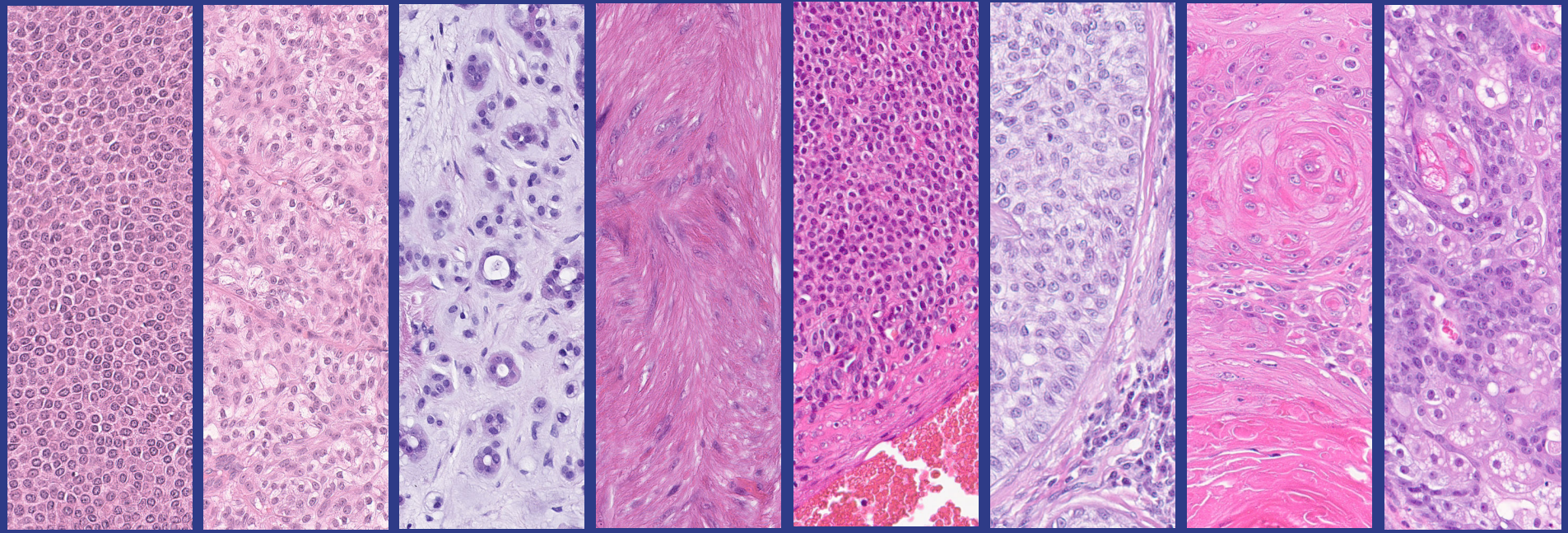


The Dermatlas Project:

Cross-species oncogenomics of melanoma and other malignancies to define disease drivers

David Adams, Experimental Cancer Genetics

@David_J_Adams

www.dermatlasproject.org

Skin structures

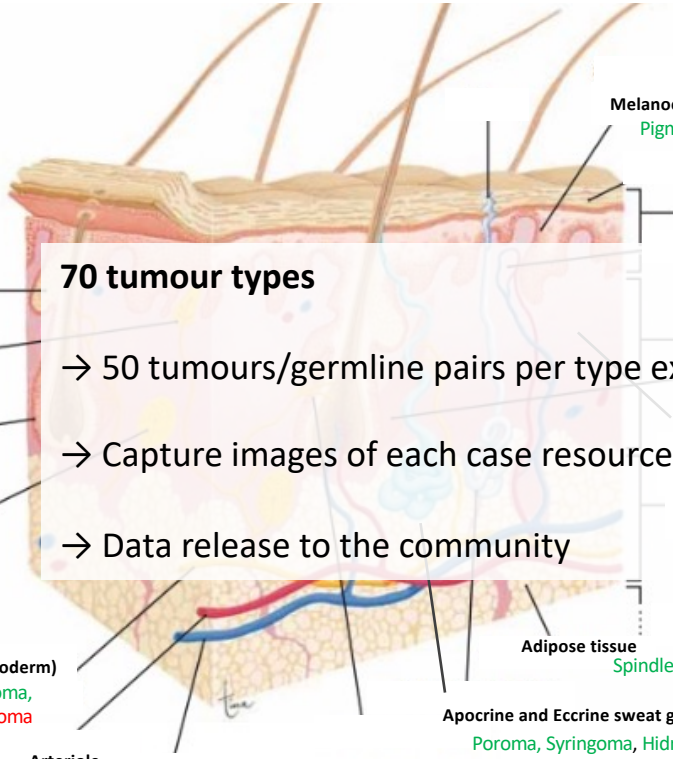
Benign, Intermediate, Malignant

Other

Cutaneous myxoma, Non neural dermal granular cell tumour, Superficial acral fibromyxoma, Extramammary Paget disease

