

# Novel Activating Mutations in *CSF1R* and Additional Receptor Tyrosine Kinases in Histiocytic Neoplasms

Erdheim-Chester Disease Medical Symposium  
Orlando, FL, United States  
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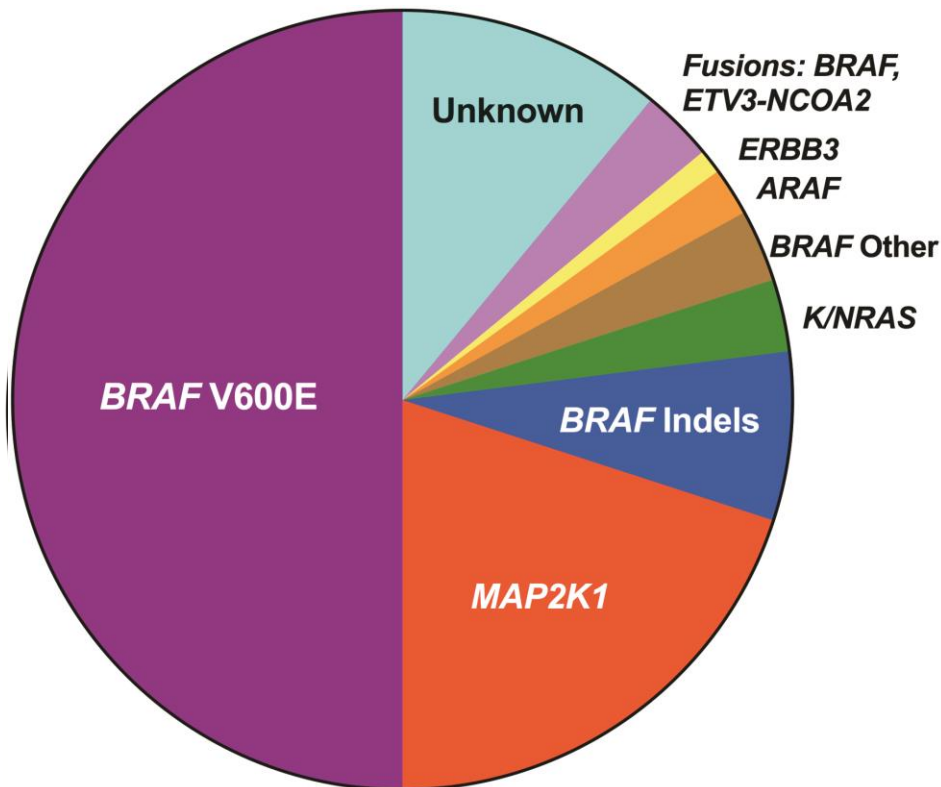
Memorial Sloan Kettering  
Cancer Center

# Outline

- **Published Kinase Alterations in the Histiocytoses**
- **New Insights into the Molecular Pathogenesis of the Histiocytoses**
- **Emergence of Targeted Therapeutics in the Histiocytic Neoplasms**

# Summary of Published Kinase Alterations in the Histiocytoses

## Langerhans Cell Histiocytosis



Badalian-Very, *et al. Blood* 2010

Kansal, *et al. Genes Chrom Cancer* 2013

Nelson, *et al. Blood* 2014

Brown NA, *et al. Blood* 2014

Chakraborty, *et al. Blood* 2014

Nelson, *et al. Genes Chrom Cancer* 2015

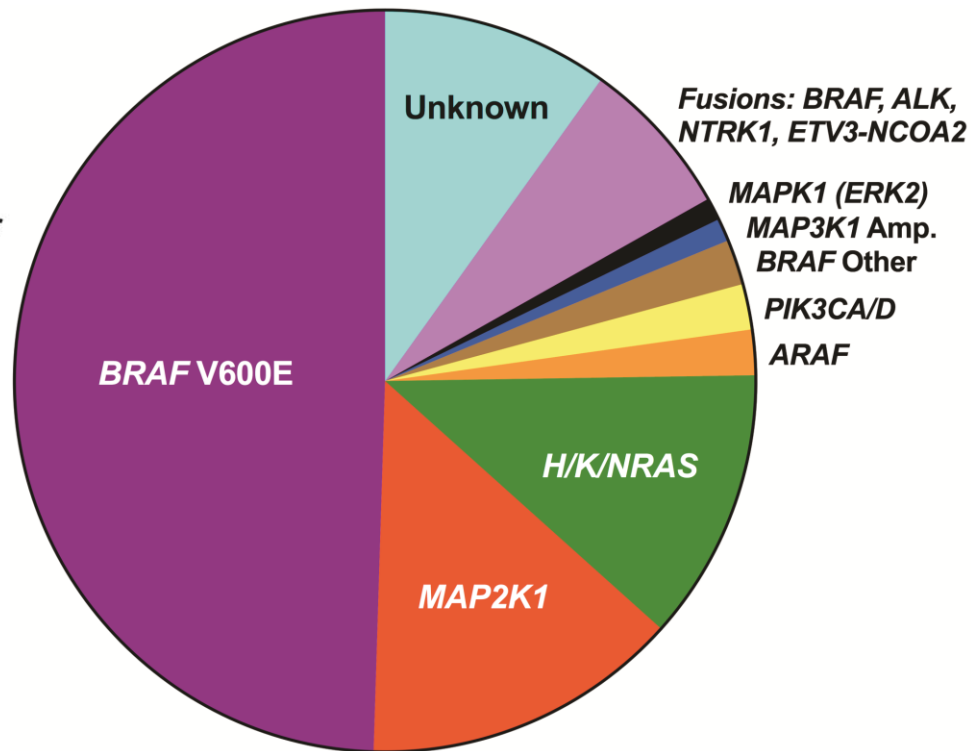
Chakraborty *et al. Blood* 2016

Lee, *et al. JCI Insight* 2017

Zarnegar, Durham, *et al. Pediatr Blood Cancer*. 2017

Héritier, *et al. Mol Cancer*. 2017

## Non-Langerhans Cell Histiocytosis



Haroche, *et al. Blood* 2012

Diamond, *et al. Blood* 2013

Go, *et al. Histopathology* 2014

Emile, Diamond, *et al. Blood* 2014

Chakraborty, *et al. Blood* 2014

O'Malley, *et al. Ann Diagn Pathol* 2015

Kordes, *et al. Leukemia* 2015

Brown RA, *et al. Blood* 2015

Diamond, Durham, Haroche, *et al.*

*Cancer Discovery* 2016.

Shanmugan, *et al. Head Neck Pathol*. 2016

Lee, *et al. JCI Insight* 2017

Chakraborty *et al. Oncotarget* 2017

Techavichit, *et al. Hum Pathol*. 2017

Garces, *et al. Mod. Pathol*. 2017

Bentel *et al. BMJ Case Rep*. 2017.

Meyer *et al. Am J Ophthalmol*.

*Case Rep*. 2018.

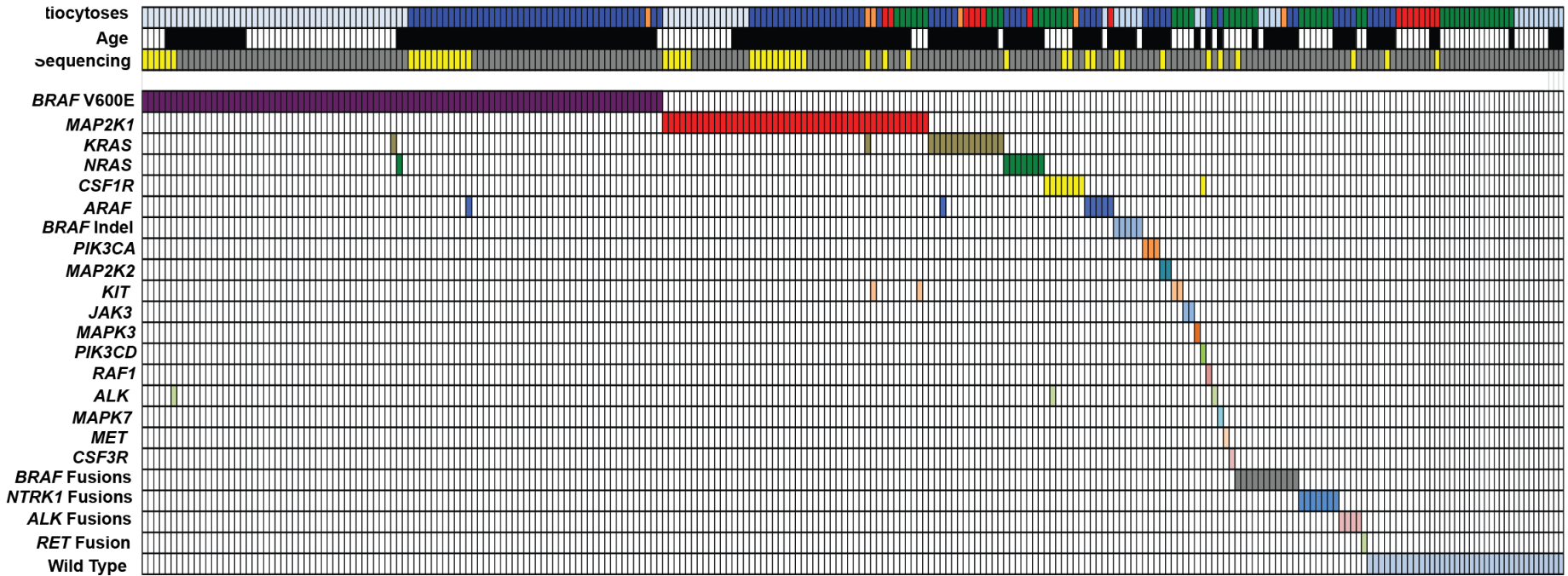
# Remaining Questions

- **What other alterations drive histiocytic neoplasms?**
- **Are there genomic differences across the diverse histiocytoses subsets?**
- **Are targeted therapies other than RAF inhibitors effective in the histiocytoses?**

# Outline

- **Published Kinase Alterations in the Histiocytoses**
- **New Insights into the Molecular Pathogenesis of the Histiocytoses**
- **Emergence of Targeted Therapeutics in the Histiocytic Neoplasms**

# Overall Histiocytoses Cohort (N=250)



## Histiocytoses Subsets

- Langerhans Cell Histiocytosis (LCH)
- Rosai-Dorfman Disease (RDD)
- Erdheim-Chester Disease (ECD)
- Histiocytic Sarcoma (HS)
- Juvenile Xanthogranuloma (JXG)

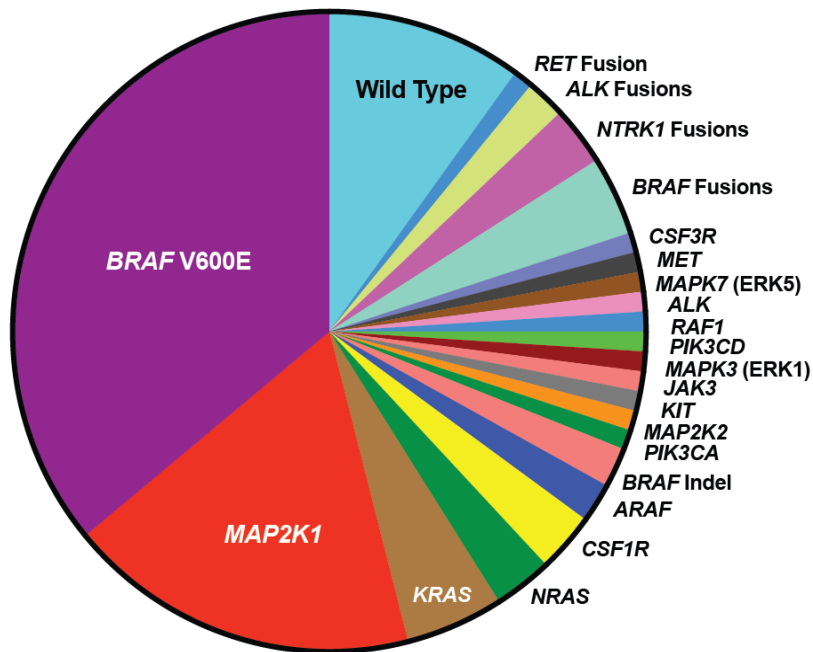
## Age

- Pediatric
- Adult

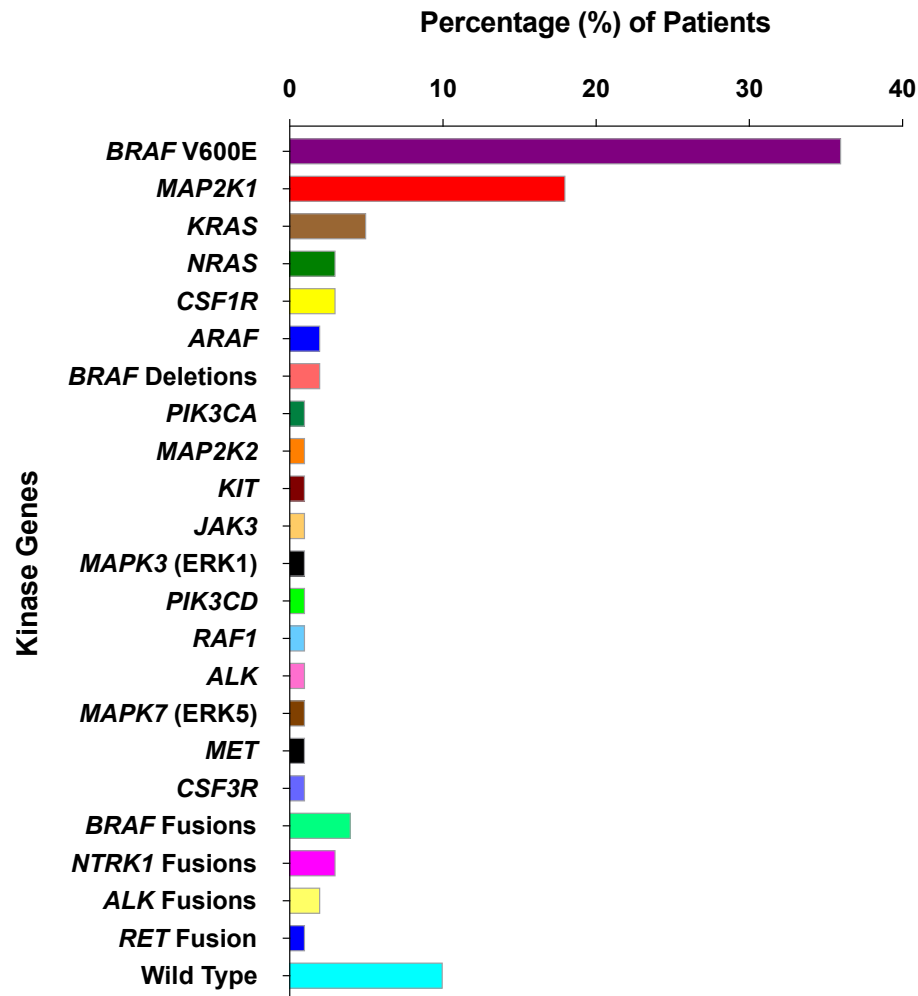
## Sequencing Analyses

- Whole Exome Sequencing (WES) and/or Whole Transcriptome Sequencing (WT)
- Targeted DNA and/or RNA Sequencing

# Relative Frequency of Kinase Alterations Identified (N = 250)

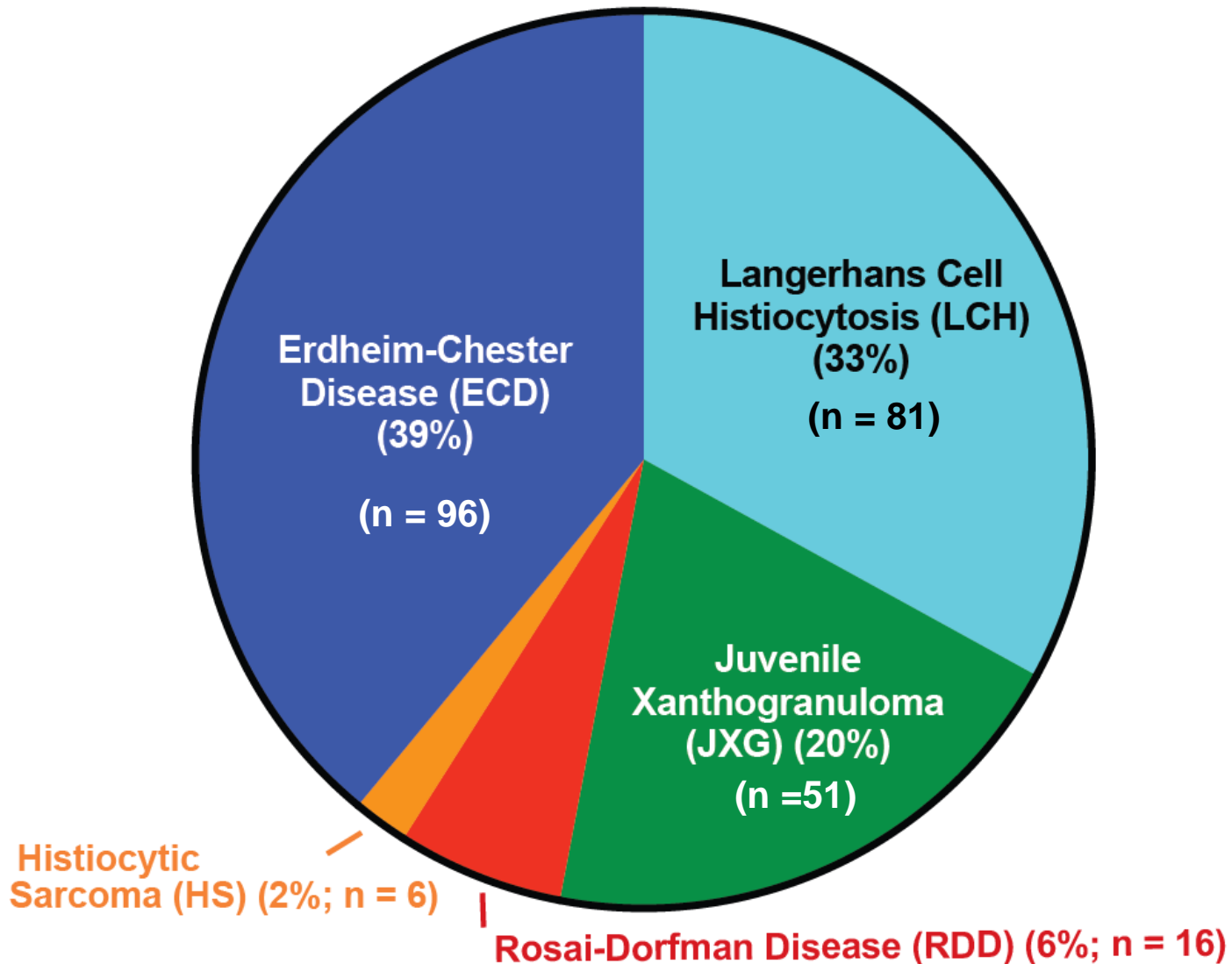


N = 250



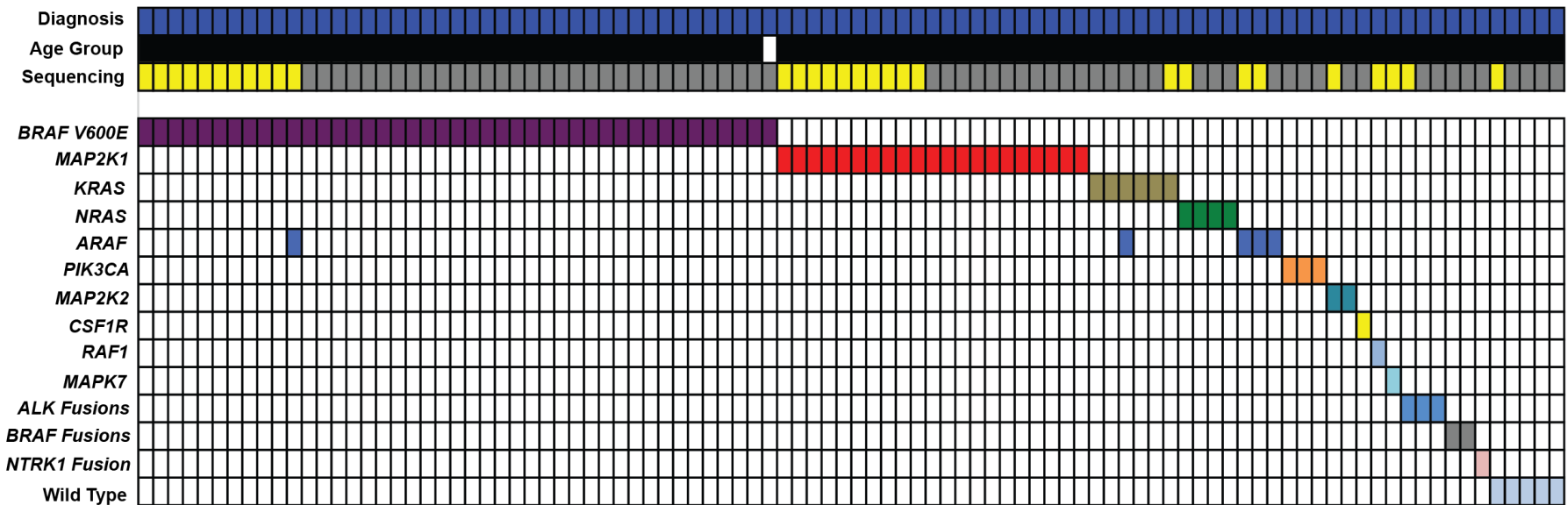
N = 250

# Histiocytoses Subsets Sequenced in Study (N=250)



**N = 250**

# Erdheim-Chester Disease Cohort (N = 96)



**Histiocytoses Subsets**

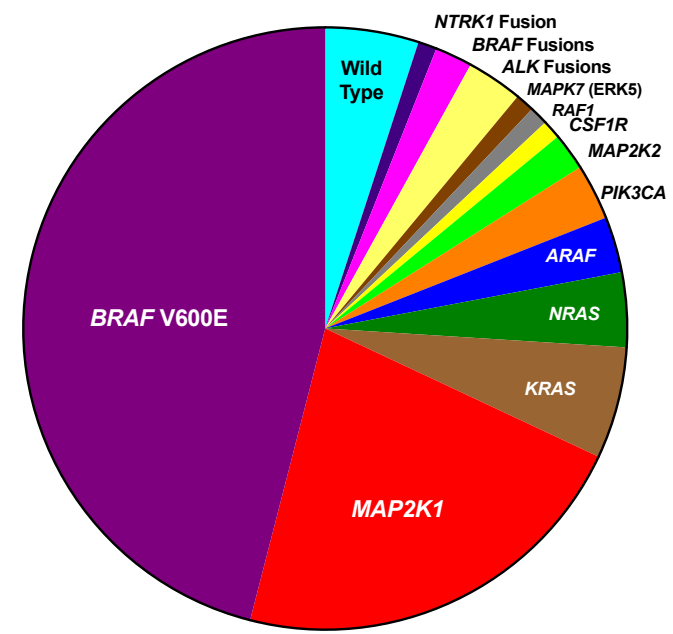
- Langerhans Cell Histiocytosis (LCH)
- Rosai-Dorfman Disease (RDD)
- Erdheim-Chester Disease (ECD)
- Histiocytic Sarcoma (HS)
- Juvenile Xanthogranuloma (JXG)

