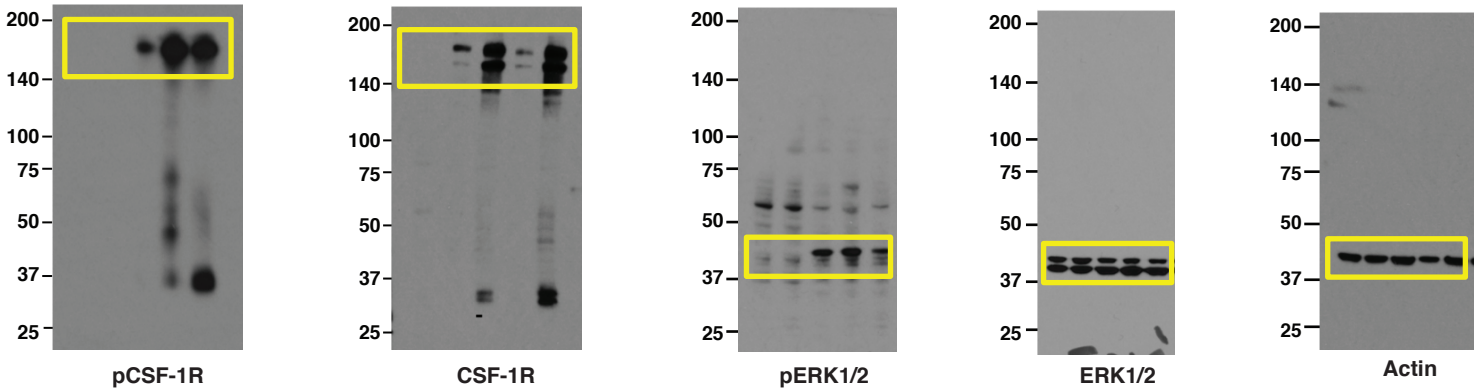
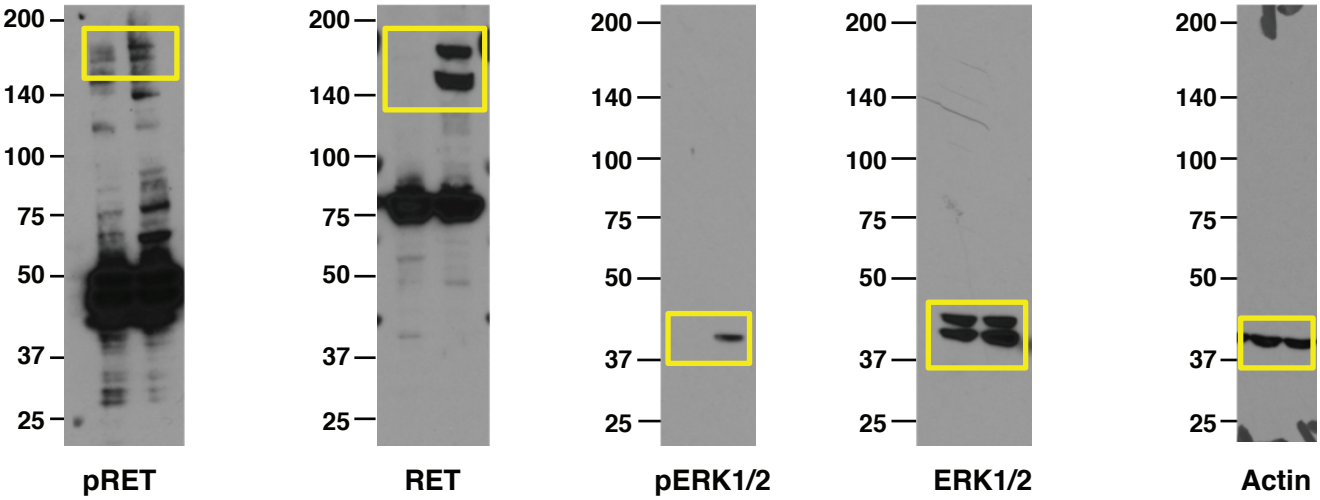
Supplementary Figure 1

Figure 2c



Supplementary Figure 2

Extended Data Figure 10f



Supplementary Table 1: Clinical features of histiocytoses patients in the current study.

Study ID	Age (years)	Sex	Histiocytosis Subtype	Tissue Site
ECD-1	75	Male	Erdheim-Chester Disease	Bone
ECD-2	76	Female	Erdheim-Chester Disease	Skin
ECD-3	65	Female	Erdheim-Chester Disease	Bone; Pituitary; Retroperitoneum
ECD-4	50	Female	Erdheim-Chester Disease	Cerebellum
ECD-5	70	Male	Erdheim-Chester Disease	Bone; Oral Mucosa
ECD-6	65	Female	Erdheim-Chester Disease	Femur; Mastoid
ECD-7	37	Male	Erdheim-Chester Disease	Dura; Testicle; Bone; Skin
ECD-8	59	Male	Erdheim-Chester Disease	Bone; Skin
ECD-9	47	Female	Erdheim-Chester Disease	Bone
ECD-10	47	Female	Erdheim-Chester Disease	Bone
ECD-11	36	Female	Erdheim-Chester Disease	Bone; Lung
ECD-12	47	Male	Erdheim-Chester Disease	Bone; Retroperitoneum
ECD-13	48	Female	Erdheim-Chester Disease	Brain; Bone; Retroperitoneum
ECD-14	73	Male	Erdheim-Chester Disease	Bone; Retroperitoneum
ECD-15	74	Male	Erdheim-Chester Disease	Brain; Bone; Lung; Retroperitoneum
ECD-16	65	Female	Erdheim-Chester Disease	Bone; Lung; Retroperitoneum
ECD-17	52	Female	Erdheim-Chester Disease	Bone; Pituitary; Skin; Soft Tissue
ECD-18	51	Female	Erdheim-Chester Disease	Bone; Skin; Soft Tissue
ECD-19	67	Male	Erdheim-Chester Disease	Bone; Lung; Pleura; Skin; Soft Tissue
ECD-20	65	Male	Erdheim-Chester Disease	Bone; Skin; Soft Tissue
ECD-21	55	Female	Erdheim-Chester Disease	Bone; Retroperitoneum; Soft Tissue
ECD-22	52	Female	Erdheim-Chester Disease	Bone; Maxilla; Skin; Soft Tissue
ECD-23	73	Male	Erdheim-Chester Disease	Bone; Brain; Retroperitoneum
ECD-24	55	Male	Erdheim-Chester Disease	Bone; Brain; Retroperitoneum
ECD-25	47	Female	Erdheim-Chester Disease	Bone; Orbit; Retroperitoneum
ECD-26	51	Male	Erdheim-Chester Disease	Bone; Epidural Soft Tissue; Orbit
ECD-27	66	Female	Erdheim-Chester Disease	Bone; Brain; Retroperitoneum; Skin
ECD-28	64	Female	Erdheim-Chester Disease	Bone
ECD-29	50	Male	Erdheim-Chester Disease	Bone; Brain; Retroperitoneum; Heart
ECD-30	58	Male	Erdheim-Chester Disease	Bone; Orbit; Retroperitoneum
ECD-31	75	Male	Erdheim-Chester Disease	Bone; Orbit; Retroperitoneum
ECD-32	59	Male	Erdheim-Chester Disease	Bone; Orbit; Retroperitoneum
ECD-33	35	Male	Erdheim-Chester Disease	Bone; Brain; Cavernous Sinus; Skull; Heart; Retroperitoneum
ECD-34	41	Male	Erdheim-Chester Disease	Orbit
ECD-35	45	Female	Erdheim-Chester Disease	Bone
ECD-36	47	Male	Erdheim-Chester Disease	Brain; Orbit; Heart; Bone
ECD-37	58	Female	Erdheim-Chester Disease	Skin; Bone; Brain
ECD-38	53	Male	Erdheim-Chester Disease	Retroperitoneum
ECD-39	65	Female	Erdheim-Chester Disease	Dura; Temporalis Muscle; Bone; Brain
ECD-40	56	Female	Erdheim-Chester Disease	Cerebellum
ECD-41	64	Female	Erdheim-Chester Disease	Bone; Lung; Pleura
ECD-42	67	Female	Erdheim-Chester Disease	Skin
ECD-43	43	Female	Erdheim-Chester Disease	Bone
ECD-44	56	Male	Erdheim-Chester Disease	Skin; Bone
ECD-45	45	Male	Erdheim-Chester Disease	Bone; Skin
ECD-46	7	Male	Erdheim-Chester Disease	Bone; Orbit; Sinonasal
ECD-47	53	Male	Erdheim-Chester Disease	Kidney
ECD-48	58	Male	Erdheim-Chester Disease	Perirenal; Tibia
ECD-49	48	Male	Erdheim-Chester Disease	Bone; Skin
ECD-50	37	Male	Erdheim-Chester Disease	Testicle; Bone; Peritoneum; Retroperitoneum; Omentum
ECD-51	30	Male	Erdheim-Chester Disease	Epidural; Tibia

