HISTOLOGICAL EVIDENCE OF MAPK PATHWAY ACTIVATION ACROSS ALL SUBTYPES OF ADULT ORBITAL XANTHOGRANULOMATOUS DISEASE IRRESPECTIVE OF PATHOGENIC MUTATIONS

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9th Annual
International Summit on
Erdheim-Chester Disease

oog
het oogziekenhuis rotterdam
the rotterdam eye hospital

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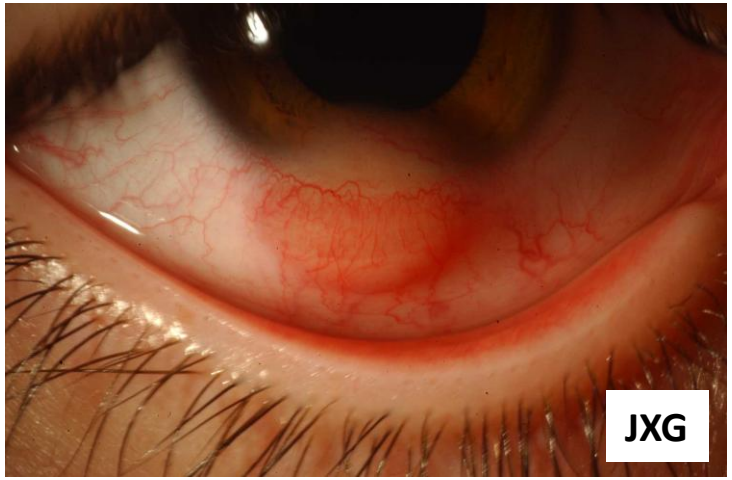
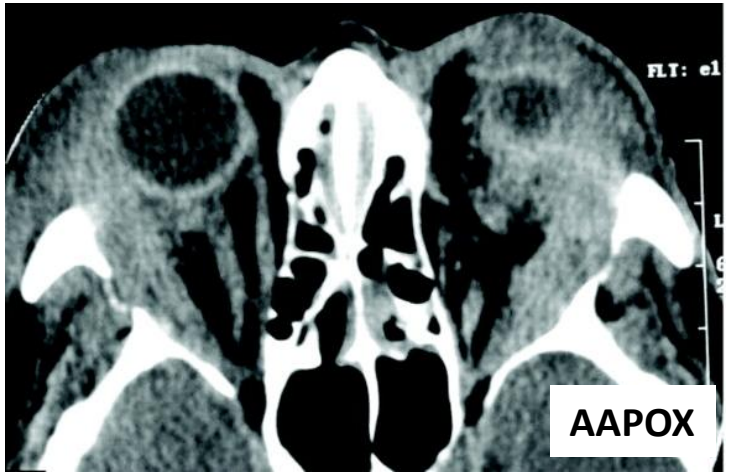
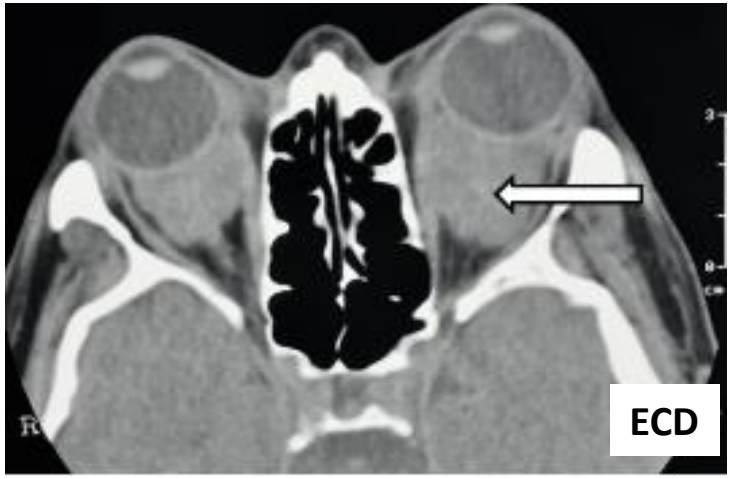
adult xanthogranulomatous diseases (AOXGD):