**Age**

- Pediatric
- Adult

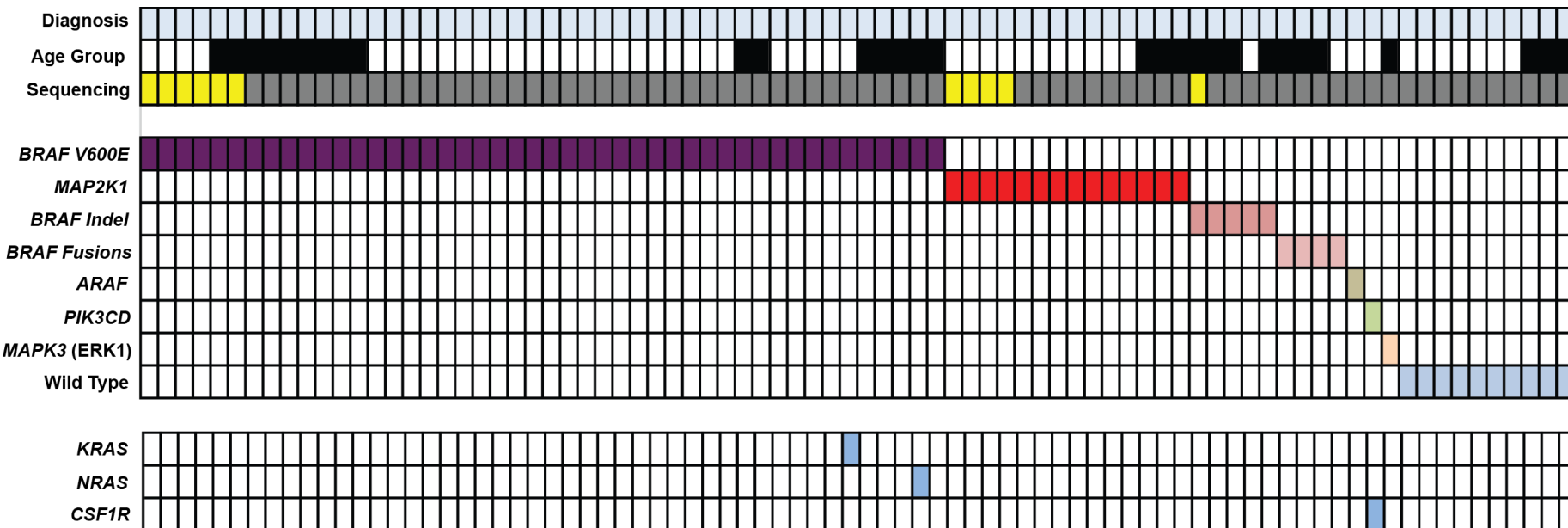
**Sequencing Analyses**

- Whole Exome Sequencing (WES) and/or Whole Transcriptome Sequencing (WT)
- Targeted DNA and/or RNA Sequencing



N = 96

# Langerhans Cell Histiocytosis Cohort (N = 81)



## Histiocytoses Subsets

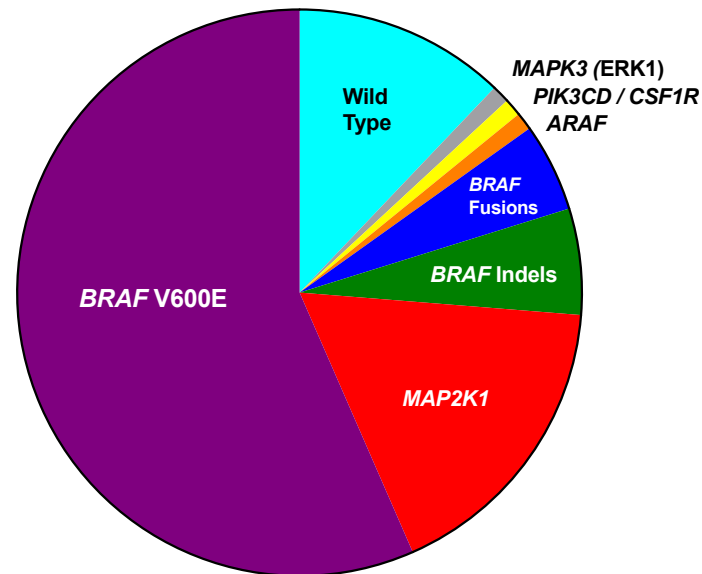
- Langerhans Cell Histiocytosis (LCH)
- Rosai-Dorfman Disease (RDD)
- Erdheim-Chester Disease (ECD)
- Histiocytic Sarcoma (HS)
- Juvenile Xanthogranuloma (JXG)

## Age

- Pediatric
- Adult

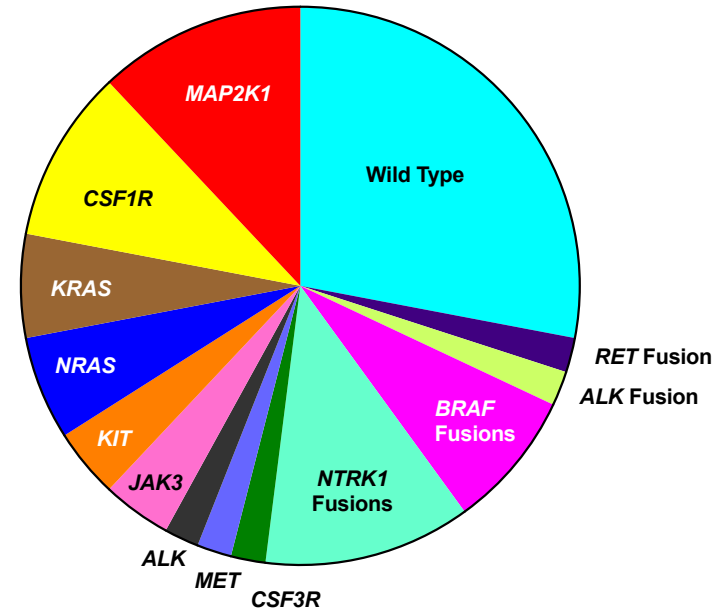
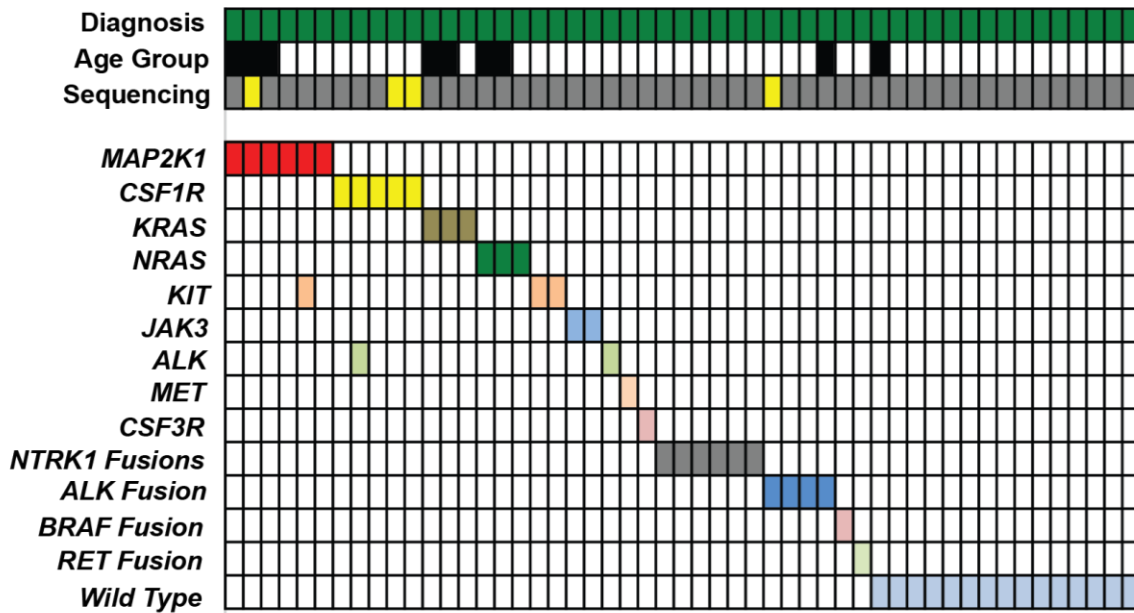
## Sequencing Analyses

- Whole Exome Sequencing (WES) and/or Whole Transcriptome Sequencing (WT)
- Targeted DNA and/or RNA Sequencing



**N = 81**

# Juvenile Xanthogranuloma Cohort (N = 51)



N = 51

## Histiocytoses Subsets

- Langerhans Cell Histiocytosis (LCH)
- Rosai-Dorfman Disease (RDD)
- Erdheim-Chester Disease (ECD)
- Histiocytic Sarcoma (HS)
- Juvenile Xanthogranuloma (JXG)

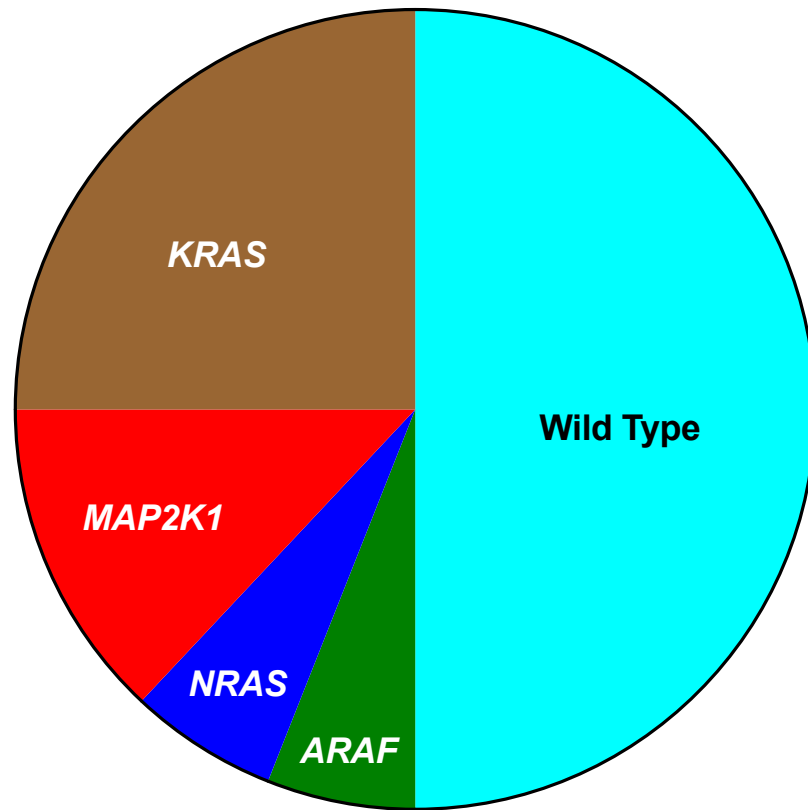
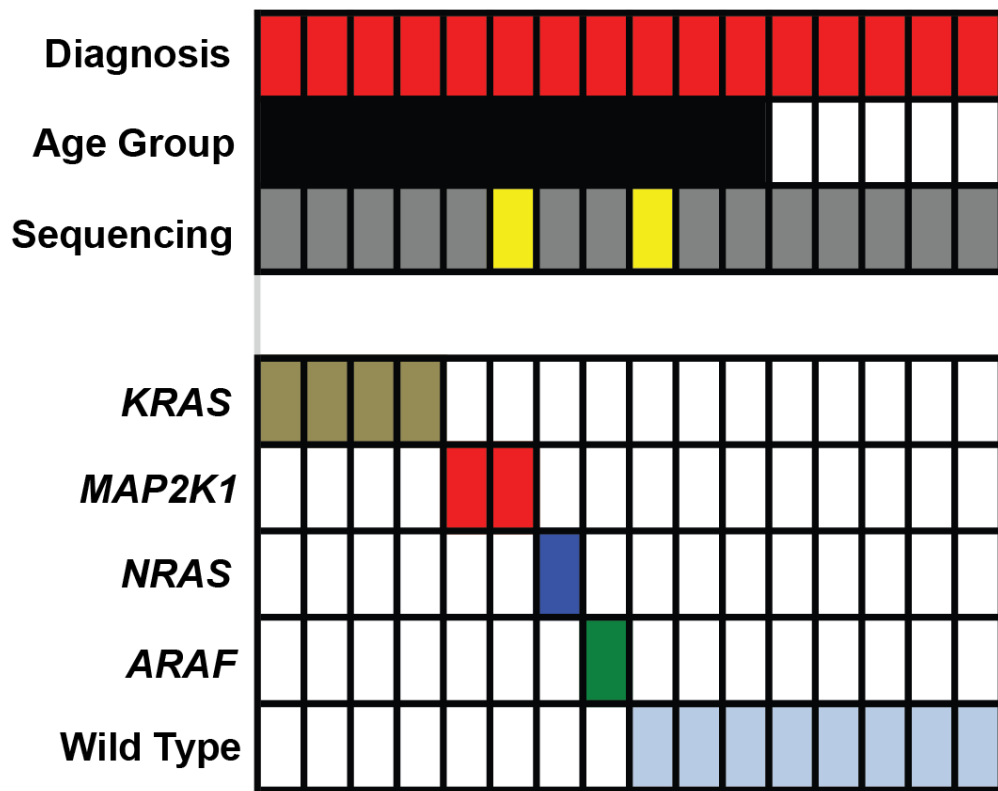
## Age

- Pediatric
- Adult

## Sequencing Analyses

- Whole Exome Sequencing (WES) and/or Whole Transcriptome Sequencing (WT)
- Targeted DNA and/or RNA Sequencing

# Rosai-Dorfman Disease Cohort (N = 16)



N = 16

## Histiocytoses Subsets

- Langerhans Cell Histiocytosis (LCH)
- Rosai-Dorfman Disease (RDD)
- Erdheim-Chester Disease (ECD)
- Histiocytic Sarcoma (HS)
- Juvenile Xanthogranuloma (JXG)

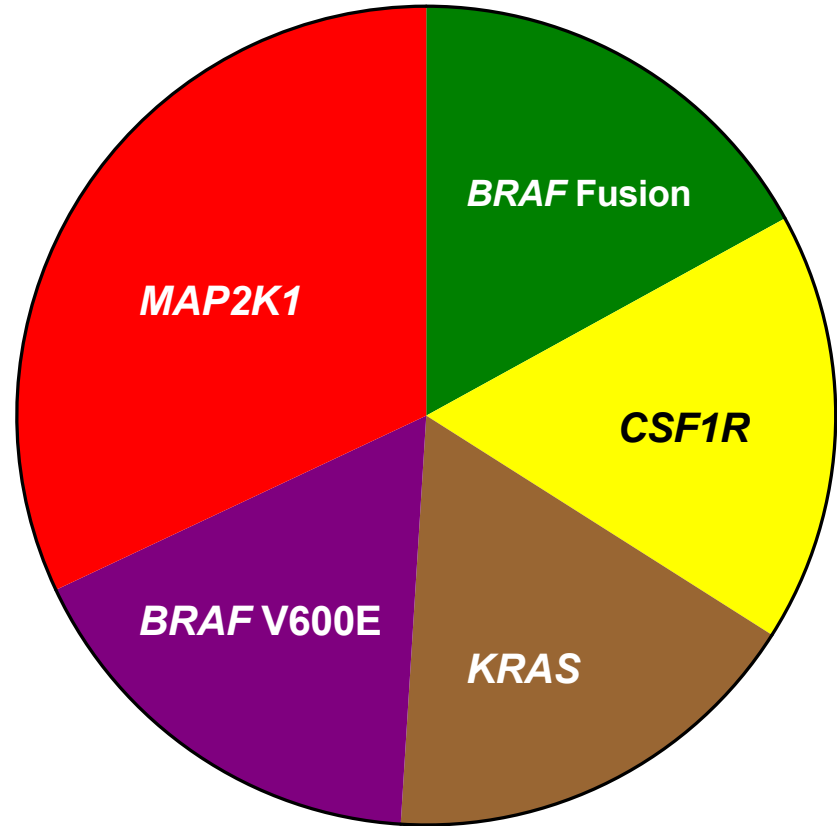
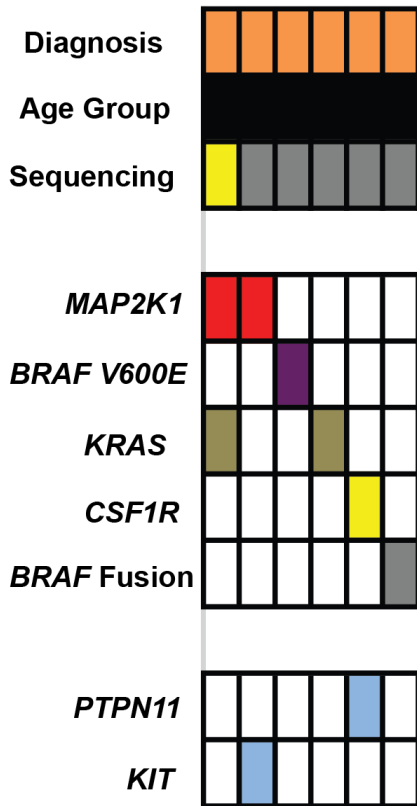
## Age

- Pediatric
- Adult

## Sequencing Analyses

- Whole Exome Sequencing (WES) and/or Whole Transcriptome Sequencing (WT)
- Targeted DNA and/or RNA Sequencing

# Histiocytic Sarcoma (HS) Cohort (N = 6)



**N = 6**

## Histiocytoses Subsets

- Langerhans Cell Histiocytosis (LCH)
- Rosai-Dorfman Disease (RDD)
- Erdheim-Chester Disease (ECD)
- Histiocytic Sarcoma (HS)
- Juvenile Xanthogranuloma (JXG)

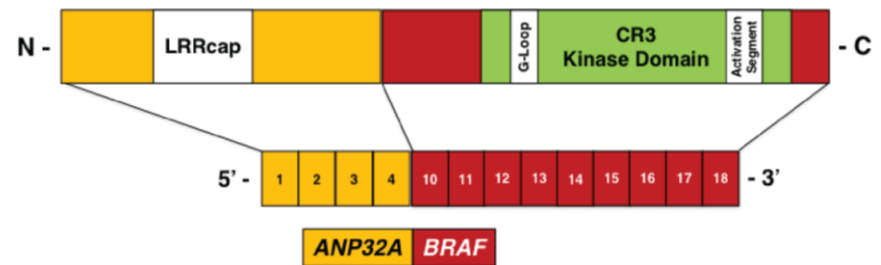
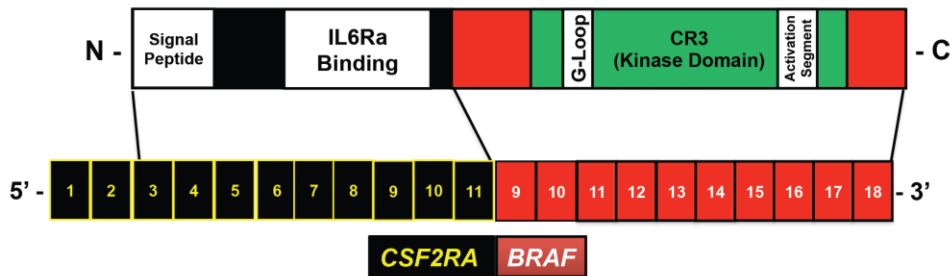
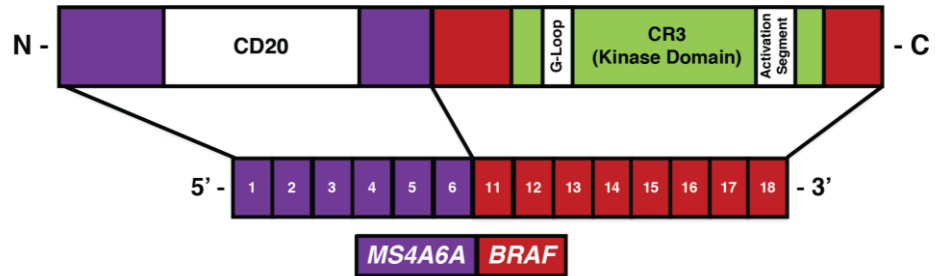
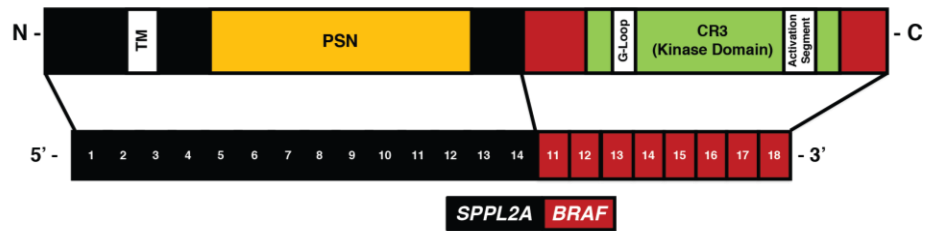
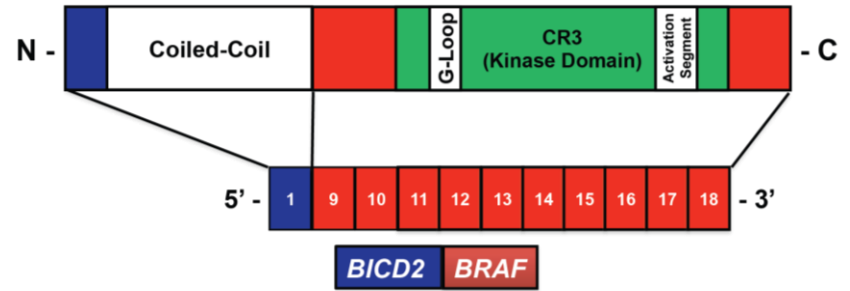
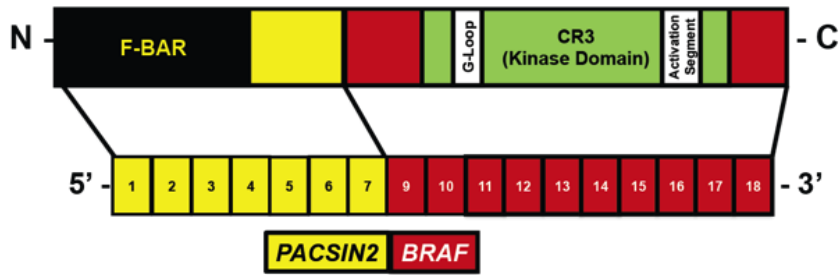
## Age