ECD-52	67	Male	Erdheim-Chester Disease	Testicle; Prostate; Bone
ECD-53	60	Male	Erdheim-Chester Disease	Retroperitoneum; Femur
ECD-54	51	Male	Erdheim-Chester Disease	Perirenal; Tibia
ECD-55	60	Female	Erdheim-Chester Disease	Bone (WES)
ECD-56	31	Female	Erdheim-Chester Disease	Dura
ECD-57	56	Female	Erdheim-Chester Disease	Bone; Soft Tissue; Skin
ECD-58	45	Male	Erdheim-Chester Disease	Soft Tissue
ECD-59	82	Female	Erdheim-Chester Disease	Skin
ECD-60	55	Male	Erdheim-Chester Disease	Skin
ECD-61	71	Male	Erdheim-Chester Disease	Retroperitoneum
ECD-62	54	Male	Erdheim-Chester Disease	Mesentery
ECD-63	52	Male	Erdheim-Chester Disease	Mesentery
ECD-64	47	Male	Erdheim-Chester Disease	Skin
ECD-65	71	Male	Erdheim-Chester Disease	Skin
ECD-66	55	Male	Erdheim-Chester Disease	Heart
ECD-67	53	Male	Erdheim-Chester Disease	Pleura; Lung
ECD-68	66	Female	Erdheim-Chester Disease	Heart; Mediastinum; Bone
ECD-69	46	Female	Erdheim-Chester Disease	Soft Tissue
ECD-70	33	Male	Erdheim-Chester Disease	Skin; Larynx
ECD-71	54	Male	Erdheim-Chester Disease	Skin; Bone
ECD-72	64	Female	Erdheim-Chester Disease	Lymph Node; Mesentery
ECD-73	42	Male	Erdheim-Chester Disease	Brain; Lung; Soft Tissue; Bone
ECD-74	66	Male	Erdheim-Chester Disease	Dura; Soft Tissue; Bone
ECD-75	64	Male	Erdheim-Chester Disease	Pleura
ECD-76	65	Male	Erdheim-Chester Disease	Pleura
ECD-77	73	Male	Erdheim-Chester Disease	Peritoneum (N)
ECD-78	58	Male	Erdheim-Chester Disease	Skin; Lung (A)
ECD-79	59	Female	Erdheim-Chester Disease	Skull; Femur; Skin
ECD-80	55	Female	Erdheim-Chester Disease	Skin; Bone
ECD-81	65	Female	Erdheim-Chester Disease	Bone; Skin
ECD-82	37	Male	Erdheim-Chester Disease	Bone
ECD-83	33	Male	Erdheim-Chester Disease	Bone
ECD-84	31	Male	Erdheim-Chester Disease	Tibia
ECD-85	66	Male	Erdheim-Chester Disease	Perirenal; Soft Tissue; Bone
ECD-86	52	Male	Erdheim-Chester Disease	Pericardium; Retroperitoneum
ECD-87	45	Female	Erdheim-Chester Disease	Skin
ECD-88	34	Female	Erdheim-Chester Disease	Hypothalamus
ECD-89	43	Female	Erdheim-Chester Disease	Bone; Lymph Node
ECD-90	25	Female	Erdheim-Chester Disease	Skin
ECD-91	42	Female	Erdheim-Chester Disease	Polyradiculopathy; Skin; Lymph Node
ECD-92	50	Male	Erdheim-Chester Disease	Liver
ECD-93	50	Female	Erdheim-Chester Disease	Lung; Stomach; Colon; Bone
ECD-94	47	Male	Erdheim-Chester Disease	Perinephric Soft Tissue
ECD-95	27	Male	Erdheim-Chester Disease	Skin; Ankle
ECD-96	49	Male	Erdheim-Chester Disease	Soft Tissue of Shoulder; Bone
ECD-97	31	Male	Erdheim-Chester Disease	Paravertebral
ECD-98	58	Male	Erdheim-Chester Disease	Perirenal
ECD-99	82	Female	Erdheim-Chester Disease	Skin
ECD-100	48	Female	Erdheim-Chester Disease	Soft Tissue
LCH-1	1	Male	Langerhans Cell Histiocytosis	Left Maxillary Sinus
LCH-2	1	Male	Langerhans Cell Histiocytosis	Epidural Space
LCH-3	9	Male	Langerhans Cell Histiocytosis	Scapula
LCH-4	10	Male	Langerhans Cell Histiocytosis	Brain
LCH-5	78	Female	Langerhans Cell Histiocytosis	Skin
LCH-6	72	Female	Langerhans Cell Histiocytosis	Skin
LCH-7	37	Female	Langerhans Cell Histiocytosis	Bone
LCH-8	34	Male	Langerhans Cell Histiocytosis	Bone
LCH-9	45	Female	Langerhans Cell Histiocytosis	Bone; Skin

LCH-10	32	Male	Langerhans Cell Histiocytosis	Bone; Skin; Soft Tissue
LCH-11	18	Female	Langerhans Cell Histiocytosis	Bone; Soft Tissue
LCH-12	39	Male	Langerhans Cell Histiocytosis	Bone
LCH-13	33	Male	Langerhans Cell Histiocytosis	Skin
LCH-14	70	Male	Langerhans Cell Histiocytosis	Lung; Spleen
LCH-15	4 mo.	Female	Langerhans Cell Histiocytosis	Bone; Liver; Spleen
LCH-16	2	Male	Langerhans Cell Histiocytosis	Bone; Intestine; Liver; Skin
LCH-17	2	Female	Langerhans Cell Histiocytosis	Bone; Pituitary; Skin
LCH-18	13	Male	Langerhans Cell Histiocytosis	Bone (Frontal); CNS Risk
LCH-19	4	Female	Langerhans Cell Histiocytosis	Bone (Maxilla); CNS Risk
LCH-20	7	Female	Langerhans Cell Histiocytosis	Bone (Frontal); CNS Risk
LCH-21	3	Male	Langerhans Cell Histiocytosis	Bone
LCH-22	12	Male	Langerhans Cell Histiocytosis	Bone (Frontal); CNS Risk
LCH-23	2	Male	Langerhans Cell Histiocytosis	Bone (Frontal); CNS Risk
LCH-24	3	Male	Langerhans Cell Histiocytosis	Bone; Pituitary; Skin
LCH-25	10	Male	Langerhans Cell Histiocytosis	Bone (Parietal); CNS Risk; Skin
LCH-26	9	Male	Langerhans Cell Histiocytosis	Bone; Pituitary
LCH-27	1	Female	Langerhans Cell Histiocytosis	Bone (Iliac)
LCH-28	7	Female	Langerhans Cell Histiocytosis	Bone; Mastoid
LCH-29	14	Female	Langerhans Cell Histiocytosis	Femur
LCH-30	4	Male	Langerhans Cell Histiocytosis	Bone; Palate; Pituitary
LCH-31	13	Male	Langerhans Cell Histiocytosis	Bone (Frontal); CNS Risk
LCH-32	10	Male	Langerhans Cell Histiocytosis	Humerus
LCH-33	2	Male	Langerhans Cell Histiocytosis	Skull
LCH-34	4	Male	Langerhans Cell Histiocytosis	Mandible
LCH-35	2	Male	Langerhans Cell Histiocytosis	Lymph Node; Skin
LCH-36	3	Female	Langerhans Cell Histiocytosis	Skin
LCH-37	5	Male	Langerhans Cell Histiocytosis	Bone
LCH-38	12	Female	Langerhans Cell Histiocytosis	Bone; Skin
LCH-39	15	Male	Langerhans Cell Histiocytosis	Bone; Skin
LCH-40	71	Female	Langerhans Cell Histiocytosis	Skin
LCH-41	25	Female	Langerhans Cell Histiocytosis	Bone
LCH-42	35	Female	Langerhans Cell Histiocytosis	Bone
LCH-43	19	Male	Langerhans Cell Histiocytosis	Bone; Brain; Pituitary
LCH-44	9	Female	Langerhans Cell Histiocytosis	Bone
LCH-45	9	Female	Langerhans Cell Histiocytosis	Bone
LCH-46	2	Female	Langerhans Cell Histiocytosis	Bone; Brain; Pituitary
LCH-47	5 mo.	Male	Langerhans Cell Histiocytosis	Bone; Brain; Pituitary; Skin
LCH-48	8	Female	Langerhans Cell Histiocytosis	Bone
LCH-49	53	Female	Langerhans Cell Histiocytosis	Bone; Brain; Liver; Lung; Skin
LCH-50	58	Female	Langerhans Cell Histiocytosis	Lung
LCH-51	31	Male	Langerhans Cell Histiocytosis	Bone
LCH-52	54	Female	Langerhans Cell Histiocytosis	Bone; Spleen
LCH-53	33	Male	Langerhans Cell Histiocytosis	Skin
LCH-54	2	Male	Langerhans Cell Histiocytosis	Femur
LCH-55	8	Female	Langerhans Cell Histiocytosis	Tibia
LCH-56	4	Female	Langerhans Cell Histiocytosis	Skin (Forehead)
LCH-57	2	Male	Langerhans Cell Histiocytosis	Skull
LCH-58	8	Male	Langerhans Cell Histiocytosis	Bone
LCH-59	1	Female	Langerhans Cell Histiocytosis	Bone
LCH-60	1	Male	Langerhans Cell Histiocytosis	Lymph Node
LCH-61	17	Male	Langerhans Cell Histiocytosis	Bone
LCH-62	13	Male	Langerhans Cell Histiocytosis	Skin
LCH-63	2	Male	Langerhans Cell Histiocytosis	Bone
LCH-64	2	Female	Langerhans Cell Histiocytosis	Bone; Lung
LCH-65	24	Female	Langerhans Cell Histiocytosis	Oral Mucosa
LCH-66	53	Female	Langerhans Cell Histiocytosis	Lung
LCH-67	33	Male	Langerhans Cell Histiocytosis	Lymph Node; Skin; Oral Mucosa
LCH-68	39	Male	Langerhans Cell Histiocytosis	Bone; Dura

