Novel Alterations in *CSF1R*, *RET*, and Other Diverse Kinases in the Histiocytoses with Biochemical and Structural Insights into Their Mechanisms of Activation

Erdheim-Chester Disease Medical Symposium
Milan, Italy
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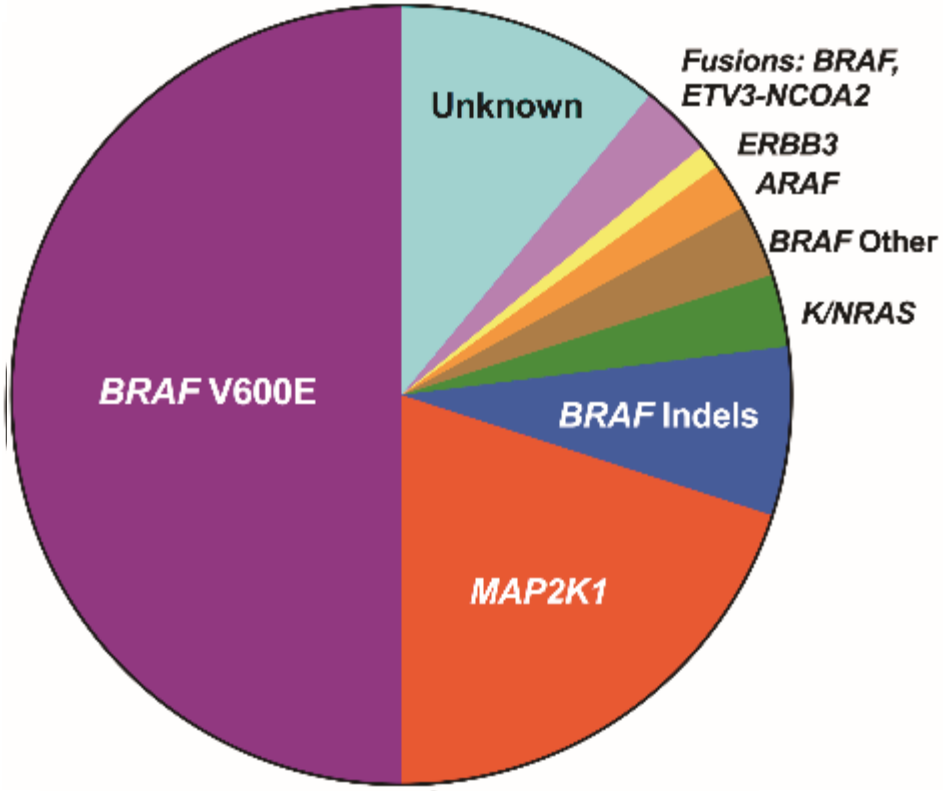
Memorial Sloan Kettering Cancer Center

Published Kinase Alterations in the Histiocytoses

Langerhans Cell HIstiocytosis

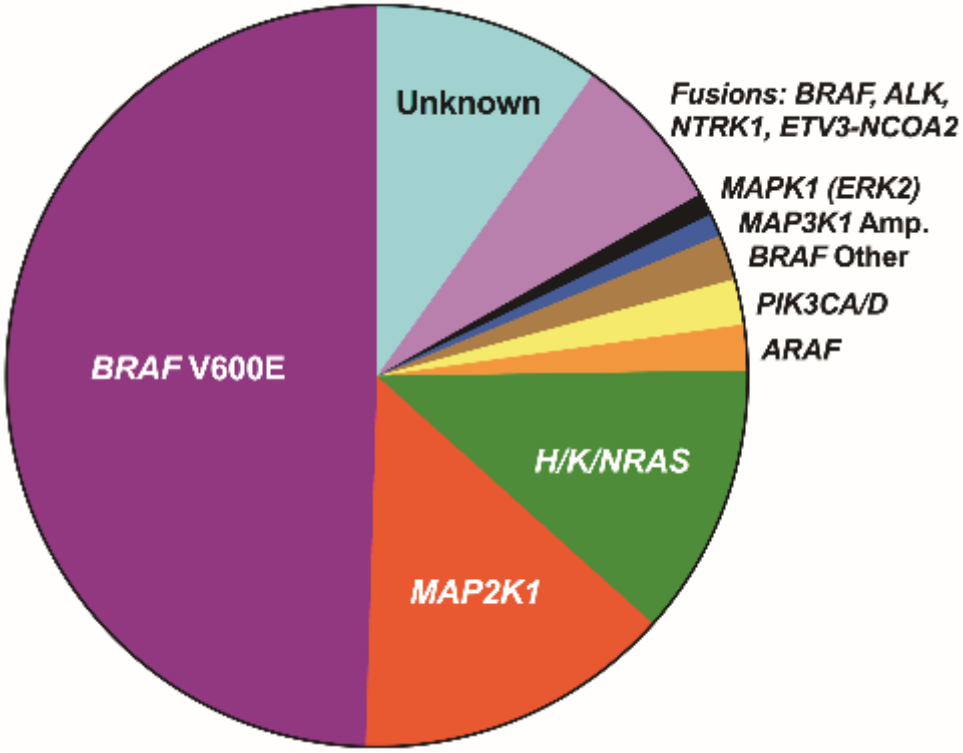


Badalian-Very, *et al. Blood* 2010

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

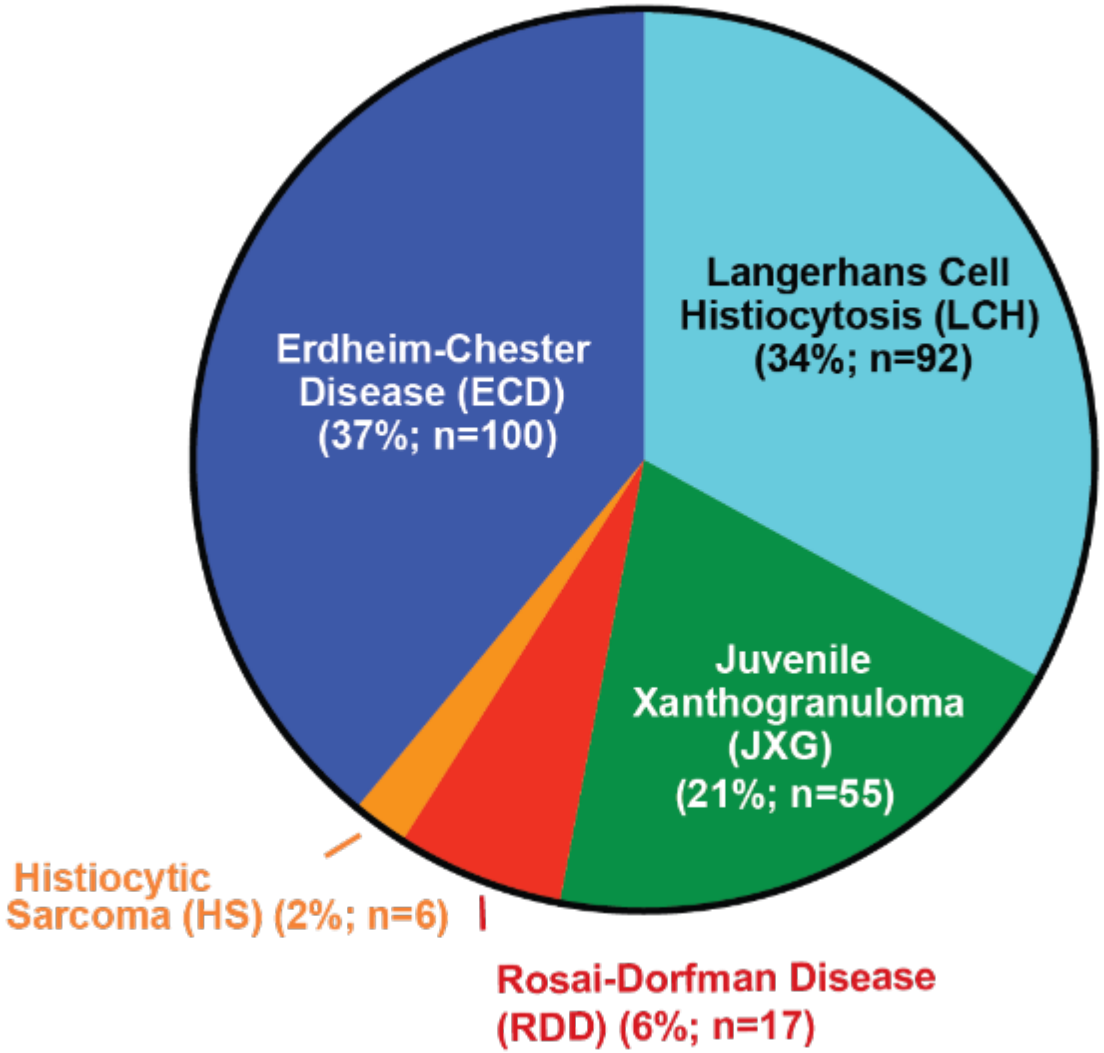
Lee, *et al. JCI Insight* 2017
Charkraborty *et al. Oncotarget* 2017
Techavichit, *et al. Hum Pathol.* 2017
Garces, *et al. Mod. Pathol.* 2017
Bentel et al. *BMJ Case Rep.* 2017.

Brown RA, *et al. Blood* 2015
Diamond, Durham, Haroche, *et al. Cancer Discovery* 2016
Durham, *et al. Curr Opin Hematol.* 2016
Shanmugan, *et al. Head Neck Pathol.* 2016

Questions

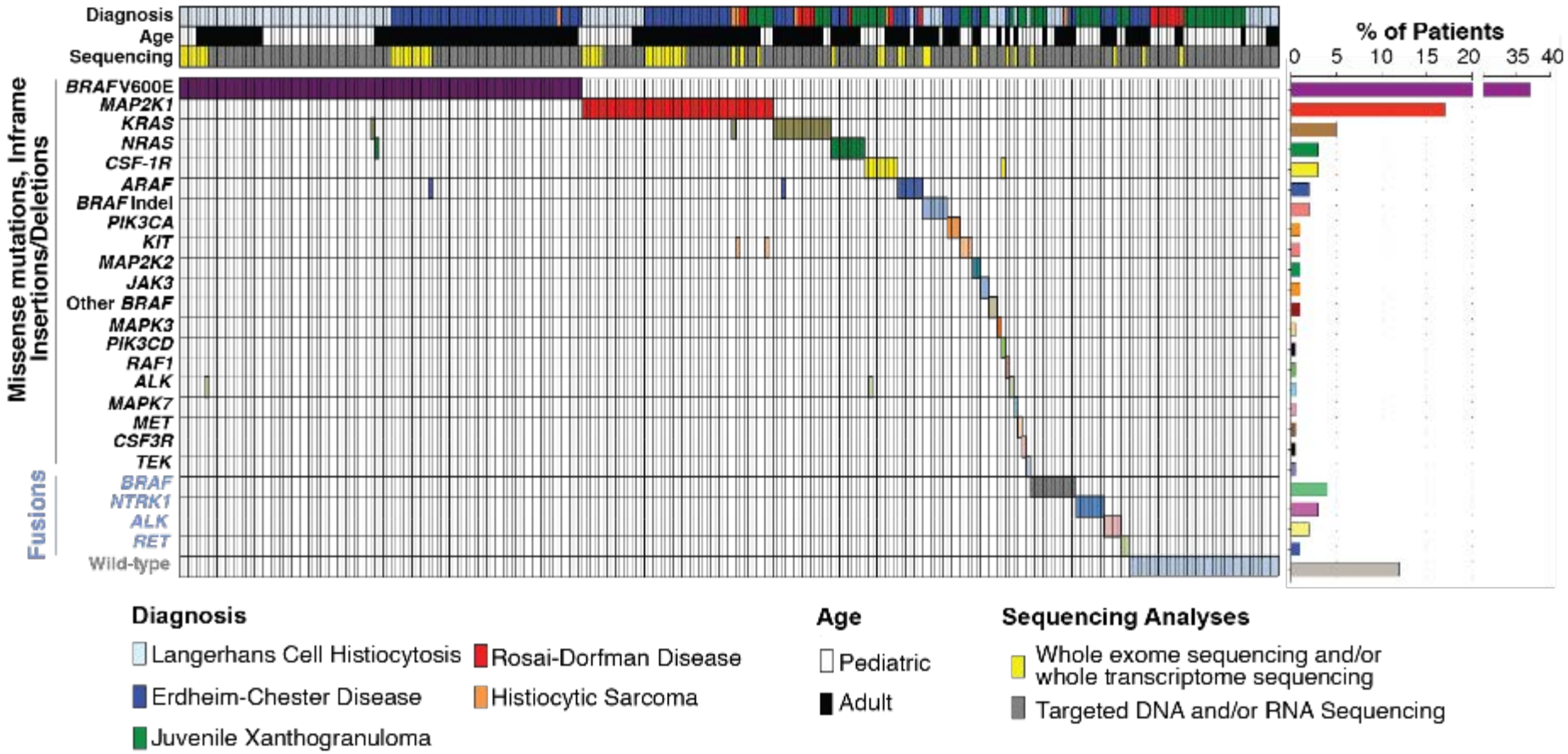
- **What other novel alterations drive histiocytic neoplasms?**
- **Are there genetic differences across the diverse clinical and histologic subtypes of histiocytoses?**
- **What is/are the cell(s)-of-origin in the histiocytoses?**
- **What is the basis for familial histiocytoses?**

Histiocytic Neoplasms Sequenced (n=270)