spectrum of histiocytoses presenting as (peri)ocular & orbital masses







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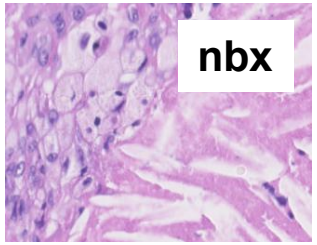
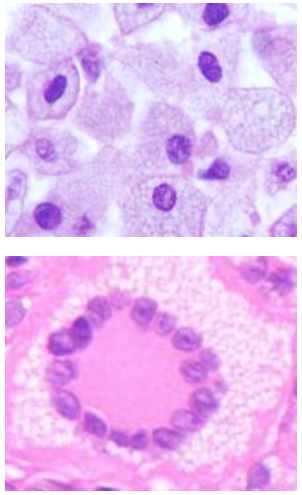
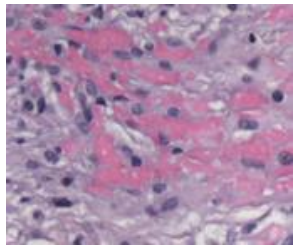
AOXGD

type		presentation
AOX	**A**dult-**o**nset **x**anthogranuloma	mostly solitary lesions often affecting lacrimal gland & eye muscles;
AAPOX	**A**dult-onset **a**sthma and **p**eri**o**cular **x**anthogranuloma	mostly isolated, but sometimes associated with lymphadenopathy and B-cell dysfunction
NBX	**N**ecro**b**iotic **x**anthogranuloma	mostly affecting eyelids and can be associated with hematological neoplasms/lymphoma
ECD	Erdheim-Chester disease	retrobulbar/apical involvement often as part of systemic disease

Histological features	shared
AOX	foamy CD68$^+$ CD163$^+$ histiocytes Touton giant cells fibrosis IgG4 plasma cells
AAPOX	
NBX	
ECD	







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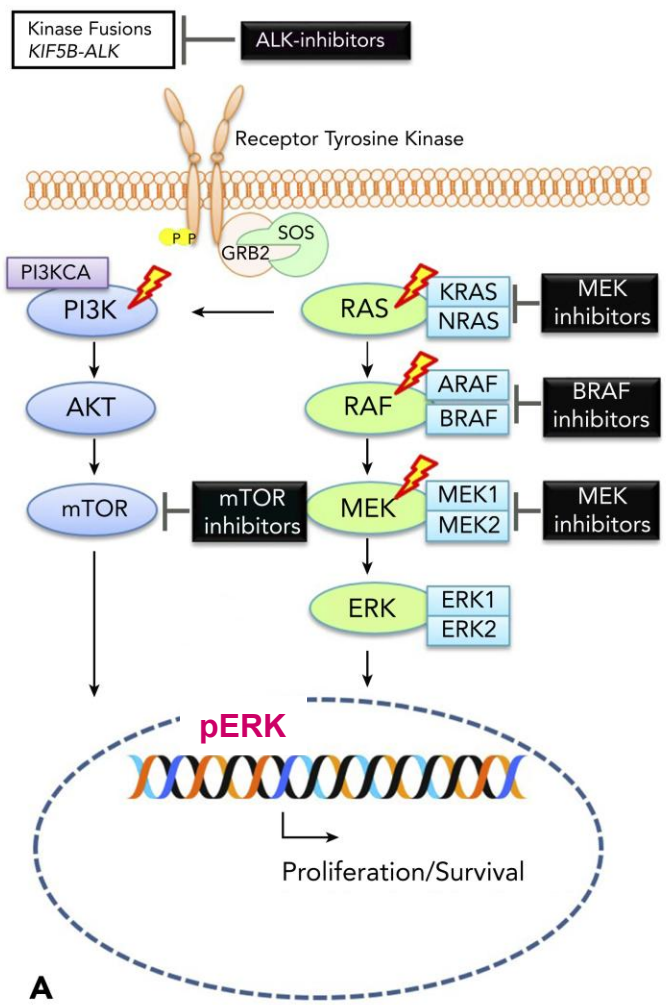
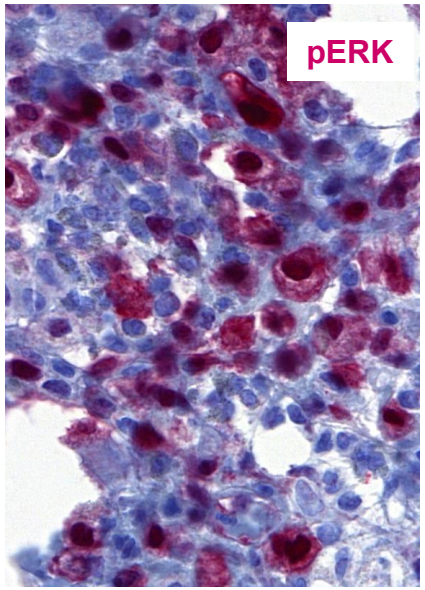
pERK and Cyclin D1 are indicators of MAPK pathway activation