LCH-69	33	Male	Langerhans Cell Histiocytosis	Skin
LCH-70	24	Female	Langerhans Cell Histiocytosis	Skull
LCH-71	55	Male	Langerhans Cell Histiocytosis	Skin; Colon
LCH-72	4	Male	Langerhans Cell Histiocytosis	Femur
LCH-73	37	Female	Langerhans Cell Histiocytosis	Thyroid; Lymph Node; Salivary Gland
LCH-74	57	Male	Langerhans Cell Histiocytosis	Lymph Node; Oral Mucosa
LCH-75	29	Female	Langerhans Cell Histiocytosis	Skin
LCH-76	7	Male	Langerhans Cell Histiocytosis	Skull; Dura; Skin
LCH-77	17	Male	Langerhans Cell Histiocytosis	Skin
LCH-78	3	Male	Langerhans Cell Histiocytosis	Skull
LCH-79	11	Female	Langerhans Cell Histiocytosis	Bone; CNS Risk Frontal
LCH-80	14	Male	Langerhans Cell Histiocytosis	Bone; Lymph Nodes
LCH-81	6	Female	Langerhans Cell Histiocytosis	Skin
LCH-82	32	Male	Langerhans Cell Histiocytosis	Lymph Node; Skin; Soft Tissue
LCH-83	26	Male	Langerhans Cell Histiocytosis	Dura
LCH-84	1	Male	Langerhans Cell Histiocytosis	Humerus
LCH-85	8	Male	Langerhans Cell Histiocytosis	Mandible; CNS Risk
LCH-86	3	Male	Langerhans Cell Histiocytosis	Scapula
LCH-87	10	Male	Langerhans Cell Histiocytosis	Bone (Iliac Crest)
LCH-88	7	Female	Langerhans Cell Histiocytosis	Lymph Node; Vertebra
LCH-89	7	Female	Langerhans Cell Histiocytosis	Skin
LCH-90	55	Female	Langerhans Cell Histiocytosis	Bone Marrow; Muscle; Hypothalamus
LCH-91	56	Female	Langerhans Cell Histiocytosis	Lung
LCH-92	60	Male	Langerhans Cell Histiocytosis	Skin
JXG-1	46	Male	Juvenile Xanthogranuloma	Soft Tissue
JXG-2	50	Female	Juvenile Xanthogranuloma	Breast Soft Tissue; Lacrimal Gland
JXG-3	63	Female	Juvenile Xanthogranuloma	Skin
JXG-4	29	Male	Juvenile Xanthogranuloma	Skin
JXG-5	16	Male	Juvenile Xanthogranuloma	Skin (Genitourinary)
JXG-6	2	Male	Juvenile Xanthogranuloma	Skin
JXG-7	4.5 mo.	Male	Juvenile Xanthogranuloma	Skin (Genitourinary)
JXG-8	5 mo.	Male	Juvenile Xanthogranuloma	Skin (Lower Extremity)
JXG-9	13.5 mo.	Female	Juvenile Xanthogranuloma	Skin (Head)
JXG-10	1	Female	Juvenile Xanthogranuloma	Skin; Eye
JXG-11	1	Female	Juvenile Xanthogranuloma	Skin
JXG-12	21.5 mo.	Female	Juvenile Xanthogranuloma	Skin (Genitourinary)
JXG-13	15.5 mo.	Female	Juvenile Xanthogranuloma	Skin (Head)
JXG-14	30	Female	Juvenile Xanthogranuloma	Skin
JXG-15	23	Male	Juvenile Xanthogranuloma	Skin
JXG-16	17	Female	Juvenile Xanthogranuloma	Skin
JXG-17	9	Male	Juvenile Xanthogranuloma	Skin (Head)
JXG-18	35	Male	Juvenile Xanthogranuloma	Skin
JXG-19	22	Female	Juvenile Xanthogranuloma	Skin
JXG-20	30	Male	Juvenile Xanthogranuloma	Skin
JXG-21	4	Female	Juvenile Xanthogranuloma	Skin (Lower Extremity)
JXG-22	3	Female	Juvenile Xanthogranuloma	Skin (Head)
JXG-23	2.5 mo.	Male	Juvenile Xanthogranuloma	Skin (Head)
JXG-24	3	Female	Juvenile Xanthogranuloma	Skin (Head)
JXG-25	6.5 mo.	Male	Juvenile Xanthogranuloma	Skin (Trunk)
JXG-26	3	Male	Juvenile Xanthogranuloma	Skin (Lower Extremity)
JXG-27	17	Male	Juvenile Xanthogranuloma	Skin (Trunk)
JXG-28	12.5 mo.	Female	Juvenile Xanthogranuloma	Skin (Head)
JXG-29	2.5 mo.	Male	Juvenile Xanthogranuloma	Skin (Head)
JXG-30	3	Male	Juvenile Xanthogranuloma	Skin (Head)
JXG-31	11 mo.	Male	Juvenile Xanthogranuloma	Skin (Head)
JXG-32	4	Male	Juvenile Xanthogranuloma	Skin (Trunk)
JXG-33	10	Male	Juvenile Xanthogranuloma	Skin (Head)
JXG-34	4 mo.	Male	Juvenile Xanthogranuloma	Skin (Head)

JXG-35	**14**	**Male**	**Juvenile Xanthogranuloma**	**Brain**
JXG-36	**12**	**Female**	**Juvenile Xanthogranuloma**	**Skin; Bone; Lymph Node; Lung**
JXG-37	**15**	**Male**	**Juvenile Xanthogranuloma**	**Skin**
JXG-38	**29**	**Male**	**Juvenile Xanthogranuloma**	**Brain; Vertebra**
JXG-39	**36**	**Male**	**Juvenile Xanthogranuloma**	**Skin (Disseminated)**
JXG-40	**4**	**Female**	**Juvenile Xanthogranuloma**	**Skin (Chest)**
JXG-41	**21 mo.**	**Female**	**Juvenile Xanthogranuloma**	**Skin (Head)**
JXG-42	**20 mo.**	**Female**	**Juvenile Xanthogranuloma**	**Skin (Extremity)**
JXG-43	**9 mo.**	**Male**	**Juvenile Xanthogranuloma**	**Skin (Head)**
JXG-44	**12**	**Male**	**Juvenile Xanthogranuloma**	**Skin (Head)**
JXG-45	**29.5 mo.**	**Male**	**Juvenile Xanthogranuloma**	**Skin (Upper Extremity)**
JXG-46	**30.5 mo.**	**Female**	**Juvenile Xanthogranuloma**	**Skin (Head)**
JXG-47	**25 mo.**	**Male**	**Juvenile Xanthogranuloma**	**Skin (Upper Extremity)**
JXG-48	**8**	**Male**	**Juvenile Xanthogranuloma**	**Skin**
JXG-49	**3**	**Male**	**Juvenile Xanthogranuloma**	**Skin**
JXG-50	**27**	**Female**	**Juvenile Xanthogranuloma**	**Skin**
JXG-51	**39**	**Female**	**Juvenile Xanthogranuloma**	**Skin**
JXG-52	**5**	**Male**	**Juvenile Xanthogranuloma**	**Skin**
JXG-53	**11**	**Male**	**Juvenile Xanthogranuloma**	**Skin (Genitourinary)**
JXG-54	**7**	**Female**	**Juvenile Xanthogranuloma**	**Skin (Upper Extremity)**
JXG-55	**4**	**Male**	**Juvenile Xanthogranuloma**	**Skin (Head)**
RDD-1	**25**	**Female**	**Rosai-Dorfman Disease**	**Lymph Node**
RDD-2	**27**	**Male**	**Rosai-Dorfman Disease**	**Lymph Node**
RDD-3	**35**	**Female**	**Rosai-Dorfman Disease**	**Soft Tissue**
RDD-4	**59**	**Female**	**Rosai-Dorfman Disease**	**Brain; Breast Soft Tissue**
RDD-5	**43**	**Male**	**Rosai-Dorfman Disease**	**Soft Tissue**
RDD-6	**60**	**Male**	**Rosai-Dorfman Disease**	**Brain; Spinal Cord**
RDD-7	**19**	**Female**	**Rosai-Dorfman Disease**	**Lymph Node**
RDD-8	**49**	**Female**	**Rosai-Dorfman Disease**	**Pituitary Stalk**
RDD-9	**52**	**Female**	**Rosai-Dorfman Disease**	**Sinuses**
RDD-10	**30**	**Male**	**Rosai-Dorfman Disease**	**Brain; Cornea**
RDD-11	**6**	**Male**	**Rosai-Dorfman Disease**	**Cheek**
RDD-12	**30**	**Female**	**Rosai-Dorfman Disease**	**Meninges**
RDD-13	**62**	**Male**	**Rosai-Dorfman Disease**	**Axillary Soft Tissue**
RDD-14	**3**	**Female**	**Rosai-Dorfman Disease**	**Lymph Node**
RDD-15	**4**	**Female**	**Rosai-Dorfman Disease**	**Lymph Node**
RDD-16	**25**	**Female**	**Rosai-Dorfman Disease**	**Tibia**
RDD-17	**58**	**Female**	**Rosai-Dorfman Disease**	**Brain**
HS-1	**76**	**Male**	**Histiocytic Sarcoma**	**Soft Tissue; Lung; Brain**
HS-2	**61**	**Male**	**Histiocytic Sarcoma**	**Lymph Node**
HS-3	**60**	**Female**	**Histiocytic Sarcoma**	**Lymph Node**
HS-4	**25**	**Male**	**Histiocytic Sarcoma**	**Soft Tissue**
HS-5	**31**	**Male**	**Histiocytic Sarcoma**	**Left Cervical Bone (Bone Marrow)**
HS-6	**38**	**Female**	**Histiocytic Sarcoma**	**Retroperitoneum**

Abbreviations: Erdheim-Chester Disease (ECD); Langerhans Cell Histiocytosis (LCH); Juvenile Xanthogranuloma (JXG); Rosai-Dorfman Disease (RDD); Histiocytic Sarcoma (HS); months (mo).

Supplementary Table 2: Somatic mutations and fusions in Erdheim-Chester Disease Cohort.

Study ID	Gene	Genomic Coordinates	Genomic Variant	Amino Acid Change	VAF
ECD-1	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	15%
ECD-2	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	9%
	EP400	chr12:132547093	c.8181_8182insCAG	p.Q2727delinsQQ	15%
	KMT2C	chr7:151962265	c.G1042G>A	p.D348N	4%
	ATXN1	chr6:16327948	c.593_594insGCA	p.Q198delinsQQ	24%
	HMGXB4	chr22:35661543	c.1163insA	p.E388fs	10%
ECD-3	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	12%
	FIP1L1	chr4:54319248	c.1447_1448del	p.R483fs	11%
	TOX3	chr16:52502453	c.109G>A	p.E37K	15%
ECD-4	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	19%
	MED15	chr22:20918916	c.631_633del	p.Q211del	10%
	INO80E	chr16:30016629	c.602dupC	p.T201fs	12%
	SETD8	chr12:123889486	c.713G>C	p.R238P	9%
	SETD8	chr12:123889492	c.A719C	p.D240A	8%
	USP8	chr15:50784990	c.2327T>C	p.L776P	5%
	CSPG4	chr15:75982085	c.1321G>A	p.E441K	10%
ECD-5	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	8%
	FGFR1	chr8:38285914	c.396_398delTGA	p.D133delD	12%
	SMARCD3	chr7:150972220	c.19C>T	p.H7Y	9%
	BTAF1	chr10:93699809	c.239C>T	p.P80L	7%
ECD-6	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	2%
ECD-7	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	3%
ECD-8	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	8%
	AMER1	chrX:63410516	c.2651C>T	p.P884L	12%
ECD-9	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	7%
	MAP3K19	chr2:135756487	c.395G>T	p.R132M	6%
	JAK2	chr9:5069154	c.1459C>A	p.R487S	5%
	TAB3	chrX:30872481	c.1301C>A	p.P434Q	4%
	TAB3	chrX:30873066	c.716C>A	p.S239X	5%
	FGF5	chr4:81196141	c.434C>A	p.S145X	6%
	FAT1	chr4:187557879	c.3832G>T	p.D1278Y	4%
	CSNK1G1	chr15:64508874	c.331G>T	p.G111W	19%
	DDX43	chr6:74104738	c.110G>T	p.R37L	8%
	NCOA1	chr2:24933824	c.2443G>T	p.D815Y	8%
	WDR33	chr2:128471212	c.3253G>T	p.E1085X	8%
	ZMYND8	chr20:45915981	c.721G>T	p.E241X	5%
	DNMT3A	chr2:25467132	c.1743G>T	p.W581C	12%
	TTI1	chr20:36640424	c.1795G>T	p.E599X	7%
	TRIO	chr5:14474171	c.6048C>A	p.F2016L	7%