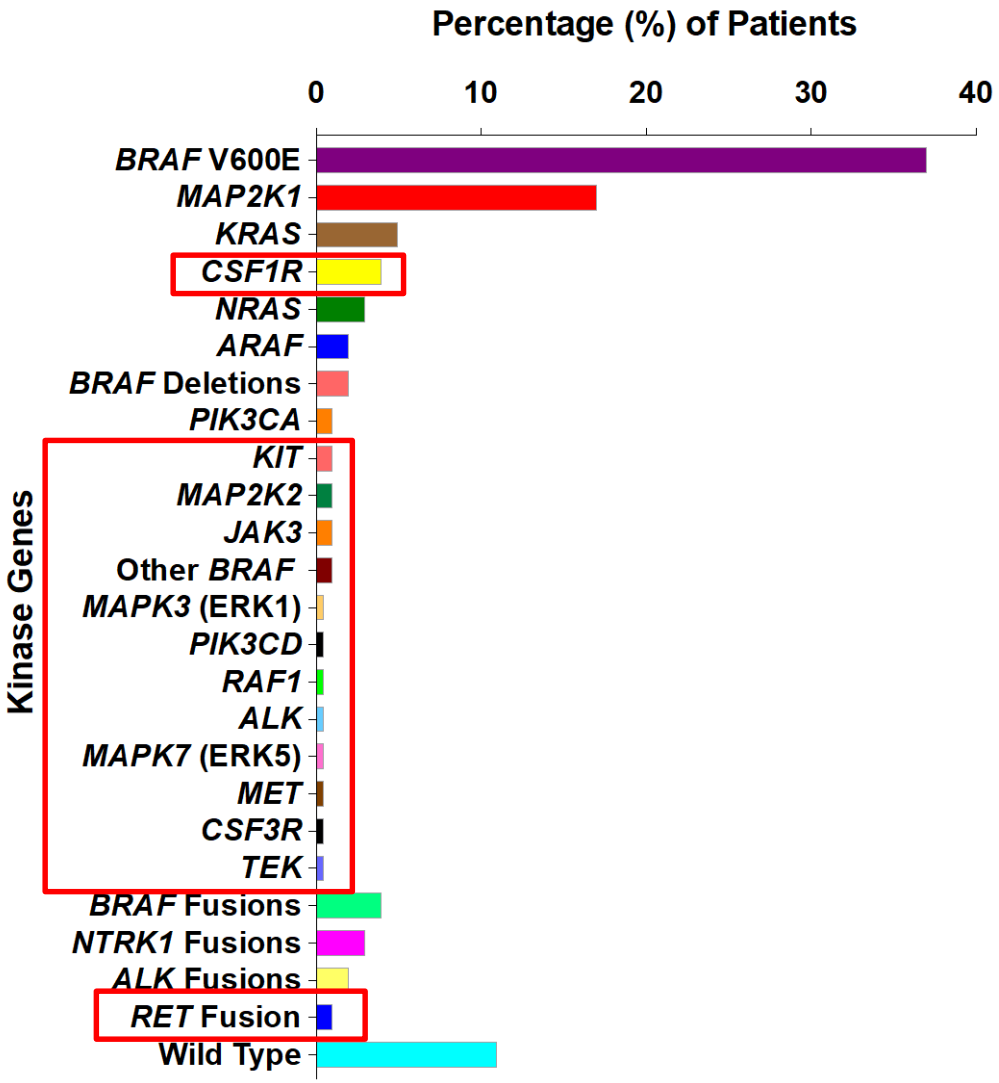


N = 270

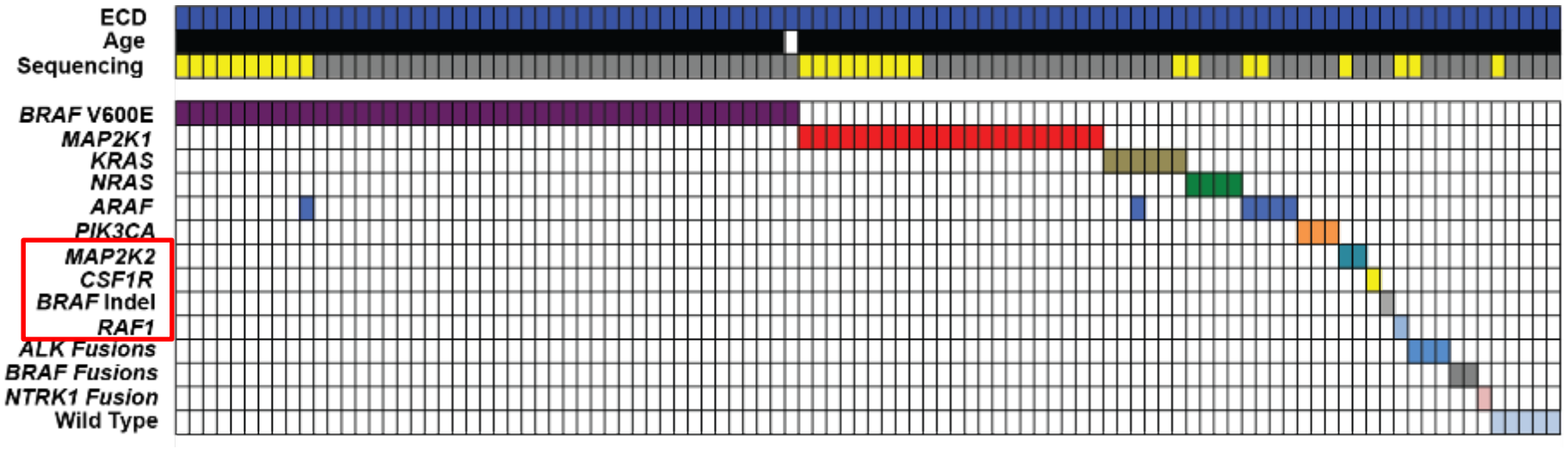
Overall Histiocytoses Cohort (n=270)

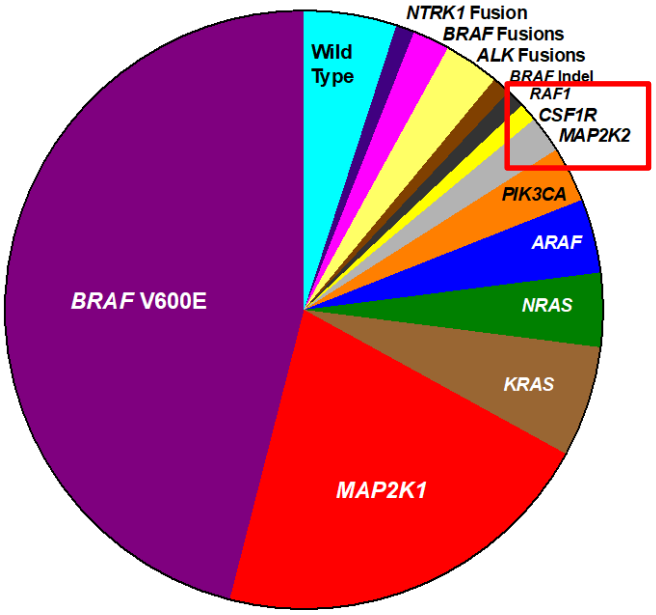


Frequency of Kinase Alterations Identified (n = 270)



Erdheim-Chester Disease Cohort (N = 100)





N = 100

Histiocytoses Subsets

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

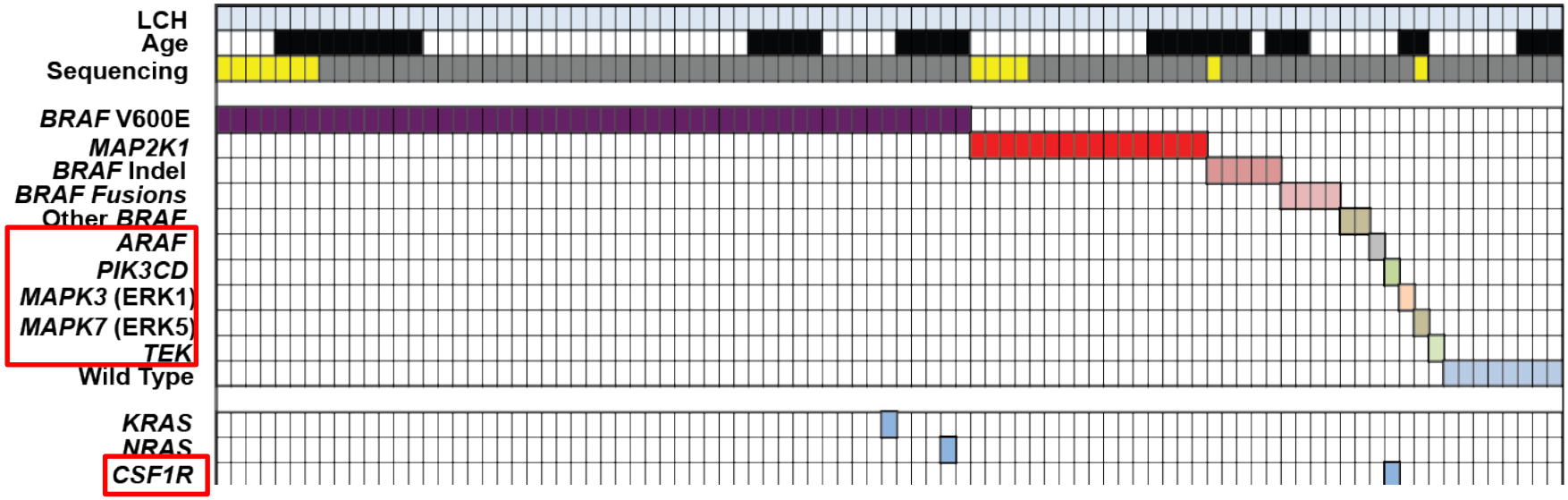
Age

- Pediatric
- Adult

Sequencing Analyses

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

Langerhans Cell Histiocytosis Cohort (N = 92)



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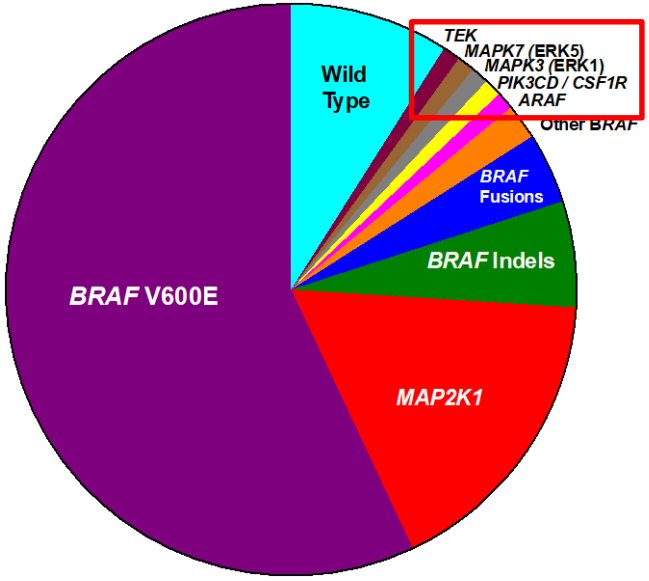
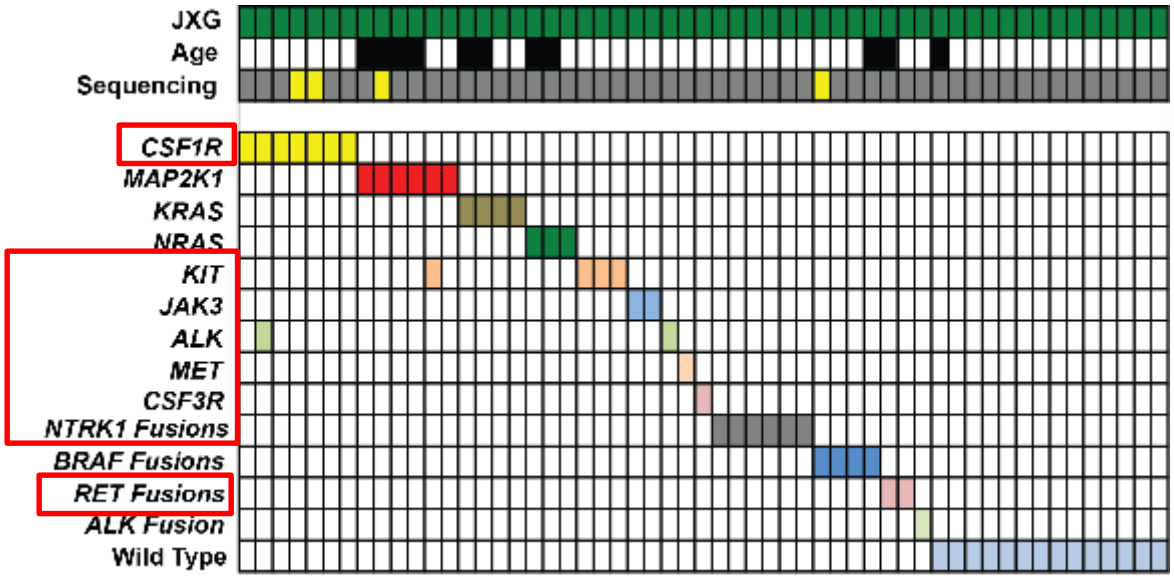
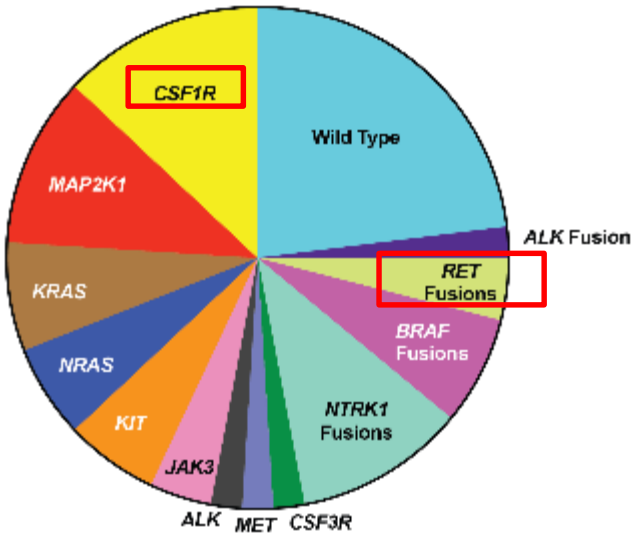


N = 91

Juvenile Xanthogranuloma Cohort (N = 55)





N = 55

Histiocytoses Subsets

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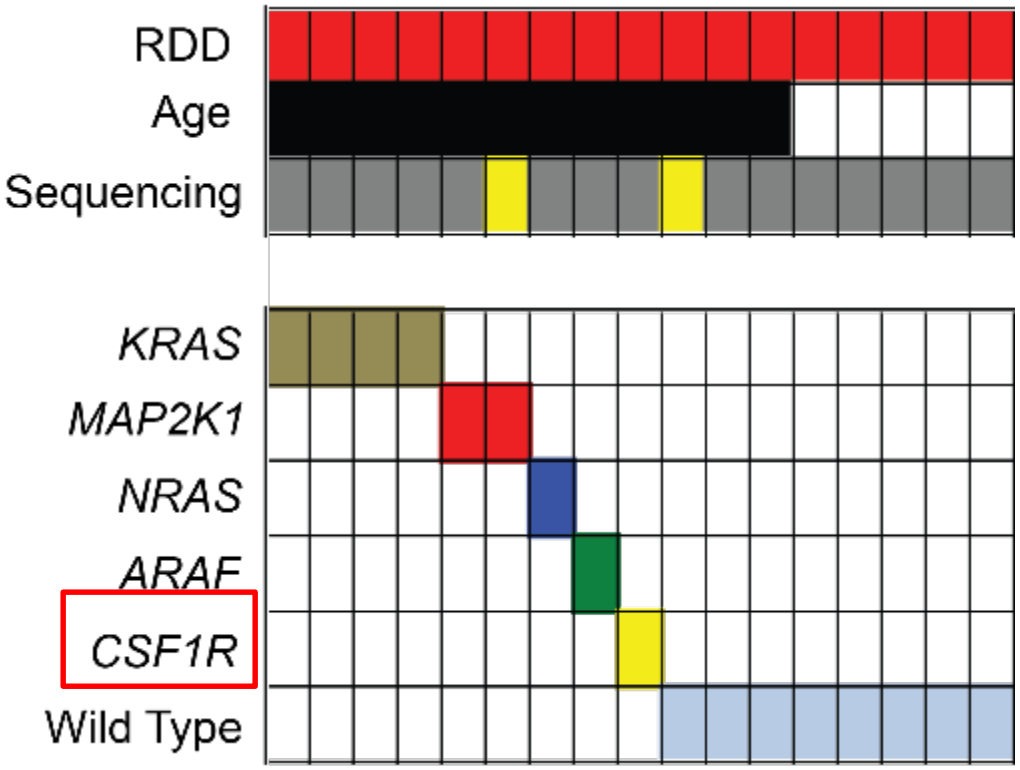
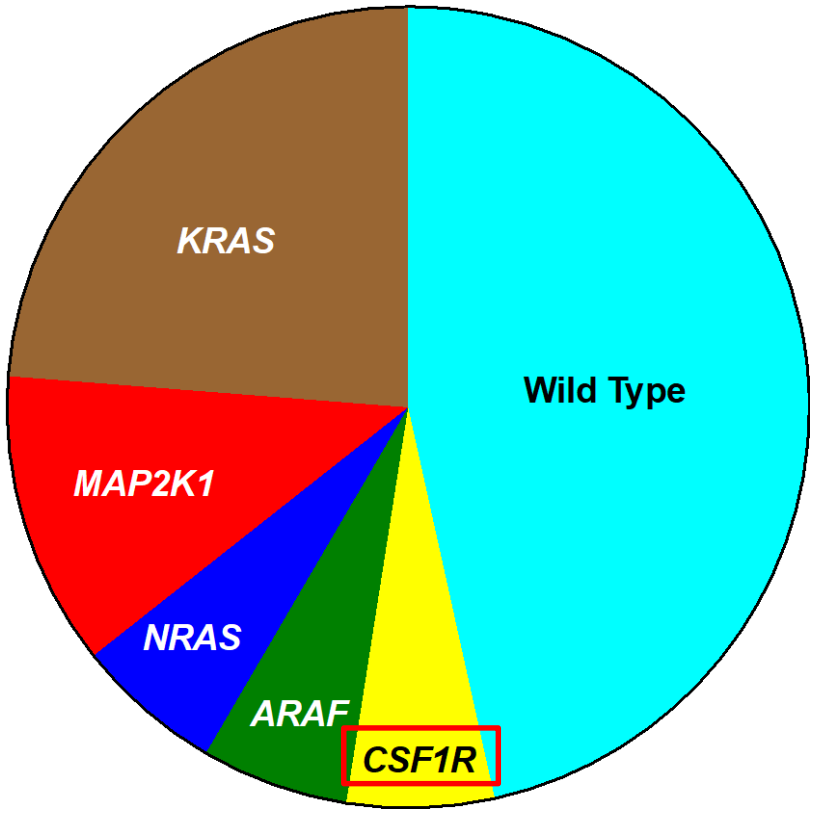
Jennifer Picarsic and Ronald Jaffe

Rosai-Dorfman Disease Cohort (N = 17)





N = 17

Histiocytoses Subsets

- Langerhans Cell Histiocytosis (LCH)
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Age