- Pediatric
- Adult

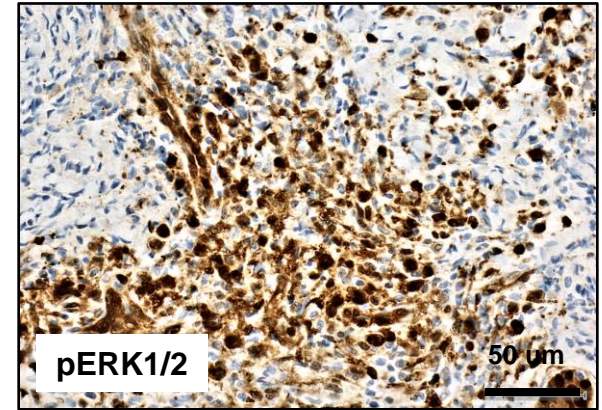
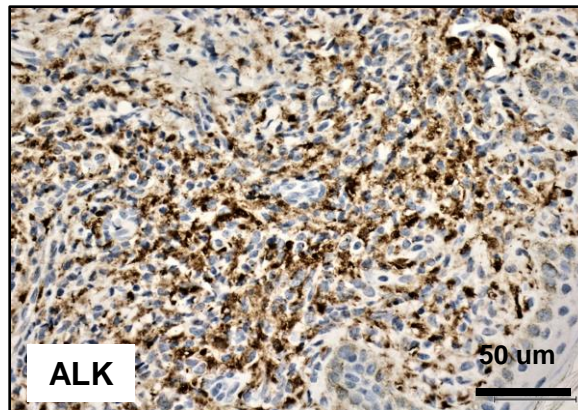
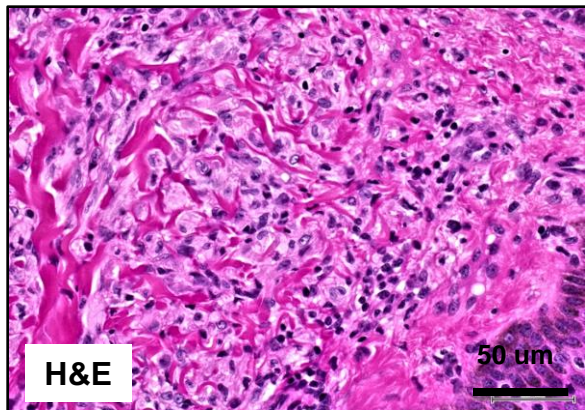
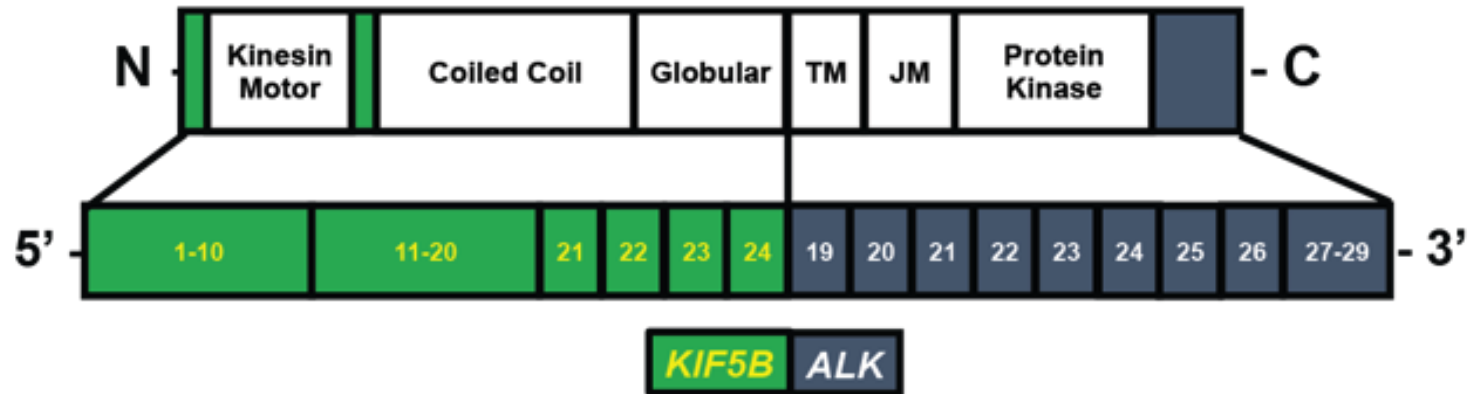
## Sequencing Analyses

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- Targeted DNA and/or RNA Sequencing

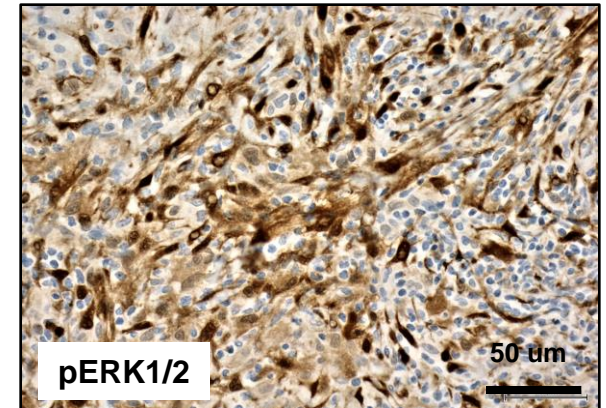
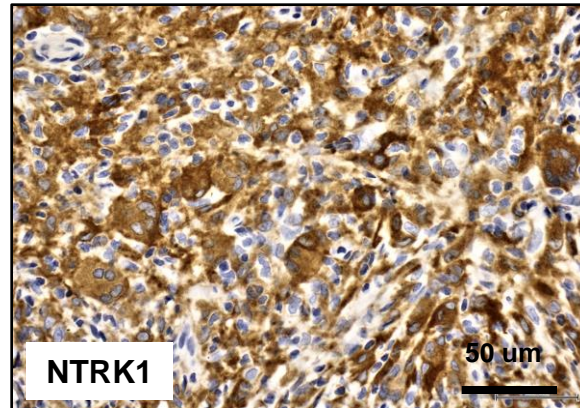
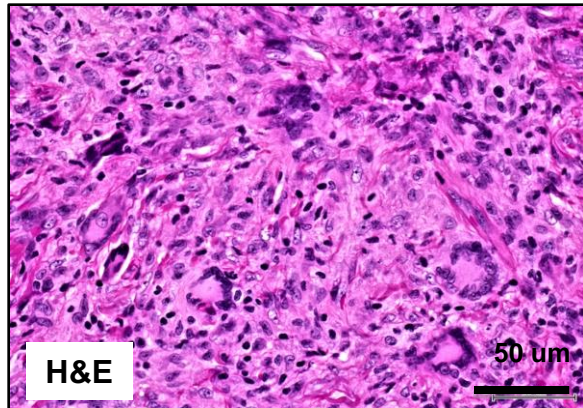
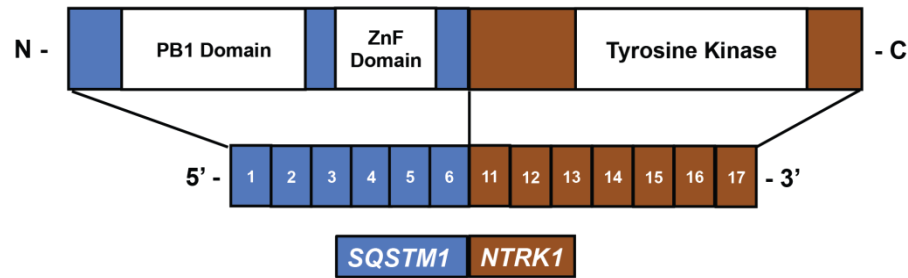
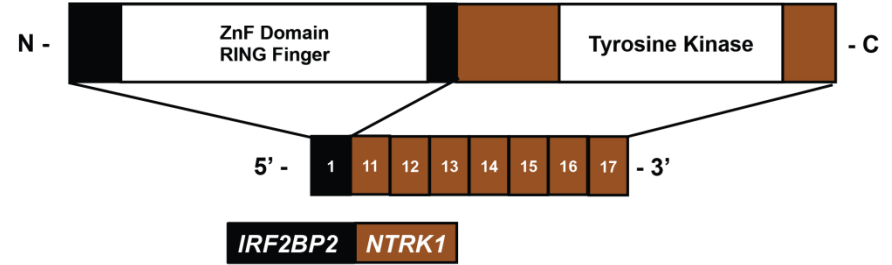
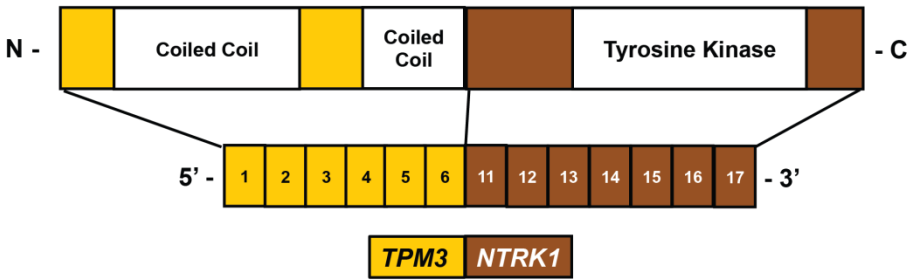
# New *BRAF* Fusions in LCH, JXG, and ECD



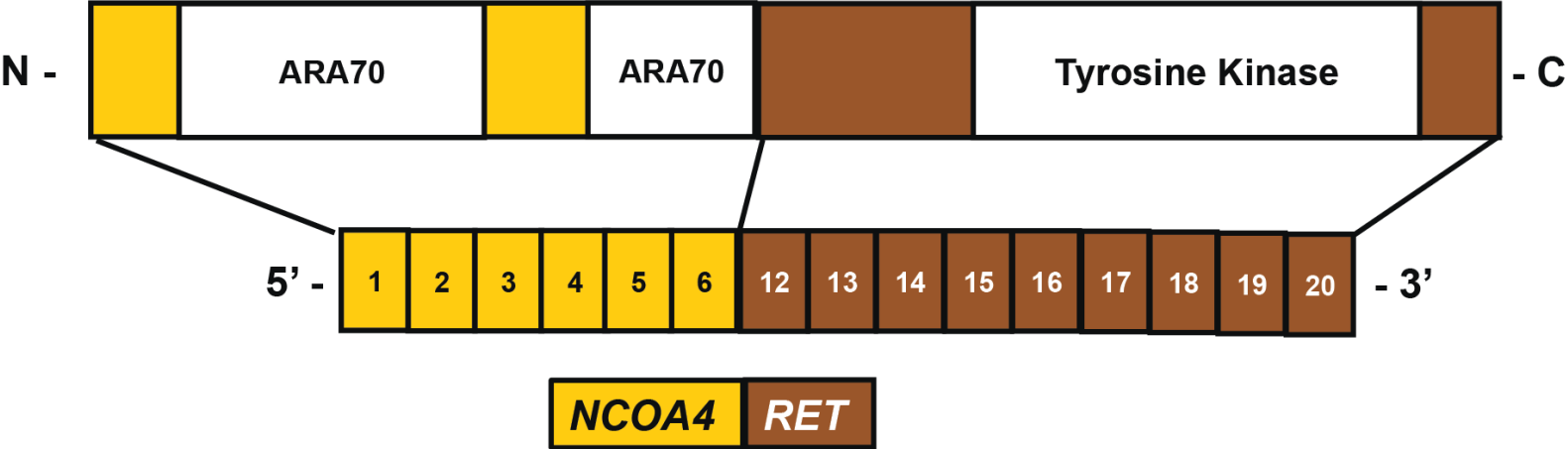
# *KIF5B-ALK* Fusion in JXG



# Recurrent *NTRK1* Fusions in JXG

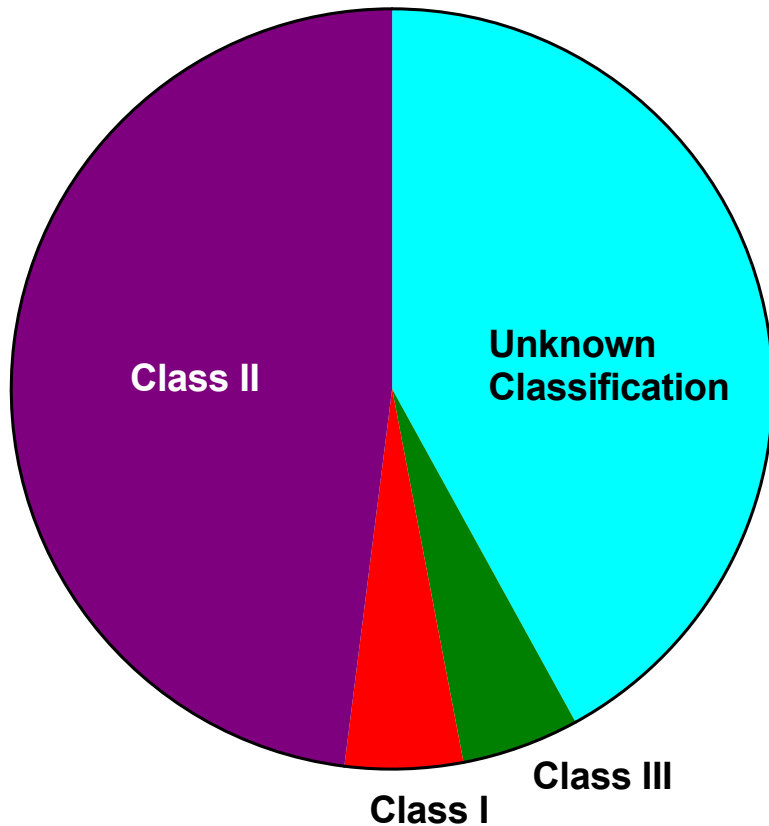


# *RET* Fusion in JXG



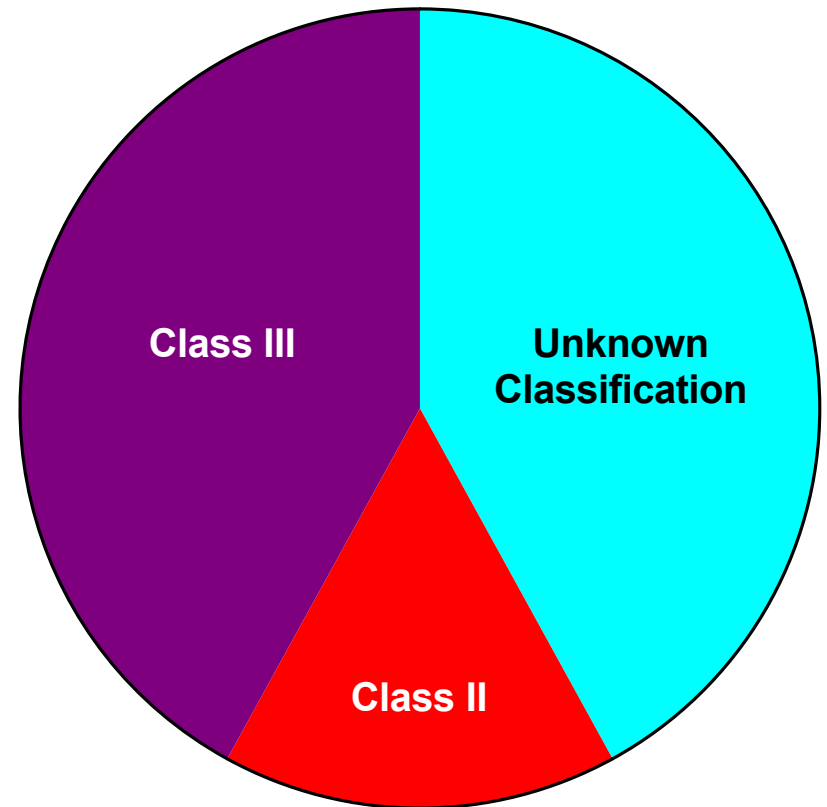
# MAP2K1 Mutations Occur Across Histiocytoses Subtypes but have Different Properties Based on MEK1 Class

Erdheim-Chester Disease



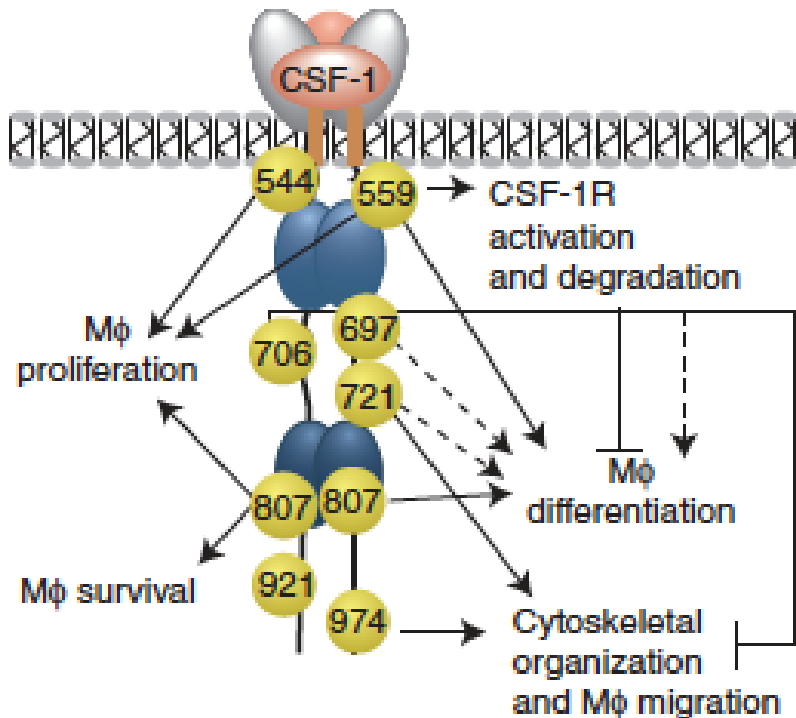
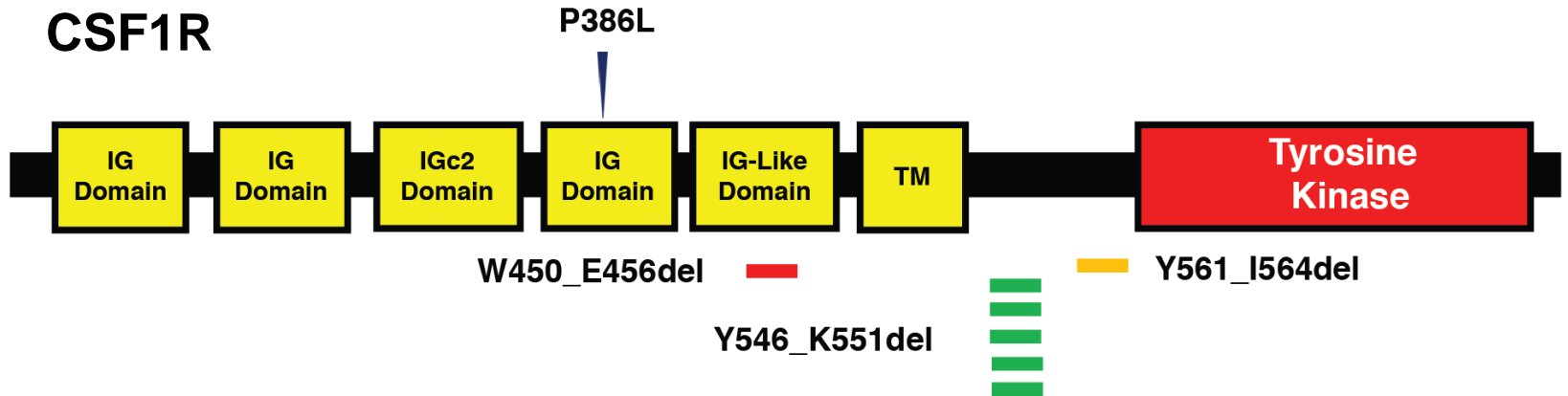
N = 21