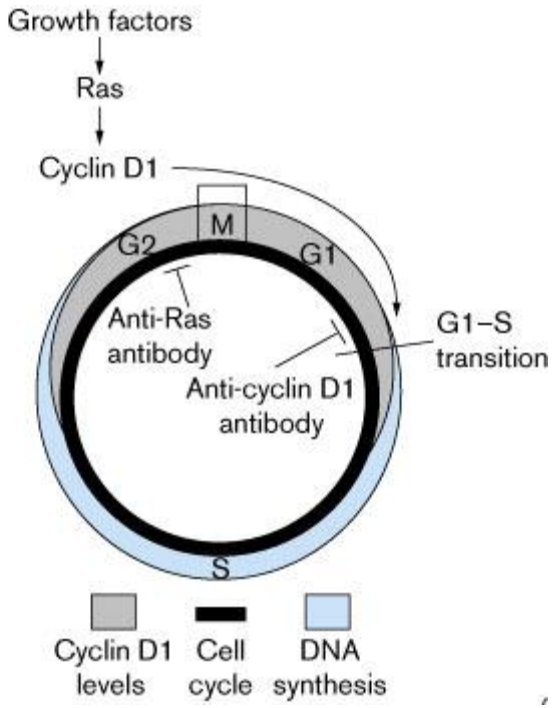


Source	Gene Alterations(s)
Haroche *et al. Blood* 2012[13] Emile *et al. J Clin Oncol.* 2013[11] Bentel et al. *BMJ Case Rep.* 2017[9]	*BRAF* p.V600E *BRAF* p.T599_ V600>RE *BRAF* p. L485W*
Diamond *et al. Blood* 2013[10] Aitken *et al. Histopathology* 2015[22] Emile *et al. Blood* 2014[12] Janku *et al. Mol Cancer Ther.* 2019[15]	*NRAS* p.Q61R *NRAS* p.Q61K *NRAS* p.G60R*
Emile *et al. Blood* 2014[12]	*PIK3CA* p.E542K *PIK3CA* p.E545K *PIK3CA* p.A1046T *PIK3CA* p.H1047L *PIK3CA* p.H1047R
Hyman *et al. Cancer Discov.* 2015[14] Nordmann *et al. Blood* 2017[20] Janku *et al. Mol Cancer Ther.* 2019[15]	*KRAS* p.G12S *KRAS* p.Q61H *KRAS* p.G12R*
Diamond *et al. Cancer Discov.* 2016[2] Diamond *et al. Blood* 2016[17] Estrada-Veras *et al. Blood Adv.* 2017[6] Lee *et al. JCI Insight* 2017[19] Papo *et al. Blood* 2017[21] Goyal *et al. Blood* 2019[18] Diamond *et al. Nature* 2019[16] Janku *et al. Mol Cancer Ther.* 2019[15] Durham *et al.* Nat Med. 2019[23]	*ARAF* p.S214A *ARAF* p.P216A *ARAF* p.A225V *ARAF* p. D228V *ARAF* p.P539H *KRAS* p.G12R *KRAS* p.R149G *NRAS* p.G12D *NRAS* p.G13D *MAP2K1* p.F53L *MAP2K1* p. Q56P *MAP2K1* p.K57N *MAP2K1* p.K57E *MAP2K1* p.F68L *MAP2K1* p.C121S *MAP2K1* p.S123T *MAP2K1* p.S123P *MAP2K1* p.P124L *MAP2K1* p.P124Q *MAP2K1* p.E144K *MAP2K1* p.E51_Q58del *MAP2K1* p.Q58_E62del *MAP2K1* p.E102_I103del *MAP2K1* p.P105_I107del *MAP2K2* p.Y134H* *RAF1* p.K106N *PTCH1* loss *NF1* p.R1132H* *ASXL1* p.E635fs*15 *ASXL1* p.G646fs*12 *ASXL1* p.R693 *U2AF1* p.Q157P *MPL* p.W515L* *ERBB2* amplification* *KIF5B-ALK* fusion *LMNA-NTRK1* fusion *CSF1R* c.1157C>T