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- Adult

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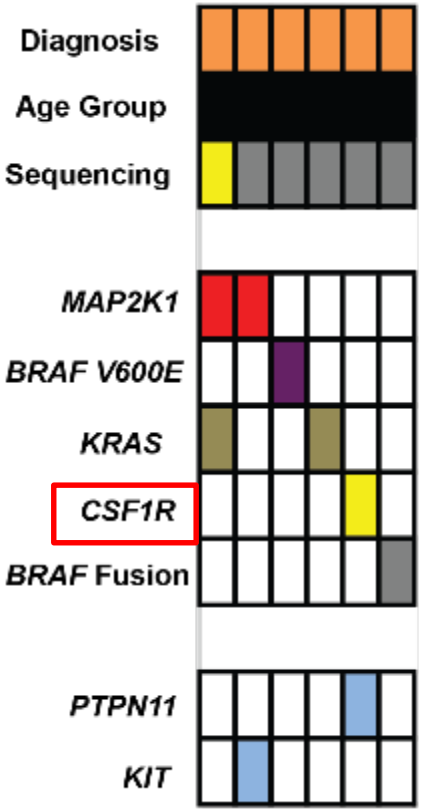
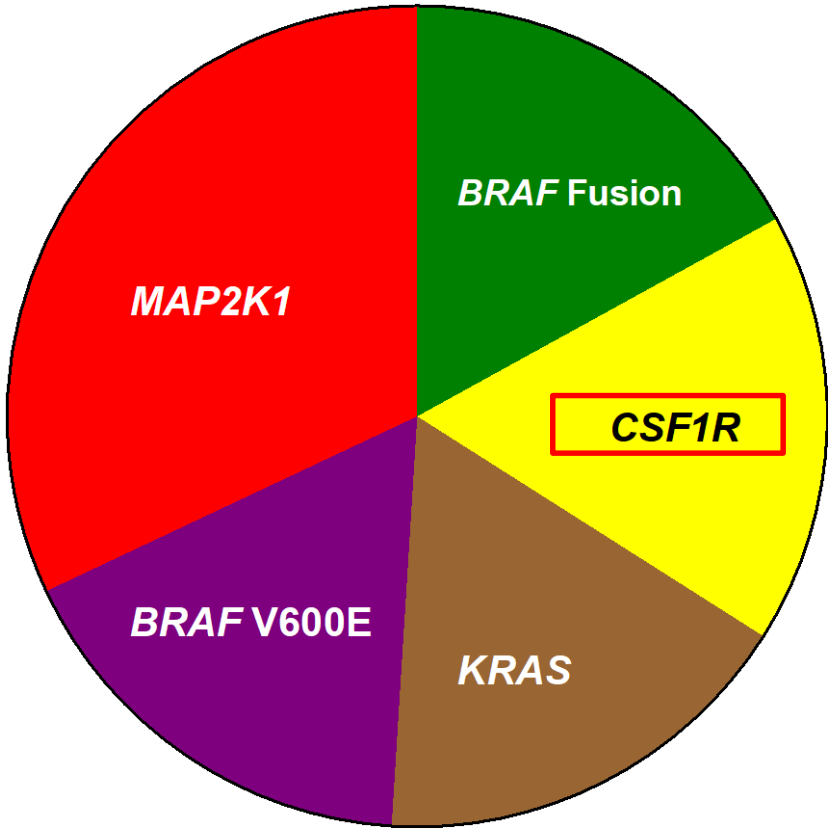
- Targeted DNA and/or RNA Sequencing

Histiocytic Sarcoma (HS) Cohort (N = 6)





N = 6

Histiocytoses Subsets

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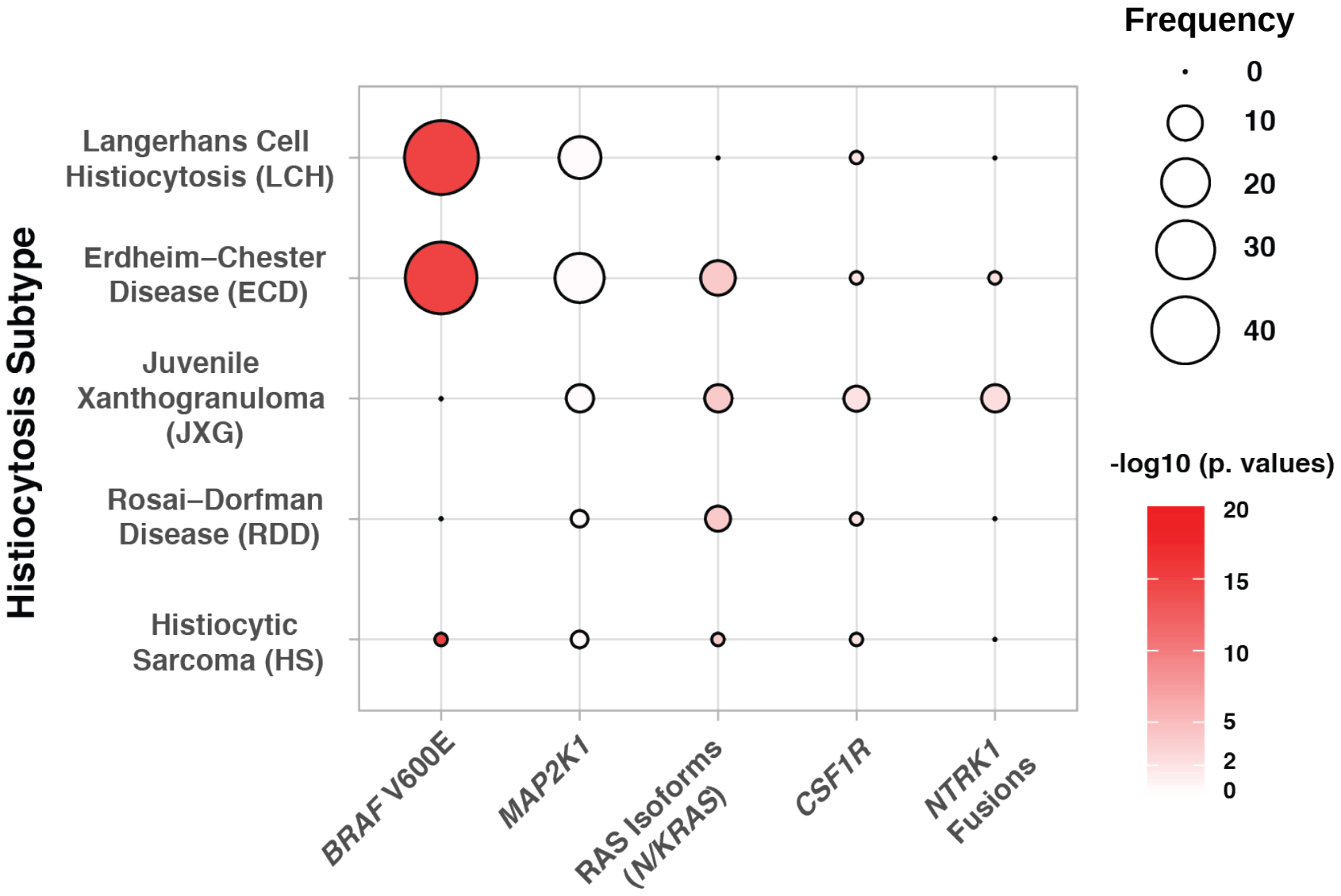
Age

- Pediatric
- Adult

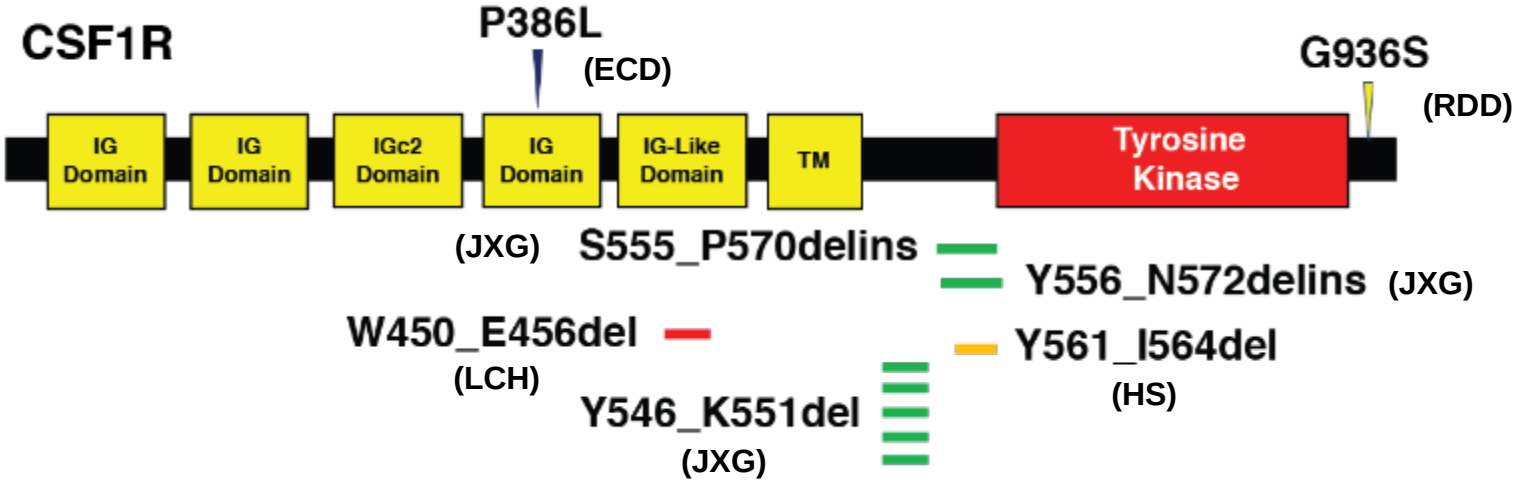
Sequencing Analyses

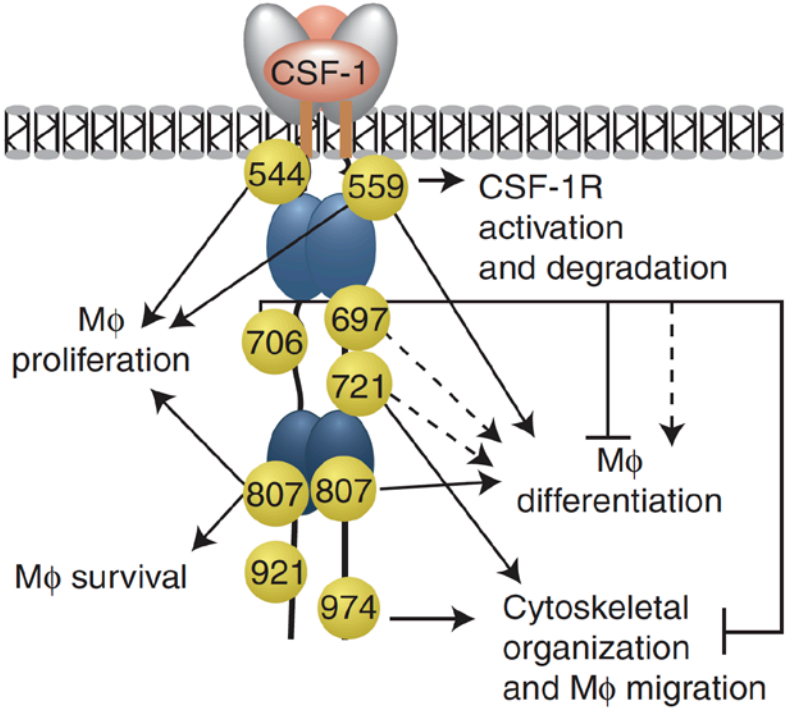
- Whole Exome Sequencing (WES) and/or Whole Transcriptome Sequencing (WT)
- Targeted DNA and/or RNA Sequencing

Correlation of Kinase Mutations with Histiocytosis Subtype



Recurrent *CSF1R* Mutations





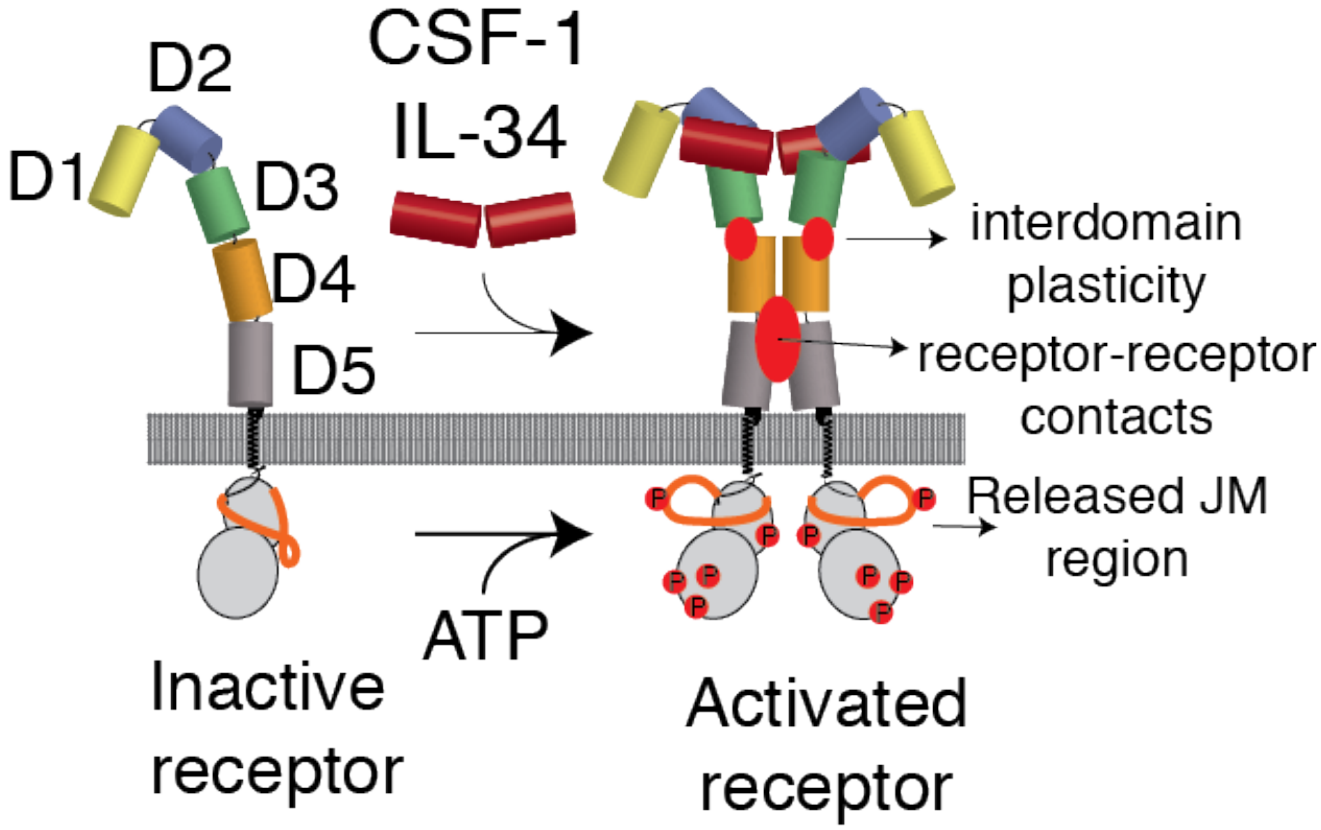
CSF1R: The receptor for MCSF (Macrophage Colony Stimulating Factor) and IL-34

Controls production, differentiation, and function of macrophages

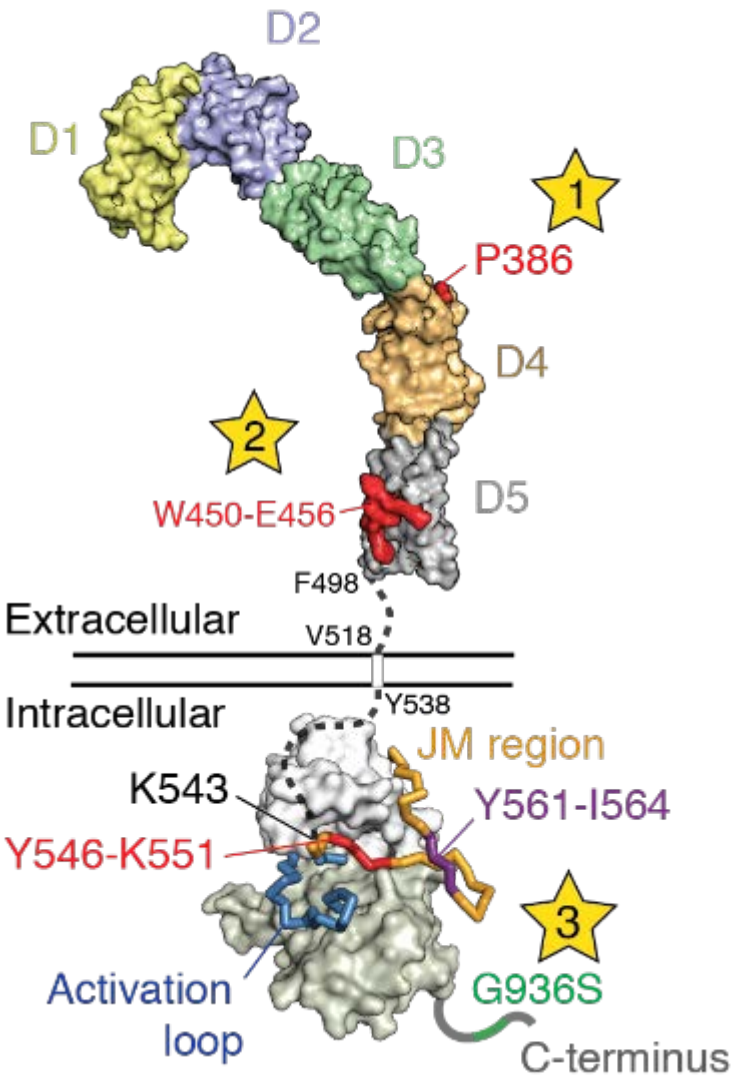
Expression is restricted to progenitor cells committed to the monocyte/macrophage lineage.