ECD-10	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	5%
	ARAF	chrX:47430341	c.1616C>A	p.P539H	2%
	MAPK9	chr5:179663476	c.1183G>T	p.D395Y	7%
	STAT2	chr12:56737909	c.2101G>T	p.E701X	6%
	BCL2	chr18:60795947	c.631G>T	p.D211Y	10%
	AURKB	chr17:8110666	c.226G>T	p.D76Y	7%
	YES1	chr18:743416	c.725-1G>T	N/A	5%
	GAK	chr4:887695	c.844G>T	p.D282Y	6%
ECD-11	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-12	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	4%
ECD-13	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	2%
ECD-14	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-15	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-16	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-17	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-18	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-19	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-20	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-21	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	5%
	ARID5B	chr10:63700037	c.372C>G	p.F124L	6%
ECD-22	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-23	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-24	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-25	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-26	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-27	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-28	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-29	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-30	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-31	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A

ECD-32	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-33	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-34	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-35	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-36	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-37	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-38	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	3%
ECD-39	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-40	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-41	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-42	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-43	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-44	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-45	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	N/A
ECD-46	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	2%
ECD-47	*MAP2K1*	chr15:66727455	c.171G>C	p.K57N	7%
	CHD4	chr12:6692417	c.4007G>A	p.G1336E	9%
ECD-48	*MAP2K1*	chr15:66727486	c.202T>C	p.F68L	11%
ECD-49	*MAP2K1*	chr15:66729153	c.361T>A	p.C121S	3%
	MAP4K5	chr14:50930796	c.293delA	p.R265Dfs*8	4%
ECD-50	*MAP2K1*	chr15: 66729100	c.308_316delAAAACCCGC	p.I103_A106del	12%
	MAP4K3	chr2:39535126	c.1077G>C	p.L359F	14%
	ETV1	chr7:14027776	c.68A>C	p.N23T	16%
ECD-51	*MAP2K1*	chr15: 66729163	c.371C>T	p.P124L	2%
ECD-52	*MAP2K1*	chr15: 66729106	c.314_319del	p. P105_I107delinsL	6%
	NF1	chr17:29486043	c.220G>T	p.A74S	6%
	STAT3	chr17:40485757	c.983G>A	p.C328Y	6%
	ROR2	chr9:94486813	c.1963C>A	p.P655T	7%
	WNT7A	chr3:13896197	c.402C>A	p.D134E	10%
	SETD2	chr3:47098416	c.6858C>A	p.Y2286X	7%
	APAF1	chr12:99080525	c.2179-1G>T	N/A	8%
	PLCE1	chr10:96022489	c.4053G>T	p.Q1351H	7%
	GRIN2A	chr16:10274124	c.145C>A	p.R49S	7%

ECD-53	*MAP2K1*	chr15: 66727451	c.167A>C	p.Q56P	2%
	NDRG2	chr14:21489989	c.352C>A	p.L132M	7%
	FOXO4	chrX:70316418	c.40G>T	p.A14S	8%
	NDRG1	chr8:134276808	c.187C>A	p.H63Q	5%
	PTPN13	chr4:87692395	c.4890G>T	p.E1630D	7%
	THBS1	chr15:39884902	c.2666G>T	p.G889V	9%
ECD-54	*MAP2K1*	chr15:66727434	c.151_174delGAGGCCTTTCTTACCCAGAAGCAG	p.E51_Q58del	7%
	STAT5A	chr17:40462649	c.2347G>T	p.A783S	14%
	KMT2C	chr7:151878809	c.6136C>A	p.P2046T	5%
	EGR1	chr5:137801684	c.234_236delCAG	p.S84delS	10%
	CASP5	chr11:104879687	c.66_67delAA	p.R23K*fs**3	3%
	KDSR	chr18:61002524	c.845C>A	p.A282D	15%
ECD-55	*MAP2K1*	chr15:66729163	c.371C>A	p.P124Q	2%
	MAP3K10	chr19:40719615	c.2029G>A	p.G677S	8%
	ARID1A	chr1:27023246	c.352A>C	p.T118P	13%
	EWSR1	chr22:29684681	c.880A>T	p.M300L	6%
	CCAR1	chr10:70516223	c.1819G>A	p.E607K	15%
	CEBPA	chr19:33793295	c.26C>T	p.A9V	12%
	NPAS2	chr2:101565835	c.491G>A	p.S164N	9%
ECD-56	*MAP2K1*	chr15:66727443	c.159T>A	p.F53L	9%
ECD-57	*MAP2K1*	chr15:66727451	c.167A>C	p.Q56P	3%
ECD-58	*MAP2K1*	chr15:66727443	c.159_173delTCTTACCCAGAAGCA	p.F53_Q58delinsL	18%
ECD-59	*MAP2K1*	chr15:66727457	c.169_183delCAGAAGGTGGGAGAA	p.Q58_E62del	N/A
ECD-60	*MAP2K1*	chr15:15:66729094	c.302_307delTGGAGA	p.E102_I103delEI	N/A
ECD-61	*MAP2K1*	chr15:66729159	c.367T>C	p.S123P	N/A
ECD-62	*MAP2K1*	chr15:66729222	c.430G>A	p.E144K	N/A
ECD-63	*MAP2K1*	chr15:66729222	c.430G>A	p.E144K	N/A
ECD-64	*MAP2K1*	chr15:66729159	c.367T>A	p.S123T	N/A
ECD-65	*MAP2K1*	chr15:66727453	c.169A>G	p.K57E	N/A
ECD-66	*MAP2K1*	chr15:66727451	c.167A>C	p.Q56P	8%
	EP400	chr12:132547093	c.8181_8182insCAG	p.Q2727delinsQQ	12%
ECD-67	*MAP2K1*	chr15:66729222	c.430G>A	p.E144K	N/A
ECD-68	*MAP2K1*	chr15:66727443	c.159T>A	p.F53L	22%
ECD-69	*KRAS*	chr12:25398285	c.34G>A	p.G12S	30%

ECD-70	***KRAS***	**chr12:25398262**	**c.57G>C**	**p.L19F**	**2%**
ECD-71	***KRAS***	**chr12:25398286**	**c.34G>C**	**p.G12R**	**23%**
	ARAF	**chrX:47426126**	**c.646C>G**	**p.P216A**	**11%**
	DNMT3A	**chr2:25466799**	**c.1904G>C**	**p.R635P**	**20%**
	DNMT3A	**chr2:25463286**	**c.2207G>A**	**p.R736H**	**19%**
ECD-72	***KRAS***	**chr12:25398281**	**c.38G>A**	**p.G13D**	**32%**
	TP53	**chr17:7578274**	**c.572_574delCTC**	**p.P191del**	**57%**
	PTEN	**chr10:89685281**	**c.179delA**	**p.K60fs**	**59%**
ECD-73	***KRAS***	**chr12:25398284**	**c.35G>A**	**p.G12D**	**18%**
ECD-74	***KRAS***	**chr12:25378553**	**c.445A>G**	**p.R49G**	**2%**
	MAP4K5	**chr14:50930796**	**c.293delA**	**p.R265D*fs**8**	**6%**
ECD-75	***NRAS***	**chr1:115256529**	**c.182A>G**	**p.Q61R**	**50%**
	GTF2F1	**chr19:6381791**	**c.751_753del**	**p.K251del**	**11%**
	ATXN1	**chr6:16327915**	**c.626_627insGCA**	**p.H209delinsQH**	**20%**
	CHD7	**chr8:61766036**	**c.6752C>T**	**p.S2251L**	**47%**
ECD-76	***NRAS***	**chr1:115256530**	**c.181C>A**	**p.Q61K**	**N/A**
ECD-77	***NRAS***	**chr1:115256529**	**c.182A>G**	**p.Q61R**	**N/A**
ECD-78	***NRAS***	**chr1:115258747**	**c.35G>A**	**p.G12D**	**N/A**
ECD-79	***ARAF***	**chrX:47426154**	**c.C674C>T**	**p.A225V**	**3%**
	TAOK2	**chr16:29994531**	**c.1138_1140del**	**p.E380del**	**10%**
	AR	**chrX:66766390**	**c.1402delG**	**p.G468fs**	**25%**
	MUC4	**chr 3:195508402**	**c.10049C>A**	**p.T3350N**	**4%**
ECD-80	***ARAF***	**chrX:47426120**	**c.640T>G**	**p.S214A**	**8%**
	HUNK	**chr21:33312540**	**c.610+8T>-**	**N/A**	**13%**
	INO80E	**chr16:30016629**	**c.602dupC**	**p.T201fs**	**24%**
	CSPG4	**chr15:75982058**	**c.1348T>A**	**p.R450W**	**7%**
ECD-81	***ARAF***	**chrX: 47426163**	**c.683A>T**	**p.D228V**	**N/A**
ECD-82	***ARAF***	**chrX:47426121**	**c.641C>T**	**p.S214F**	**22%**
	DNMT3A	**chr2:25497943**	**c.505delC**	**p.R169G*fs**56**	**8%**
	DNMT3A	**chr2:25457287**	**c.2599delG**	**p.V867Yfs*14**	**25%**
ECD-83	***PIK3CA***	**chr3:178936082**	**c.1624G>A**	**p.E542K**	**N/A**
ECD-84	***PIK3CA***	**chr3:178936091**	**c.1633G>A**	**p.E545K**	**N/A**
ECD-85	***PIK3CA***	**chr3:178952085**	**c.3140A>G**	**p.H1047R**	**N/A**
ECD-86	***MAP2K2***	**chr19: 4110557**	**c.400T>C**	**p.Y134H**	**6%**
	NOTCH3	**chr19:15311677**	**c.29_40del12**	**p.R10_R13delRRRR**	**12%**

ECD-87	***MAP2K2***	**chr19: 4110557**	**c.400T>C**	**p.Y134H**	**12%**
ECD-88	***CSF1R***	**chr5:149450060**	**c.1157C>T**	**p.P386L**	**44%**
ECD-89	***BRAF***	**chr7:140477836**	**c.1457_1471delATGTGACAG CACCTA**	**p.N486_P490del**	**14%**
ECD-90	***RAF1***	**chr3:12653451**	**c.318A>C**	**p.K106N**	**2%**
ECD-91	***KIF5B-ALK***	**N/A**	**N/A**	**N/A**	**N/A**
	MAP4K4	**chr2:102456430**	**c.923G>A**	**p.R308H**	**30%**
	RALGAPA1	**chr14:36142064**	**c.3696+9A>C**	**N/A**	**17%**
	HUNK	**chr21:33312540**	**c.610+8T>-**	**N/A**	**36%**
	EP400	**chr12:132539513**	**c.7729-6A>T**	**N/A**	**7%**
	KMT2C	**chr7:151932897**	**c.2769+5G>T**	**N/A**	**6%**
	KMT2C	**chr7:151962113**	**c.1184+10C>A**	**N/A**	**4%**
	INO80E	**chr16:30016629**	**c.602dupC**	**p.T201fs**	**20%**
	AFF3	**chr2:100218011**	**c.1255_1257del**	**p.S419del**	**11%**
ECD-92	***KIF5B-ALK***	**N/A**	**N/A**	**N/A**	**N/A**
	DNMT3A	**chr2:25457242**	**c.2645G>A**	**p.R882H**	**34%**
	BRCA1	**chr7:41199675**	**c.5452G>A**	**p.D1818N**	**5%**
ECD-93	***KIF5B-ALK***	**N/A**	**N/A**	**N/A**	**N/A**
ECD-94	***BRAF-PICALM***	**N/A**	**N/A**	**N/A**	**N/A**
ECD-95	***ANP32A-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
ECD-96	***LMNA-NTRK1***	**N/A**	**N/A**	**N/A**	**N/A**
ECD-97	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
	WISP3	**chr6:112389433**	**c.669_670insA**	**p.C227M*fs**21**	**5%**
ECD-98	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
ECD-99	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
ECD-100	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**

Abbreviations: Erdheim-Chester Disease (ECD); variant allele frequency (VAF); wild type (WT); not applicable (N/A)

Supplementary Table 3: Somatic genetic alterations in Langerhans Cell Histiocytosis Cohort.

