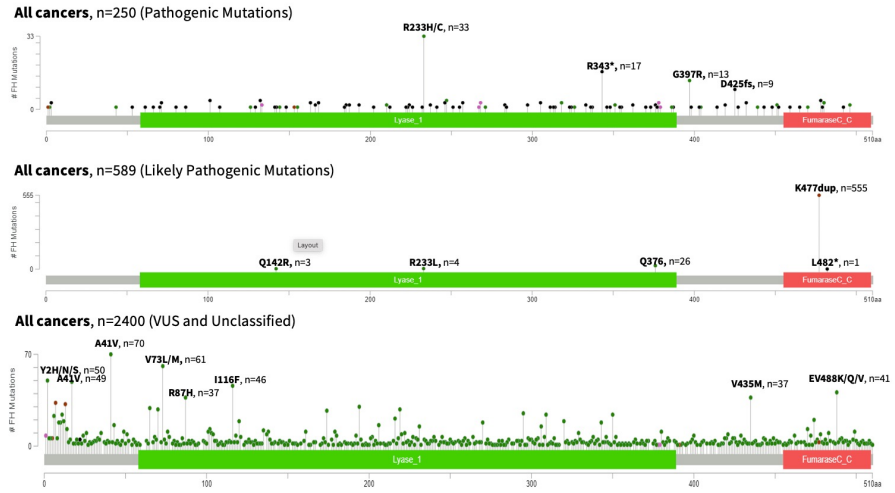
FH mutation in all cancers

Table 1. Patient demographics

Characteristics	All	P+LP	VUS
N	3,149	833 (26.5)	2316 (73.5)
Age, median (range)	65 (7-90)	66 (18-90)	65 (7-90)
Gender, N (%)			
Female	1767 (56.1)	458 (55)	1309 (56.5)
Male	1382 (43.9)	375 (45)	1007 (43.5)

- 3,239 *FH* mutations were seen in 45 tumor types in 3,149 FH-mutated tumors
- NSCLC, colorectal and endometrial cancers harbored the most mutations

Figure 1. Lollipop plots showing distribution of *FH* mutations



- The most common mutations: R233H (P; n=37), K477dup (LP; n=555), and A41V (VUS; n=70) *(Fig 1)*
- VUS had increased *CREBBP* mutations (5.1% vs 1.6%, q=0.012) *(Fig 2)* and TMB-H (40.4% vs 29.8%, q=0.004) *(Fig 3)* compared to P+LP

Fig 2. Top Co-Mutations in *FH*-mt tumors (P+LP vs VUS)

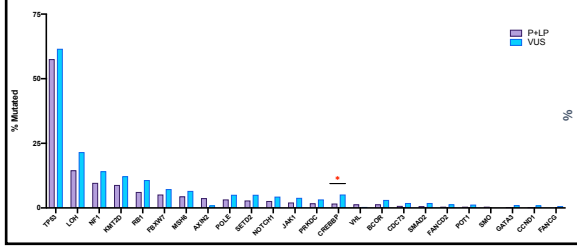
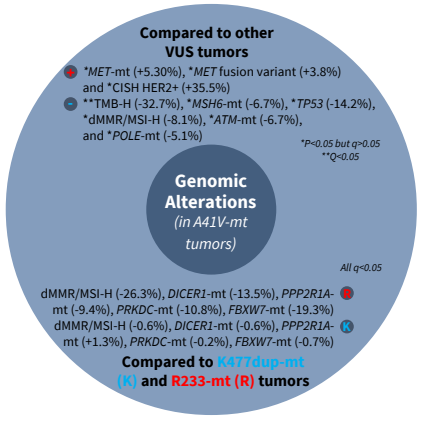


Fig 3. IO Therapy Biomarkers in *FH*-mt tumors (P+LP vs VUS)

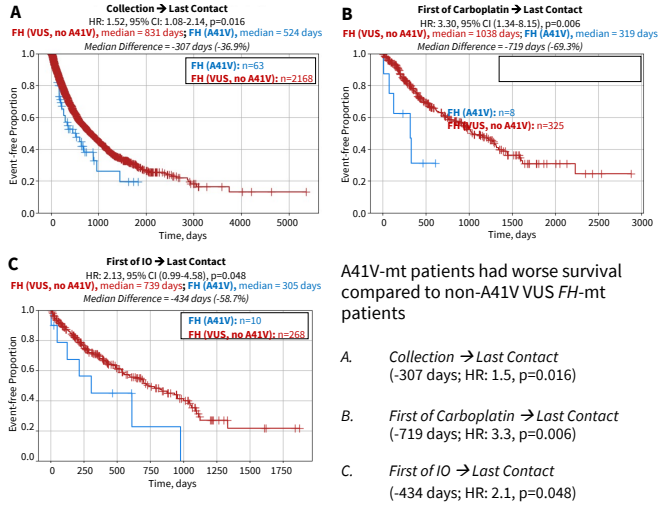
A41V-mt tumors

Figure 4. Molecular differences of A41V-mt tumors compared to other VUS *FH*-mt tumors and K477-dup/R233-mt tumors



- A41V-mt tumors had significantly lower TMB-H than other VUS (8.8% vs 41.5%, q=0.002) and lower MSI-H (3.13% vs 3.69% vs 29.4%, q=0.003) and *DICER1*, *PRKDC*, *FBXW7* mutations (q<0.05) compared to K477dup and R233 (Figure 4)

Figure 5. The A41V *FH* mutation is associated with worse survival compared to non-A41V VUS *FH* mutations



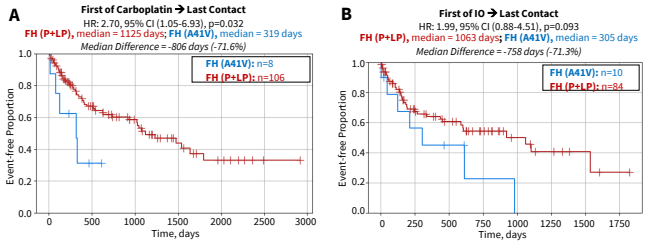
A41V-mt patients had worse survival compared to non-A41V VUS *FH*-mt patients

A. *Collection → Last Contact* (-307 days; HR: 1.5, p=0.016)

B. *First of Carboplatin → Last Contact* (-719 days; HR: 3.3, p=0.006)

C. *First of IO → Last Contact* (-434 days; HR: 2.1, p=0.048)

Figure 6. The A41V *FH* mutation is associated with worse survival compared to K477dup/R233 *FH*-mt patients



A41V-mt patients had worse survival compared to P+LP *FH*-mt patients

A. *First of Carboplatin → Last Contact* (-806 days; HR: 2.70, p=0.032)

B. *First of IO → Last Contact* (-758 days; HR: 1.99, p=0.093)

CONCLUSION

FH alterations are found in multiple cancers. A41V was the most common VUS mutation and is associated with a distinct molecular profile compared to K477dup-mt and R233-mt tumors; it was associated with worse survival in all-comers and after carboplatin compared to P+LP mutations. This highlights the significance of this mutation and the need for further investigation into how this specific and other FH mutations contribute to cancer progression and treatment outcomes.