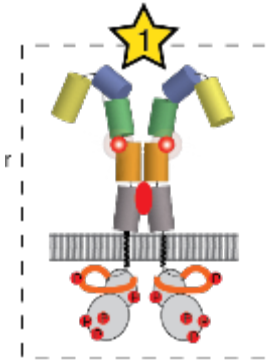
Stanley, Chitu. *Cold Spring Harb Perspect Biol* 2014;6:a021857

Principles of Activation of Human *CSF1R*



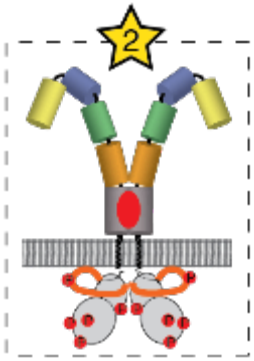
Structural Mapping of *CSF1R* Activating Mutations and Proposed Impact of CSF1R Activation





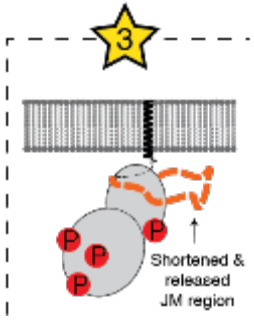
Enhance dimerization propensity in the absence of ligand

***CSF1R*^{P386L}**



Enhance dimerization propensity in the absence of ligand

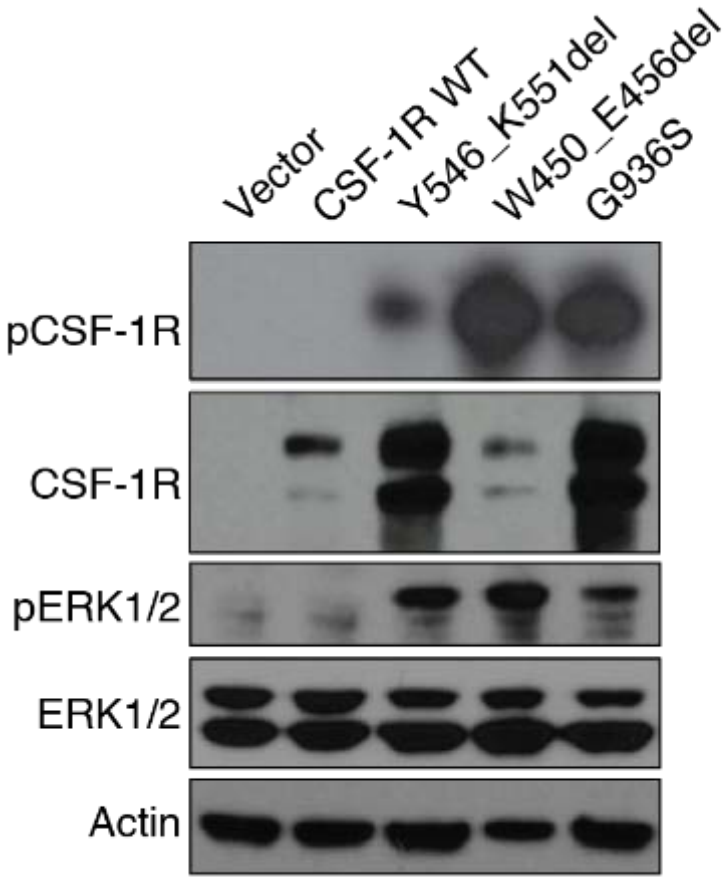
***CSF1R*$^{W450\_E456del}$**



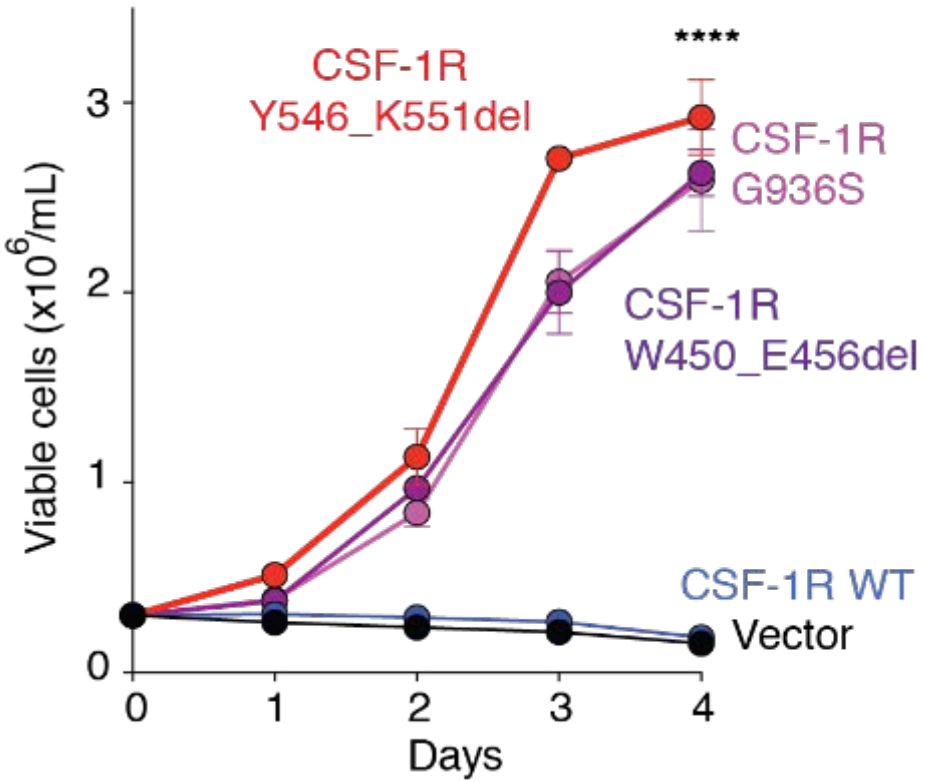
Promotion of the receptor's Intrinsic kinase activity
- Affect intracellular regions critical to enforcing the inactive state of the kinase domain in the absence of ligand

***CSF1R*$^{Y546\_K551del}$**

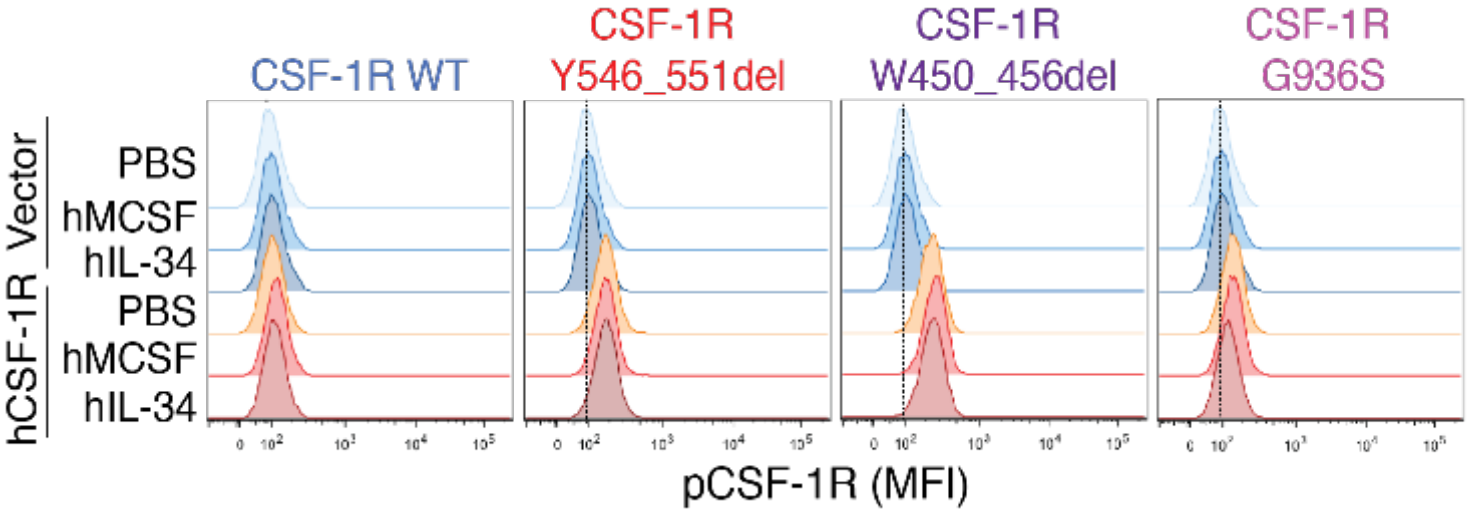
CSF1R Mutations in the Histiocytoses are Activating