Study ID	Gene	Genomic Coordinates	Genomic Variant	Amino Acid Change	VAF
LCH-1	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	28%
	DIAPH1	chr5:140907266	c.3149-2->TTT	N/A	27%
	KMT2C	chr7:151932949	c.2722G>T	p.G908C	5%
	PDS5B	chr13:33344888	c.4161delA	p.P1387fs	11%
	TOX3	chr16:52473513	c.1338_1340del	p.Q447del	15%
	KRT1	chr12:53069223	c.1669_1689del	p.S557_G563del	43%
	CSPG4	chr15:75982085	c.G1321G>A	p.E441K	7%
LCH-2	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	11%
	BRAF	chr7:140453127	c.G1808C>T	p.R603Q	13%
	MED12	chrX:70361098	c.6286_6288del	p.Q2096del	11%
	PHF2	chr9:96439004	c.2961_2962insCCTGCCTCCACCACA	p.T987delinsTPASTT	30%
	MN1	chr22:28195603	c.927_929del	p.Q309del	11%
LCH-3	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	14%
	GTF2F1	chr19:6381410	c.976_978del	p.E326del	15%
	EP400	chr12:132547068	c.8156_8157insGCA	p.R2719delinsRQ	39%
	MED15	chr22:20918916	c.631_633del	p.Q211del	16%
	PHF2	chr9:96439004	c.2961_2962insCCTGCCTCCACCACA	p.T987delinsTPASTT	48%
	THAP11	chr16:67876824	c.367_369del	p.Q123del	19%
	ATXN1	chr6:16327915	c.626_627insGCA	p.H209delinsQH	20%
	HMGXB4	chr22:35661543	c.1163dupA	p.E388fs	11%
	MN1	chr22:28194913	c.1617_1619del	p.Q539del	10%
LCH-4	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	9%
	AR	chrX:66765159	c.171_173del	p.Q58del	14%
	AR	chrX:66766356	c.1368_1369insGGC	p.G456delinsGG	25%
	CCNT1	chr12:49087434	c.1561_1563del	p.H521del	15%
LCH-5	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	5%
	GTF2F1	chr19:6381791	c.751_753del	p.K251del	11%
LCH-6	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	7%
	SYNGAP1	chr6:33409086	c.2050G>A	p.D684N	12%
	FAT1	chr4:187541913	c.5827C>T	p.Q1943X	6%
	CHD4	chr12:6711207	c.355_357del	p.K119del	17%
	CHD4	chr12:6682390	c.5407G>A	p.A1803T	15%
	MED12	chrX:70361098	c.6286_6288del	p.Q2096del	11%
	MED15	chr22:20918817	c.532_534del	p.Q178del	11%
	NCOA6	chr20:33334734	c.2793-2->T	N/A	27%
	WDR33	chr2:128467115	c.3514C>T	p.R1172C	5%
	ATRX	chrX:76907782	c.4377_4379del	p.E1459del	11%
	USP8	chr15:50784950	c.2287C>T	p.R763W	16%
	GAK	chr4:887704	c.835C>T	p.P279S	8%
	DNMT3B	chr20:31395621	c.2474C>T	p.A825V	12%

LCH-7	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**13%**
	ALK	**chr2:29917863**	**c.805G>T**	**p.D269Y**	**9%**
	MAPK11	**chr22:50704972**	**c.679G>T**	**p.D227Y**	**9%**
	MAP3K9	**chr14:71227812**	**c.908G>T**	**p.R303L**	**5%**
	RALGAPA1	**chr14:36217952**	**c.1090G>T**	**p.E364X**	**4%**
	JAK2	**chr9:5069158**	**c.1463C>A**	**p.S488X**	**5%**
	STAT6	**chr12:57502001**	**c.61G>T**	**p.D21Y**	**5%**
	CSNK1G1	**chr15:64496755**	**c.884G>T**	**p.R295L**	**5%**
	AMER2	**chr13:25745341**	**c.416_417insC**	**p.G140fs**	**12%**
	DDX11	**chr12:31254916**	**c.2202G>T**	**p.K734N**	**7%**
	DDX43	**chr6:74115452**	**c.701G>T**	**p.R234L**	**5%**
	NCOA1	**chr2:24952429**	**c.2946G>T**	**p.L982F**	**5%**
	ZMYND8	**chr20:45915981**	**c.721G>T**	**p.E241X**	**5%**
	AURKB	**chr17:8110078**	**c.527G>T**	**p.R176L**	**7%**
	YES1	**chr18:736929**	**c.1170G>T**	**p.M390I**	**6%**
	MUC4	**chr3:195508598**	**c.9853G>T**	**p.D3285Y**	**8%**
	CCNT1	**chr12:49108266**	**c.203G>T**	**p.R68L**	**6%**
	CHD7	**chr8:61766944**	**c.6798G>T**	**p.K2266N**	**7%**
	TTI1	**chr20:36627633**	**c.2750G>T**	**p.R917L**	**7%**
	CSPG4	**chr15:75982702**	**c.704G>T**	**p.R235L**	**6%**
LCH-8	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**11%**
LCH-9	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**16%**
LCH-10	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**16%**
LCH-11	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**18%**
	FAT1	**chr4:187539564**	**c.8176C>T**	**p.R2726***	**17%**
LCH-12	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**15%**
LCH-13	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**N/A**
LCH-14	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**15%**
	RET	**chr10:43613908**	**c.2372A>T**	**p.Y791F**	**52%**
	TNFAIP3	**chr6:138202365**	**c.2282G>A**	**p.R761H**	**12%**
	SMO	**chr7:128829195**	**c.203C>G**	**p.A68G**	**45%**
	FBXO11	**chr2:48132717**	**c.143C>T**	**p.P48L**	**53%**
	KMT2C	**chr7:151932996**	**c.2675G>A**	**p.G892E**	**42%**
	ASXL1	**chr20:31023288**	**c.2773C>T**	**p.Q925X**	**23%**
	TET2	**chr4:106158497**	**c.3398G>A**	**p.C1133Y**	**17%**
	NSD1	**chr5:176637725**	**c.2325A>T**	**p.Q775H**	**44%**
LCH-15	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**15%**
	ASXL1	**chr20:31022851**	**c.2336C>T**	**p.P779L**	**42%**
	TET2	**chr4:106196382**	**c.4715G>A**	**p.R1572Q**	**44%**
	TRAF7	**chr16: 2220633**	**c.250C>T**	**p.R84C**	**44%**
LCH-16	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**11%**
	INSR	**chr19:7141693**	**c.2677G>A**	**p.D893N**	**44%**
LCH-17	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**21%**

	STK19	**chr6:31939866**	**c.94_96del**	**p.K32del**	**43%**
	TP53	**chr17: 7577099**	**c.839G>C**	**p.R280T**	**4%**
LCH-18	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**18%**
	BRCA2	**chr13: 32911562**	**c.3071_3073del**	**p. I1024del**	**52%**
LCH-19	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**10%**
	LATS1	**chr6:150022977**	**c.286C>T**	**p.R96W**	**56%**
	MDC1	**chr6:30681077**	**c.618_642delinsG**	**p.G207_F214delGL GPPFAF**	**38%**
	FANCA	**chr16: 89813084**	**c.3421G>A**	**p.A1141T**	**55%**
LCH-20	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**13%**
	FAT1	**chr4:187557941**	**c.3770G>T**	**p.R1257L**	**31%**
	HIST1H3A	**chr6: 26020781**	**c.64G>C**	**p.A22T**	**49%**
LCH-21	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**4%**
	SETD4	**chr21: 37420648**	**c.254C>A**	**p.T85K**	**55%**
	PARP1	**chr1: 226558164**	**c.2125G>A**	**p.A709T**	**48%**
LCH-22	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**8%**
	NOTCH3	**chr19:15271928**	**c.6511G>A**	**p.D2171N**	**39%**
	EP400	**chr12: 132547058**	**c.8146C>T**	**p.Q2716***	**37%**
	FGF3	**chr11: 69625189**	**c.604C>T**	**p.P202S**	**42%**
LCH-23	***BRAF***	**chr7:140453135**	**c.1799_1800delinsAT**	**p.V600E**	**25%**
	NKX2-1	**chr14:36986875**	**c.805_813dupGGCGGGGGC**	**p.G269_G271dup**	**48%**
	SETD1A	**chr16: 30991240**	**c.4147_4149dup**	**p.S1383dup**	**39%**
	CD58	**chr1:117057436**	**c.752G>C**	**p.*251Sext*15**	**36%**
	NF1	**chr17:29533315**	**c.1318C>T**	**p.R440X**	**2%**
LCH-24	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**13%**
	KEAP1	**chr19:10610439**	**c.271G>A**	**p.A91T**	**27%**
	MDC1	**chr6:30671949**	**c.5011A>G**	**p.T1671A**	**53%**
	ESCO2	**chr8: 27645520**	**c.1131+1G>A**	**p.X377_splice**	**36%**
LCH-25	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**6%**
LCH-26	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**23%**
LCH-27	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**30%**
LCH-28	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**18%**
LCH-29	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**9%**
LCH-30	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**13%**
LCH-31	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**14%**
LCH-32	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**25%**
LCH-33	***BRAF***	**chr7:140453136**	**c.1799A>T**	**p.V600E**	**36%**