B

G Goyal et al. *Blood* 2020





M Hitomi et al. *Current Biol* 1999

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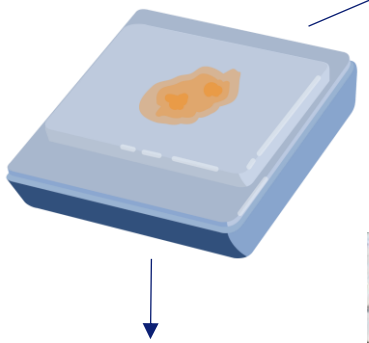
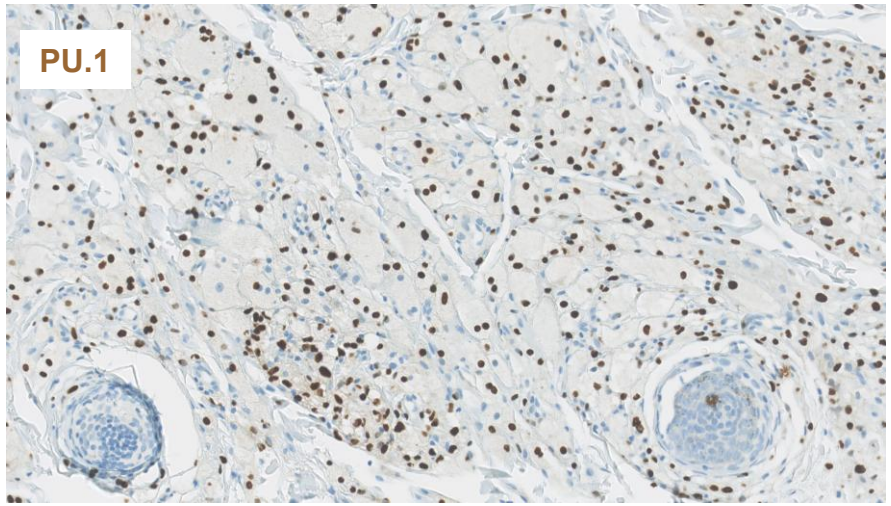
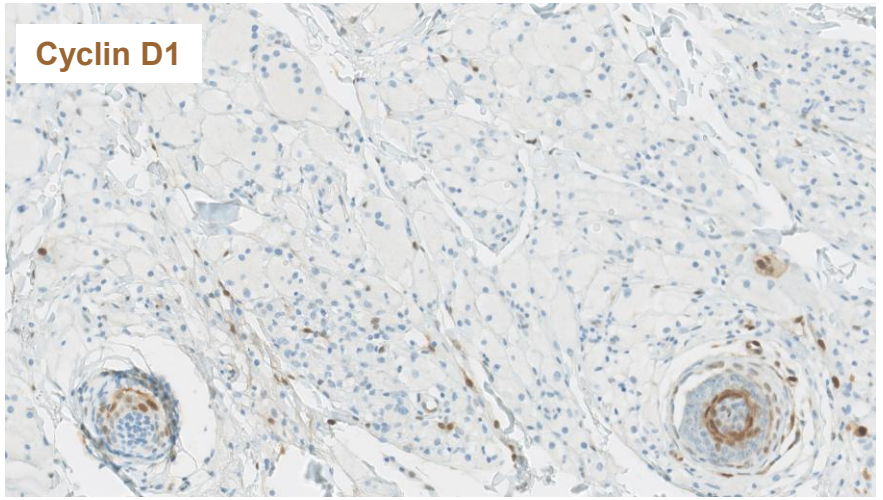
Methods

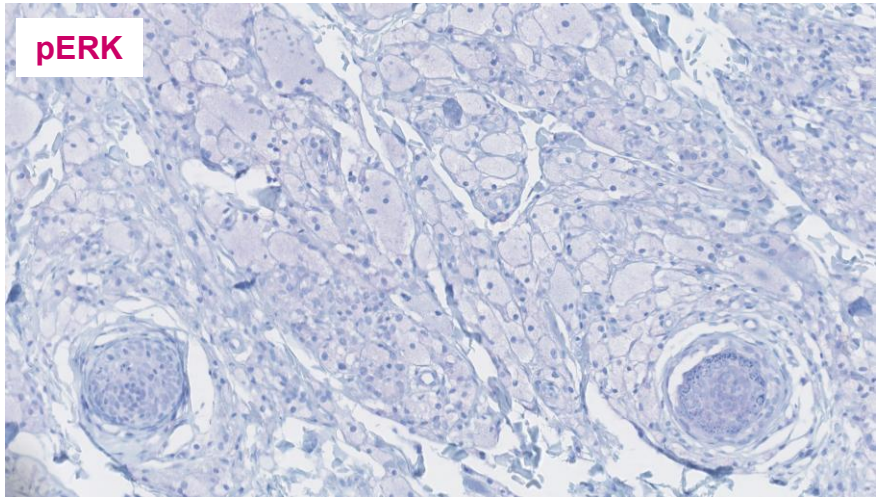
immunohistochemical staining for PU.1, Cyclin D1 and pERK