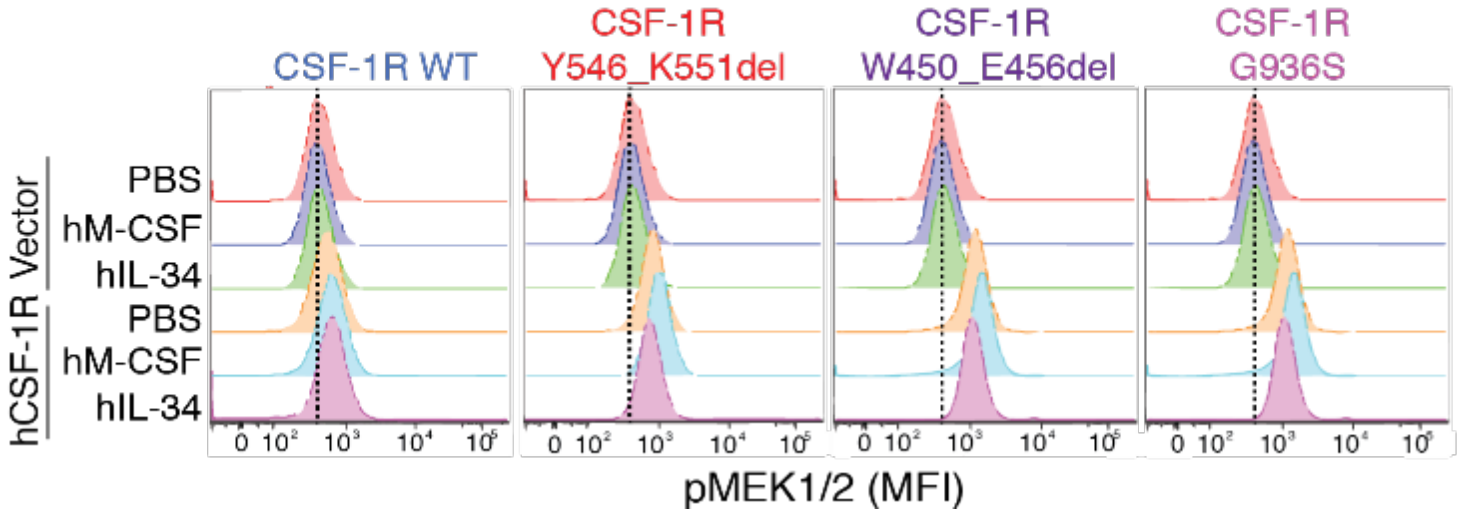


Ba/F3 Cell Cytokine-Independent Growth

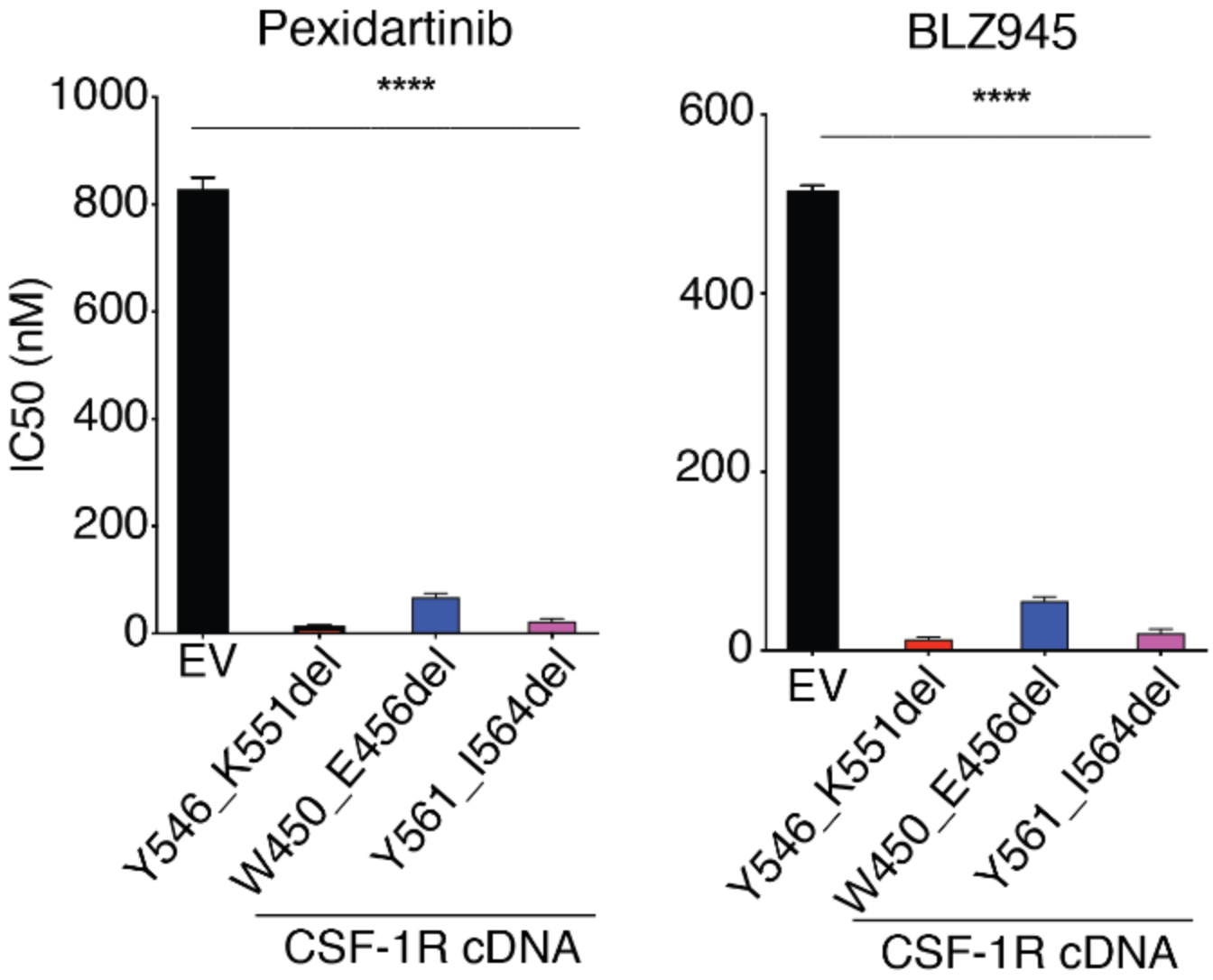


CSF1R Mutations in Histiocytoses are Activating via Phospho-Flow Cytometry



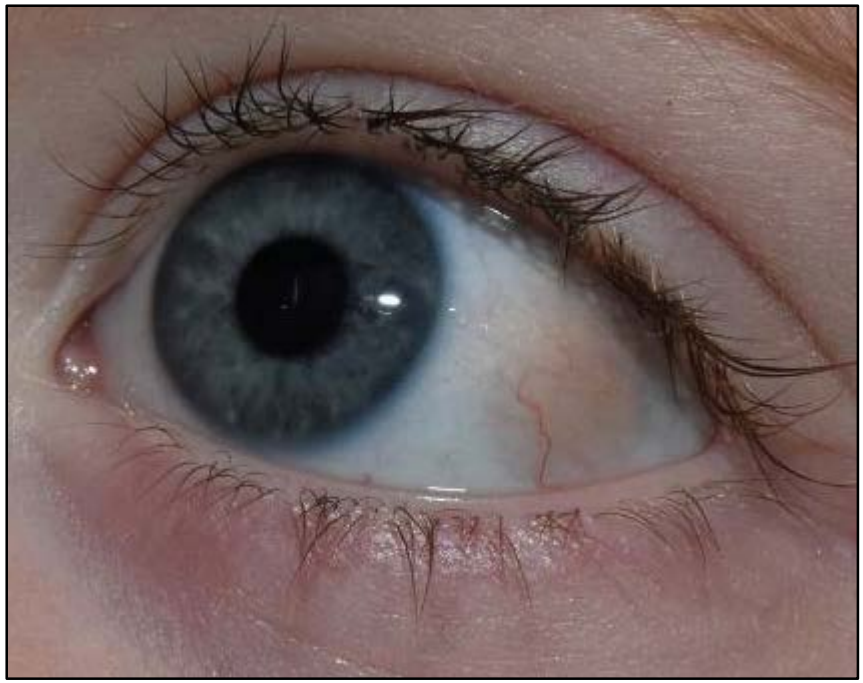


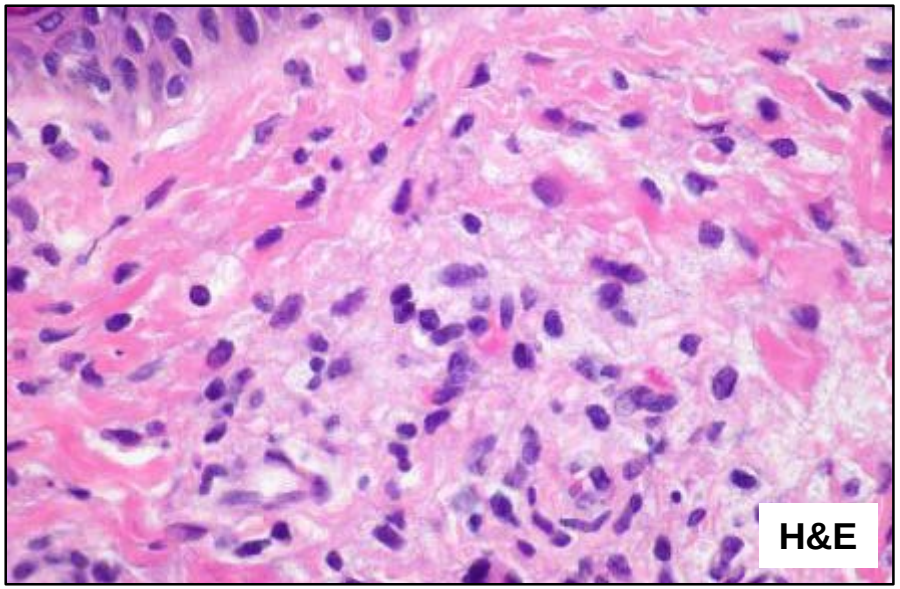
CSF1R Deletion Mutations are Sensitive to CSF1R Inhibitors (Pexidartinib and BLZ 945)

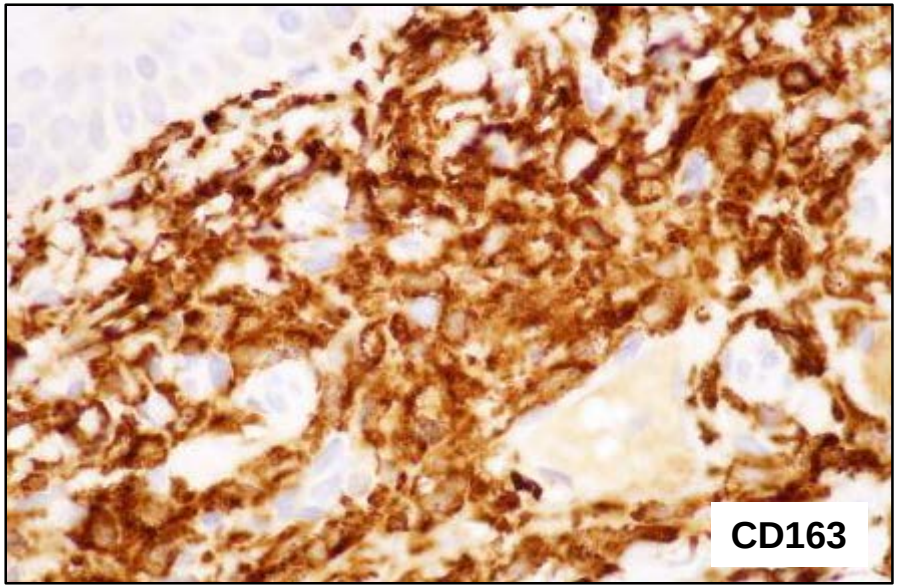


Identical Twins with Histiocytosis

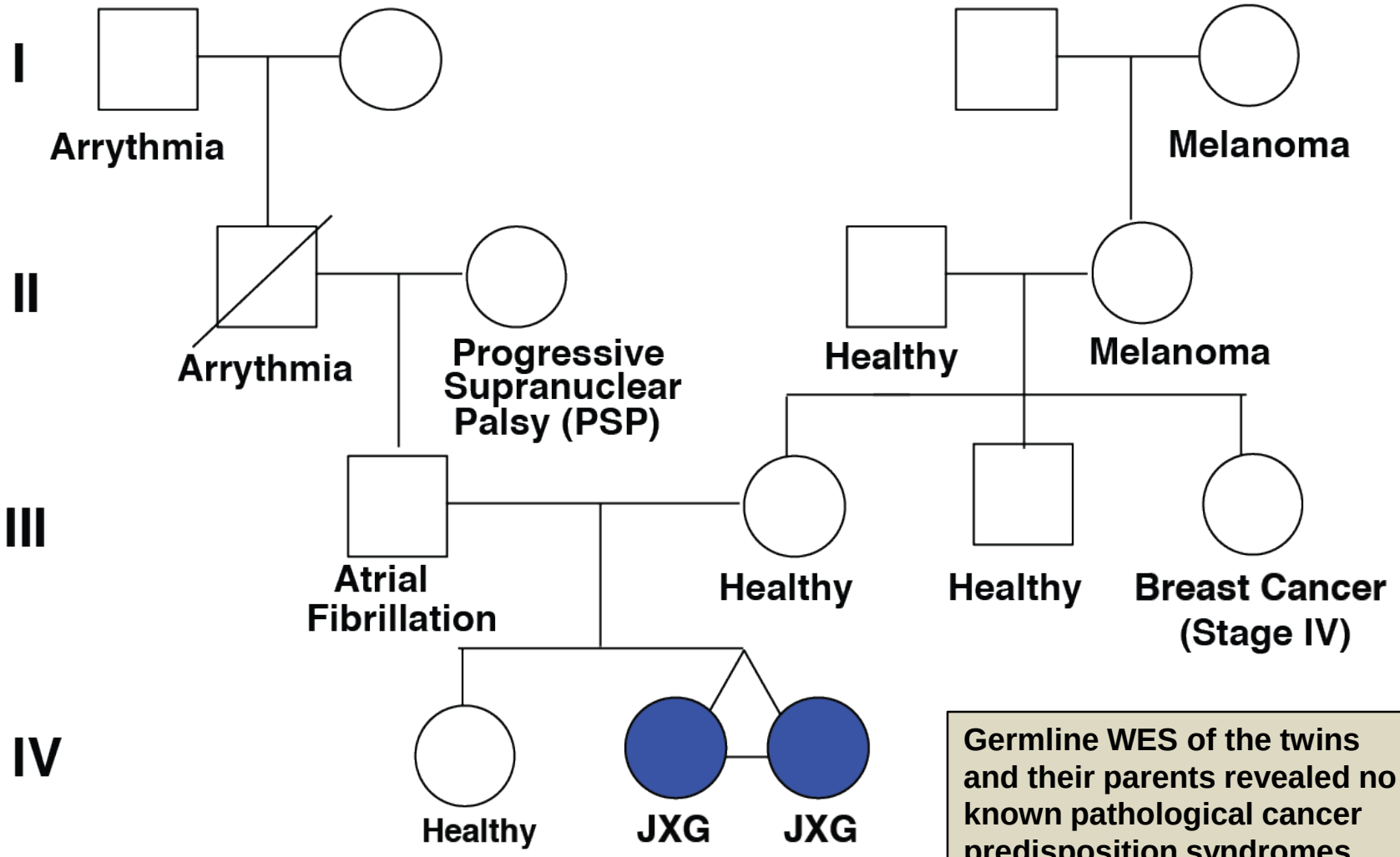
Monozygotic, dichorionic
Identical twin girls







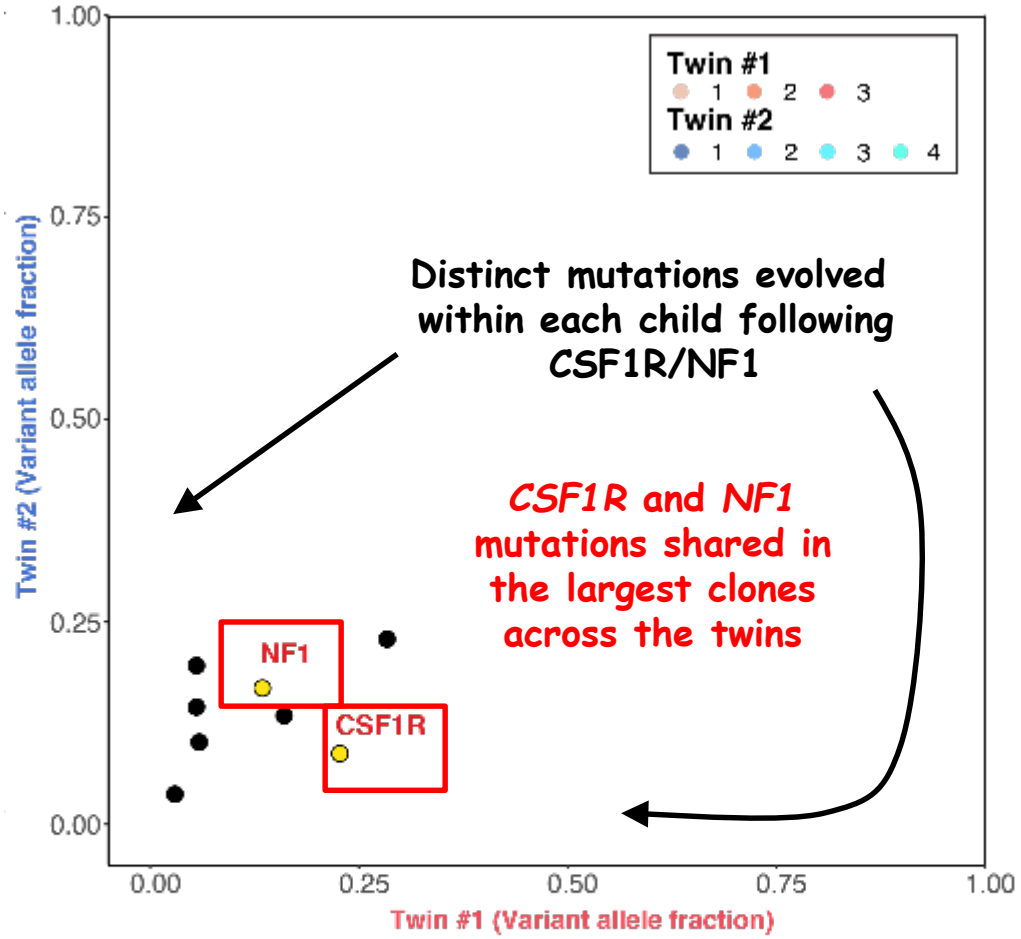
JXG in Monozygotic Twins – Family History



Germline WES of the twins and their parents revealed no known pathological cancer predisposition syndromes.

Shared *Somatic* *CSF1R* and *NF1* Mutations in Monozygotic Twins

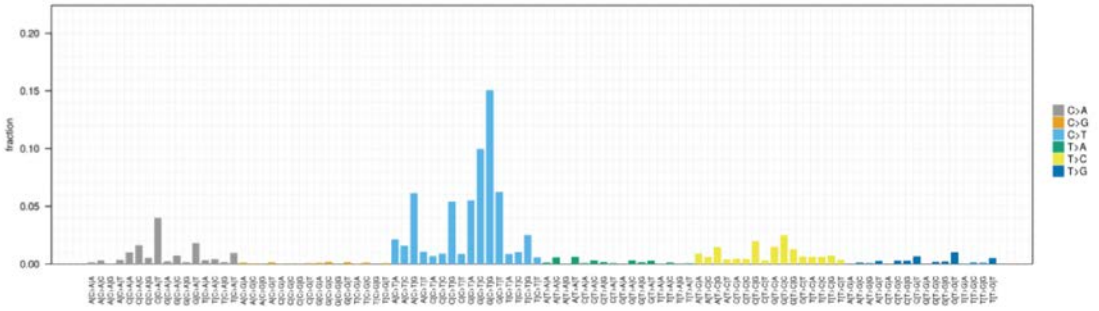
Twin 2

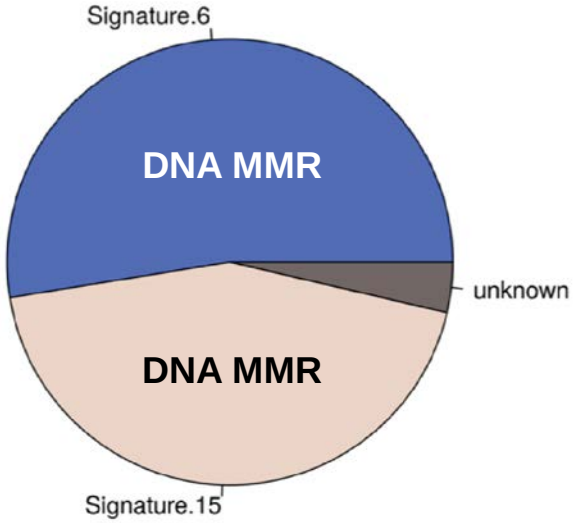


Twin 1

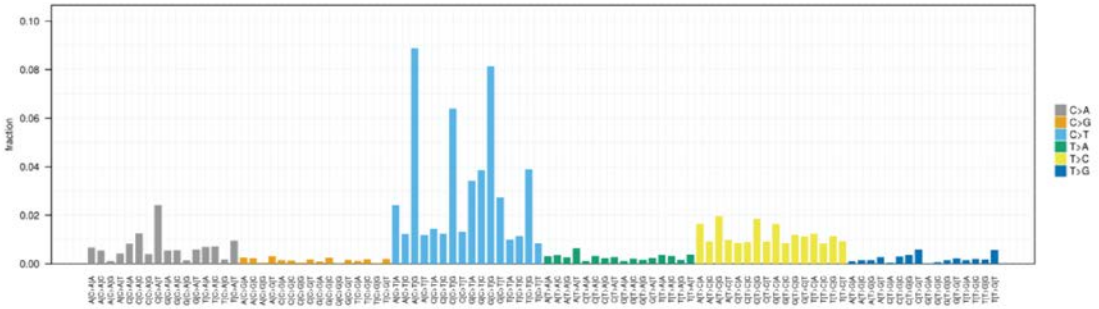
JXG Mutational Signatures in Monozygotic Twins with the Highest Ranked Signature Being DNA Mismatch Repair

