KRAS Mutations in Histiocytic Neoplasms: Mutation Spectrum and Response to MEK Inhibition

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BACKGROUND

Histiocytic neoplasms (HN) are rare hematologic disorders derived from myeloid dendritic lineages. The most common forms include Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), and Rosai-Dorfman disease (RDD).[1] Recurrent MAPK pathway mutations have enabled targeted therapy with BRAF and MEK inhibitors (MEKi), producing durable responses.[2,3] However, the impact of specific *KRAS* variants on treatment response remains unclear.[4] We aimed to characterize the spectrum of *KRAS* mutations in HN and evaluate responses to MEKi.

METHODS

We retrospectively reviewed consecutive patients with HN at Mayo Clinic and the University of Alabama at Birmingham. Patients with a *KRAS* mutation identified by next-generation sequencing were included. Response was assessed radiographically according to the latest Histiocyte Society consensus guidelines.

RESULTS

We identified 36 patients, including 23 women (63.9%), with a median age at diagnosis of 64 years (range, 20–86 years). Diagnoses included RDD (55.6%, n=20), ECD (16.7%, n=6), and LCH (5.6%, n=2) and other HN (22.2%, n=8). The most frequent *KRAS* variants were p.K117N (31.6%), p.G12D (13.9%), p.G13D (11.1%), p.A146T (11.1%), and p.G13C (8.3%). *KRAS* distribution differed by disease subtype: p.G12D was enriched in ECD compared with RDD (50.0% vs 5.0%, $P<0.05$) and absent in LCH, whereas p.K117N was observed in 45.0% of RDD cases and absent in ECD. Sixteen patients (44.4%) received MEKi therapy, predominantly cobimetinib. The overall response rate was 68.8%, including 3 complete and 8 partial responses. One patient who progressed on cobimetinib subsequently responded to trametinib. Among 5 non-responders, *KRAS* variants included p.K117N (n=2), p.G12D (n=1), and p.A146T (n=1). Notably, four of five patients with codon 146 mutations achieved partial responses, although no statistically significant genotype-response associations were identified.

Characteristic	N=36
Median age at diagnosis (range) — yr	64 (20-86)
Female sex — no. (%)	23 (63.9%)
Institution of enrollment — no. (%)	
Mayo	33 (91.7%)
UAB	3 (8.3%)
Diagnosis — no. (%)	
RDD	20 (55.6%)
ECD	6 (16.7%)
LCH	2 (5.6%)
Histiocytic Sarcoma	3 (8.3%)
Xanthogranuloma	2 (5.6%)
Others	3 (8.3%)
Treated with MEKi — no. (%)	16 (44.4%)
Cobimetinib	15 (41.7)
Trametinib	2 (5.6%)

Table 1. Patient characteristics. Yr, year; RDD, Rosai-Dorfman disease; ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; UAB, University of Alabama at Birmingham; MEKi, MEK inhibitor.

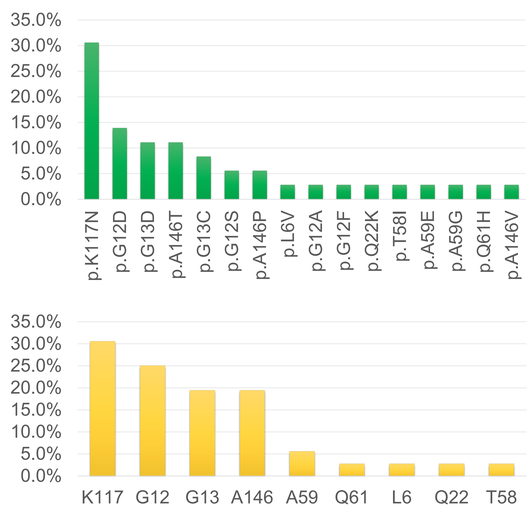

Figure 2. Spectrum of *KRAS* mutations in histiocytic neoplasms.

(A) Frequency of individual *KRAS* variants.

(B) Distribution of *KRAS* mutations by affected codon. Percentages are calculated among the 36 patients with *KRAS*-mutated histiocytic neoplasms.

ID	Sex	Mutations	Diagnosis	1st MEKi	Response	Time to Best Response	2nd MEKi	Response
1	F	p.K117N	RDD	Cobimetinib	CR	13 mo	-	
2	M	p.K117N	RDD	Cobimetinib	PR	5 mo	-	
3	F	p.K117N	RDD	Cobimetinib	PR	4 mo	-	
4	F	p.K117N	RDD	Cobimetinib	No response	2 mo	-	
5	F	p.K117N	RDD	Cobimetinib	No response	22 mo	-	
6	F	p.K117N	RDD	Cobimetinib	No response	5 mo	Trametinib	PR in 2 mo
7	F	p.G12D	ECD	Cobimetinib	CR	23 mo	-	
8	F	p.G12D	RDD	Cobimetinib	No response	3 mo	-	
9	F	p.G13C	RDD	Cobimetinib	PR	10 mo	-	
10	F	p.G13D	RDD	Cobimetinib	No response	3 mo	-	
11	F	p.A146T	RDD	Cobimetinib	PR	5 mo	-	
12	F	p.A146T	RDD	Cobimetinib	PR	6 mo	-	
13	F	p.A146P	RDD	Cobimetinib	PR	4 mo	-	
14	M	p.A146V	ECD	Cobimetinib	PR	3 mo	-	
15	M	p.A146T	LCS	Trametinib	No response	2 mo	-	
16	F	p.T58I	RDD	Cobimetinib	CR	2 mo	-	

Table 2. Clinical features and responses to MEK inhibitor therapy. MEKi, MEK inhibitor; mo, months; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RDD, Rosai-Dorfman disease; ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis.

CONCLUSIONS

KRAS mutations represent an important subset of MAPK alterations in HN and vary by disease subtype. Codon 146 mutations may be associated with improved response to MEKi. Larger cohorts are needed to validate variant-specific predictors of response and guide precision therapy.

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