ngs







N=28 AOXGD biopsies & N=10 xanthalasma biopsies

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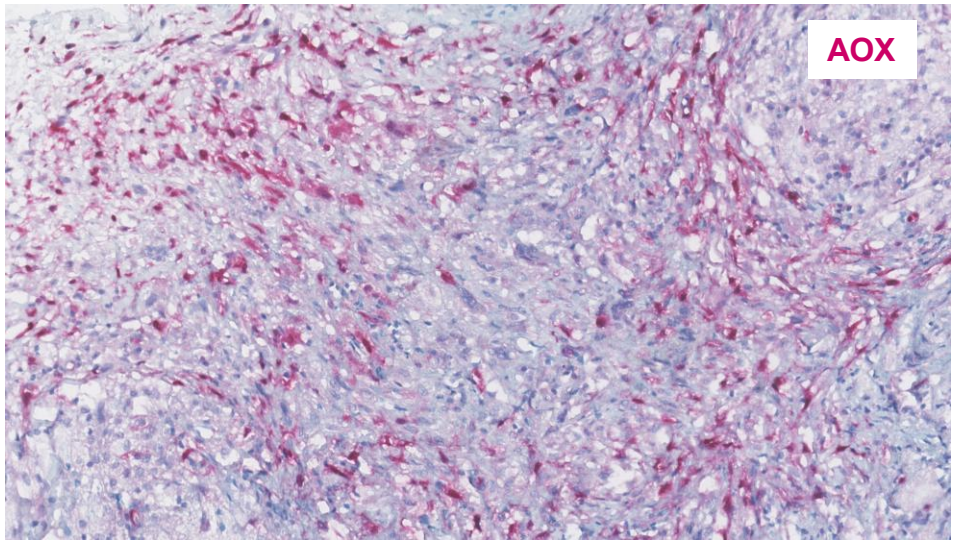