Langerhans Cell Histiocytosis



N = 12

# Recurrent *CSF1R* Mutations

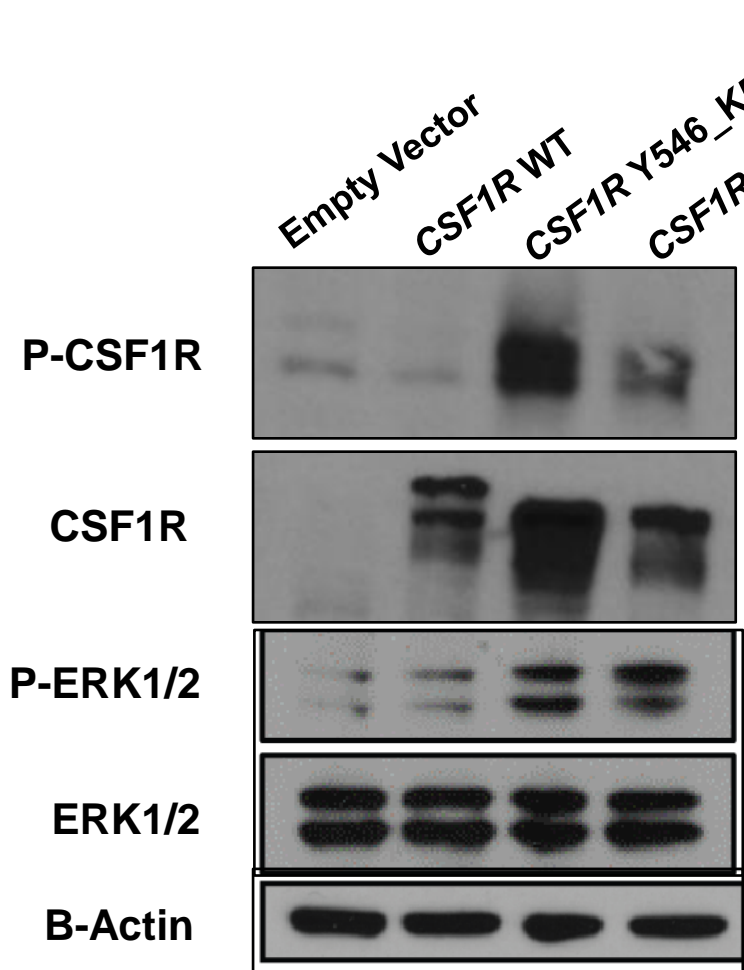


**CSF1R: The receptor for MCSF (Macrophage Colony Stimulating Factor)**

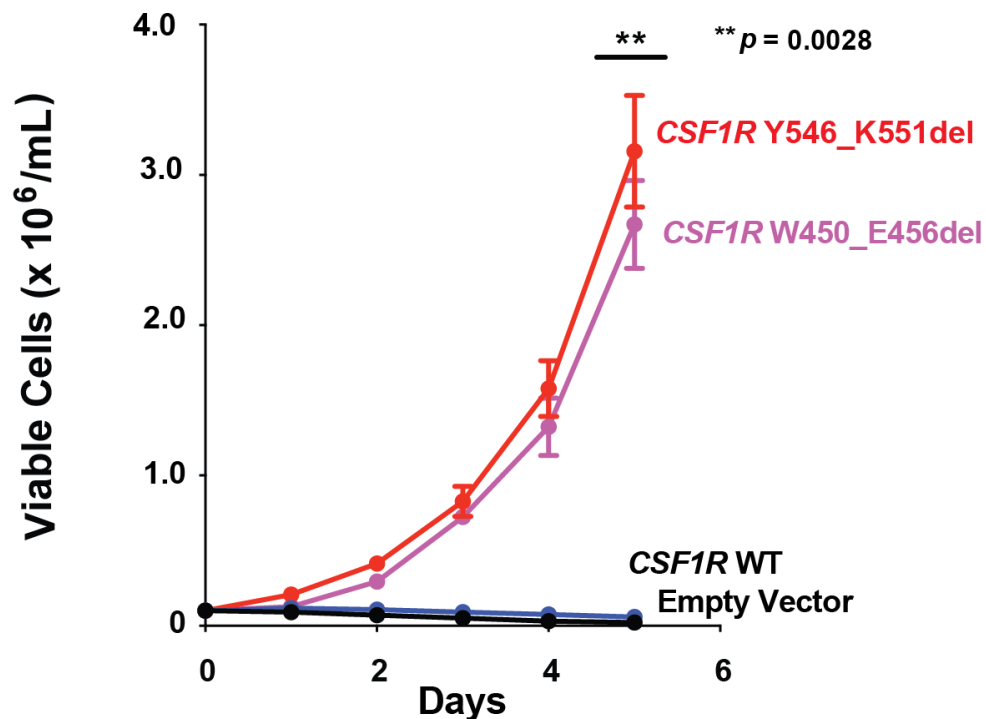
**Controls production, differentiation, and function of macrophages**

**Expression is restricted to cells committed to the monocyte/macrophage lineage.**

# CSF1R Y546\_K551del and CSF1R W450\_E456del Mutations in Histiocytoses are Activating

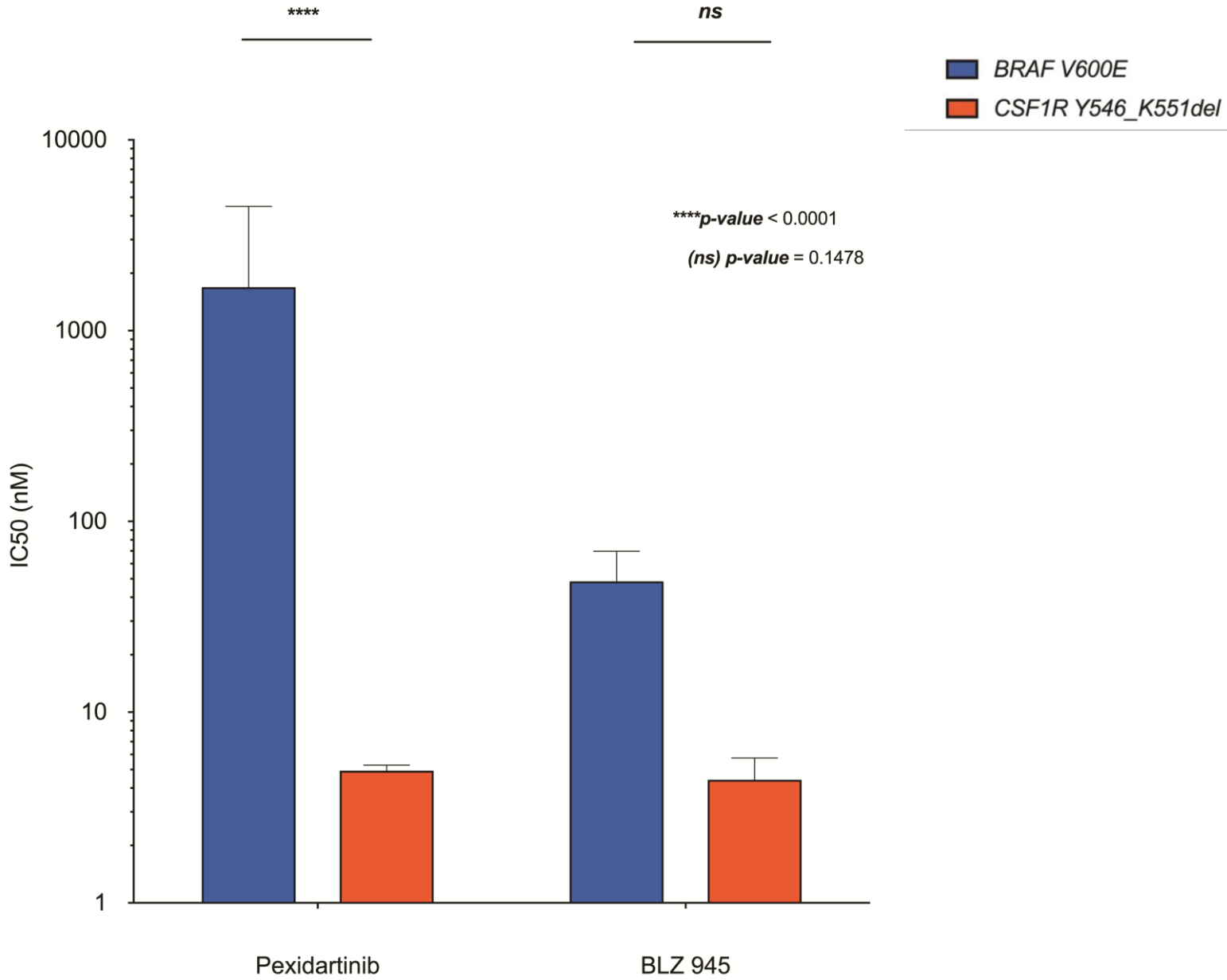


## Ba/F3 Cell Cytokine-Independent Growth



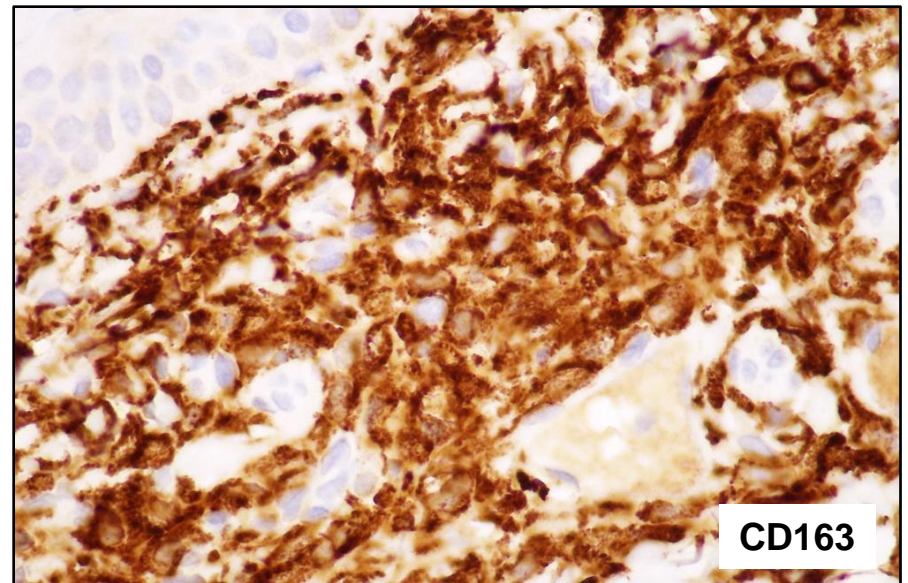
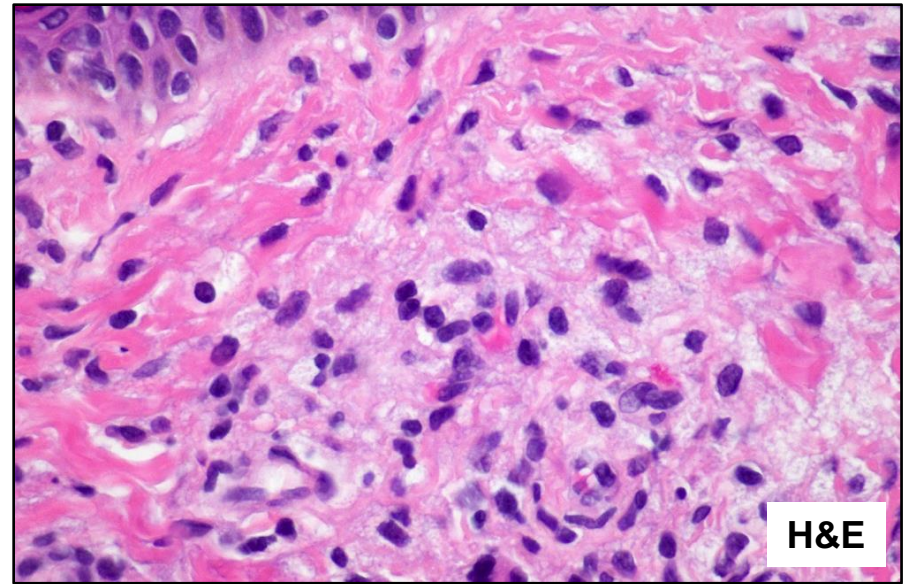
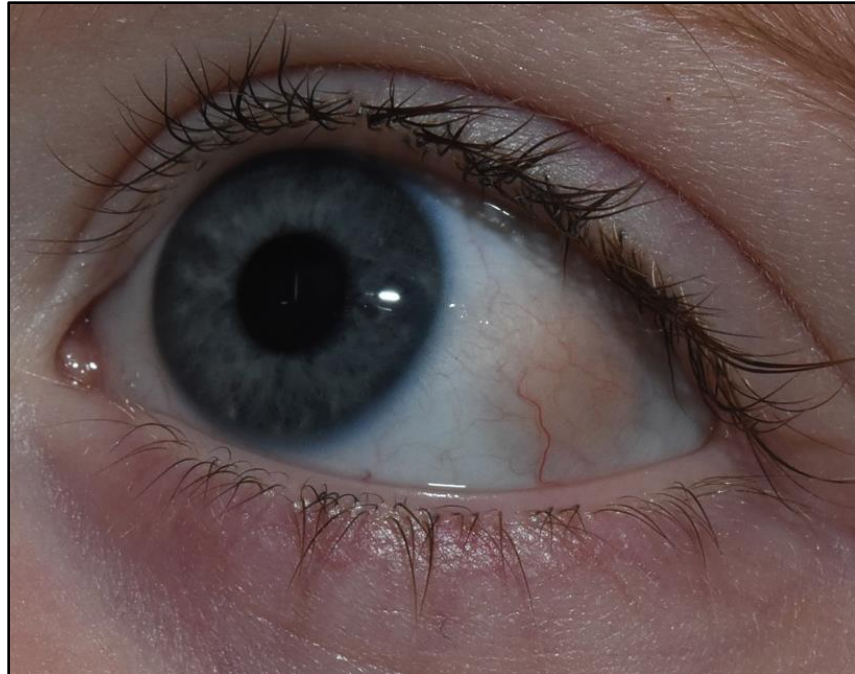
- EV
- CSF1R WT
- CSF1R W450\_E456del
- CSF1R Y546\_K551del

# CSF1R Y546\_K551del Mutation is Sensitive to CSF1R Inhibitors (Pexidartinib and BLZ 945)

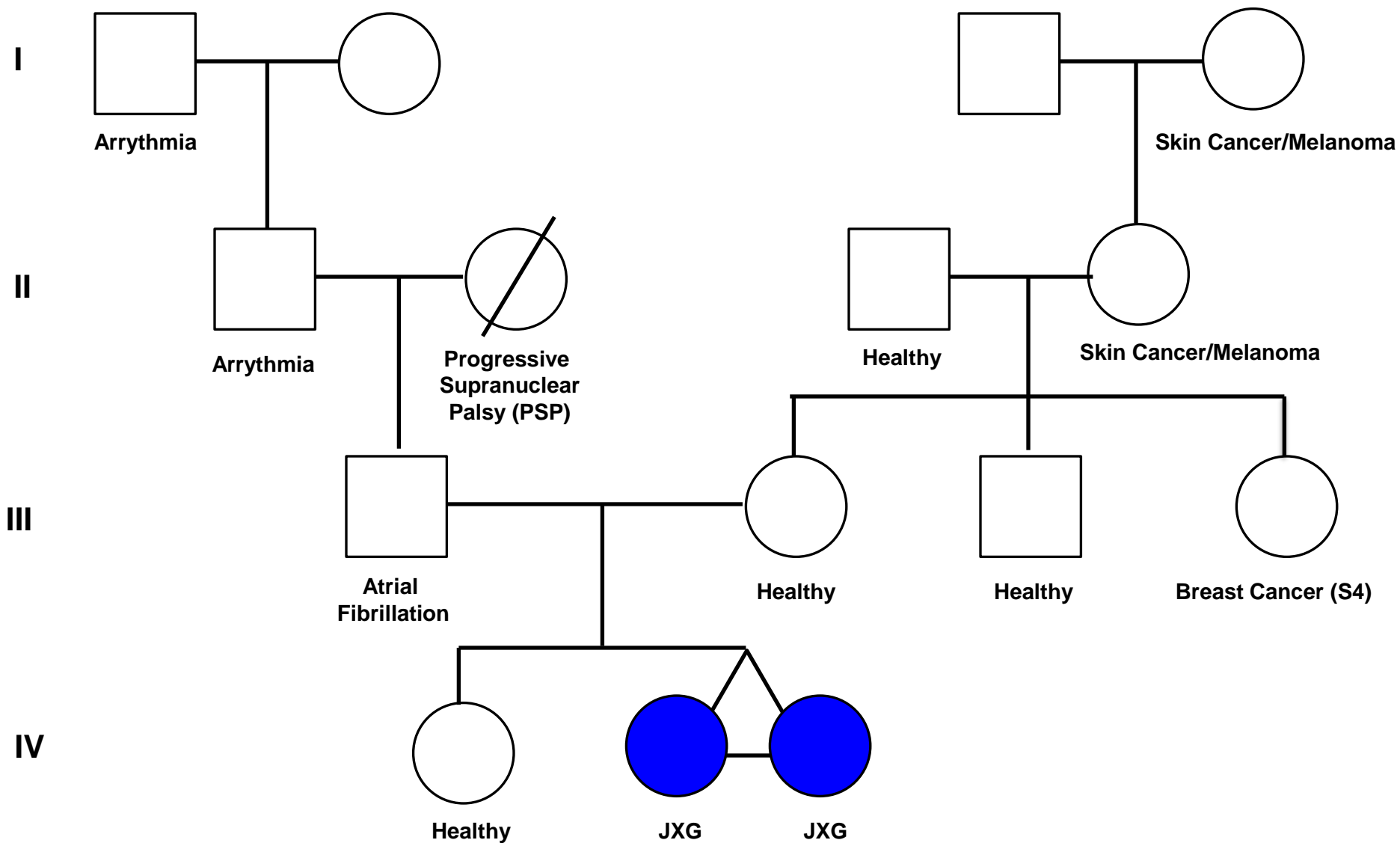


# Shared Somatic *CSF1R* Mutations in Monozygotic Twins with JXG

Monozygotic, dichorionic  
Identical twin girls

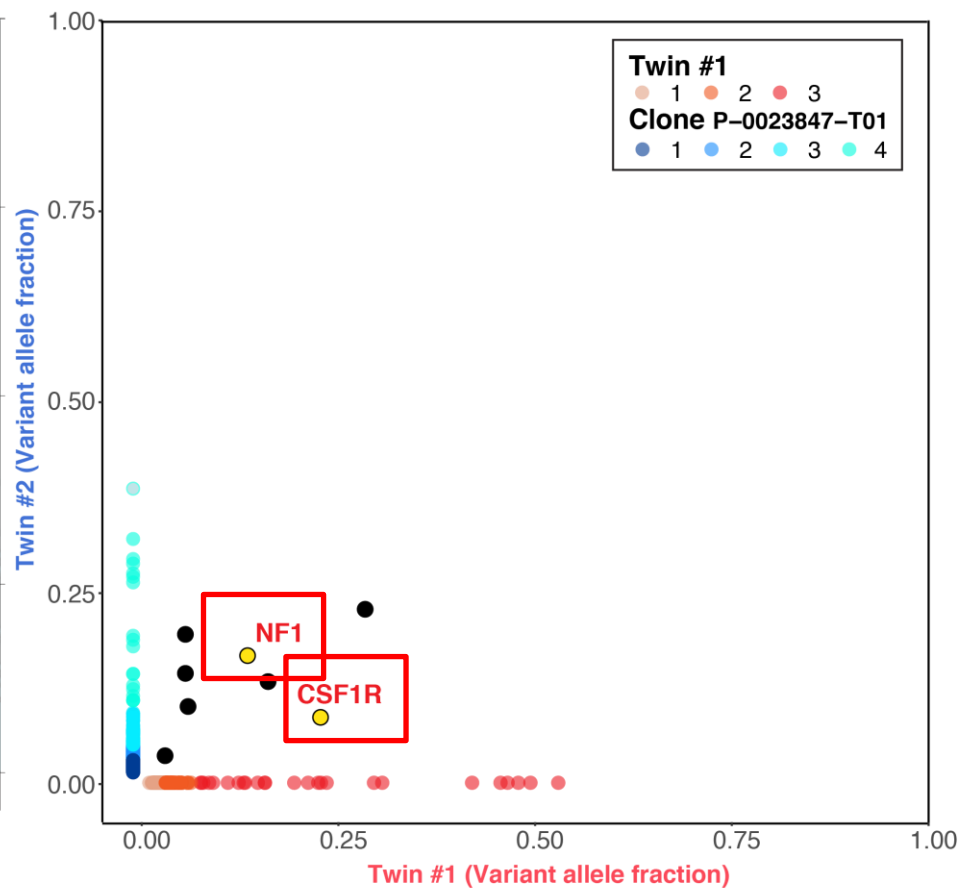


# JXG in Monozygotic Twins – Family History



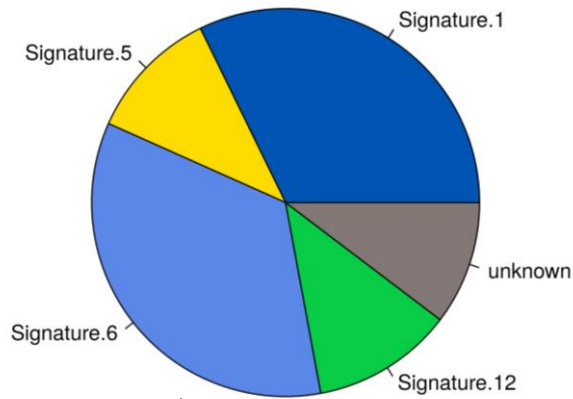
# Somatic *CSF1R* Y546\_K551del and *NF1* E19\* Shared Mutations in the Largest JXG Clone in Monozygotic Twins

Twin 2

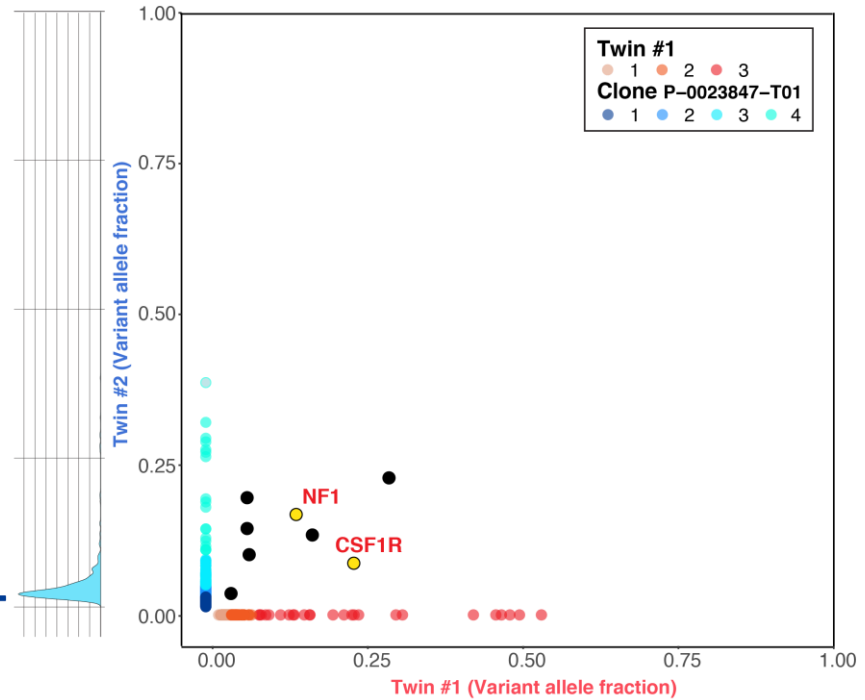


# Mutational Signatures in the JXG Twins

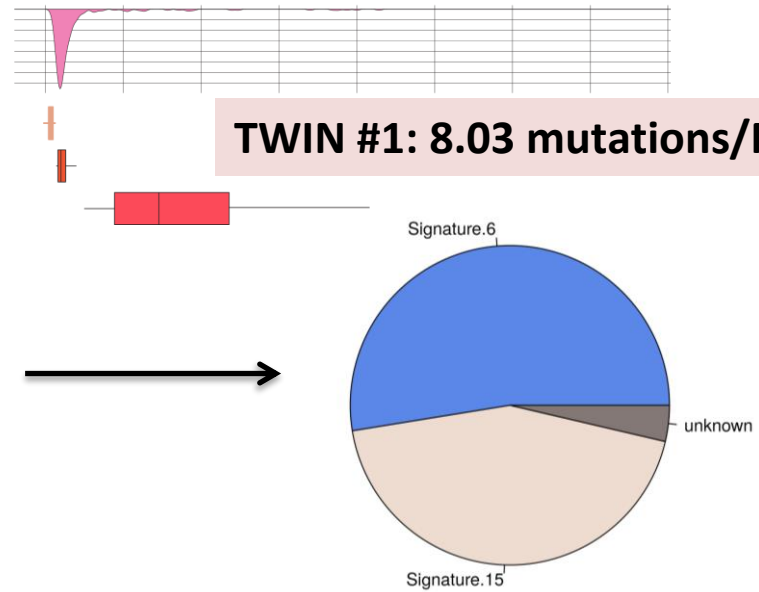
**TWIN #2: 42.5 mutations/Mb**



**Defective DNA Mismatch Repair (MMR)**



**TWIN #1: 8.03 mutations/Mb**



# Conclusions

- Diverse **kinase mutations** and **fusions** continue to drive systemic histiocytic neoplasms with recurrent ***BRAF* deletions** and **fusions** now identified in **LCH** and the first ***RET* fusion** uncovered in the histiocytoses.
- Recurrent, activating ***CSF1R*** mutations are first identified in multiple histiocytoses.
- Description of first ***MAP2K2*** (MEK2), ***MAPK7*** (ERK5), ***MAPK3*** (ERK1) ***ALK***, ***CSF1R***, ***KIT***, ***RAF1***, ***MET***, ***JAK3***, and ***CSF3R*** mutations in the histiocytoses. There is an enrichment of ***NTRK1* fusions** in **JXG**, ***BRAF* fusions** in **LCH**, and ***ALK* fusions** in **ECD** compared to other histiocytoses in this cohort.
- Kinase alterations other than ***BRAF*<sup>V600E</sup>** may have **direct therapeutic implications**:

## Genetic Alterations

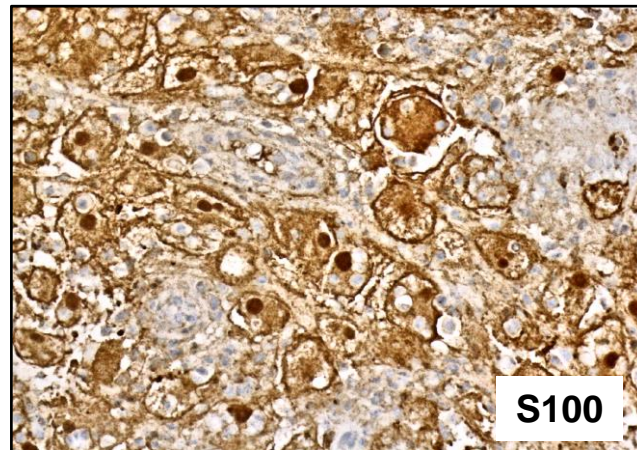
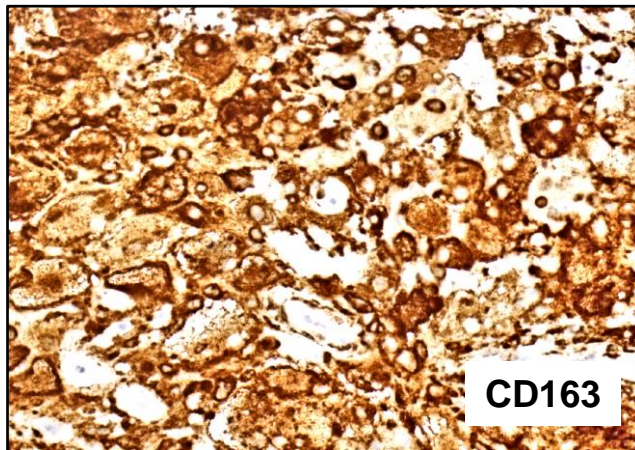
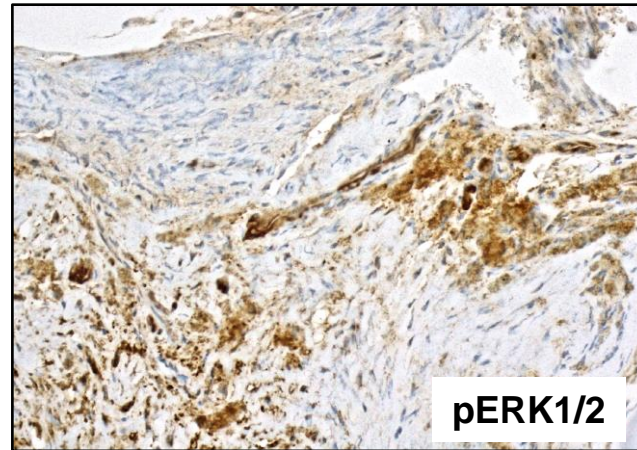
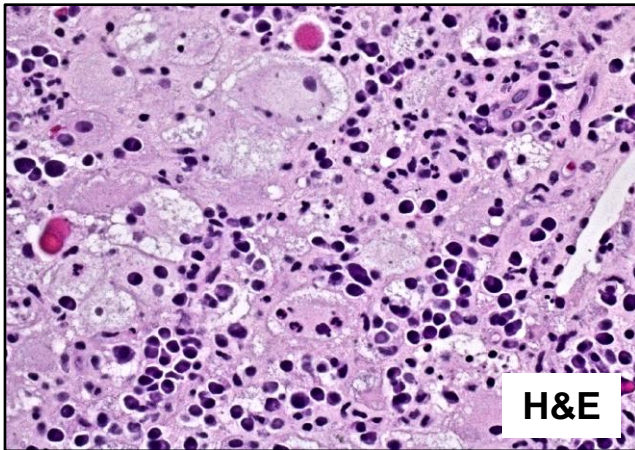
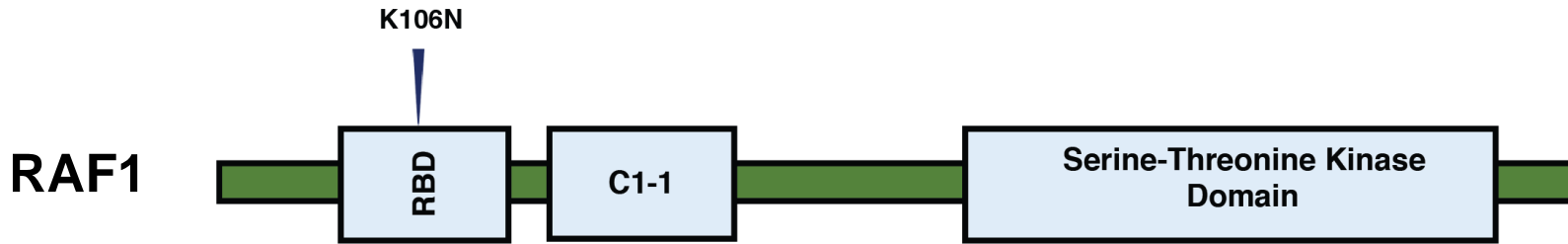
<b><i>BRAF</i> V600E</b>	<b><i>MAP2K1/2</i> mutations</b>	<b>Other <i>RAF</i> mutations</b>	<b><i>BRAF</i> fusions</b>	<b>Other MAPK mutations</b>	<b><i>ALK</i> fusions</b>	<b><i>NTRK</i> fusions</b>
<b>Vemurafenib Debrafenib</b>	<b>MEK inhibition</b>				<b>ALK inhibition</b>	<b><i>NTRK</i> inhibition</b>
<b>Interferon, Anakinra, other non-kinase drugs</b>						

## Therapy

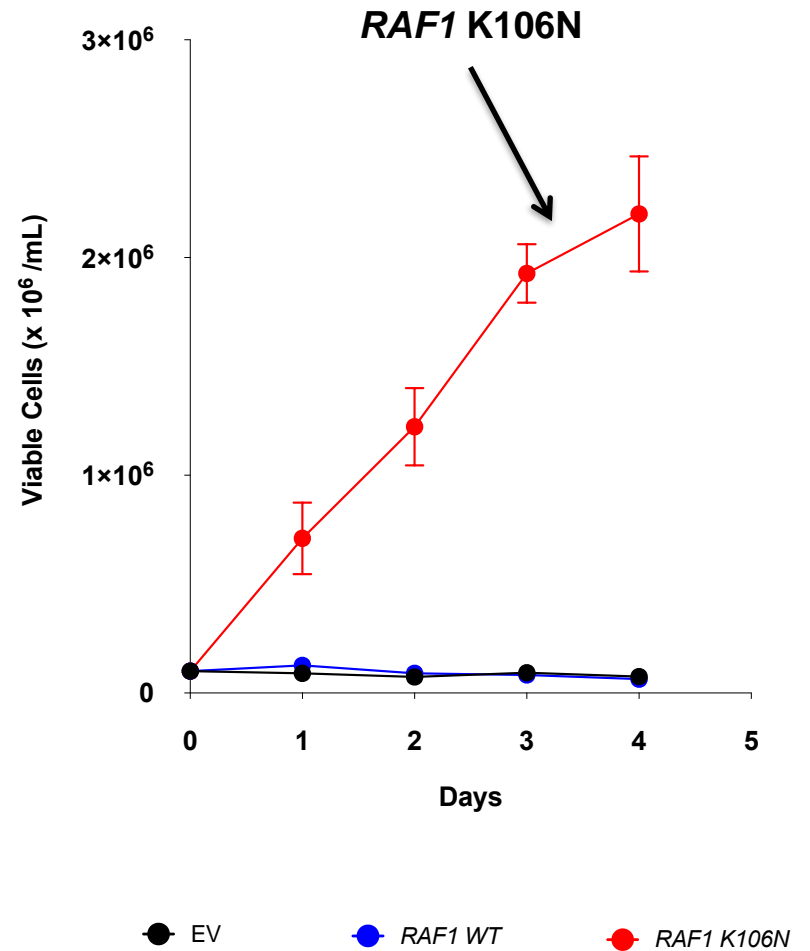
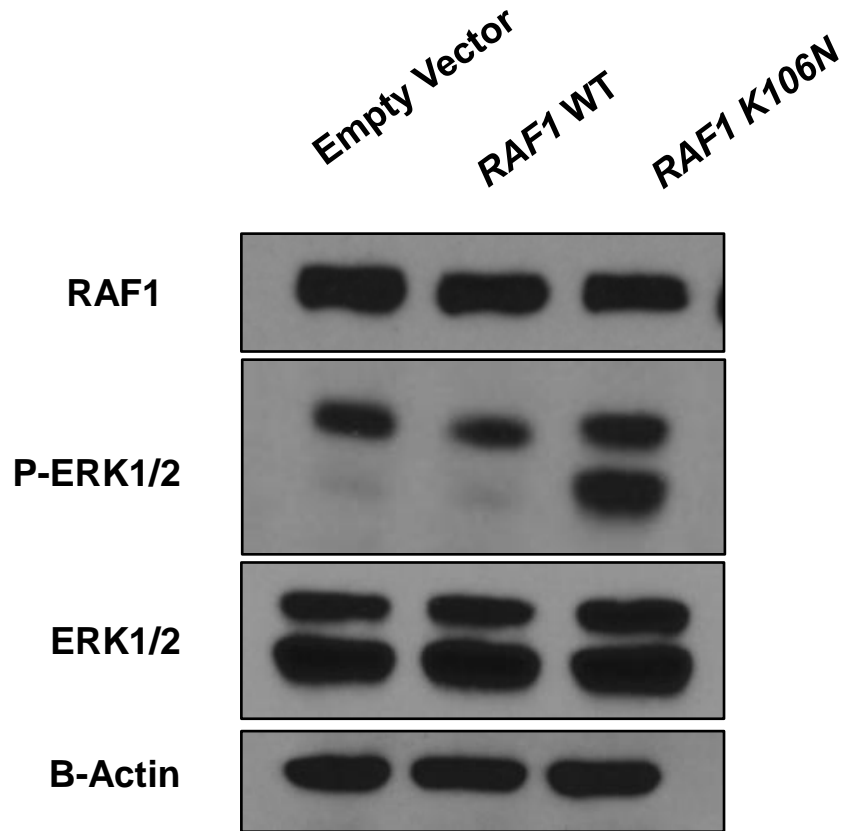
# Outline

- **Published Kinase Alterations in the Histiocytoses**
- **New Insights into the Molecular Pathogenesis of the Histiocytoses**
- **Emergence of Targeted Therapeutics in the Histiocytic Neoplasms**

# MEK Inhibitor Response in *RAF1*<sup>K106N</sup> ECD/RDD

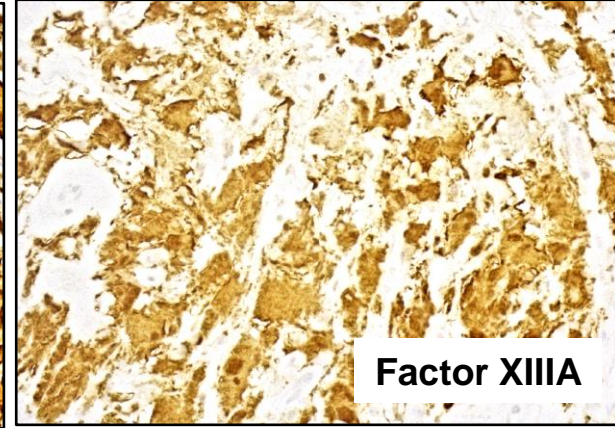
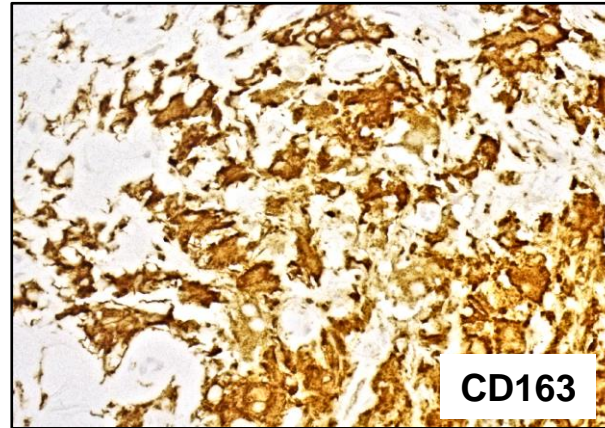
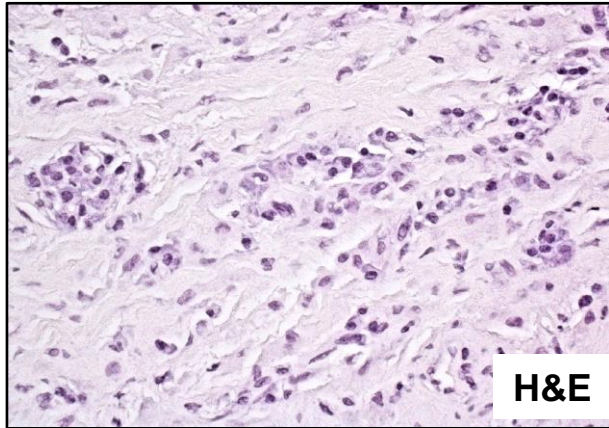


# RAF1 K106N Mutation in ECD is Activating

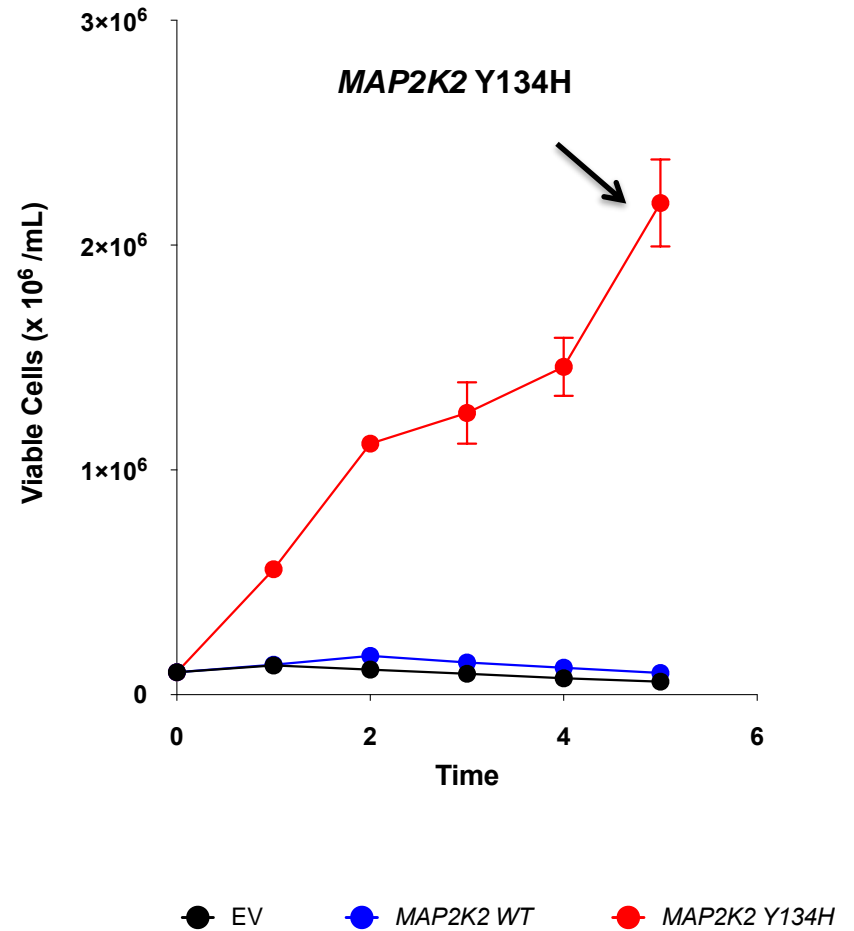
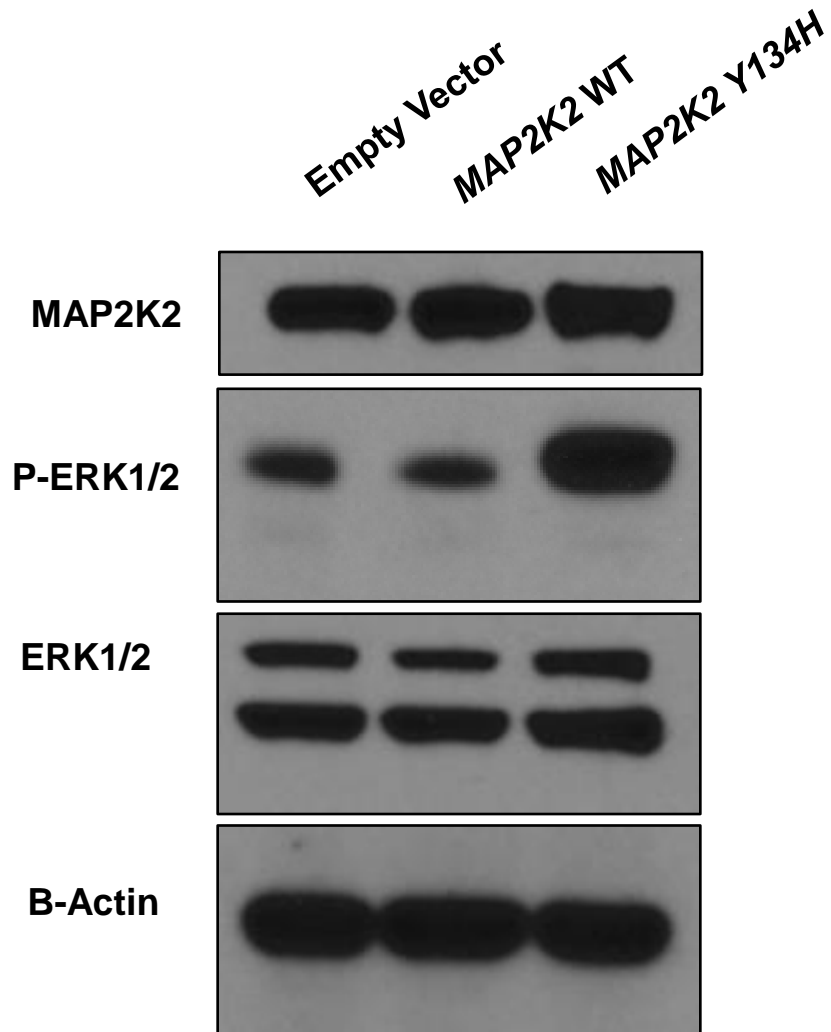