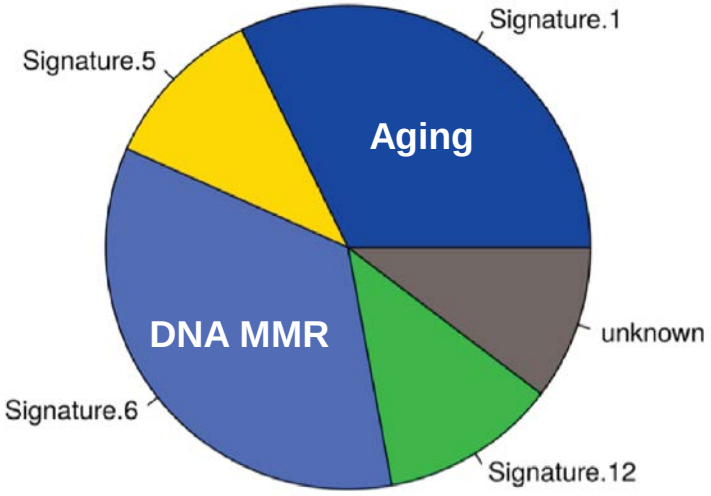
Twin 1



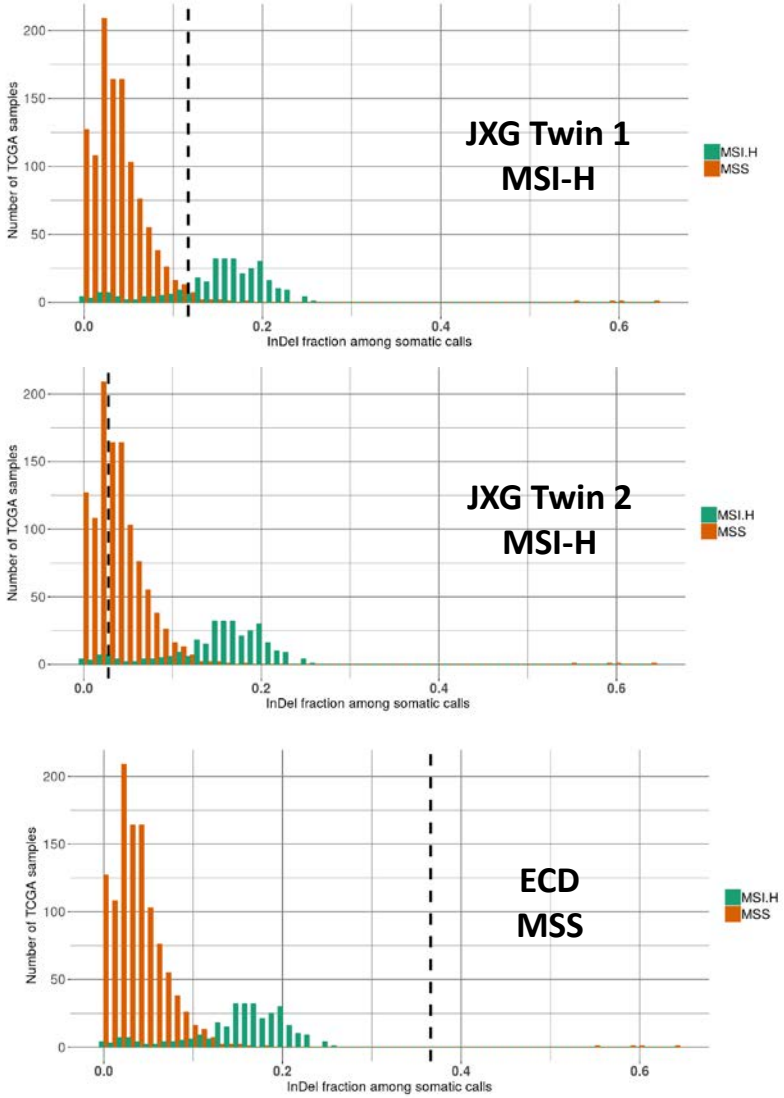


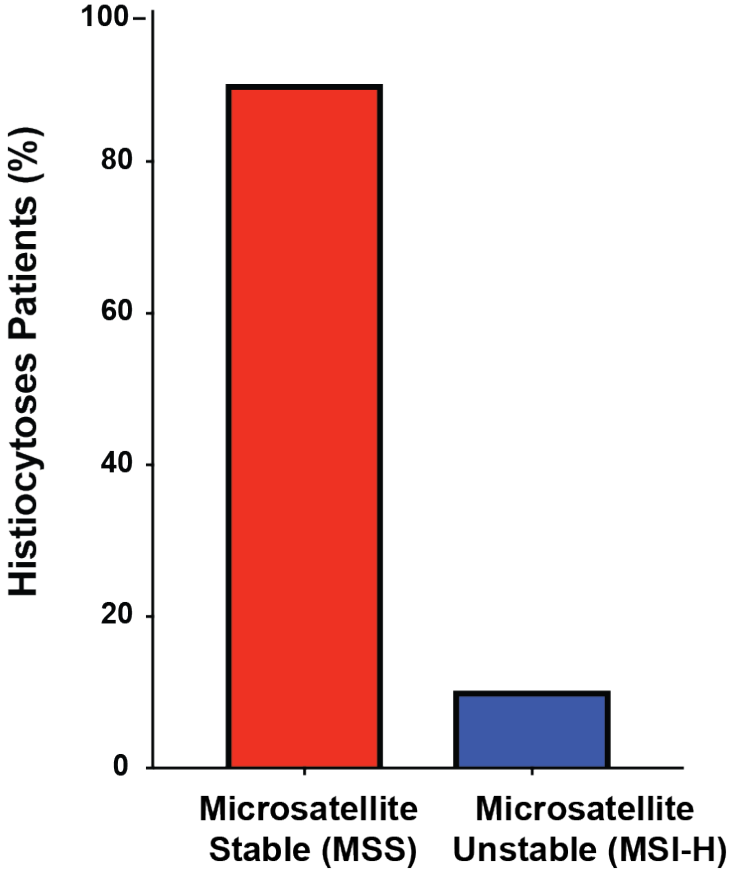
Twin 2



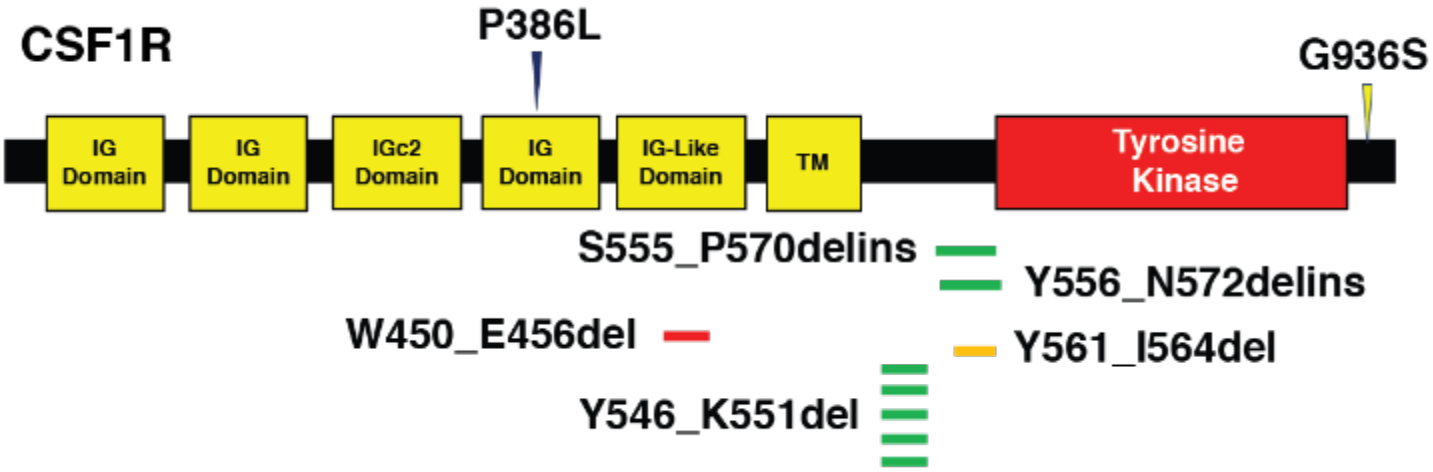


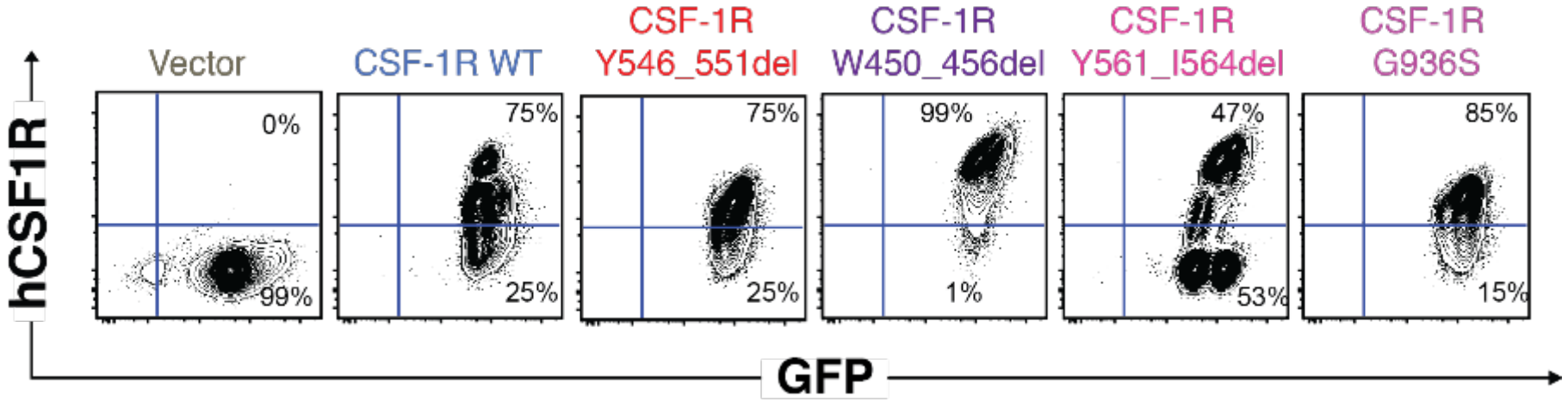
Microsatellite Instability is Rare in the Histiocytoses – However, Both Twins Show Microsatellite Instabiltiy by Next-Generation Sequencing



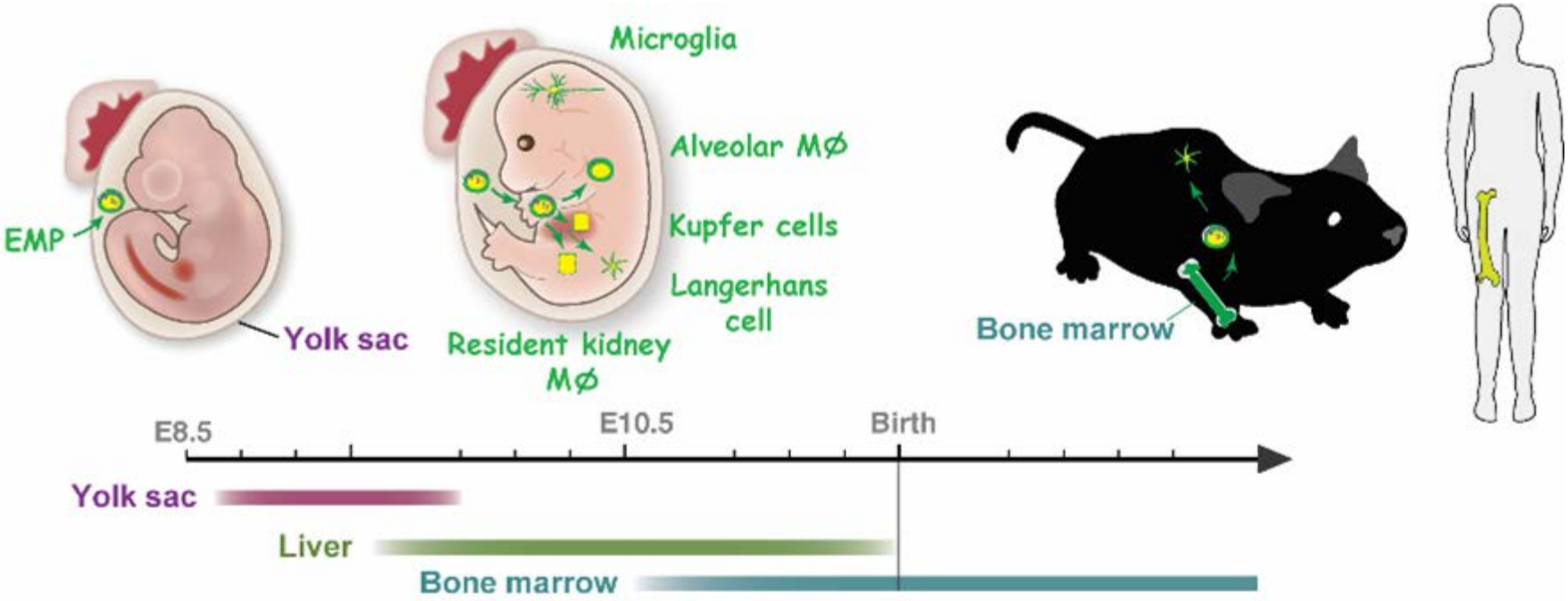


CSF1R Mutants Expressed on Cell Surface





Developmental Origins of Macrophages



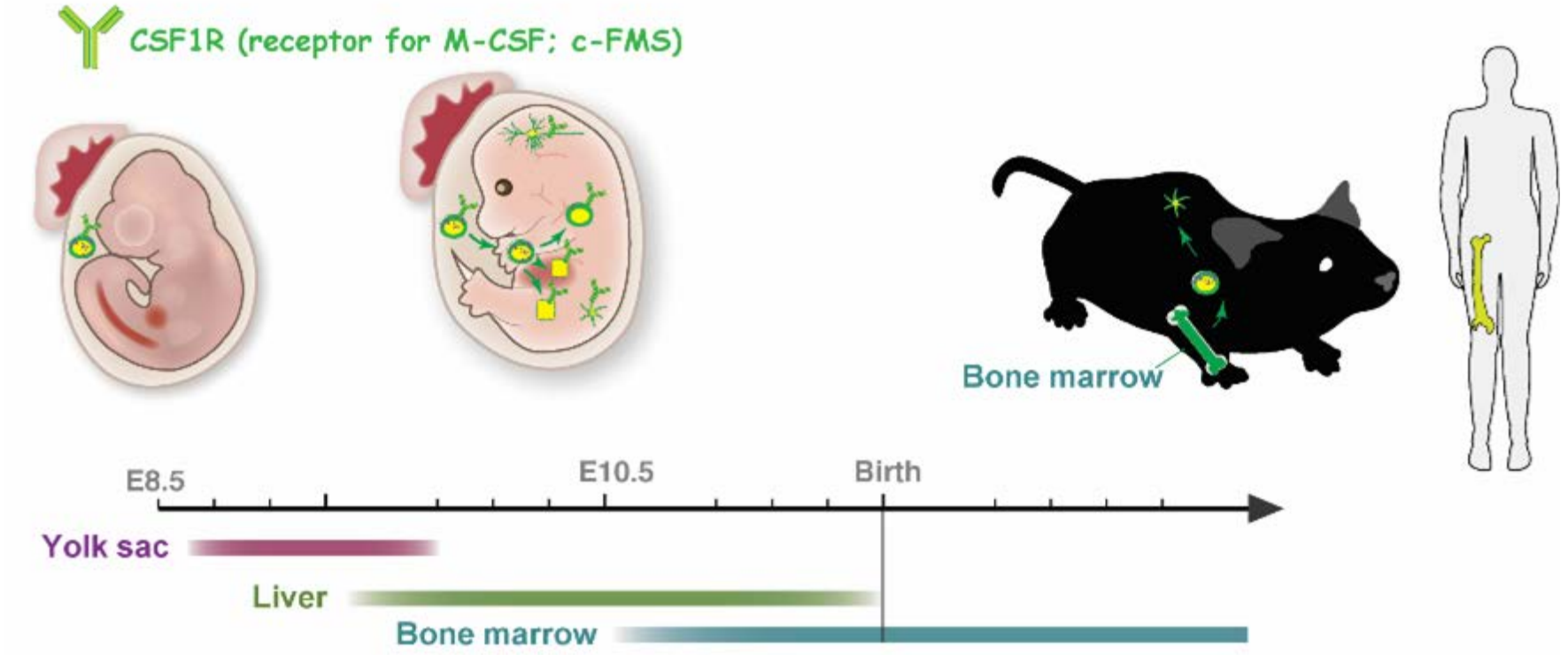
Frederic Geissmann

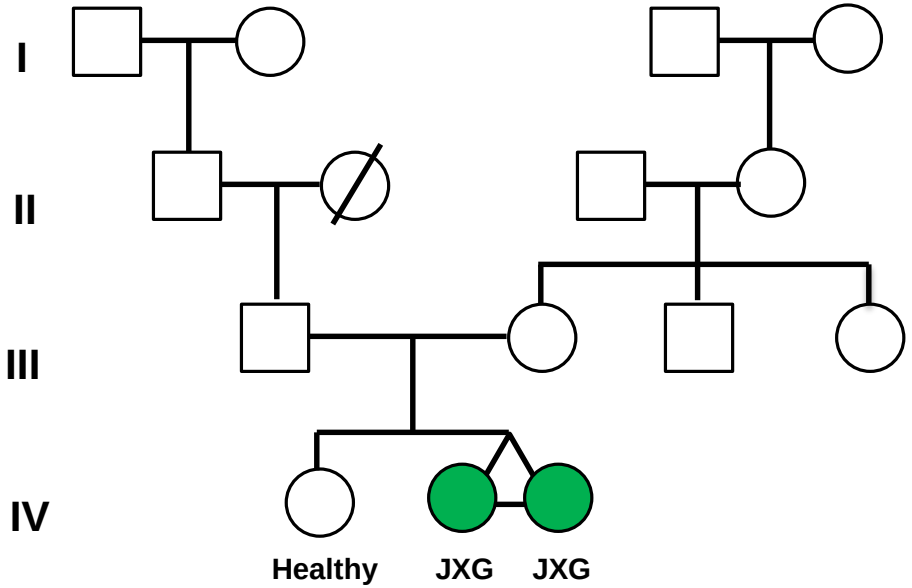
e gives rise to histiocytoses?

derived hematopoietic stem cell?

ted monocyte/dendritic cell precursor?