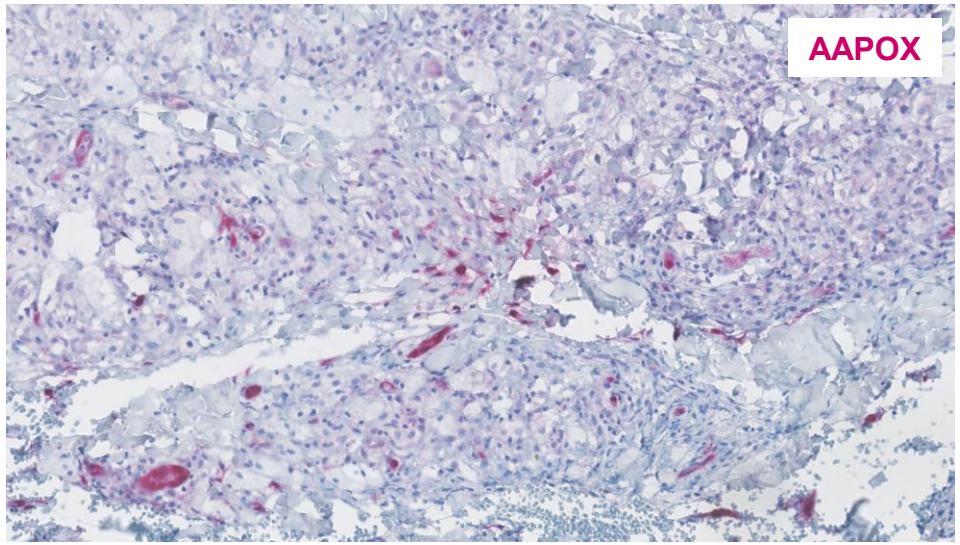
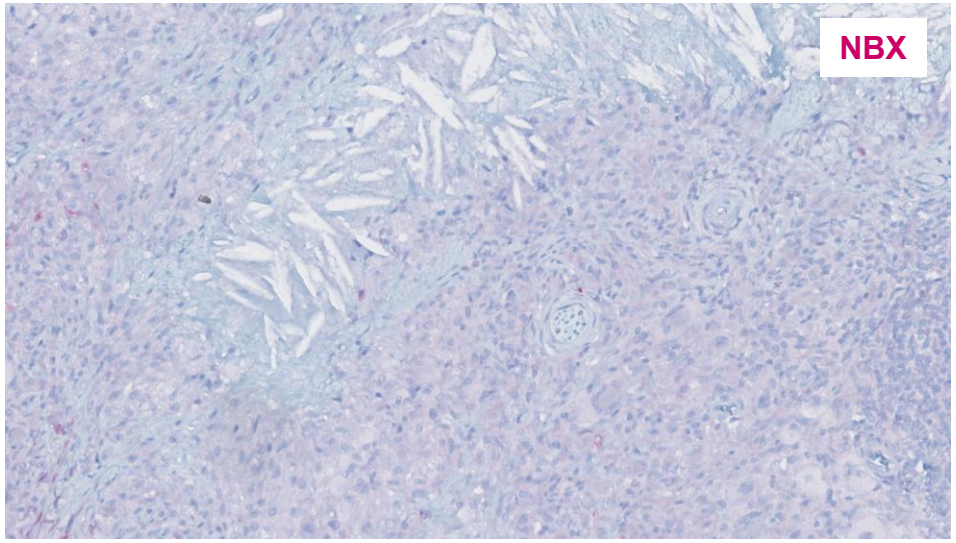
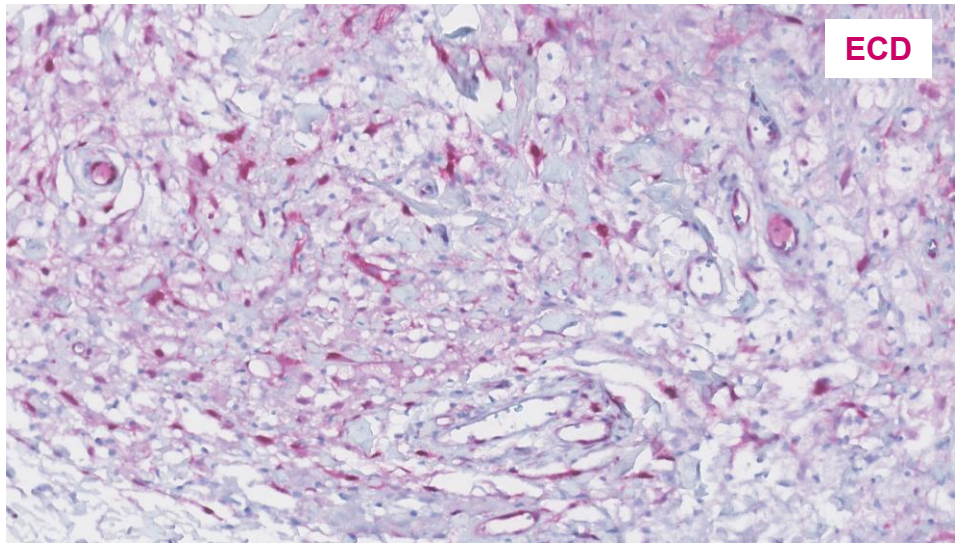
Phosphorylated ERK results