LCH-34	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	5%
LCH-35	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	18%
LCH-36	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	25%
LCH-37	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	4%
LCH-38	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	2%
LCH-39	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	18%
	FAT1	chr4:187539564	c.8176C>T	p.R2726X	17%
LCH-40	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	16%
LCH-41	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	11%
	TET2	chr4:106155916	c.817C>T	p.Q273X	30%
LCH-42	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	14%
	EPAS1	chr2:46608749	c.2060T>C	p.F687S	44%
	HIST1H1D	chr6:26235112	c.50A>G	p.K17R	47%
	NCOR2	chr12:124915248	c.968G>A	p.R323Q	47%
LCH-43	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	10%
	PTPRS	chr19:5219993	c.3722G>A	p.R1241H	38%
	CD274	chr9:5462858	c.419G>C	p.R140T	46%
LCH-44	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	10%
LCH-45	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	4%
	KRAS	chr12:25398285	c.34G>A	p.G12S	3%
LCH-46	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	16%
LCH-47	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	12%
	FLT4	chr5:180056400	c.844C>T	p.R282X	13%
LCH-48	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	3%
LCH-49	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	2%
	NRAS	chr1:115258747	c.35G>A	p.G12D	23%
LCH-50	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	9%
LCH-51	*MAP2K1*	chr15:66727443	c.159_173delTCTTACCCAGAAGCA	p.F53_Q58del	15%
	SYNGAP1	chr6:33419606	c.3956dupC	p.A1319fs	14%
	DIAPH1	chr5:140953564	c.1851_1853del	p.P618del	20%
	MED15	chr22:20918916	c.631_633del	p.Q211del	17%
	NCOA6	chr20:33334734	c.2793-2->T	N/A	29%
	KRT1	chr12:53069189	c.1722_1723insGGC	p.H575delinsGH	11%

LCH-52	***MAP2K1***	**chr15:66727457**	**c.169_183delCAGAAGGTGGGAGAA**	**p.Q58_E62del**	**21%**
	FIP1L1	**chr4:54319248**	**c.1447_1448del**	**p.R483fs**	**15%**
	AFF3	**chr2:100218011**	**c.1255_1257del**	**p.S419del**	**18%**
	KRT1	**chr12:53069223**	**c.1669_1689del**	**p.S557_G563del**	**49%**
LCH-53	***MAP2K1***	**chr15:66727457**	**c.169_183delCAGAAGGTGGGAGAA**	**p.Q58_E62del**	**23%**
LCH-54	***MAP2K1***	**chr15:66727457**	**c.169_183delCAGAAGGTGGGAGAA**	**p.Q58_E62del**	**10%**
	PLEKHG5	**chr1:6529183**	**c.2397_2399del**	**p.799_800del**	**16%**
	USP8	**chr15:50784990**	**c.2327T>C**	**p.L776P**	**5%**
	DKC1	**chrX:154005089**	**c.1492_1494del**	**p.K498del**	**13%**
LCH-55	***MAP2K1***	**chr15:66729093**	**c.303_309delGGAGAT**	**p.E102_I103delEI**	**6%**
LCH-56	***MAP2K1***	**chr15:66727443**	**c.159_173delTCTTACCCAGAAGCA**	**p.F53_Q58delinsL**	**18%**
	APC	**chr5:112173918**	**c.2627G>A**	**p.R876Q**	**49%**
	CTNNB1	**chr3:41266178**	**c.175A>G**	**p.T59A**	**50%**
	NOTCH1	**chr9:139390908**	**c.7283A>G**	**p.H2428R**	**55%**
LCH-57	***MAP2K1***	**chr15:66729093**	**c.303_309delGGAGAT**	**p.E102_I103delEI**	**9%**
	AXL	**chr19:41763451**	**c.2250T>G**	**p.S354X**	**57%**
	BARD1	**chr2: 215645537**	**c.1061C>A**	**p.Y750X**	**44%**
LCH-58	***MAP2K1***	**chr15:66727454**	**c.170A>C**	**p.K57T**	**11%**
LCH-59	***MAP2K1***	**chr15:66727457**	**c.169_183delCAGAAGGTGGGAGAA**	**p.Q58_E62del**	**14%**
LCH-60	***MAP2K1***	**chr15:66729093**	**c.303_309delGGAGAT**	**p.E102_I103delEI**	**14%**
LCH-61	***MAP2K1***	**chr15:66729093**	**c.303_309delGGAGAT**	**p.E102_I103delEI**	**23%**
LCH-62	***MAP2K1***	**chr15:66727457**	**c.169_183delCAGAAGGTGGGAGAA**	**p.Q58_E62del**	**9%**
	HGF	**chr7:81374403**	**c.659G>A**	**p.R220Q**	**45%**
	ASXL2	**chr2:25972764**	**c.1661C>T**	**p.P554L**	**48%**
LCH-63	***MAP2K1***	**chr15:66729093**	**c.303_309delGGAGAT**	**p.E102_I103delEI**	**12%**
LCH-64	***MAP2K1***	**chr15:66729093**	**c.303_309delGGAGAT**	**p.E102_I103delEI**	**7%**
LCH-65	***MAP2K1***	**chr15:66729093**	**c.303_309delGGAGAT**	**p.E102_I103delEI**	**13%**
	MPL	**chr1:43804317**	**c.317C>T**	**p.P106L**	**47%**
	STAT3	**chr17:40498652**	**c.208C>T**	**p.R70C**	**6%**
	NOTCH1	**chr9:139409061**	**c.2108G>A**	**p.R703H**	**51%**
	NOTCH3	**chr19:15296476**	**c.1966G>A**	**p.V656M**	**48%**
	ARID1B	**chr6:157100116**	**c.1069_1071del**	**p.G357del**	**44%**
	TET3	**chr2:74273751**	**c.302G>T**	**p.S101I**	**53%**
	ZRSR2	**chrX:15821844**	**c.237G>T**	**p. E79D**	**100%**
	ROBO1	**chr3:78717402**	**c.1680_1681delinsAG**	**p.P561A**	**43%**

LCH-66	***MAP2K1***	**chr15:66729093**	**c.303_309delGGAGAT**	**p.E102_I103delEI**	**13%**
	DNMT3A	**chr2:25469085**	**c.1372delC**	**p.R458G*fs**193**	**13%**
LCH-67	***BRAF***	**chr7:140477836**	**c.1457_1471del15**	**p.N486_P490del**	**1%**
	MAP2K6	**chr17:67532249**	**c.882-7C>T**	**N/A**	**10%**
	KMT2D	**chr19:36211494**	**c.1246dupC**	**p.P415fs**	**14%**
	PHF14	**chr7:11101414**	**c.2482-4C>T**	**N/A**	**18%**
	ASH1L	**chr1:155408725**	**c.5221G>A**	**p.A1741T**	**5%**
	BPTF	**chr17:65899951**	**c.2968delA**	**p.K990fs**	**11%**
	MUC4	**chr3:195508202**	**c.10202_10249del**	**p.3401_3417del**	**18%**
	CCNB3	**chrX:50037859**	**c.205-4G>T**	**N/A**	**10%**
	ACIN1	**chr14:23530733**	**c.3371dupC**	**p.P1124fs**	**12%**
	NAE1	**chr16:66855469**	**c.135-7T>-**	**N/A**	**27%**
	RANBP9	**chr6:13711709**	**c.29C>A**	**p.P10Q**	**8%**
LCH-68	***BRAF***	**chr7:140477836**	**c.1457_1471del15**	**p.N486_P490del**	**12%**
LCH-69	***BRAF***	**chr7:140477836**	**c.1457_1471del15**	**p.N486_P490del**	**6%**
LCH-70	***BRAF***	**chr7:140477836**	**c.1457_1471del15**	**p.N486_P490del**	**16%**
	KMT2C	**chr7:151859914**	**c.10748C>T**	**p.P3583L**	**49%**
LCH-71	***BRAF***	**chr7:140477836**	**c.1457_1471del15**	**p.N486_P490del**	**18%**
LCH-72	***BICD2-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
	FLT1	**chr13:28964143**	**c.1759G>A**	**p.V587I**	**9%**
	NOTCH3	**chr19:15302639**	**c.719G>C**	**p.C240S**	**8%**
	MCL1	**chr1:150551921**	**c.86C>A**	**p.T29N**	**9%**
LCH-73	***CSF2RA-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-74	***PACSIN2-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-75	***SPPL2A-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-76	***BRAF***	**chr7:140453135**	**c.1799_1800delinsAT**	**p.V600D**	**10%**
LCH-77	***BRAF***	**chr7:140494190**	**c.1058A>G**	**p.H353R**	**50%**
	BRAF	**chr7:140477788**	**c.1511_1517+2dup**	**p. X504_splice**	**33%**
	HGF	**chr7:81334774**	**c.1942G>A**	**p.G648R**	**52%**
	INPPL1	**chr11:71948712**	**c.3424C>T**	**p.R1142C**	**54%**
LCH-78	***ARAF***	**chrX:47426444**	**c.787G>A**	**p.V263M**	**93%**
	TNFRSF14	**chr1: 2494316**	**c.711_726+2del**	**p.KVIVSVQdel**	**37%**
LCH-79	***PIK3CD***	**chr1: 9787030**	**c.3061G>A**	**p.E1021K**	**26%**
	CSF1R	**chr5:149449579**	**c.1347_1367del**	**p.W450_E456del**	**23%**
	PDGFRB	**chr5:149501449**	**c.2338C>T**	**p.P780S**	**31%**
	NOTCH1	**chr9:139391176**	**c.7014_7015insT**	**p.A2339Cfs*15**	**27%**
	ASXL1	**chr20:31024701**	**c.4186G>T**	**p.V1396L**	**51%**
	CCND3	**chr6:41903803**	**c.753_754insGTCCCTC**	**p.R252Vfs*74**	**22%**

LCH-80	***MAPK3 (ERK1)***	**chr16:30129852**	**c.361G>A)**	**p.V121M**	**9%**
	TET2	**chr4:106156424**	**c.1326del**	**p.N442Kfs*5**	**7%**
	TET2	**chr4:106164778**	**c.3646C>G**	**p.R1216G**	**9%**
	TET2	**chr4:106196985**	**c.5319dupC**	**p.N1774Qfs*15**	**6%**
	ETNK1	**chr12:22811995**	**c.731A>G**	**p.N244S**	**4%**
LCH-81	***MAPK7 (ERK5)***	**chr17:19284721**	**c.1199G>T**	**p.R400L**	**6%**
	GNAQ	**chr9:80537095**	**c.303C>A**	**p.Y101X**	**6%**
	MAP3K4	**chr6:161530795**	**c.4095G>T**	**p.M1415I**	**7%**
	DNAJC27	**chr2:25179912**	**c.528G>T**	**p.Q176H**	**8%**
	CARD11	**chr7:2983990**	**c.540C>A**	**p.Y180X**	**8%**
	TCF7L2	**chr10:114925316**	**c.1394_1395insA**	**p.C469V*fs**8**	**12%**
	E2F1	**chr20:32267696**	**c.437C>A**	**p.S146X**	**8%**
	DNMT3A	**chr2:25459866**	**c.2417C>A**	**p.A806E**	**9%**
	UNC5A	**chr5:176305120**	**c.1861G>T**	**p.A621S**	**7%**
	PTPN2	**chr18:12785826**	**c.1229C>A**	**p.Thr410Asn**	**6%**
LCH-82	***TEK***	**chr9:27197448**	**c.1760A>G**	**p.D587G**	**49%**
	CIC	**chr19: 42795793**	**c.2782G>A**	**p.A928T**	**41%**
	BCL11B	**chr14: 99642361**	**c.812C>T**	**p.P271L**	**47%**
	NCOR2	**chr12:124839089**	**c.3524G>A**	**p.R1175Q**	**67%**
	MSH3	**chr5: 79950727**	**c.195_203dupGCCCCCAGC**	**p.P67_P69dup**	**37%**
LCH-83	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
	NSD1	**chr5:176721945**	**c.7576C>T**	**p.P2526S**	**49%**
	TERT	**chr5:1293767**	**c.1234C>T**	**p.H412Y**	**40%**
	ZRSR2	**chrX:15841231**	**c.1338_1343delGAGCCG**	**p.S447_R448del**	**86%**
	SAMHD1	**chr20:35526364**	**c.1609-2A>G**	**p.X537_Splice**	**48%**
LCH-84	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-85	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-86	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-87	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
	APC	**chr5:112175977**	**c.4686C>A**	**p.D1562E**	**42%**
LCH-88	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-89	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-90	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-91	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
LCH-92	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**

Abbreviations: Langerhans Cell Histiocytosis (LCH); variant allele frequency (VAF); wild type (WT); not applicable (N/A).