Melanocytes

Pigmented spindle cell nevus, Conjunctival nevi



70 tumour types

→ 50 tumours/germline pairs per type exome/transcriptome

→ Capture images of each case resource for machine learning & teaching

→ Data release to the community

MRC | Medical Research Council

Trich

(Myo-/Histio-)Fibroblasts

Cutaneous leiomyosarcoma

Striated Muscle Rhabdomyosarcoma

Adipose tissue

Spindle cell/pleomorphic lipoma, Pleomorphic Liposarcoma

Nerve (& neuroectoderm)

Solitary Circumscribed Neuroma, Perineurioma, Epithelioid schwannoma, Epithelioid MPNST, Cellular neurothecoma, Cutaneous Ewing sarcoma

Arteriole

Venule

Glomus tumour, Angioleiomyoma, Myopericytoma, Myofibroma, Epithelioid Angiomatous Nodule, Microvenular/Hobnail/Glomeruloid/Spindle cell/Tufted Hemangioma, Atypical Vascular Lesion, Kaposiform/Retiniform hemangioendothelioma, Cutaneous (epithelioid) angiosarcoma, Malignant glomus tumour

Apocrine and Eccrine sweat glands

Poroma, Syringoma, Hidradenoma, Mixed tumour, Myoepithelioma, Syringocystadenoma papilliferum, Hidradenoma papilliferum, Tubular apocrine adenoma, Porocarcinoma, Microcystic adnexal carcinoma, Endocrine mucin-producing sweat gland carcinoma, Digital papillary adenocarcinoma, Squamoid eccrine ductal carcinoma, Eccrine ductal carcinoma, Malignant mixed tumour, Malignant myoepithelioma, Hidradenocarcinoma, Mucinous carcinoma, Apocrine carcinoma, Cribriform carcinoma, Polymorphous sweat gland carcinoma

Collaborators

Australia

Dr. Peter Ferguson

Belgium

Dr. Ingrid Ferreira
Dr. Nicolas de Saint Aubain

Brazil

Dr. Carlos Bacchi

Canada

Prof. Thomas Brenn

France

Dr. Sylvie Fraitag

Germany

Prof. Wilko Weichert

Mexico

Dr. Daniela Robles-Espinoza

Spain

Dr. Carlos Monteagudo

Netherlands

Dr. Michiel van der Horst
Dr. Remco van Doorn

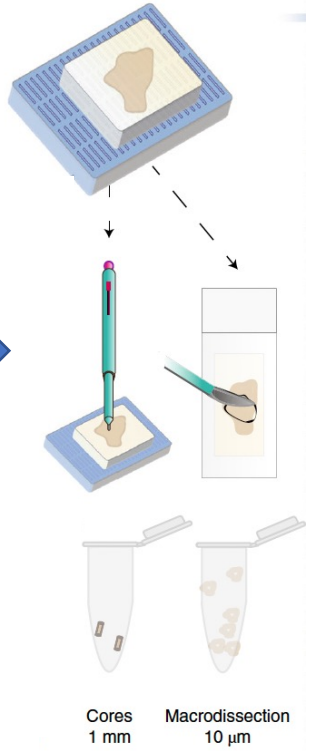
United Kingdom

Prof. Mark Arends
Dr. Emily Clarke
Dr. Eleni Ieremia
Dr. Will Merchant
Dr. Neil Rajan

United States

Dr. Ahmed Alomari
Prof. Steven Billings
Prof. Klaus Busam
Dr. Derek Frew
Dr. Paul Harms
Prof. Alex Lazar
Prof. Michael Tetzlaff