# MEK Inhibitor Response in *MAP2K2*<sup>Y134H</sup> ECD

MEK2

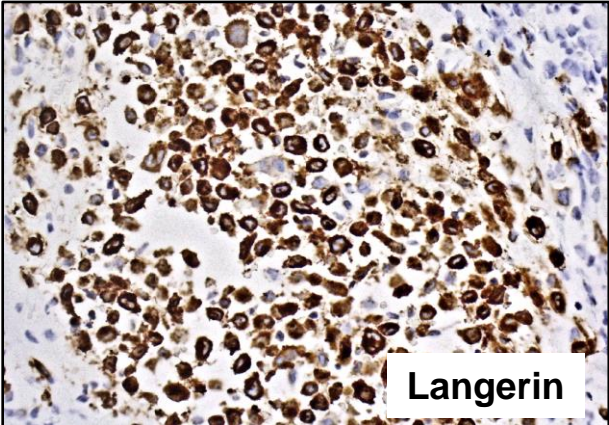
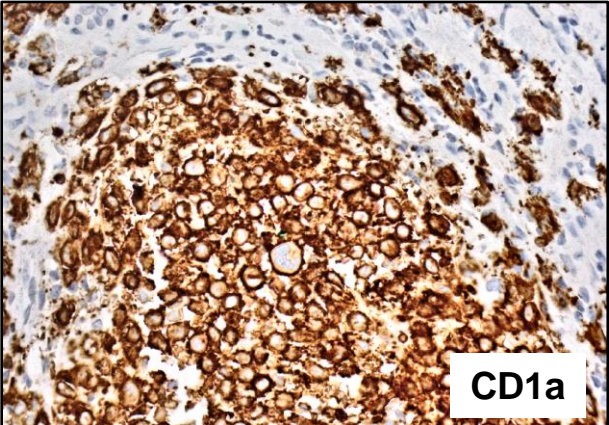
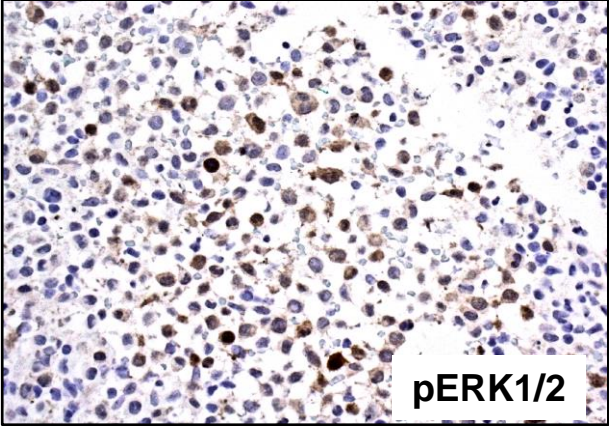
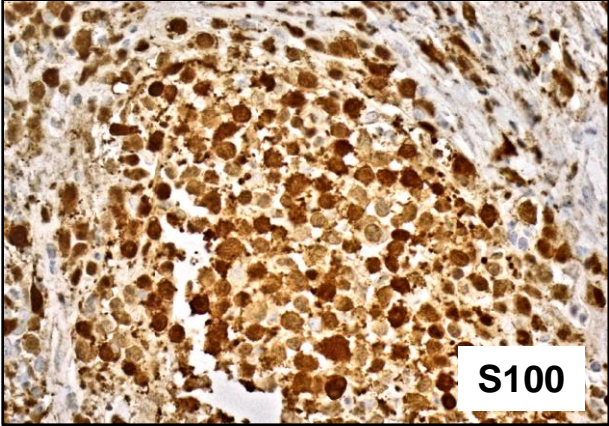
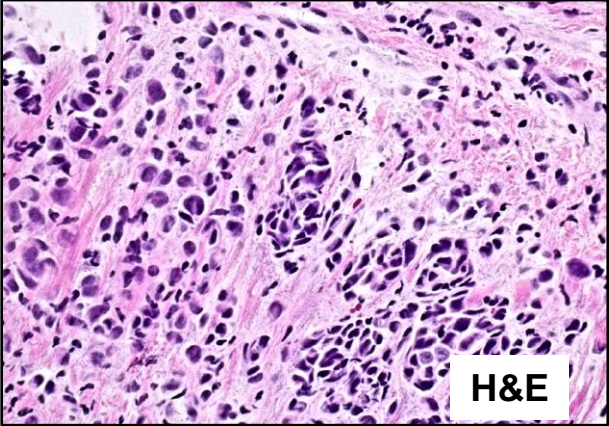
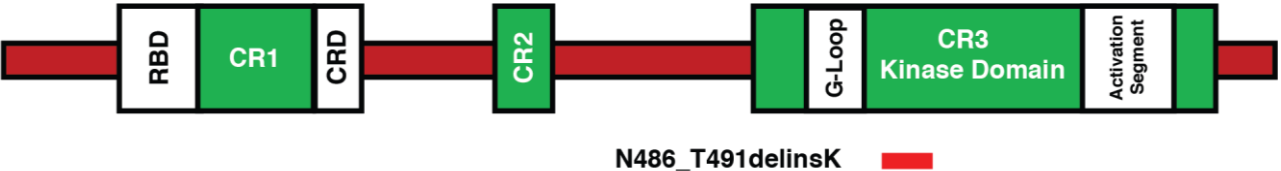


# MAP2K2 Y134H Mutation in ECD is Activating

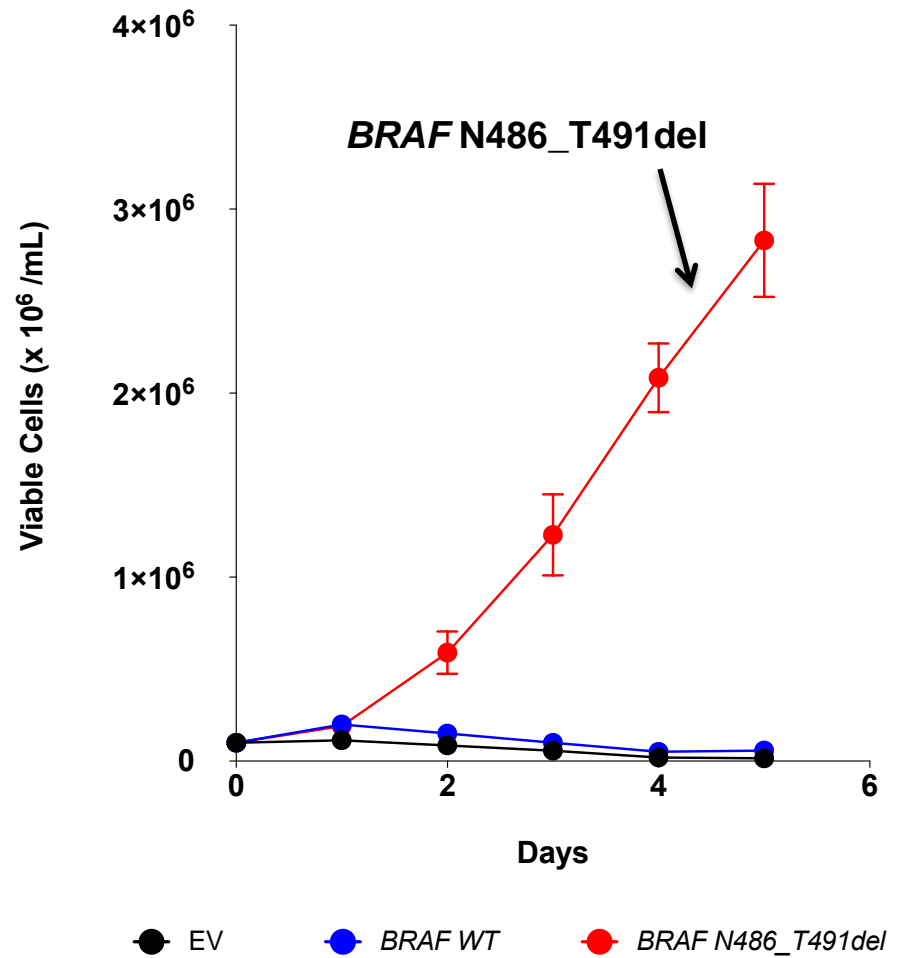
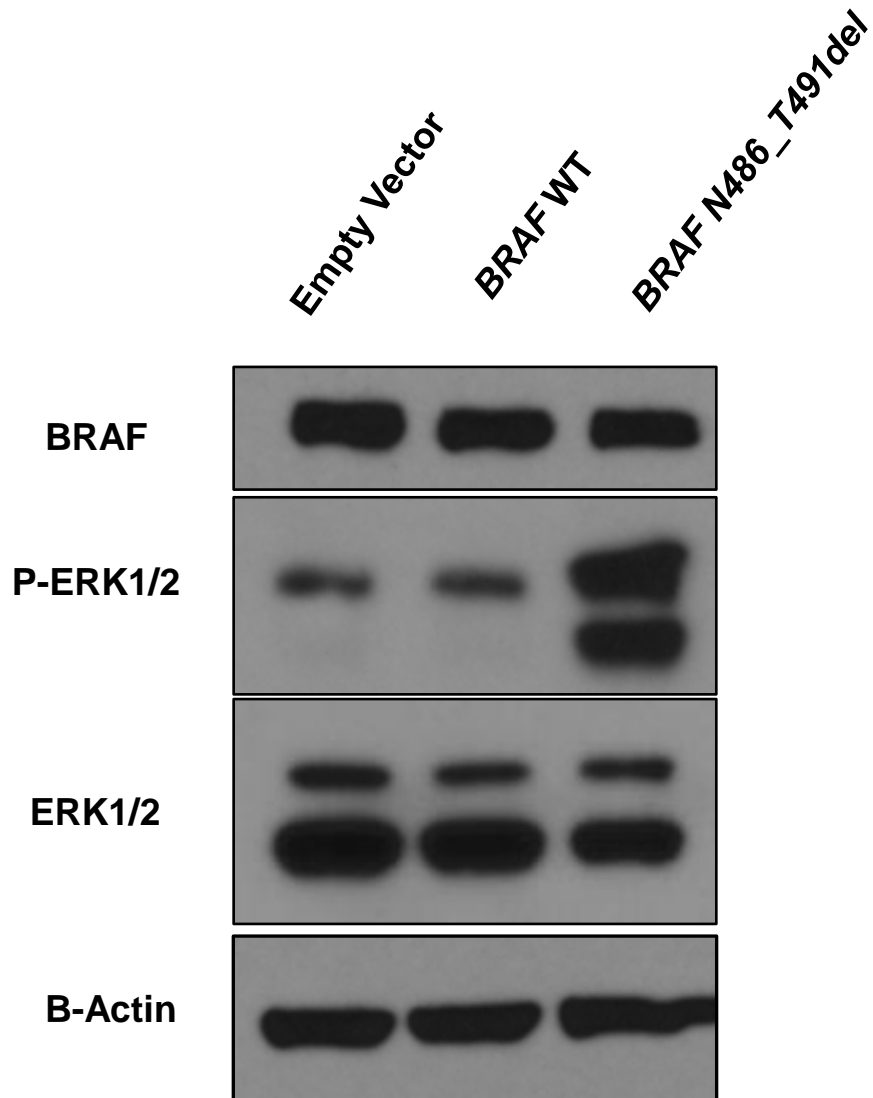


# MEK Inhibitor Response in *BRAF*<sup>N486\_T491delinsK</sup> Refractory LCH

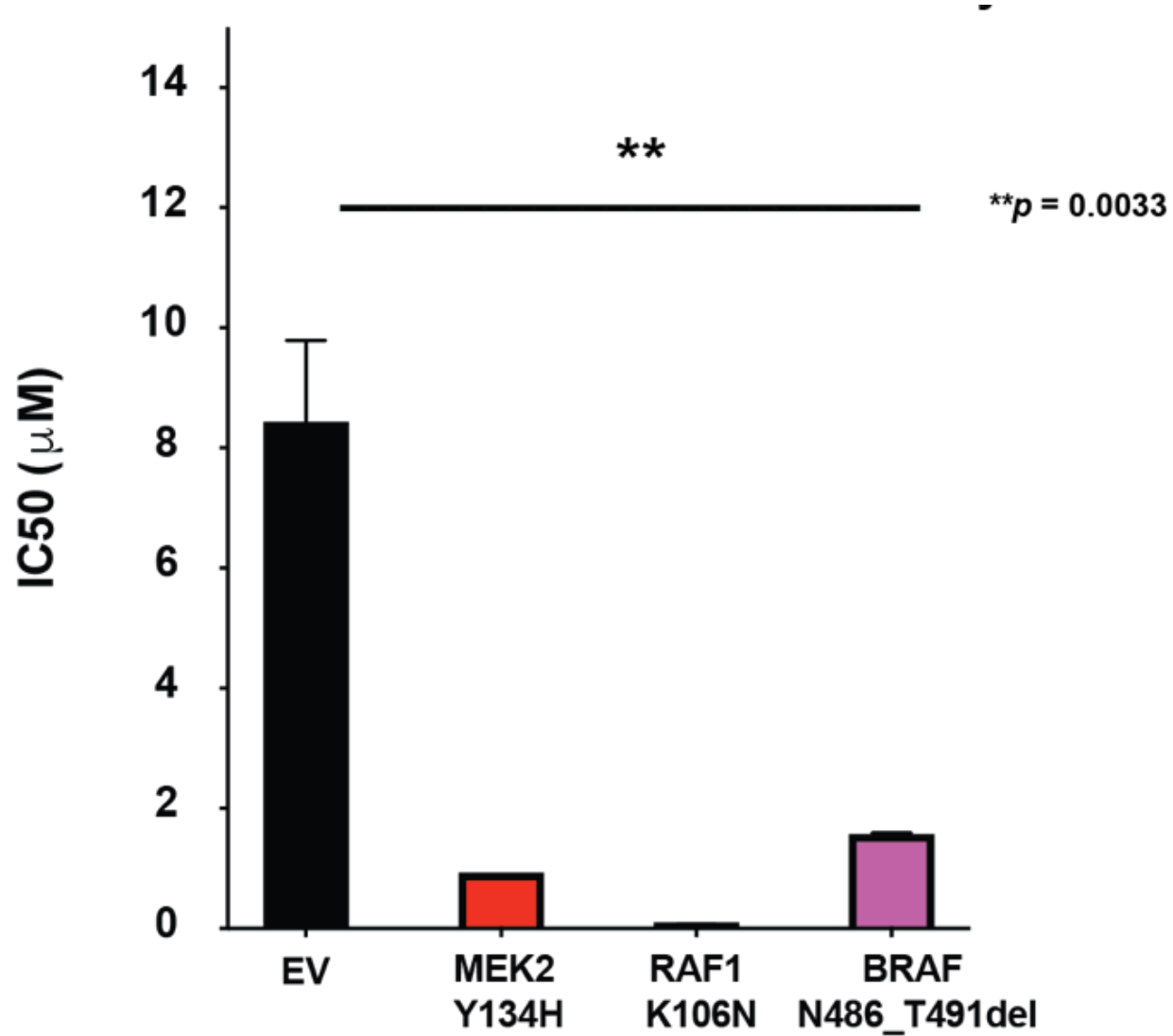
BRAF



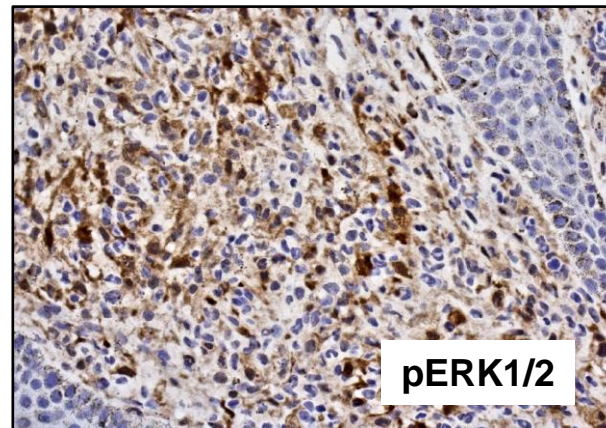
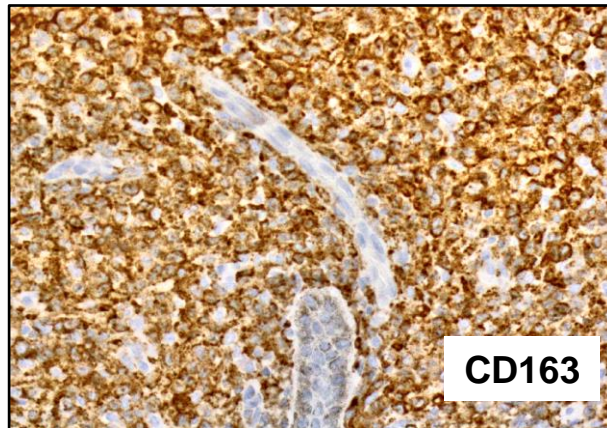
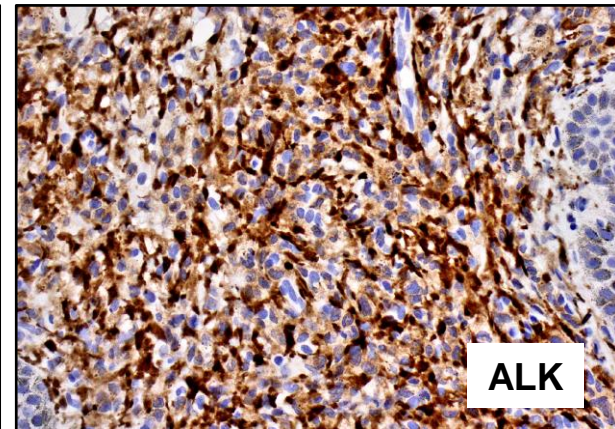
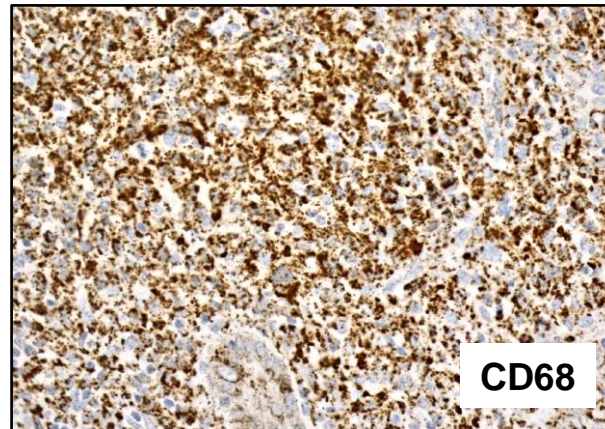
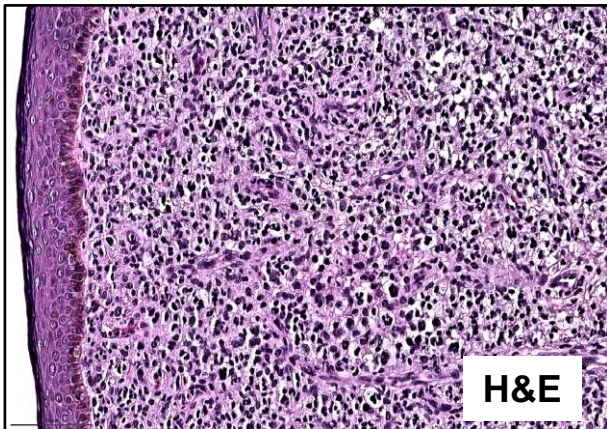
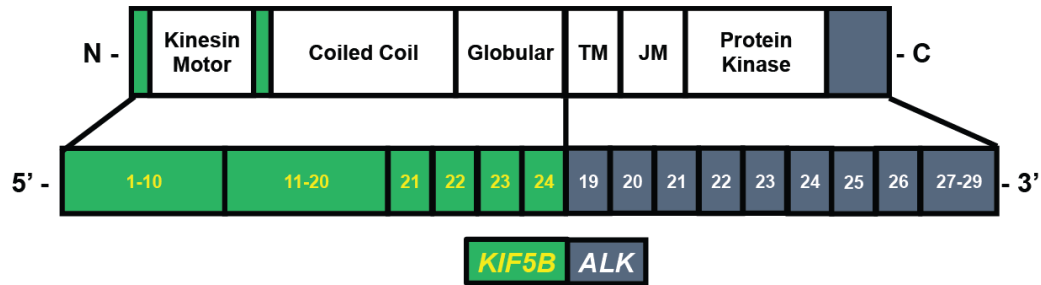
# *BRAF* N486\_T491del Mutation in LCH is Activating



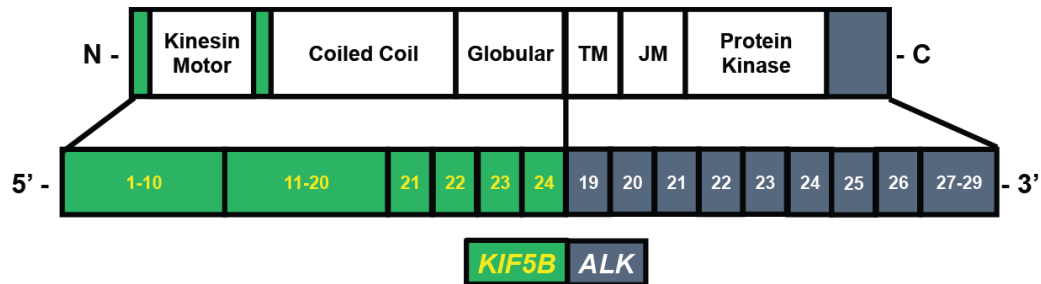
# Diverse Kinase Mutations are Sensitive to Cobimetinib



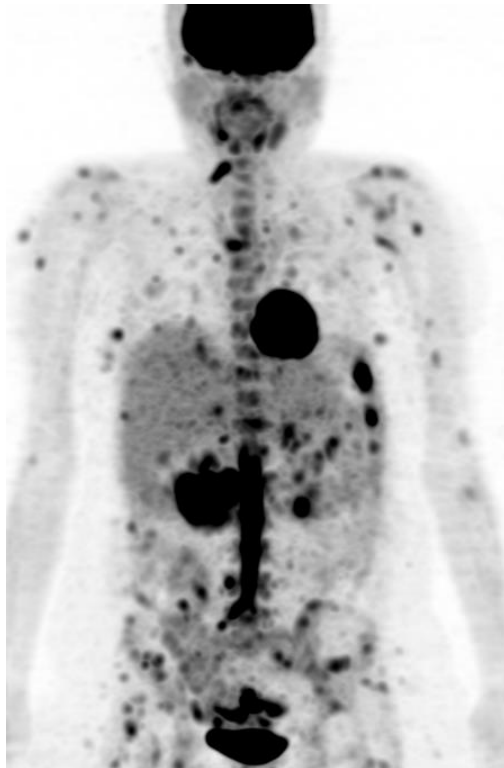
# ALK Inhibitor Response in *KIF5B-ALK* Fusion ECD



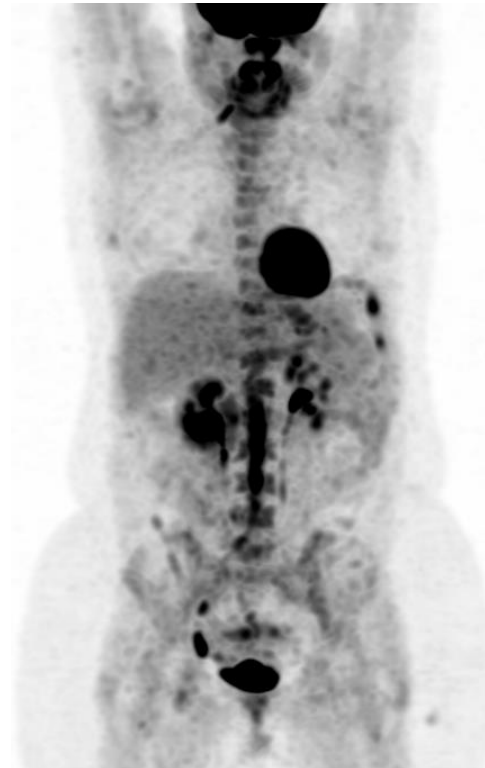
# ALK Inhibitor Response in *KIF5B-ALK* Fusion ECD



Pre-Treatment



Post-Treatment



# Conclusions II

- Kinase alterations other than *BRAF*<sup>V600E</sup> have direct therapeutic implications.
- First evidence of ALK inhibitor use and response in the systemic histiocytoses
- Single-agent cobimetinib has robust activity across histiocytic neoplasms regardless of *BRAF* mutational status
  - ECD, LCH, and RDD

# THANK YOU

## Memorial Sloan Kettering Cancer Center New York, NY, United States



**Omar Abdel-Wahab**



**Eli Diamond**

### Abdel-Wahab Lab

- **Alessandro Pastore**
- **Eunhee Kim**
- **Aki Yoshimi**
- **Justin Taylor**
- Stan Lee
- Young Rock Chung
- Daichi Inoue
- Syd Lu
- Hana Cho
- Michelle Ki
- Lillian Bitner