Supplementary Table 4: Somatic genetic alterations in juvenile xanthogranuloma (JXG) cohort.

Study ID	Gene	Genomic Coordinates	Genomic Variant	Amino Acid Change	VAF
JXG-1	*MAP2K1*	chr15:66729181	c.389A>G	p.Y130C	N/A
JXG-2	*MAP2K1*	chr15:66729162	c.370C>A	p.P124T	2%
JXG-3	*MAP2K1*	chr15:66727394	c.110T>C	p.L37P	N/A
JXG-4	*MAP2K1*	chr15:66729150	c.358G>C	p.E120Q	N/A
JXG-5	*MAP2K1*	chr15:66727561	c.277G>A	p.V93I	49%
	KIT	chr4:55593431	c.1588G>A	p.V530I	44%
	ARID1B	chr6:157100396	c.1333_1334insCGC	p.A445_P446insP	26%
JXG-6	*MAP2K1*	chr15:66729181	c.389A>G	p.Y130C	N/A
JXG-7	*CSF1R*	chr5:149441385	c.1636_1653delTACCAGGTCCGCTGGAAG	p.Y546_K551del	64%
	TSC2	chr16:2134521	c.4298C>T	p.S1433L	47%
	TET2	chr4:106196834	c.5167C>T	p.P1723S	49%
	TET2	chr4:106157698	c.2599T>C	p.Y867H	55%
	BRCA2	chr13:32910458	c.1966A>G	p.T656A	52%
JXG-8	*CSF1R*	chr5:149441385	c.1636_1653delTACCAGGTCCGCTGGAAG	p.Y546_K551del	27%
	ALK	chr2:29445273	c.3452C>T	p.T1151M	44%
	MSH3	chr5:80024783	c.1567G>A	p.E523K	36%
	AR	chrX:66765158	c.170T>A	p.L57Q	67%
JXG-9	*CSF1R*	chr5:149441385	c.1636_1653delTACCAGGTCCGCTGGAAG	p.Y546_K551del	16%
	IKBKE	chr1:206653437	c.1321C>T	p.R441W	43%
	PAX5	chr9:36882049	c.964G>A	p.A322T	46%
	NCOR2	chr12:124824739	c.5499_5500insCGGC	p.S1834Rfs*194	9%
	BRCA2	chr13:32914592	c.6100C>T	p.R2034C	42%
JXG-10	*CSF1R*	chr5:149441385	c.1636_1653delTACCAGGTCCGCTGGAAG	p.Y546_K551del	20%
	NF1	chr17:29422382	c.55G>T	p.E19X	19%
	MST1R	chr3:49940328	c.717G>A	p.P239S	5%
	ZNF185	chrX:152087569	c.495CGAG>C	p.E165del	9%
	BICRA	chr19:48197890	c.2801AC>A	p.P937Hfs*10	5%
	MLH3	chr14:75514603	c.1755_1756insA	p.E586Rfs*3	4%
JXG-11	*CSF1R*	chr5:149441385	c.1636_1653delTACCAGGTCCGCTGGAAG	p.Y546_K551del	19%
	NF1	chr17:29422382	c.55G>T	p.E19X	20%
	FGFR2	chr10:123279669	c.765G>A	p.R255W	5%
	SMARCA2	chr9:2060951	c.1659G>A	p.A553T	6%
	UVRAG	chr11:75694430	c.701_703G>GA	p.S237Kfs*2	9%
JXG-12	*KRAS*	chr12:25398284	c.35G>A	p.G12D	N/A
JXG-13	*KRAS*	chr12:25398284	c.35G>A	p.G12D	N/A
JXG-14	*KRAS*	chr12:25398284	c.35G>A	p.G12D	N/A

JXG-15	***KRAS***	**chr12:25398284**	**c.35G>C**	**p.G12A**	**18%**
	SPEN	**chr1:16256120**	**c.3385G>A**	**p.V1129I**	**48%**
JXG-16	***NRAS***	**chr1:115258744**	**c.38G>A**	**p.G13D**	**N/A**
JXG-17	***NRAS***	**chr1:115258744**	**c.38G>A**	**p.G13D**	**N/A**
JXG-18	***NRAS***	**chr1:115258744**	**c.38G>A**	**p.G13D**	**N/A**
JXG-19	***KIT***	**chr4:55593431**	**c.1588G>A**	**p.V530I**	**52%**
	ROS1	**chr6:117715381**	**c.1108T>C**	**p.S370P**	**51%**
	NOTCH4	**chr6:32164153**	**c.5245delG**	**p.A1749Pfs*34**	**50%**
	ARID1B	**chr6:157100396**	**c.1333_1334insCGC**	**p.A445_P446insP**	**23%**
	AR	**chrX:66766356**	**c.1369_1380delGGCGGCGGCGGC**	**p.457_460del**	**23%**
JXG-20	***KIT***	**chr4:55593431**	**c.1588G>A**	**p.V530I**	**24%**
JXG-21	***KIT***	**chr4:55575669**	**c.1195G>A**	**p.V399I**	**44%**
	DOT1L	**chr19:2222424**	**c.3256C>T**	**p.R1086C**	**51%**
	BRCA2	**chr13:32972744**	**c.10094_10095insGAATTATATC**	**p.S3366Nfs*5**	**39%**
	FLT1	**chr13:28971136**	**c.1621G>T**	**p.V541F**	**49%**
JXG-22	***JAK3***	**chr19:17945696**	**c.2164G>A**	**p.V722I**	**46%**
	TSC2	**chr16:2120559**	**c.1819G>A**	**p.A607T**	**49%**
JXG-23	***JAK3***	**chr19:17953950**	**c.452C>G**	**p.P151R**	**48%**
JXG-24	***ALK***	**chr2:29462643**	**c.2258G>A**	**p.R753Q**	**49%**
	INSR	**chr19:7125518**	**c.3034G>A**	**p.V1012M**	**50%**
	DOT1L	**chr19:2210451**	**c.1058C>G**	**p.A353G**	**53%**
	KMT2D	**chr12:49426729**	**c.11750_11758delAGCAGCAGC**	**p.Q3917_Q3919del**	**34%**
	SOX17	**chr8:55372258**	**c.949_954delCACCAG**	**p.317_318del**	**32%**
	LATS2	**chr13:21557529**	**c.2316C>G**	**p.I772V**	**51%**
JXG-25	***MET***	**chr7:116398608**	**c.2198C>T**	**p.T733I**	**43%**
	KMT2D	**chr12:49445189**	**c.2250_2276del GCACCTGTCCCCCCGGCCTGAGGAGCC**	**p.R755_P763del**	**36%**
	MSH3	**chr5:79950727**	**c.182_190delCAGCGCCCC**	**p.P67_P69del**	**34%**
JXG-26	***CSF3R***	**chr1:36933539**	**c.1748G>A**	**p.R583H**	**48%**
	CSF3R	**chr1:36933198**	**c.1919C>T**	**p.T640I**	**50%**
	FBXW7	**chr4:153244091**	**c.2066G>A**	**p.R689Q**	**2%**
	MAP3K13	**chr3:185198302**	**c.2785_2787delGAA**	**p.E929del**	**44%**
	TET2	**chr4:106155533**	**c.434G>A**	**p.S145N**	**47%**
	MSH3	**chr5:79950724**	**c.178_179insCCGCAGCGC**	**p.A60_A61insAAP**	**30%**
JXG-27	***IRF2BP2-NTRK1***	**N/A**	**N/A**	**N/A**	**N/A**
	MAP3K13	**chr3:185146499**	**c.130G>A**	**p.E44K**	**54%**
	TET2	**chr4:106157698**	**c.2599T>C**	**p.Y867H**	**45%**
	TET2	**chr4:106196834**	**c.5167C>T**	**p.P1723S**	**53%**

JXG-28	***IRF2BP2-NTRK1***	**N/A**	**N/A**	**N/A**	**N/A**
	NOTCH2	**chr1:120459251**	**c.6094C>A**	**p.H2032N**	**37%**
	MSH3	**chr5:79950727**	**c.181_182insCAGCGCCCC**	**p.A61_A62insAPP**	**54%**
JXG-29	***TPM3-NTRK1***	**N/A**	**N/A**	**N/A**	**N/A**
	NOTCH4	**chr6:32165201**	**c.4927C>T**	**p.R1643X**	**44%**
	PTPRD	**chr9:8486142**	**c.2675T>C**	**p.V892A**	**46%**
	FAT1	**chr4:187538942**	**c.8798A>T**	**p.Q2933L**	**39%**
JXG-30	***SQSTM1-NTRK1***	**N/A**	**N/A**	**N/A**	**N/A**
	FLT1	**chr13:28919682**	**c.2255C>T**	**p.S752L**	**39%**
JXG-31	***TPM3-NTRK1***	**N/A**	**N/A**	**N/A**	**N/A**
JXG-32	***IRF2BP2-NTRK1***	**N/A**	**N/A**	**N/A**	**N/A**
	AR	**chrX:66766356**	**c.1369_1380delGGCGGCGGCGGC**	**p.457_460del**	**34%**
JXG-33	***RNF11-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
	KMT2C	**chr7:151945330**	**c.2189C>A**	**p.S730Y**	**11%**
	DDX11	**chr12:31244665**	**c.1102C>T**	**p.P368S**	**8%**
	MED12	**chrX:70361098**	**c.6286_6288del**	**p.Q2096del**	**12%**
	MUC4	**chr3:195507020**	**c.11431G>C**	**p.V3811L**	**10%**
JXG-34	***MS4A6A-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
JXG-35	***BICD2-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
JXG-36	***BICD2-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**
JXG-37	***NCOA4-RET***	**N/A**	**N/A**	**N/A**	**N/A**
JXG-38	***NCOA4-RET***	**N/A**	**N/A**	**N/A**	**N/A**
JXG-39	***KIF5B-ALK***	**N/A**	**N/A**	**N/A**	**N/A**
JXG-40	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	FGF4	**chr11:69588217**	**c.481C>G**	**p.L161F**	**45%**
	MAP3K13	**chr3:185146499**	**c.130G>A**	**p.E44K**	**48%**
	INSR	**chr19:7117151**	**c.4065C>G**	**p.Y1355X**	**43%**
	LATS2	**chr13:21557531**	**c.2314A>G**	**p.I772V**	**49%**
	FAT1	**chr4:187538942**	**c.8798A>T**	**p.Q2933L**	**45%**