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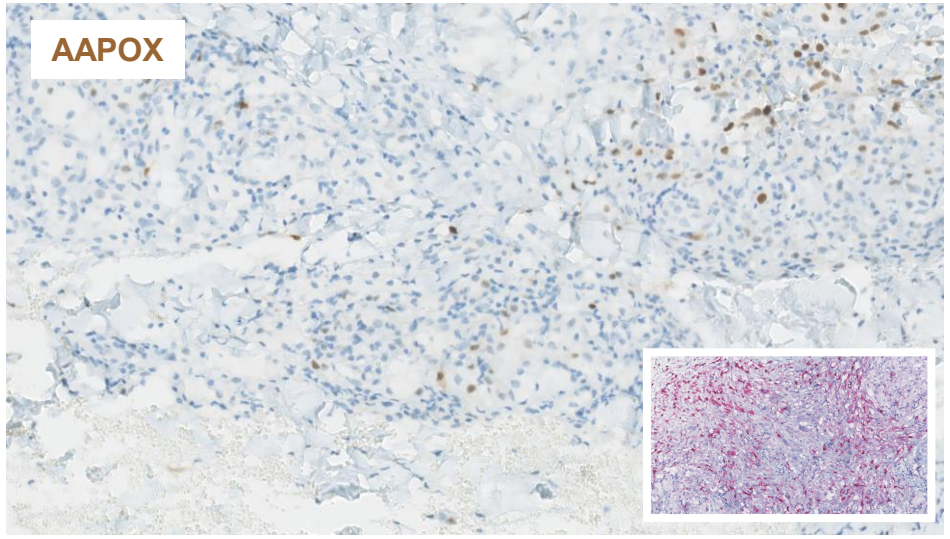
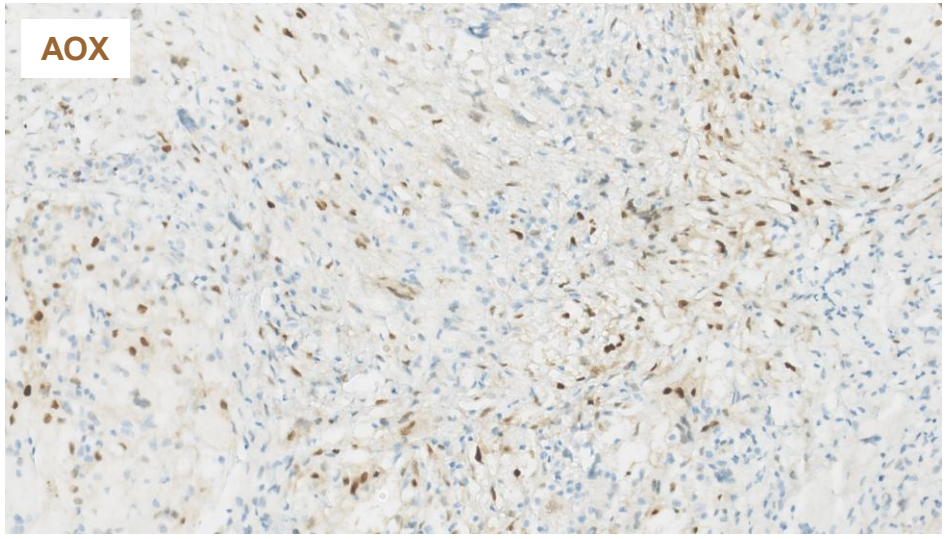
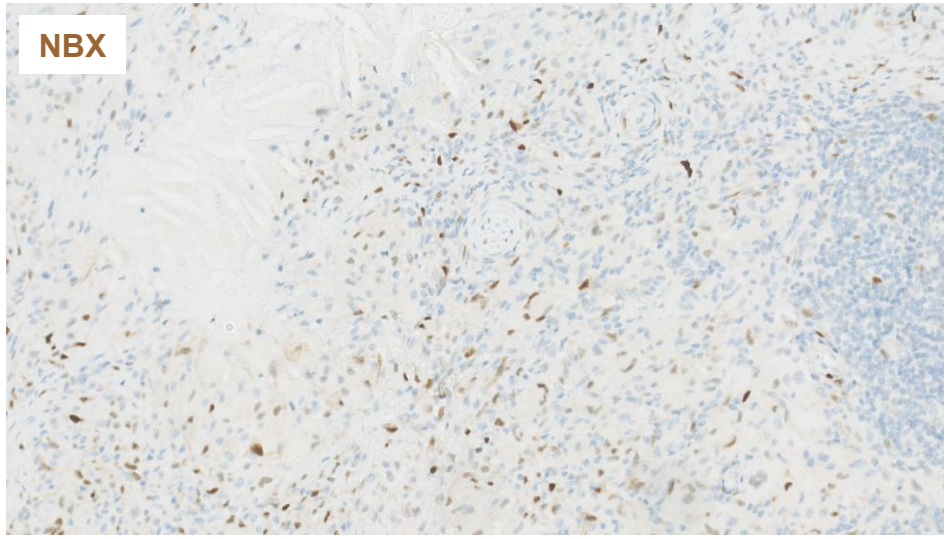
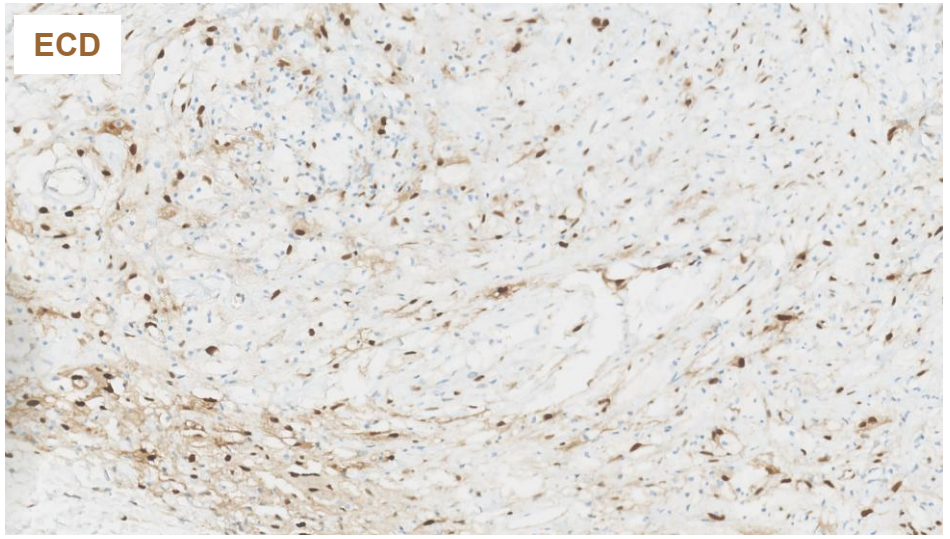
Cyclin D1 results