### Developmental Therapeutics

- **David Hyman**

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- **Yijun Gao**

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## Funding Sources



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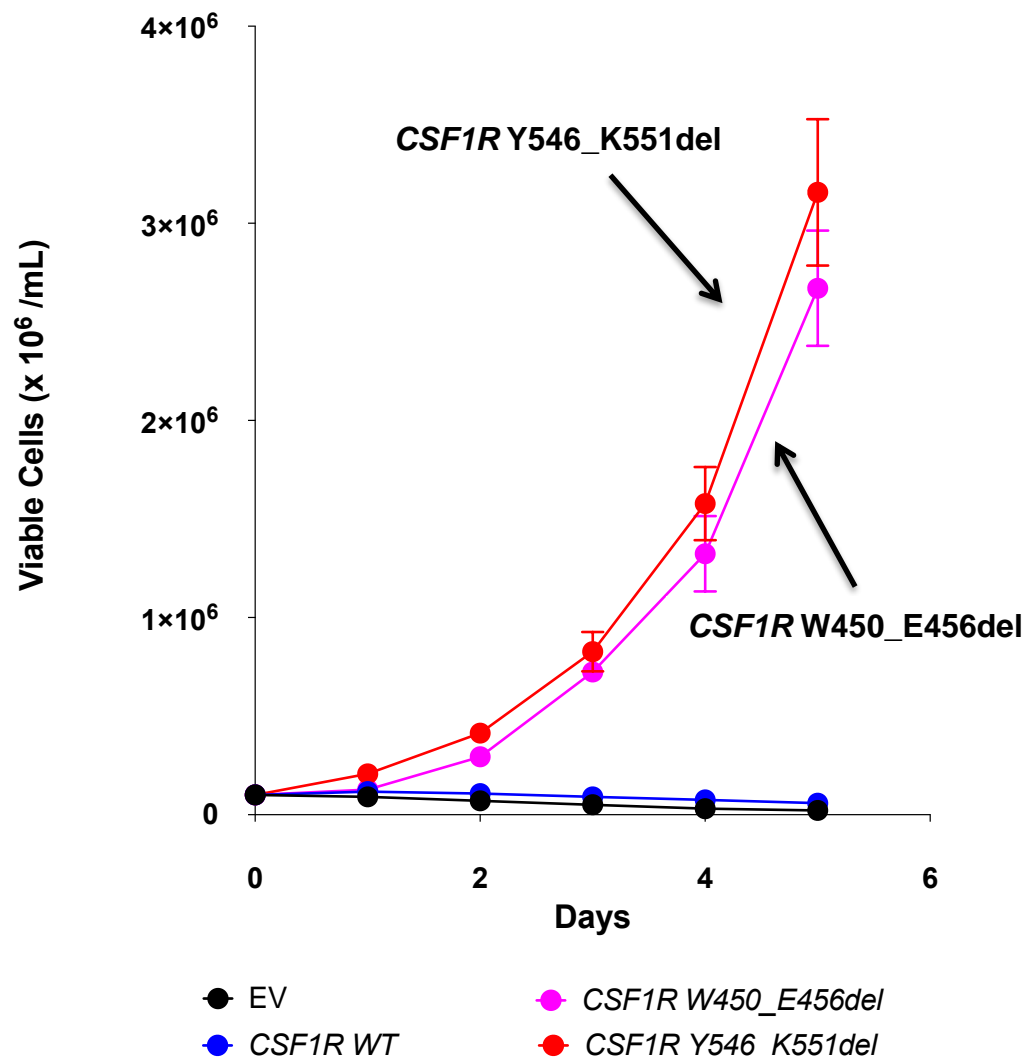
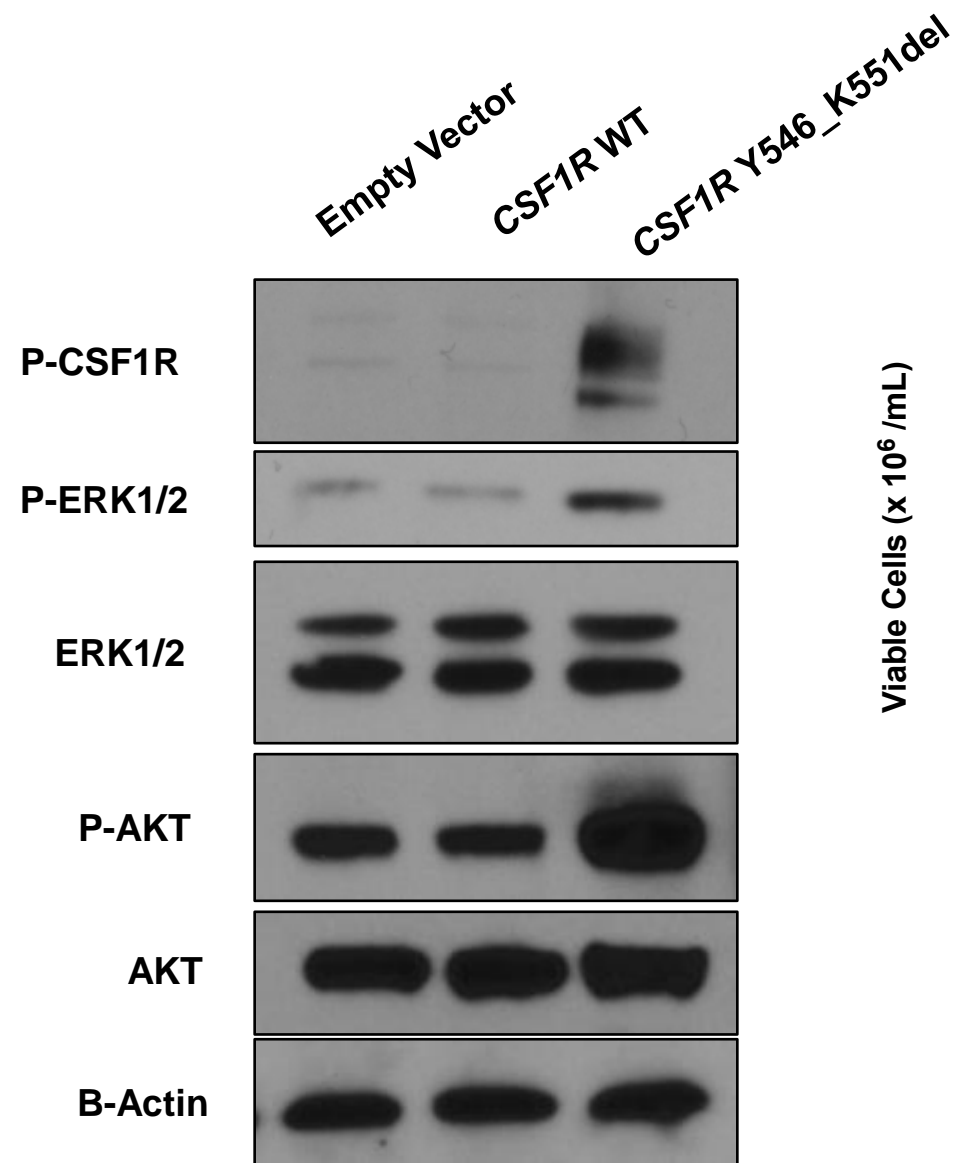


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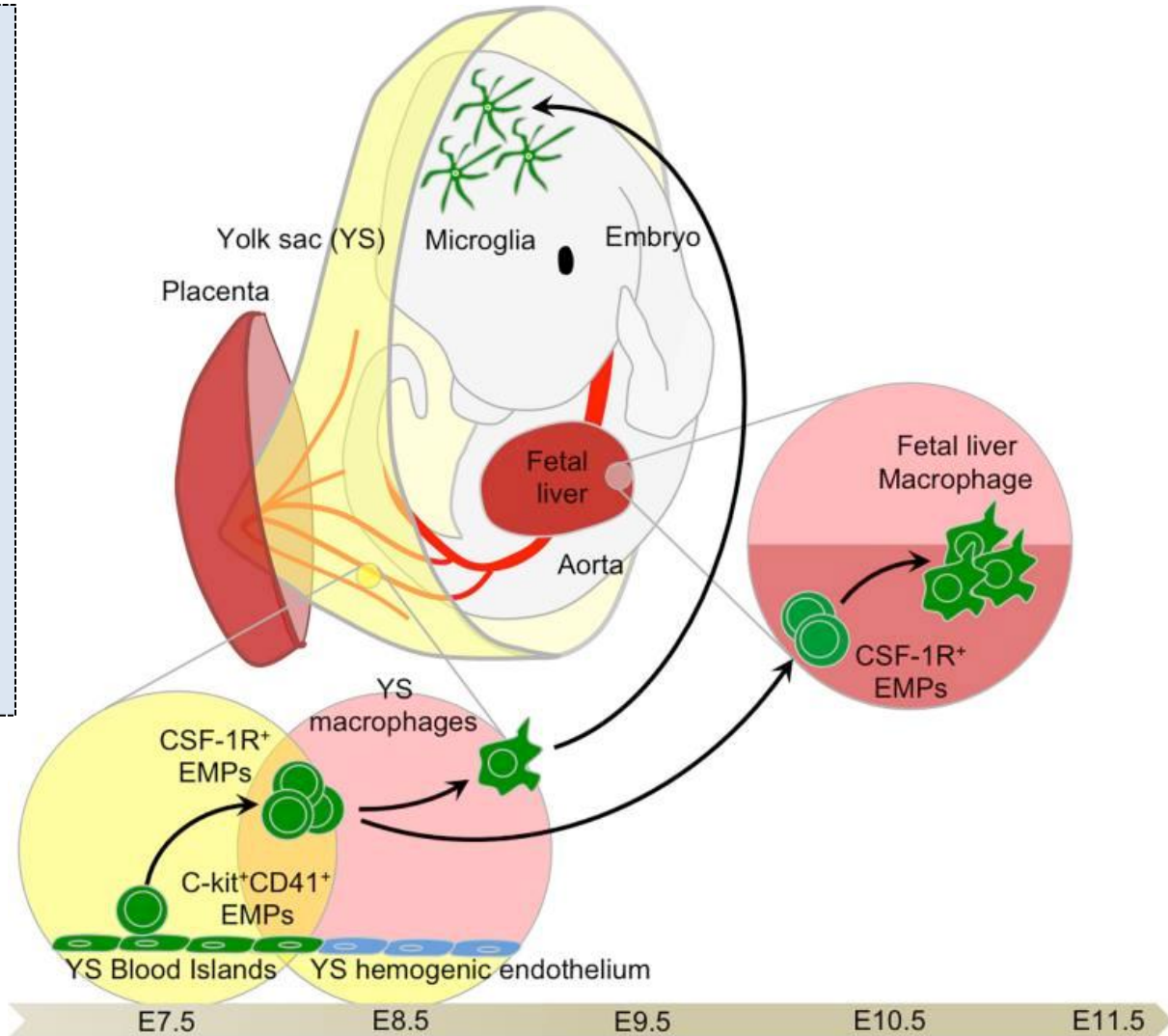
# CSF1R Y546\_K551del and CSF1R W450\_E456del Mutations in Histiocytoses are Activating



# How do we explain shared somatic mutations in twins with histiocytosis?

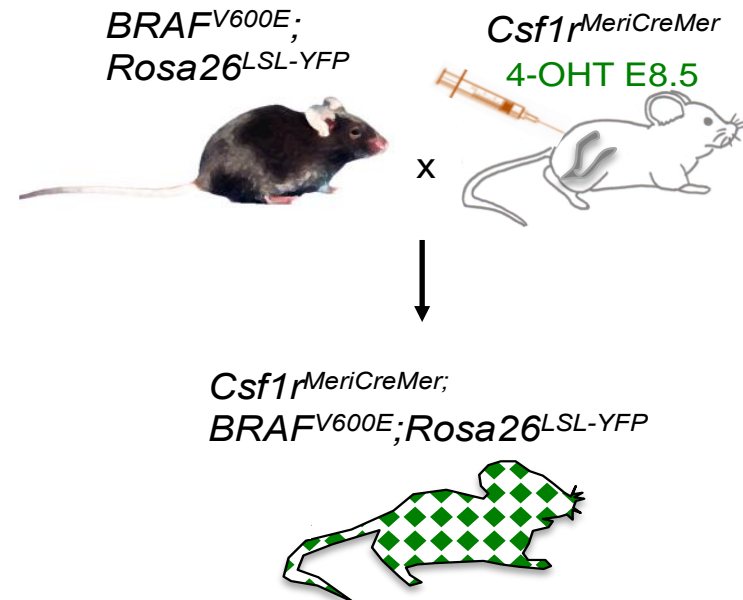
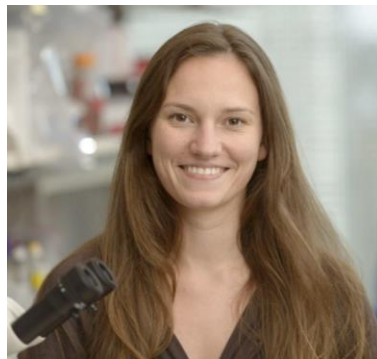
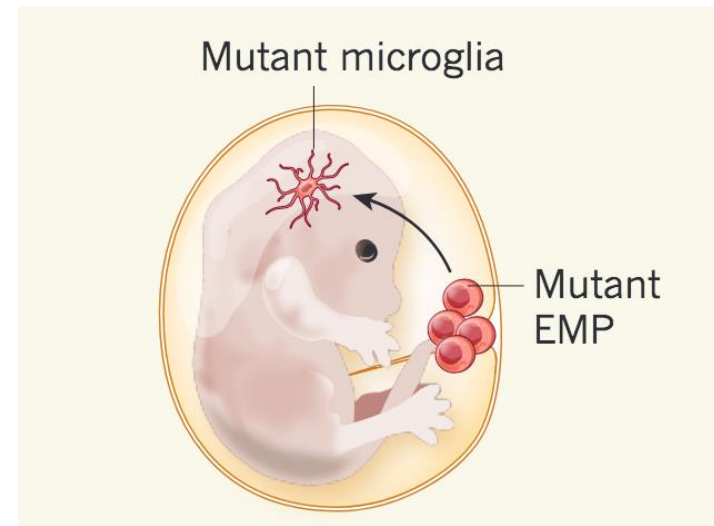
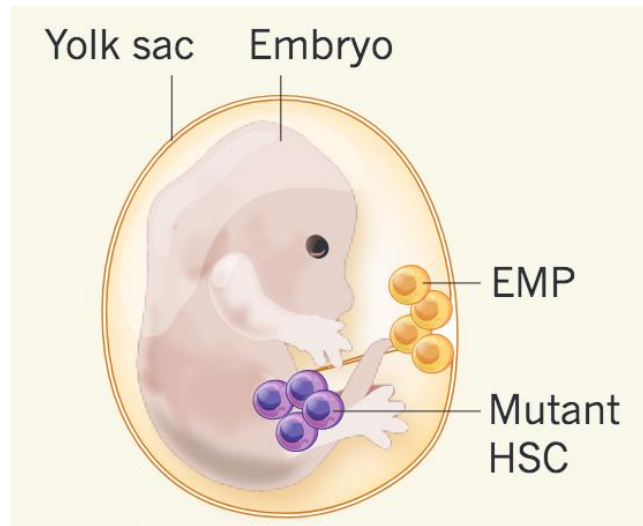
*CSF1R* drives the development of tissue-resident macrophages from progenitors in the fetal yolk sac outside of the animal's body.

**HYPOTHESIS:** Activating *CSF1R* mutations were acquired in the fetal macrophage progenitor shared for both twins.

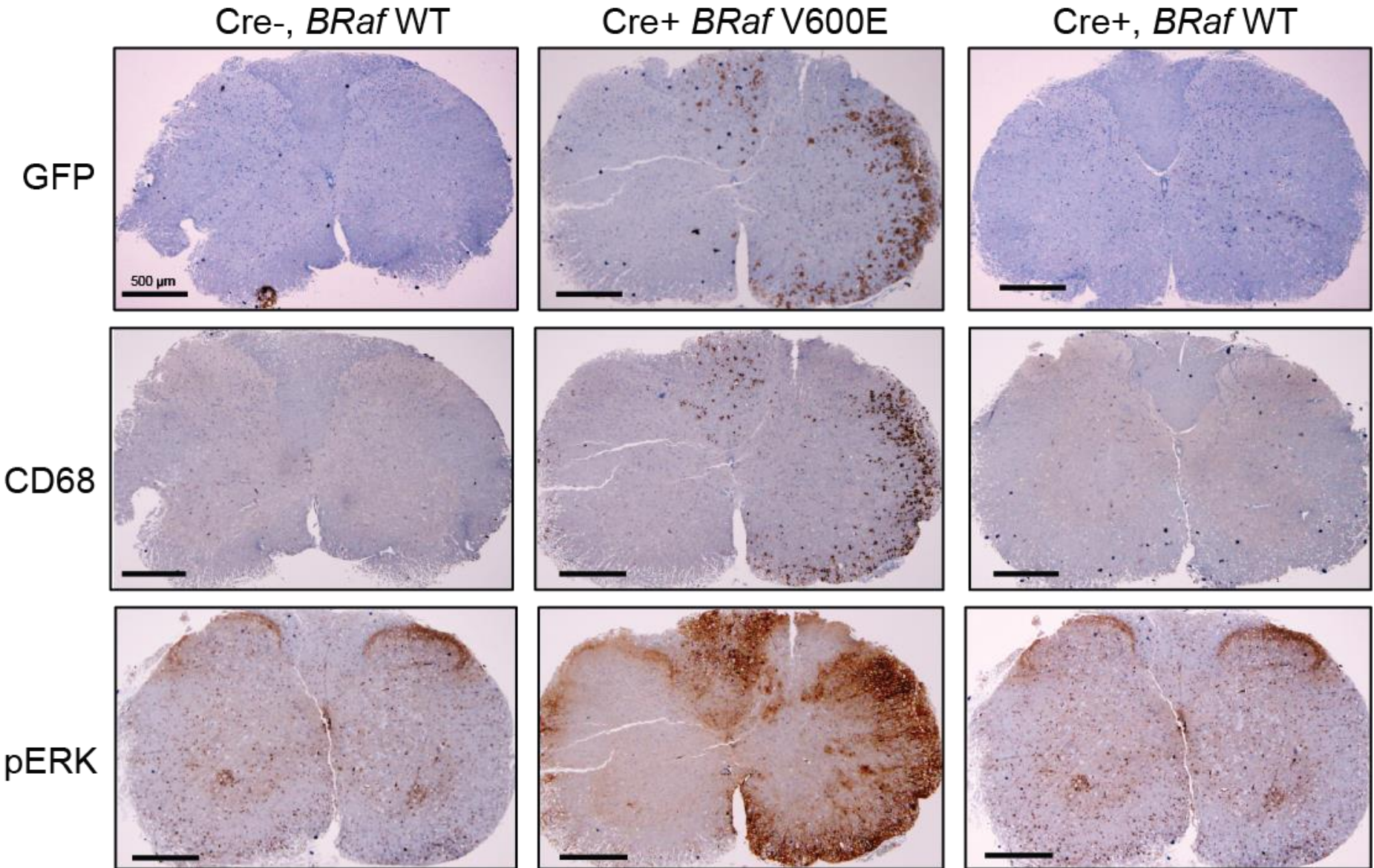


EMPs = Erythro-myeloid progenitors

# What is the effect of expressing BRAF<sup>V600E</sup> in yolk-sac precursors of macrophages?



# Neurodegeneration in *Csf1R-Cre BRaf<sup>V600E</sup>* mice



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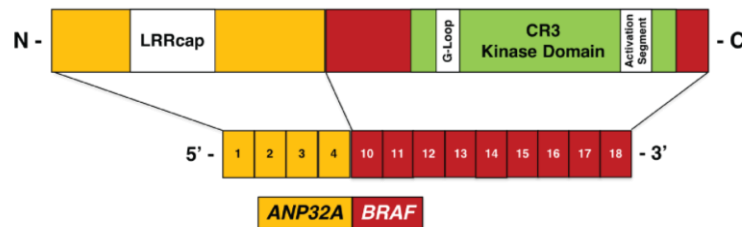
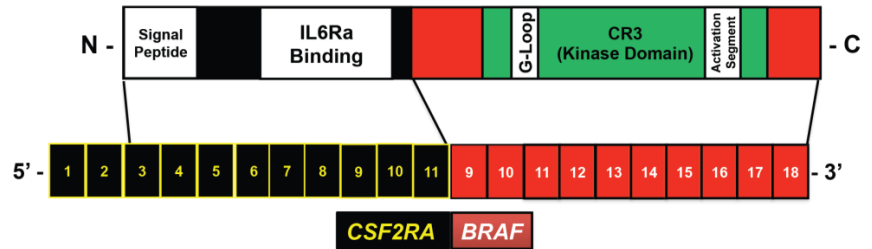
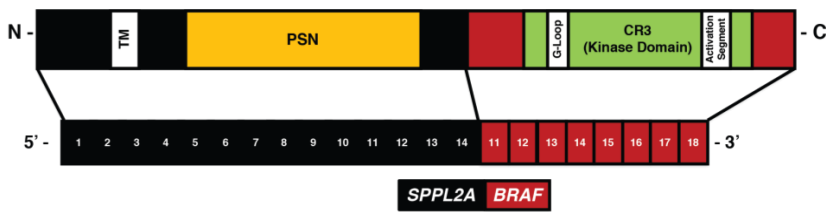
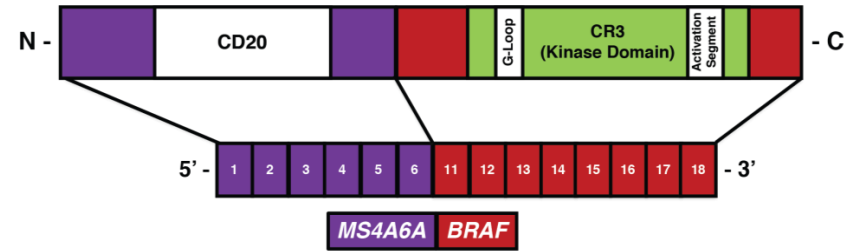
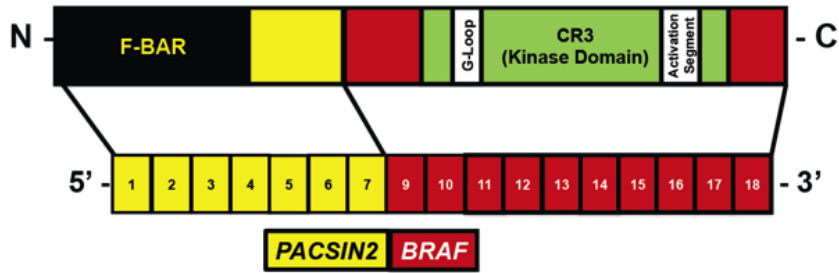
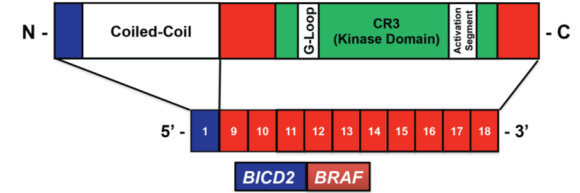
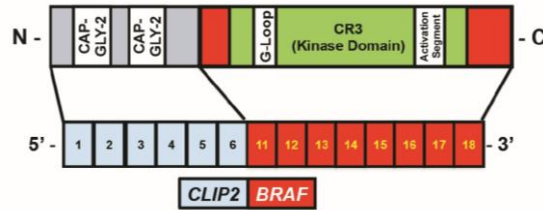
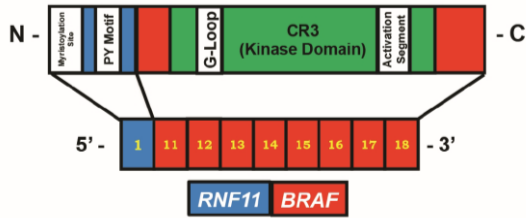