JXG-41	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
JXG-42	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	PTPRD	**chr9:8486142**	**c.2675T>C**	**p.V892A**	**35%**
JXG-43	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	ARID1B	**chr6:157527492**	**c.5218_5220delGAC**	**p.D1741del**	**46%**
JXG-44	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	FLT3	**chr13:28599077**	**c.2211G>C**	**p.M737I**	**45%**
	ARID1B	**chr6:157099981**	**c.919_924delGGCGGC**	**p.307_308del**	**32%**
	SPEN	**chr1:16259837**	**c.7102G>A**	**p.A2368T**	**44%**
JXG-45	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	FGF6	**chr12:4554549**	**c.188C>T**	**p.A63V**	**38%**
	KLF4	**chr9:110249963**	**c.712C>T**	**p.P238S**	**41%**
	BCL6	**chr3:187447543**	**c.650G>A**	**p.R217Q**	**37%**
	ERCC5	**chr13:103518178**	**c.2116G>C**	**p.E706Q**	**40%**
JXG-46	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	CBL	**chr11:119148991**	**c.1211G>T**	**p.C404F**	**71%**
	CHEK2	**chr22:29121087**	**c.470T>C**	**p.I157T**	**48%**
JXG-47	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	SOX17	**chr8:55372258**	**c.948_949insCACCAG**	**p.Q316_H317insHQ**	**59%**
JXG-48	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
JXG-49	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
JXG-50	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
JXG-51	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
JXG-52	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
JXG-53	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	INSR	**chr19:7125518**	**c.3034G>A**	**p.V1012M**	**42%**
	NCOR2	**chr12:124832415**	**c.4028A>G**	**p.H1343R**	**18%**
	SMARCA4	**chr19:11169011**	**c.4505G>A**	**p.R1502H**	**46%**
JXG-54	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
JXG-55	**Driver WT**	**N/A**	**N/A**	**N/A**	**N/A**
	EP300	**chr22:41574017**	**c.6303_6323del TGGGCAGCCTGGCATGCCCCA**	**p.2101_2108del**	**36%**
	MSH3	**chr5:79950727**	**c.181_182insCAGCGCCCC**	**p.A61_A62insAPP**	**30%**

Abbreviations: Juvenile Xanthogranuloma (JXG); variant allele frequency (VAF); wild type (WT); not applicable (N/A)

Supplementary Table 5: Somatic mutations in the Rosai-Dorfman Disease (RDD) cohort.

Study ID	Gene	Genomic Coordinates	Genomic Variant	Amino Acid Change	VAF
RDD-1	*KRAS*	chr12:25398284	c.35G>A	p.G12D	N/A
RDD-2	*KRAS*	chr12:25398284	c.35G>A	p.G12D	N/A
RDD-3	*KRAS*	chr12:25378647	c.351A>C	p.K117N	2%
RDD-4	*KRAS*	chr12:25378647	c.351A>C	p.K117N	8%
RDD-5	*MAP2K1*	chr15:66729163	c.371C>G	p.P124R	N/A
RDD-6	*MAP2K1*	chr15:66774131	c.607G>A	p.E203K	4%
	SNX24	chr5:122343374	c.443-3C>T	N/A	11%
	CIC	chr19:42799295	c.7507dupC	p.Q2502fs	12%
	INT32	chr17:59999198	c.457-10->T	N/A	12%
	SFR1	chr10:105885262	c.547-9C>T	N/A	10%
	MUC4	chr3:195510535	c.7916C>G	p.T2639S	6%
	PDS5A	chr4:39924373	c.528-5T>-	N/A	21%
	USP35	chr11:77911287	c.1038+7->CCCCTGCCTGCTGCCCCTGGTGAGG	N/A	23%
RDD-7	*NRAS*	chr1:115258744	c.38G>A	p.G13D	N/A
RDD-8	*ARAF*	chrX:47426131	c.651C>A	p.N217K	N/A
RDD-9	*CSF1R*	chr5:149433745	c.2806G>A	p.G936S	6%
RDD-10	*Driver WT*	N/A	N/A	N/A	N/A
	BRD4	chr19:15350270	c.3509C>G	p.P1170R	40%
	PHOX2B	chr4:41750401	c.227G>C	p.S76T	35%
	ERCC2	chr19:45867247	c.946C>G	p.Q316E	52%
	BRCA1	chr17:41251803	c.536A>G	p.Y179C	48%
	BRCA1	chr17:41246092	c.1456T>C	p.F486L	48%
	BRCA1	chr17:41245900	c.1648A>C	p.N550H	45%
	LATS2	chr13:21563171	c.747_748delinsTT	p.Q249_G250delinsHC	51%
	ATM	chr11:108139269	c.2771G>A	p.R924Q	44%
	RPS6KB2	chr11:67202161	c.1264G>A	p.V422I	52%
RDD-11	*Driver WT*	N/A	N/A	N/A	N/A
RDD-12	*Driver WT*	N/A	N/A	N/A	N/A
RDD-13	*Driver WT*	N/A	N/A	N/A	N/A
RDD-14	*Driver WT*	N/A	N/A	N/A	N/A
RDD-15	*Driver WT*	N/A	N/A	N/A	N/A
RDD-16	*Driver WT*	N/A	N/A	N/A	N/A

RDD-17	***Driver WT***	**N/A**	**N/A**	**N/A**	**N/A**
[redacted]					

Abbreviations: Rosai-Dorfman Disease (RDD); variant allele frequency (VAF); wild type (WT); not applicable (N/A)

Supplementary Table 6: Somatic genetic alterations in the histiocytic sarcoma cohort.

Study ID	Gene	Genomic Coordinates	Genomic Variant	Amino Acid Change	VAF
HS-1	*MAP2K1*	chr15:66727443	c.157T>C	p.F53L	13%
	KRAS	chr12:25378647	c.351A>T	p.K117N	16%
	RSU1	chr10:16824091	c.110-8C>T	N/A	13%
	GAB2	chr11:77937662	c.1055dupC	p.P352fs	26%
	TNFRSF14	chr1:2493110	c.552-2A>C	N/A	37%
	ACIN1	chr14:23530733	c.3371dupC	p.P1124fs	14%
	PHF6	chrX:133559269	c.1007_1008del	p.D336fs	36%
	SCA1	chr9:127765856	c.862-7->T	N/A	18%
	ARID4B	chr1:235419047	c.G202A	p.V68M	10%
	PTF1A	chr10:23481515	c.C56A	p.S19X	15%
	FOXG1	chr14:29236691	c.C206A	p.P69Q	8%
	ZFP36L1	chr14:69259610	c.G253C	p.V85L	21%
	CREBBP	chr16:3795336	c.T3856C	p.C1286R	19%
	SMARCA4	chr19:11141427	c.G3404A	p.R1135Q	16%
	CRTC1	chr19:18888001	c.A1762C	p.S588R	16%
	RPRD1B	chr20:36718165	c.G869T	p.R290L	17%
	MITF	chr3:69928336	c.T108A	p.S36R	15%
	POU3F2	chr6:99283408	c.A659G	p.D220G	15%
	POU4F2	chr4:147561458	c.C728T	p.S243L	15%
	PHOX2B	chr4:41747943	c.G826A	p.G276S	12%
	TLX3	chr5:170737240	c.C508T	p.R170C	15%
	HIST1H1E	chr6:26156862	c.C244A	p.L82M	15%
	HIST1H2AK	chr6:27805944	c.C174A	p.Y58X	13%
	ZNF479	chr7:57188200	c.G922T	p.V308L	5%
	MSH5	chr6:31727624	c.A1557C	p.L519F	18%
	PAXX	chr9:139886994	c.C99G	p.D33E	15%
	KPNA5	chr6:117023177	c.436-5C>T	N/A	12%
	KIF20B	chr10:91497374	c.A2656C	p.N886H	23%
	ATG12	chr5:115167564	c.364-4G>T	N/A	11%
HS-2	*MAP2K1*	chr15:66727443	c.159T>A	p.F53L	7%
	KIT	chr4:55602952	c.2662C>T	p.R888W	9%
	BCL2	chr18:60985344	c.556C>G	p.H186D	8%
	BCL2	chr18:60985530	c.367_370delinsGCCG	p.P123_F124delinsAV	8%
	BCL2	chr18:60985629	c.271C>T	p.P91S	11%
	BCL2	chr18:60985715	c.185C>T	p.S62F	11%
	BCL10	chr1:85733589	c.421_422delAG	p.S141fs	9%
	CDKN1B	chr12:12871001	c.228G>A	p.W76*	9%
	CDKN1B	chr12:12871012	c.239_242delinsTGAG	p.E80_K81delinsVR	8%
HS-3	*BRAF*	chr7:140453136	c.1799A>T	p.V600E	46%
HS-4	*KRAS*	chr12:25398281	c.38G>A	p.G13D	32%
HS-5	*CSF1R*	chr5:149441348	c.1682_1690delATACTTTCA	p.Y561_I564delinsF	24%
	PTPN11	chr12:112888210	c.226G>A	p.E76K	31%
	MED12	chrX:70349666	c.3828_3854delinsGGTC	p.D1276Efs*15	22%
	SETD2	chr3:47144879	c.4874G>A	p.R1625H	16%

	SETD2	**chr3:47058736**	**c.7541dupA**	**p.H2514Qfs*6**	**33%**
HS-6	***CLIP2-BRAF***	**N/A**	**N/A**	**N/A**	**N/A**

Abbreviations: Histiocytic Sarcoma (HS); variant allele frequency (VAF); not applicable (N/A)