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Molecular and immunohistochemical characteristics of AOXGD patients

Patient	Age at diagnosis (years)	Sex	Diagnosis	Year of biopsy	NGS (VAF)	FFPE-TLC NGS (VAF)	pERK	Cyclin D1	PU.1
1	31	M	AOX	2018	no mutation detected	no mutation detected	neg	neg	pos
2	51	M	AOX	2011		no mutation detected	neg	neg	pos
3	48	M	AOX	2006		no mutation detected	pos	pos	pos
4	50	F	AOX	1994		no mutation detected	neg	pos	pos
5	61	F	AOX	2011		no mutation detected	neg	pos	pos
6	82	F	AOX	2004		no mutation detected	neg	pos	pos
7	49	M	AOX	2005		no mutation detected	neg	pos	pos
8	80	F	AOX	1989		no mutation detected	neg	neg	pos
9	70	M	AOX	2003		no mutation detected	pos	pos	pos
10	42	M	AOX	2021	no mutation detected	no mutation detected	pos	pos	pos
11	48	M	AOX*	2021	KRASp.G12R (23%) BRAFp.G466E (21%)		neg	pos	pos
12	50	M	AAPOX	2015		No mutation detected	neg	neg	pos
13	53	F	AAPOX	2010		KRASp.K117N (23%) PIK3CAp.R992Q (5%)	pos	pos	pos
14	45	F	AAPOX	2010		NRASp.G12D (31%)	focal pos	focal pos	pos
15	68	F	AAPOX	2003		no mutation detected	pos	pos	pos
16	72	M	AAPOX	2022	no mutation detected	no mutation detected	neg	neg	pos
17	45	M	AAPOX	2021	no mutation detected	no mutation detected	neg	neg	pos
18	43	M	NBX	1999	no mutation detected	no mutation detected	pos	pos	pos
19	73	F	NBX	2002		no mutation detected	pos	neg	pos
20	49	F	NBX	2019		no mutation detected	neg	neg	pos
21	67	M	NBX	2017		no mutation detected	pos	pos	pos
22	57	F	NBX	2014		no mutation detected	pos	pos	pos
23	52	M	NBX	2018	no mutation detected	no mutation detected	*failed*	neg	*failed*
24	75	M	NBX	2022	no mutation detected	no mutation detected	*failed*	*failed*	*failed*
25	47	M	ECD	2000	*failed*	BRAFp.V600E (9%)	pos	pos	pos
26**	59	F	ECD	2018	KRASp.G12A (52%)				
27	59	F	ECD	2022	BRAFp.V600E (9.5%)		pos	*failed*	*failed*
28	67	F	ECD	2020	KRASp.K117N (28%)		*neg*	pos	pos

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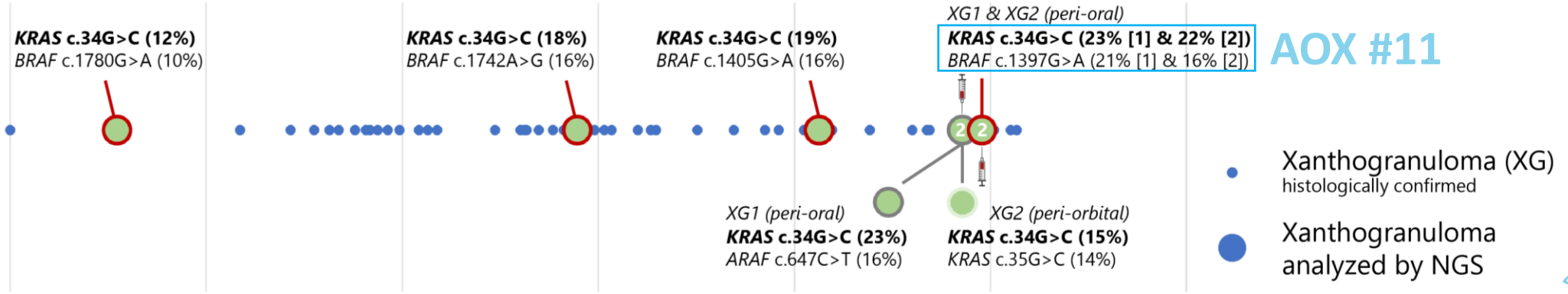
Conclusions and take home message

- pERK and Cyclin d1 are surrogate indicators of MAPK pathway activation irrespective of concurrently present driver mutation(s);
- 25% of (peri)orbital AOXGD biopsies display no pERK^{+} and/or Cyclin D1^{+} histiocytes, a situation comparable to control xanthalasma;
- 4/7 (57%) of AOXGD patients with mutation-driven MAPK activation relapsed versus 8/21 (35%) without mutation;
- Molecular analysis of (perio)orbital biopsies may help to identify patients at risk of recurrent disease



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