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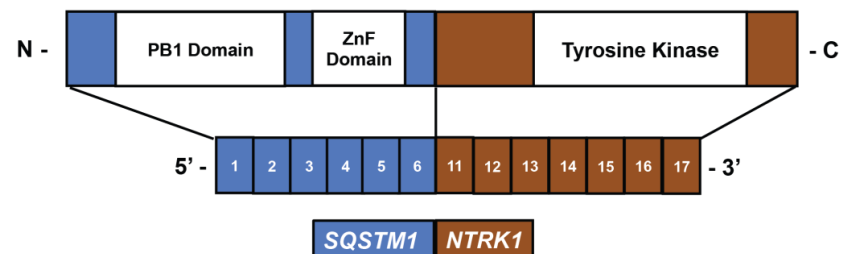
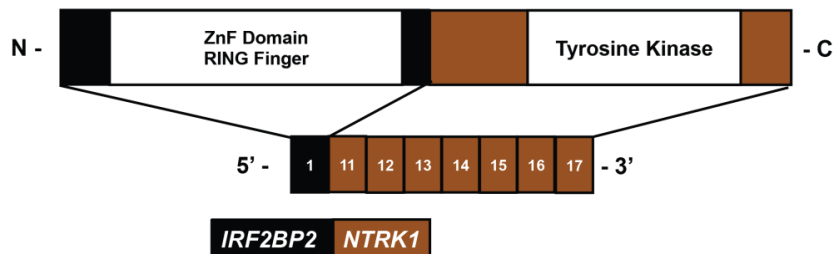
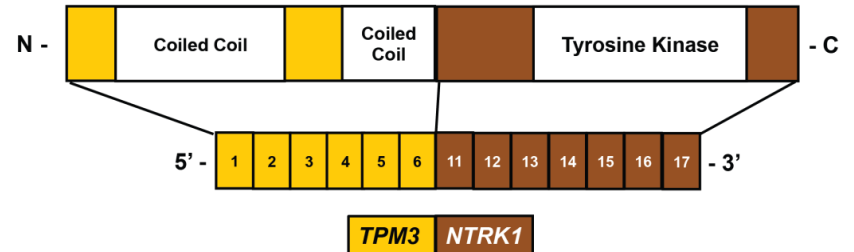
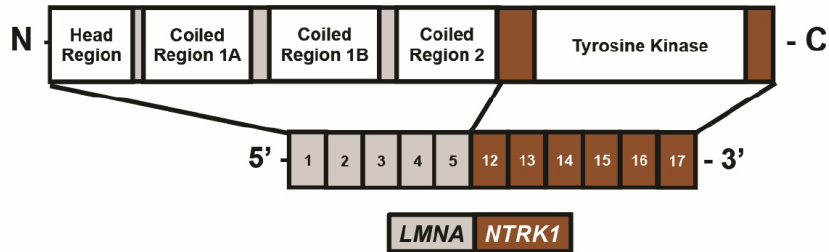
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# BRAF Fusions in LCH, JXG, ECD, and HS



# NTRK1 Fusions in ECD and JXG



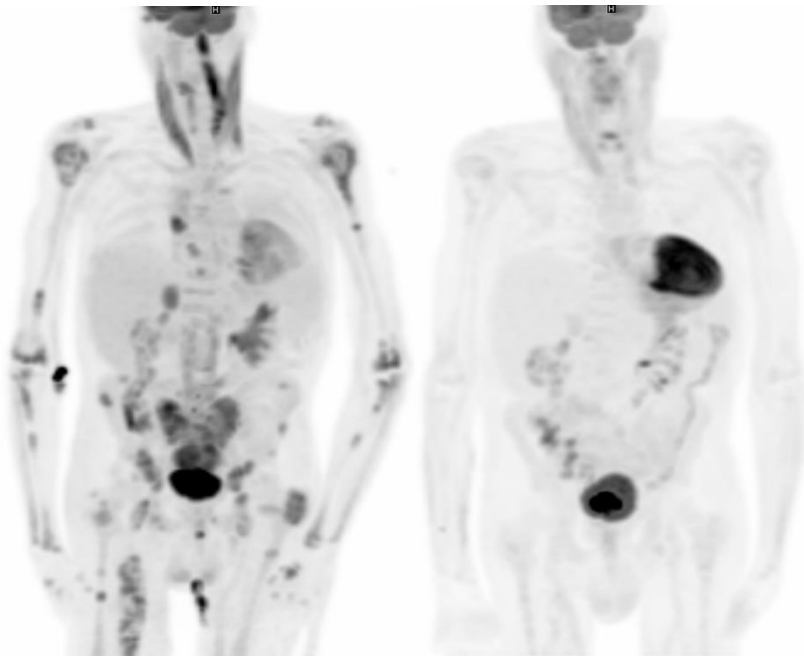
# MEK Inhibitor Response in *NRAS*<sup>Q61R</sup> ECD



*NRAS*

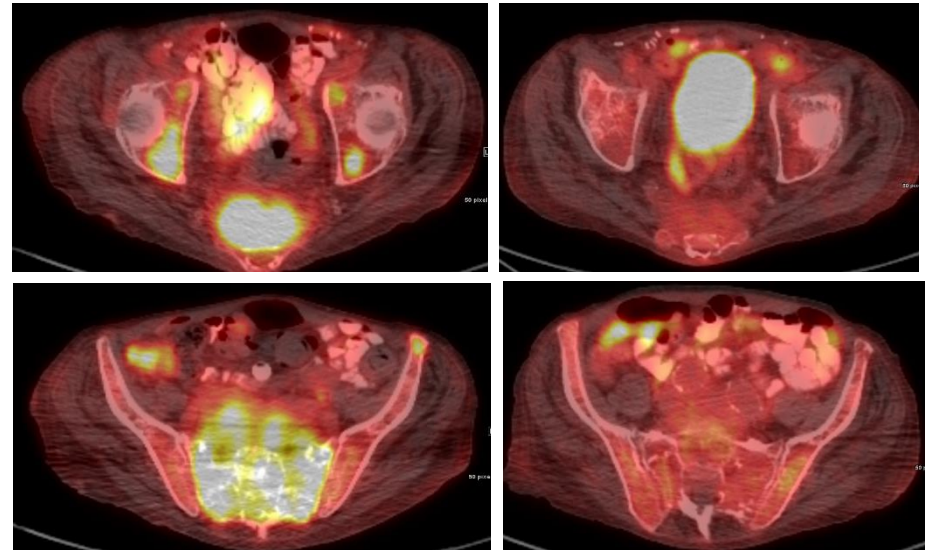
Pre-Treatment

Post-Treatment

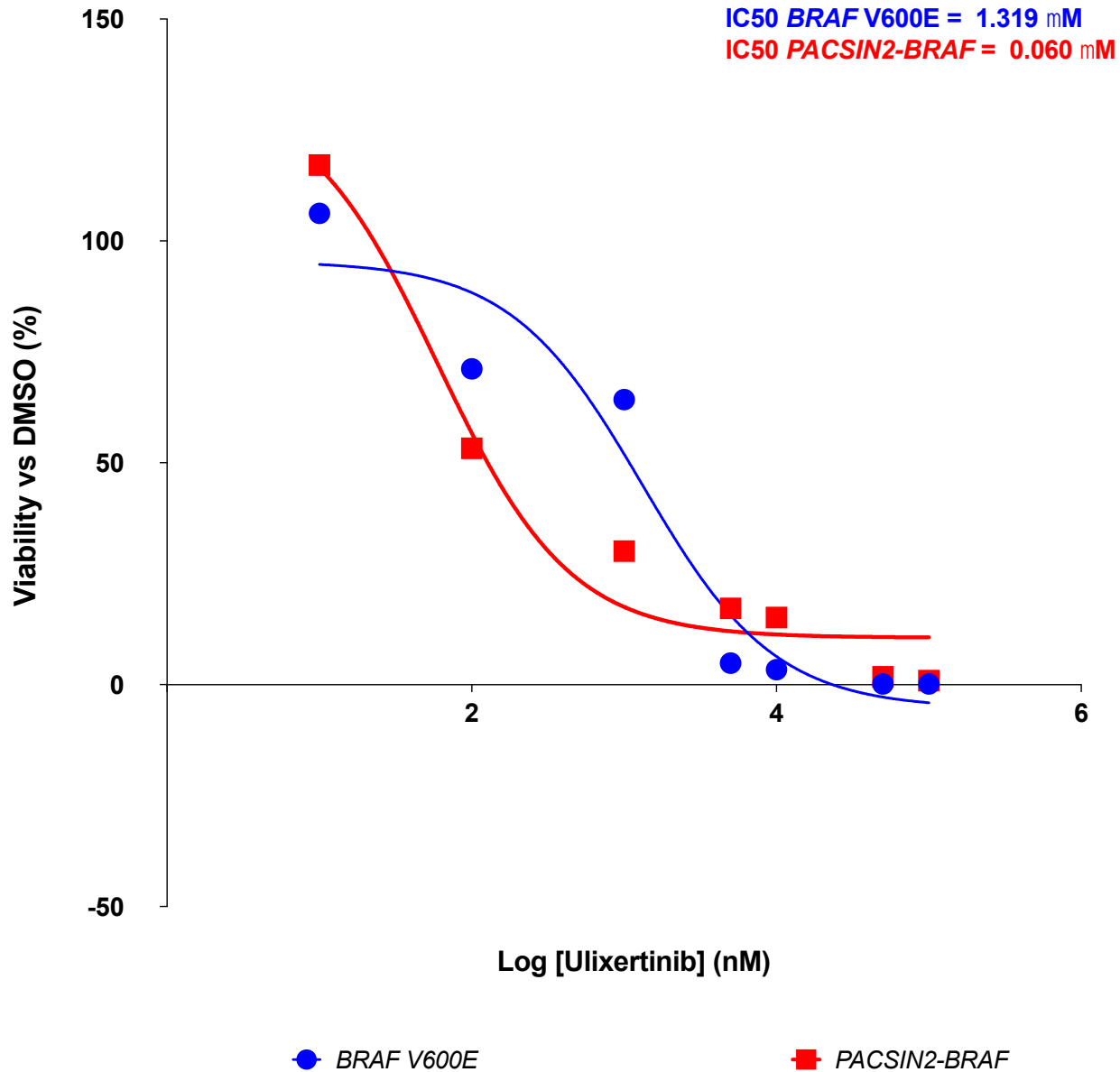


Pre-Treatment

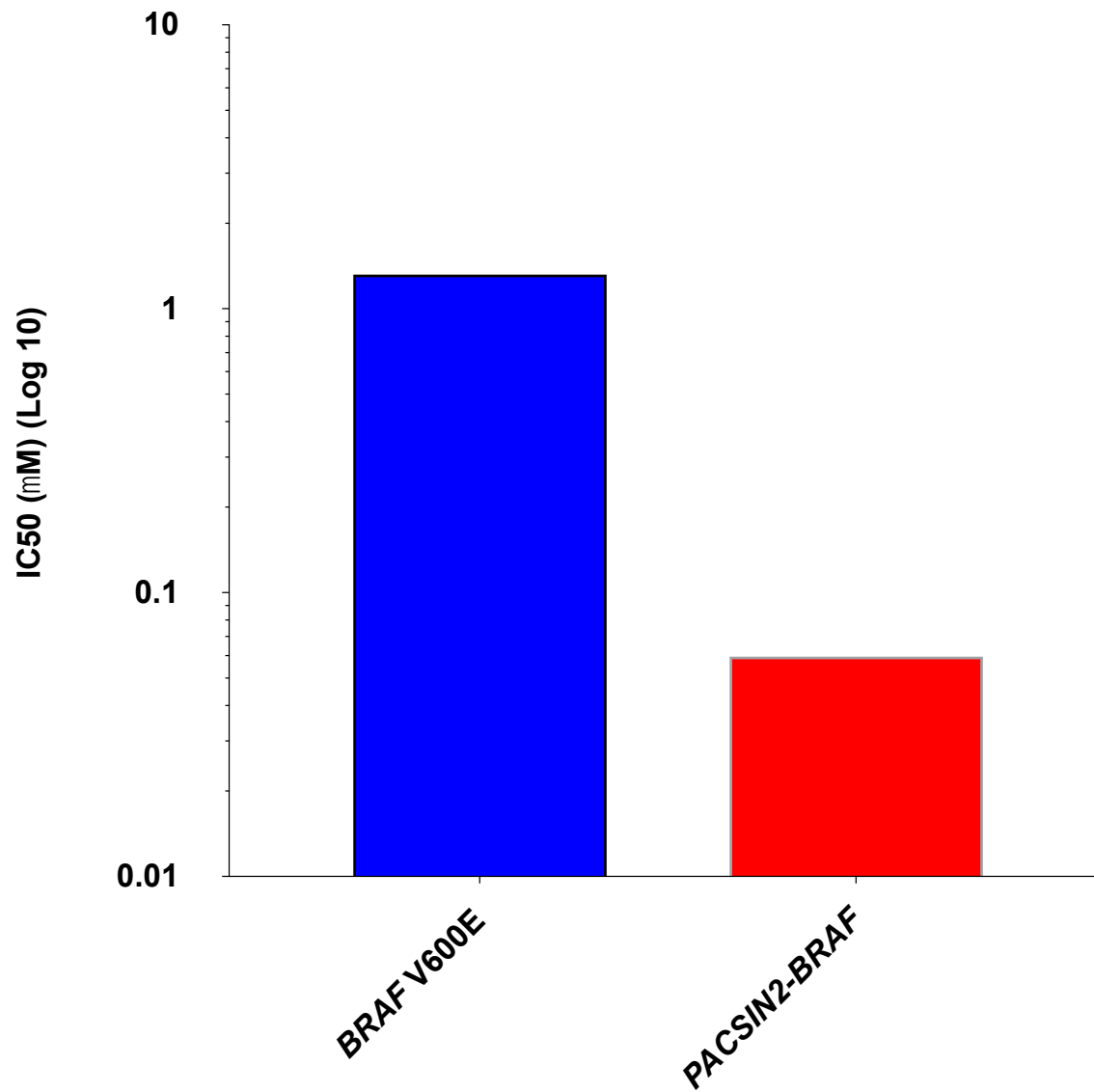
Post-Treatment



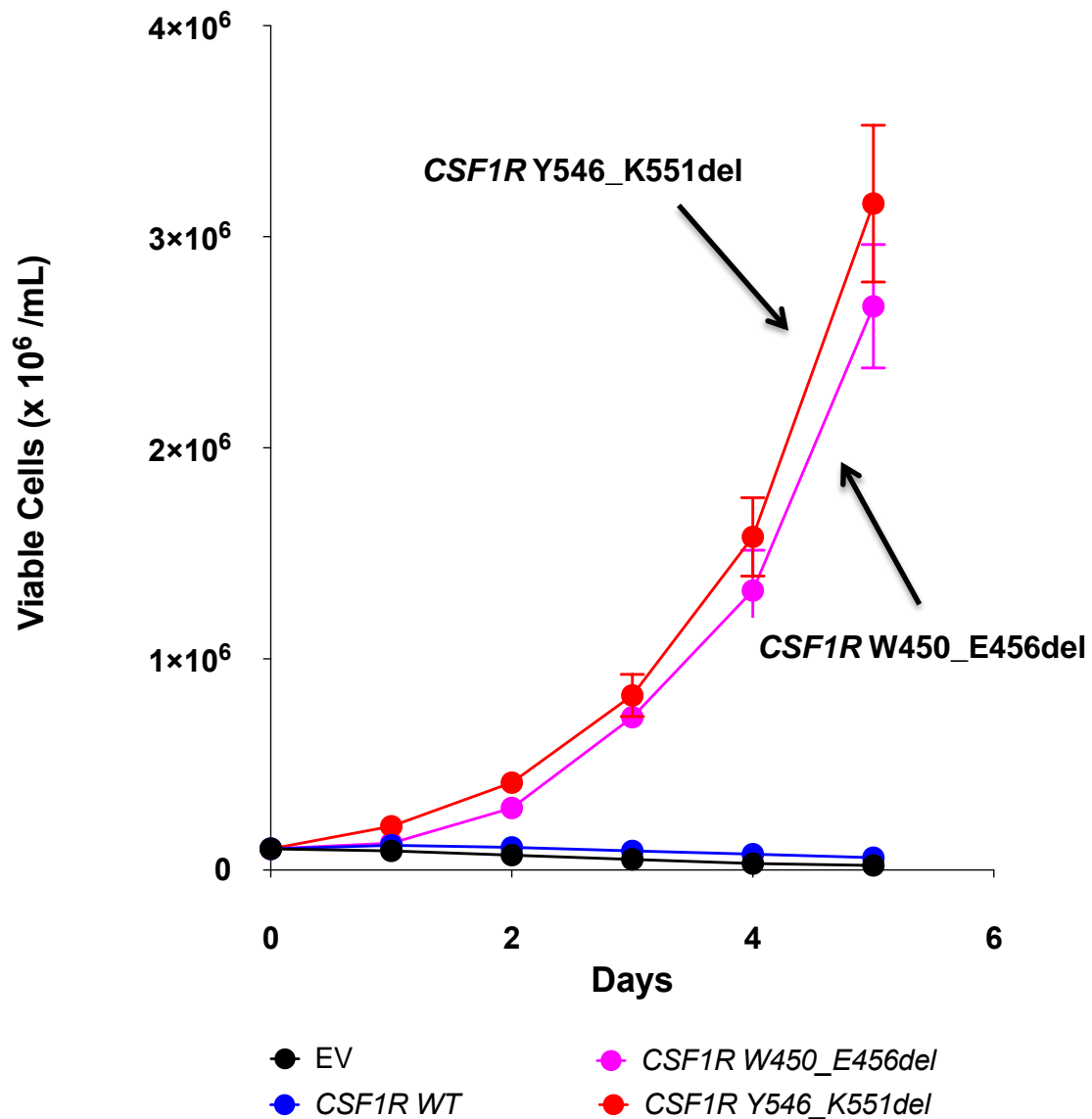
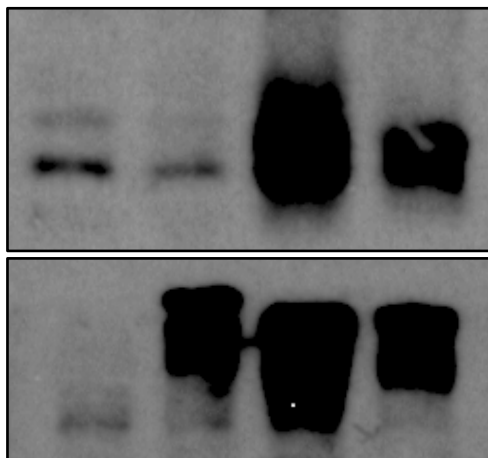
# BRAF V600E Ba/F3 Cells - IC50 to Ulixertinib (ERK1/2 Inhibitor)



# ***BRAF V600E Ba/F3 Cells - IC50 to Ulixertinib***








# CSF1R Y546\_K551del and CSF1R W450\_E456del Mutations in Histiocytoses are Activating

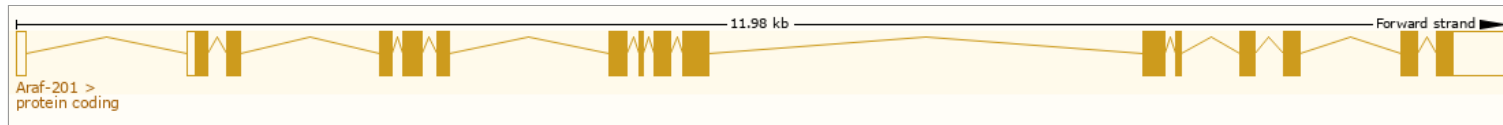







# Araf Transgenic Mouse Project (CRCm38.p6)






Transcript: Araf-201 ENSMUST00000001155.10

**Description**  **Gene Synonyms**  **Location**  **About this transcript**  **Gene** 

Name	Transcript ID	bp	Protein	Biotype	CCDS	UniProt	RefSeq	Flags
Araf-203								
Araf-201								
Araf-202								
Araf-204								
Araf-206								
Araf-207								
Araf-208								
Araf-210								
Araf-205								
Araf-209								



**Statistics**  **Exons:**  **Coding exons:**  **Transcript length:**  **Translation length:** 

**CCDS**  **Uniprot**  **Transcript Support Level (TSL)**  **Version**  **Type**  **Annotation Method**  **GENCODE basic gene** 

# Map2k1 Transgenic Mouse Project (CRCm38.p6)

Transcript: Map2k1-201 ENSMUST00000005066.8

**Description**

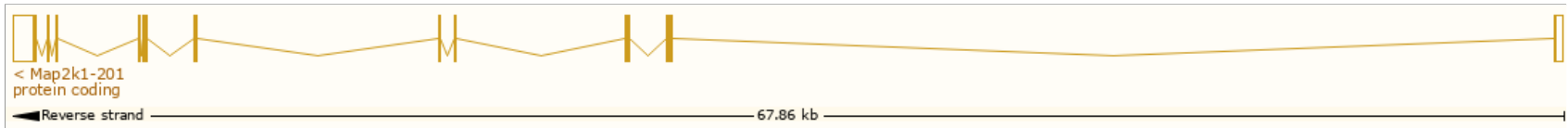
**Gene Synonyms**

**Location**

**About this transcript**

**Gene**

Name	Transcript ID	bp	Protein	Biotype	CCDS	UniProt	RefSeq	Flags
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Map2k1-203				•				
Map2k1-202				•				
Map2k1-204				•				



**Statistics** Exons: Coding exons: Transcript length: Translation length:

**CCDS**

**Uniprot**

**Transcript Support Level (TSL)**

**Version**

**Type**

**Annotation Method**

**GENCODE basic gene**