Geissman, F, *et al. Science* 2010
Schulz, *et al. Science* 2012
Gomez Perdiguero, E, *et al. Nature* 2015

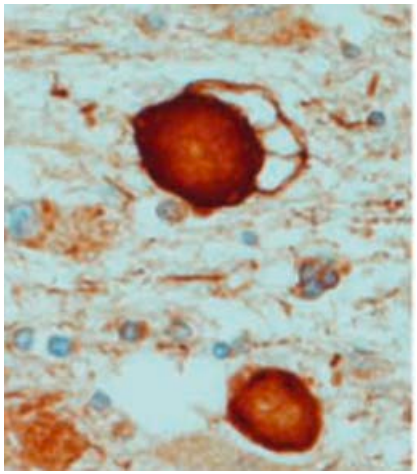




①Shared CSF1R mutant yolk-sac precursor.

② Hematogenous dissemination of shared precursor of histiocytosis *in utero.*

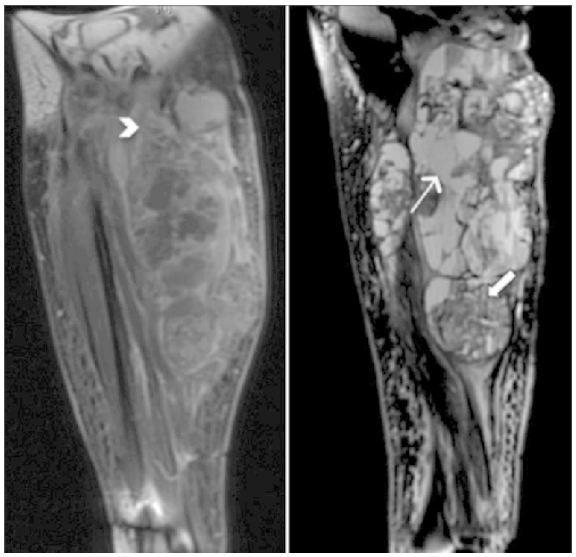
Spectrum of *CSF1R/CSF1* Mutant Diseases

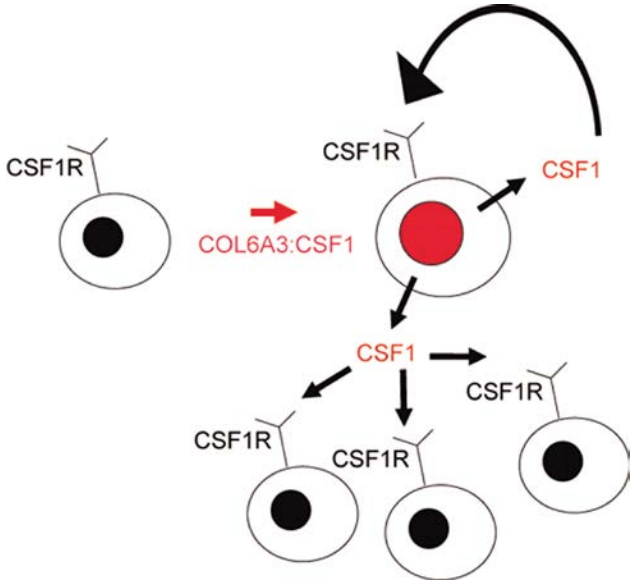


Hereditary Diffuse Leukoencepholopathy with Spheroids: Germline LOF CSF1R mutations

Rademakers, *et al. Nat Gen* 2012

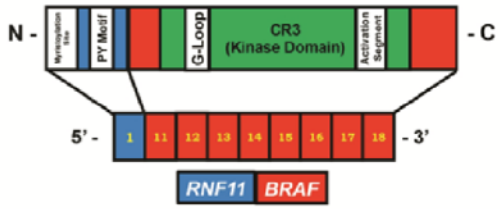
Tenosynovial Giant Cell Tumor: Ectopic overexpression of CSF1

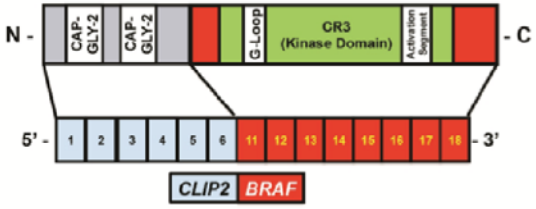


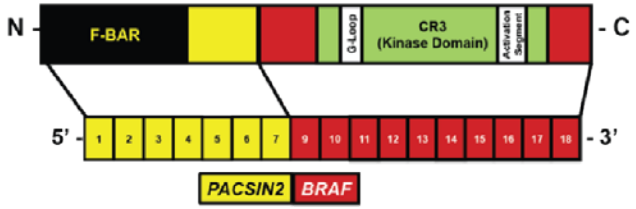


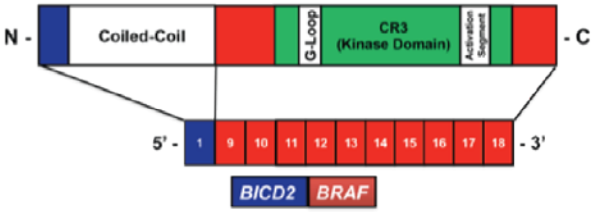
West, *et al. PNAS* 2006;
Tap, *et al. NEJM* 2015

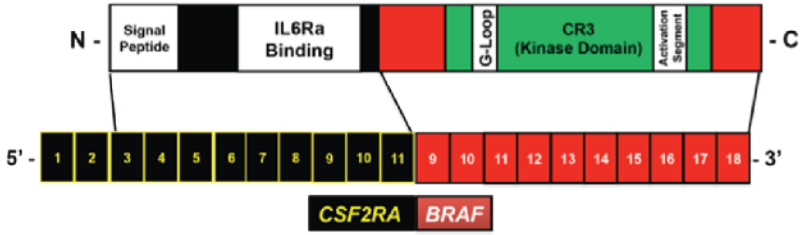
Kinase Fusions in Histiocytoses

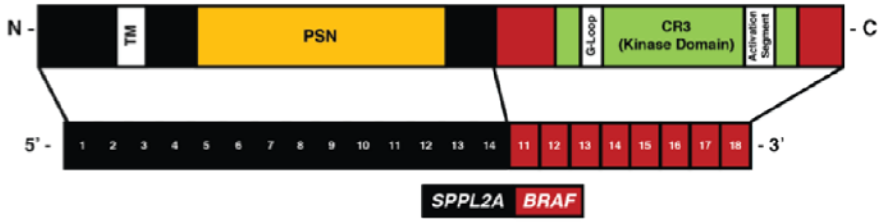


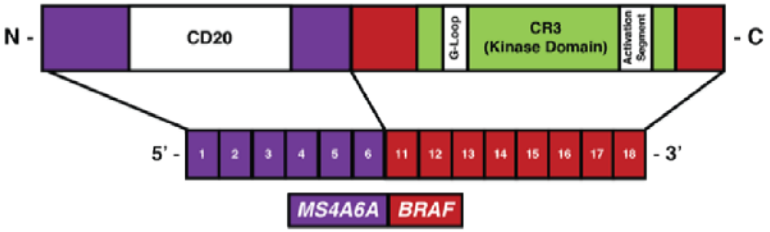




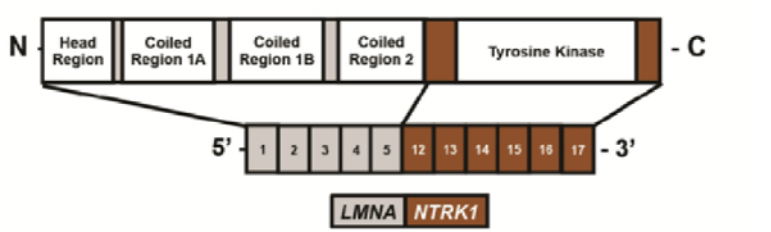


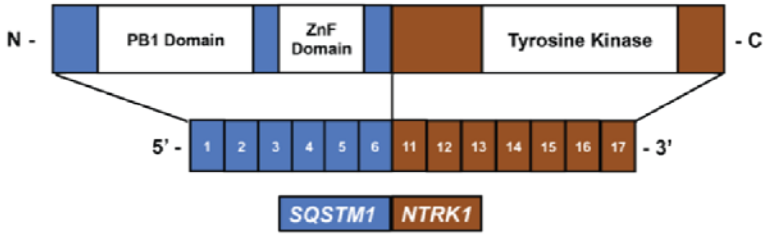


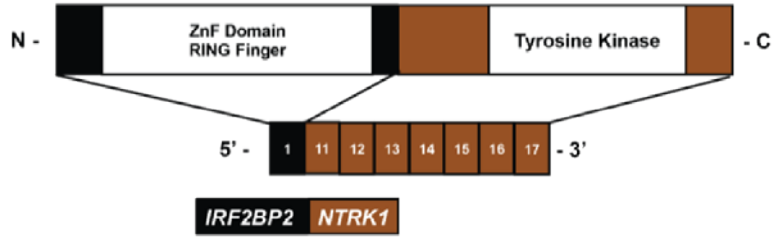


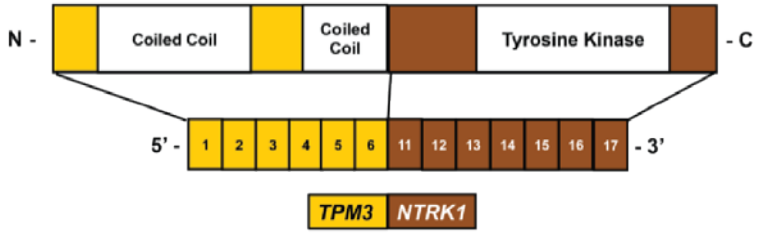


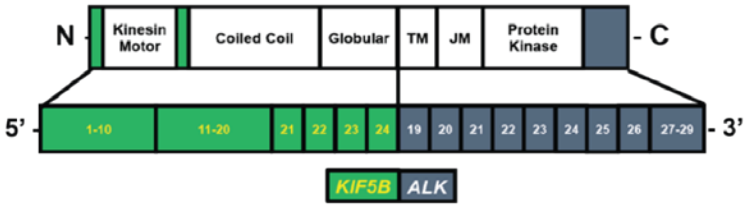
Kinase Fusions in Histiocytoses

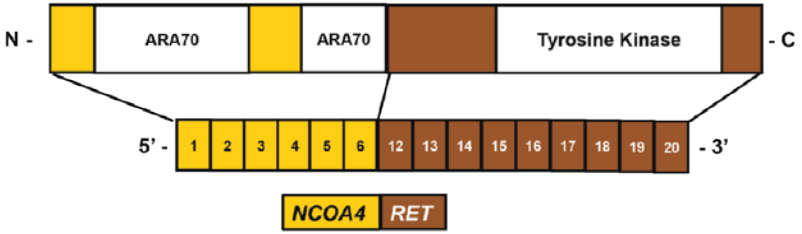




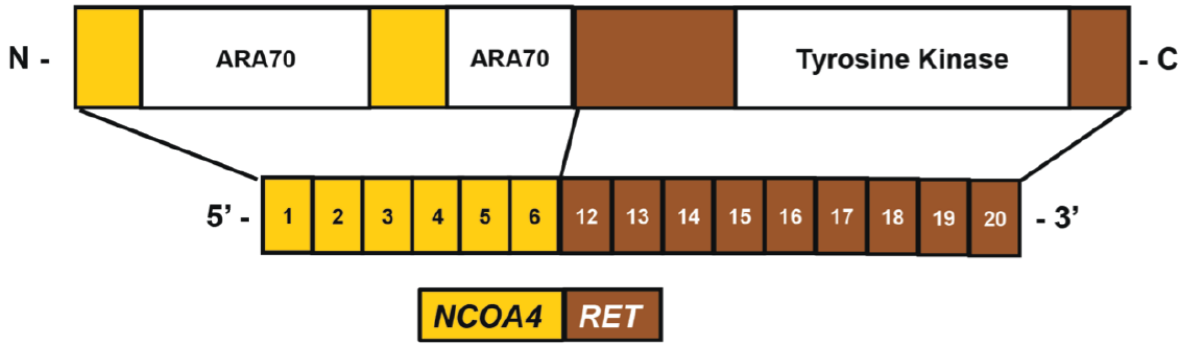


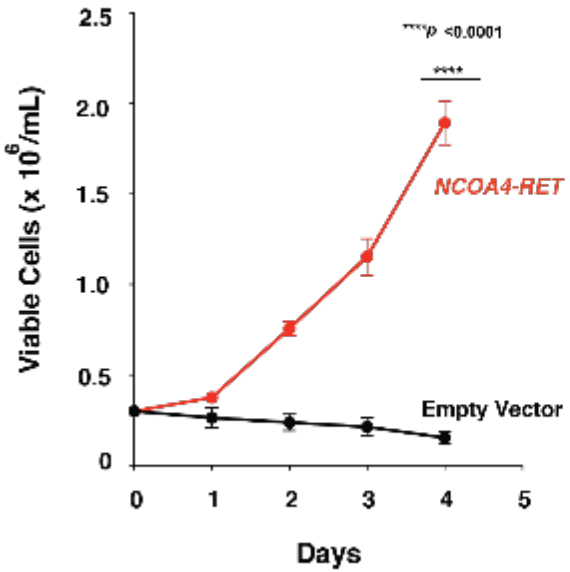


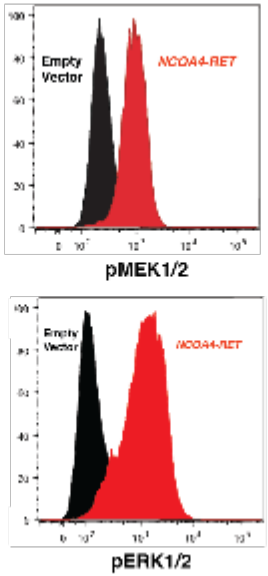


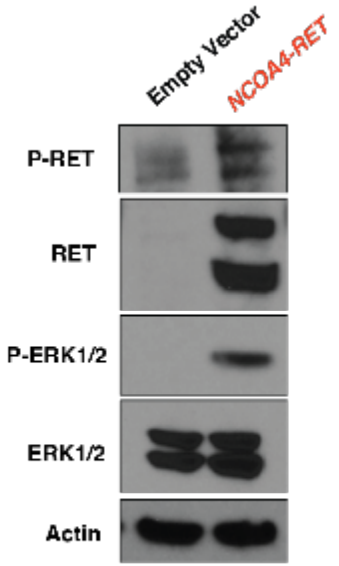


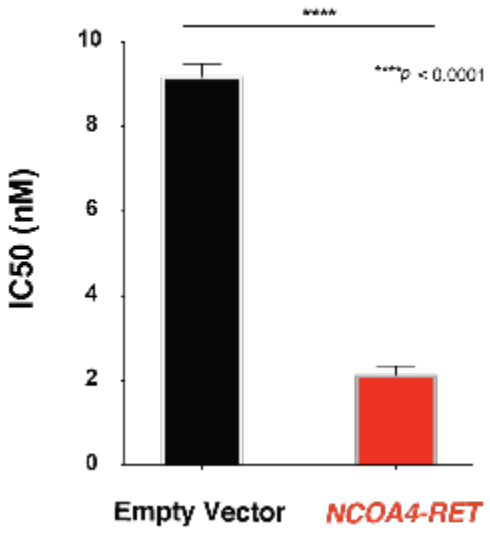
NCOA4-RET Fusions in JXG/AXG are Activating



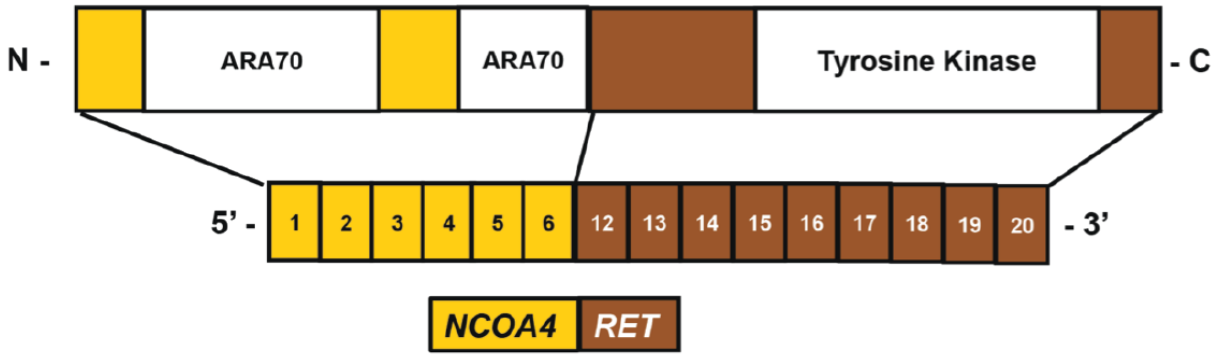




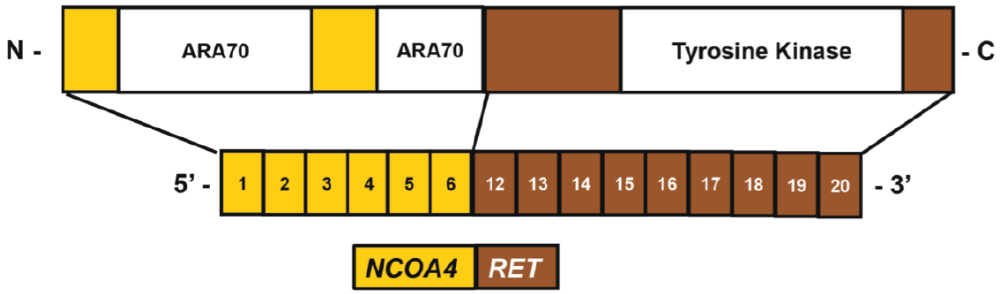


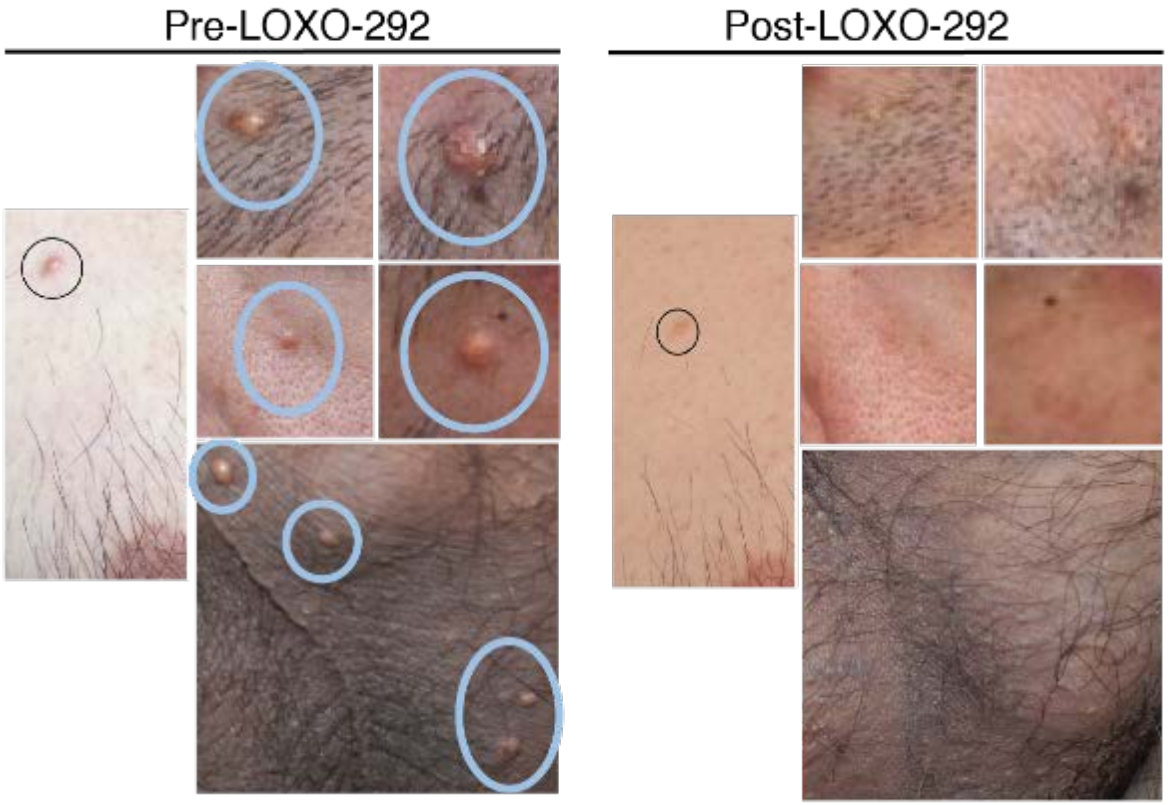


RET inhibitor Response in NCOA4-RET JXG/AXG

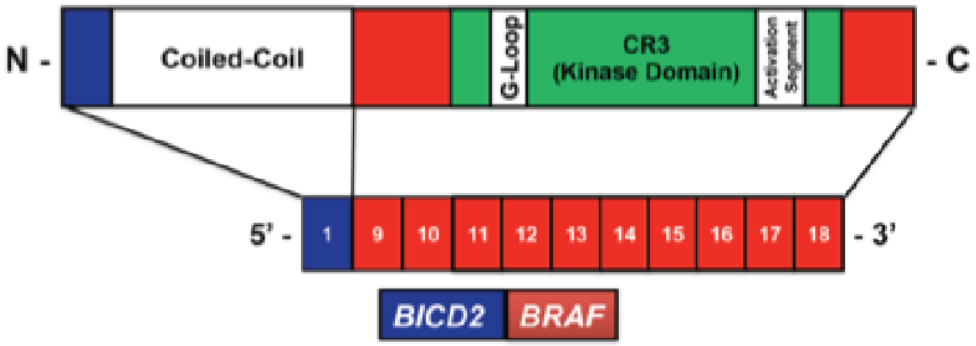


RET inhibitor Response in NCOA4-RET JXG/AXG

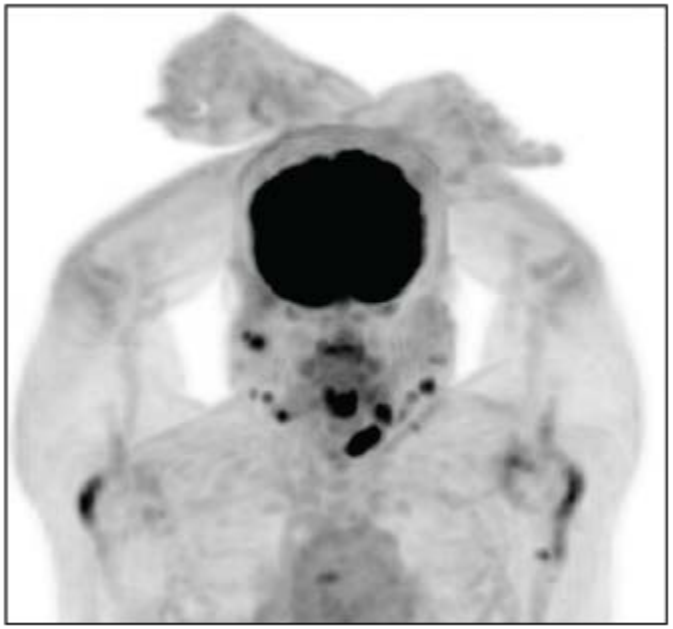




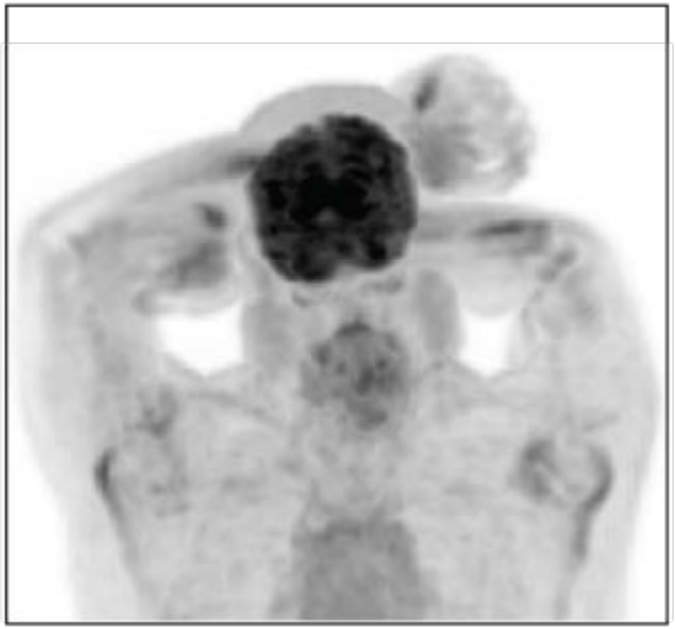
MEK Inhibitor Response in *BICD2-BRAF* Fusion LCH



Pre-Trametinib



Post-Trametinib



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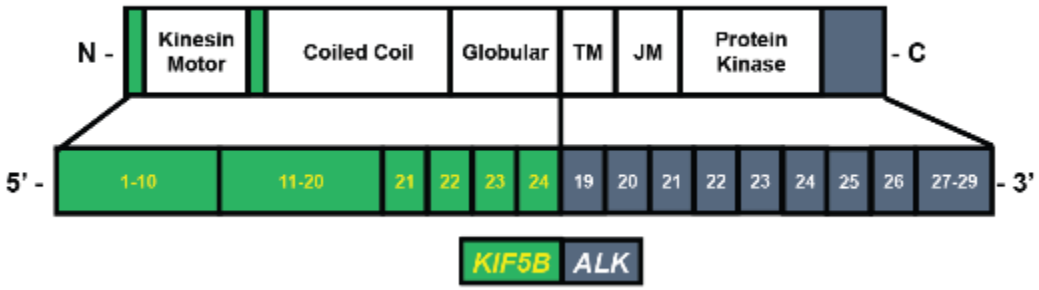
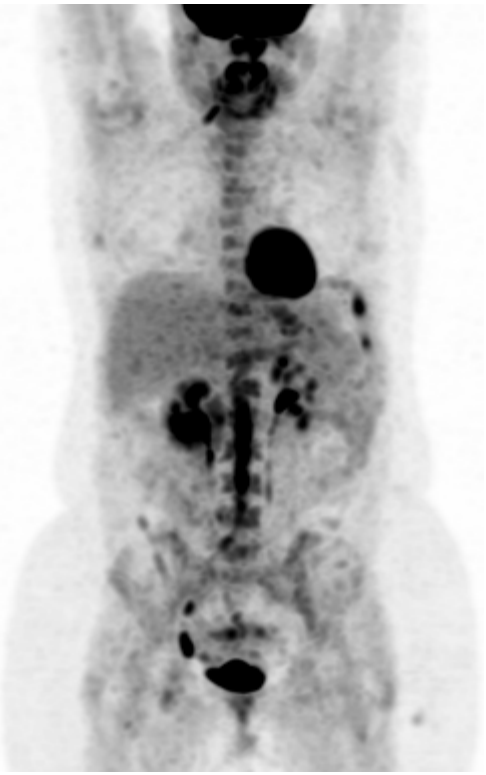
ALK Inhibitor Response in *KIF5B-ALK* Fusion ECD



Pre-Treatment

Post-Treatment



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Conclusions

- Diverse **kinase mutations** and **fusions** continue to drive systemic histiocytic neoplasms.

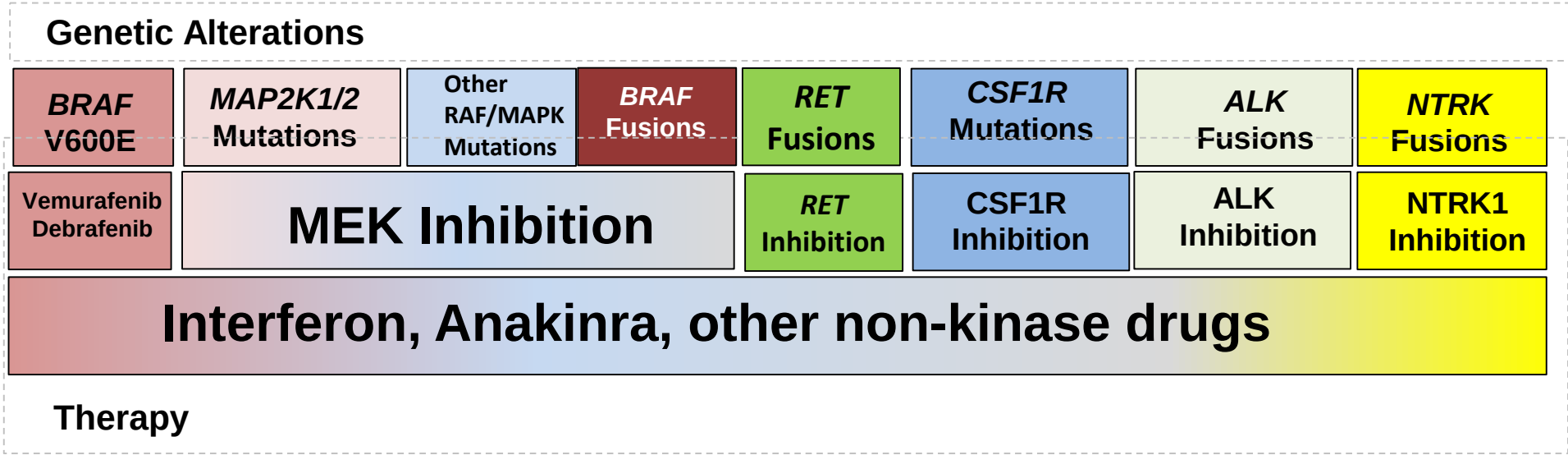
- Recurrent, activating ***CSF1R*** mutations in familial and sporadic histiocytoses,
  - Suggests the cell-of-origin belongs to committed monocyte/macrophage progenitors.
  - Highlights therapeutic potential for ***CSF1R*** inhibition in histiocytoses.

.

- First description of other kinase and receptor tyrosine kinase [***MAPK7*** (ERK5), ***MAPK3*** (ERK1) ***ALK, KIT, MET, JAK3,* and *CSF3R*]** mutations and first ***RET* fusions** uncovered in the histiocytoses.

- ***BRAF*^{V600E}** is prevalent in LCH and ECD but not in other histiocytoses subtypes. There is also an enrichment of ***NTRK1* fusions** and ***CSF1R* mutations** in **JXG and *BRAF* fusions and deletions in LCH** compared to other histocytoses in this cohor

- Kinase alterations other than *BRAF*^{V600E} have **direct therapeutic implications.**



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