Samples collection

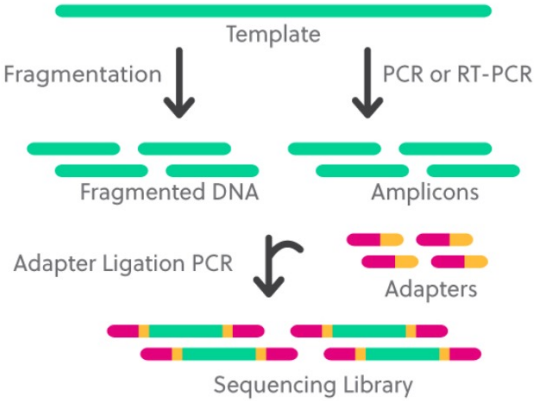


wellcome sanger institute

Workflow

STEP 1:
Extraction

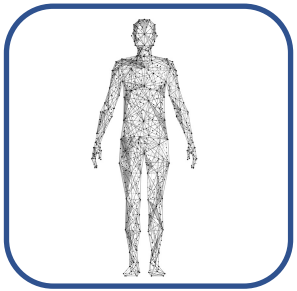
STEP 2:
Library Prep



STEP 3:
Sequencing

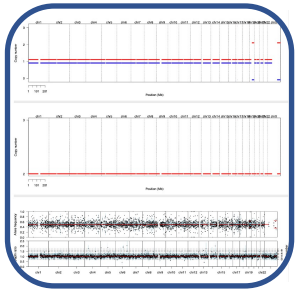
STEP 4:
Analysis

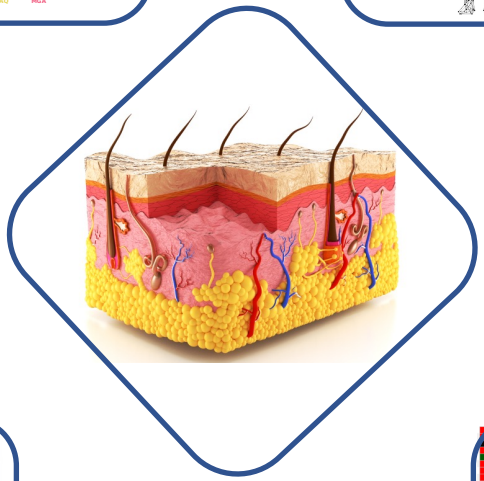
Somatic Mutations & Driver Genes

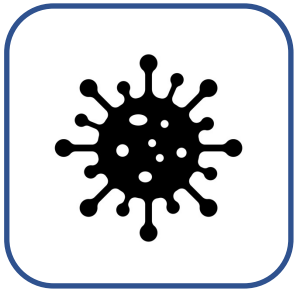


Germline Variants

Copy Number Alterations

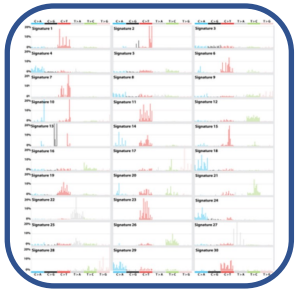




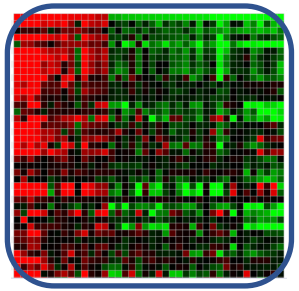


Viral Sequences

Mutational Signatures



Fusion Genes



Genes expressions

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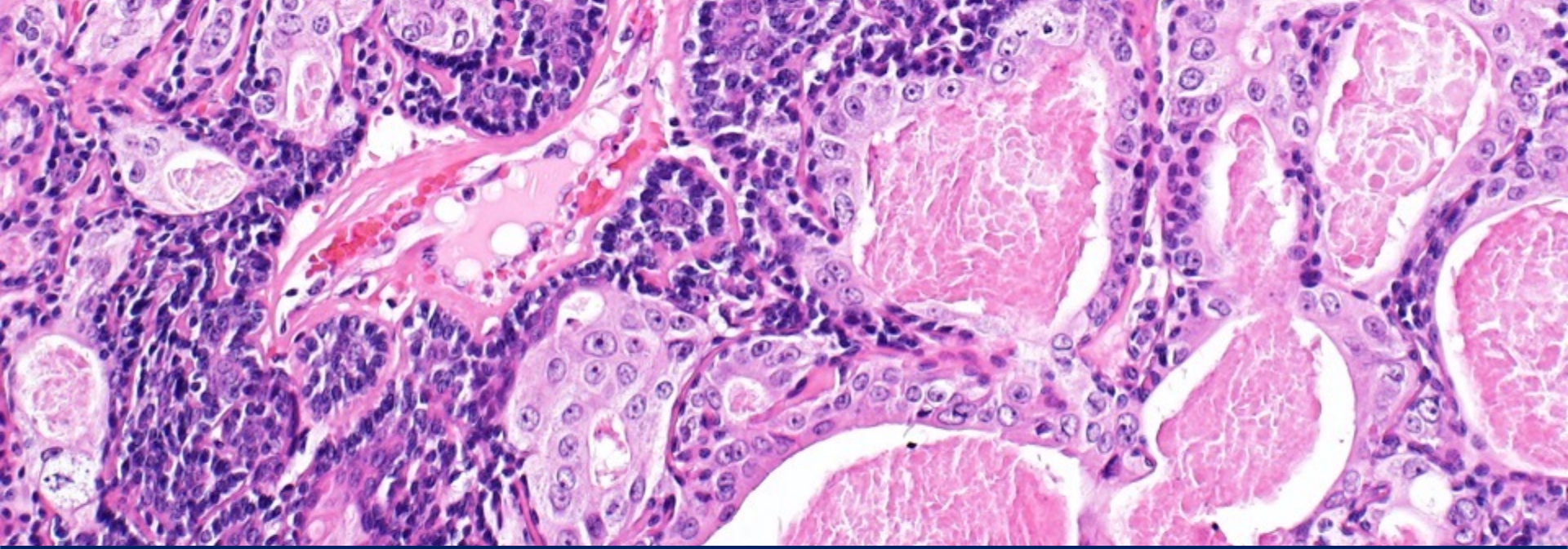
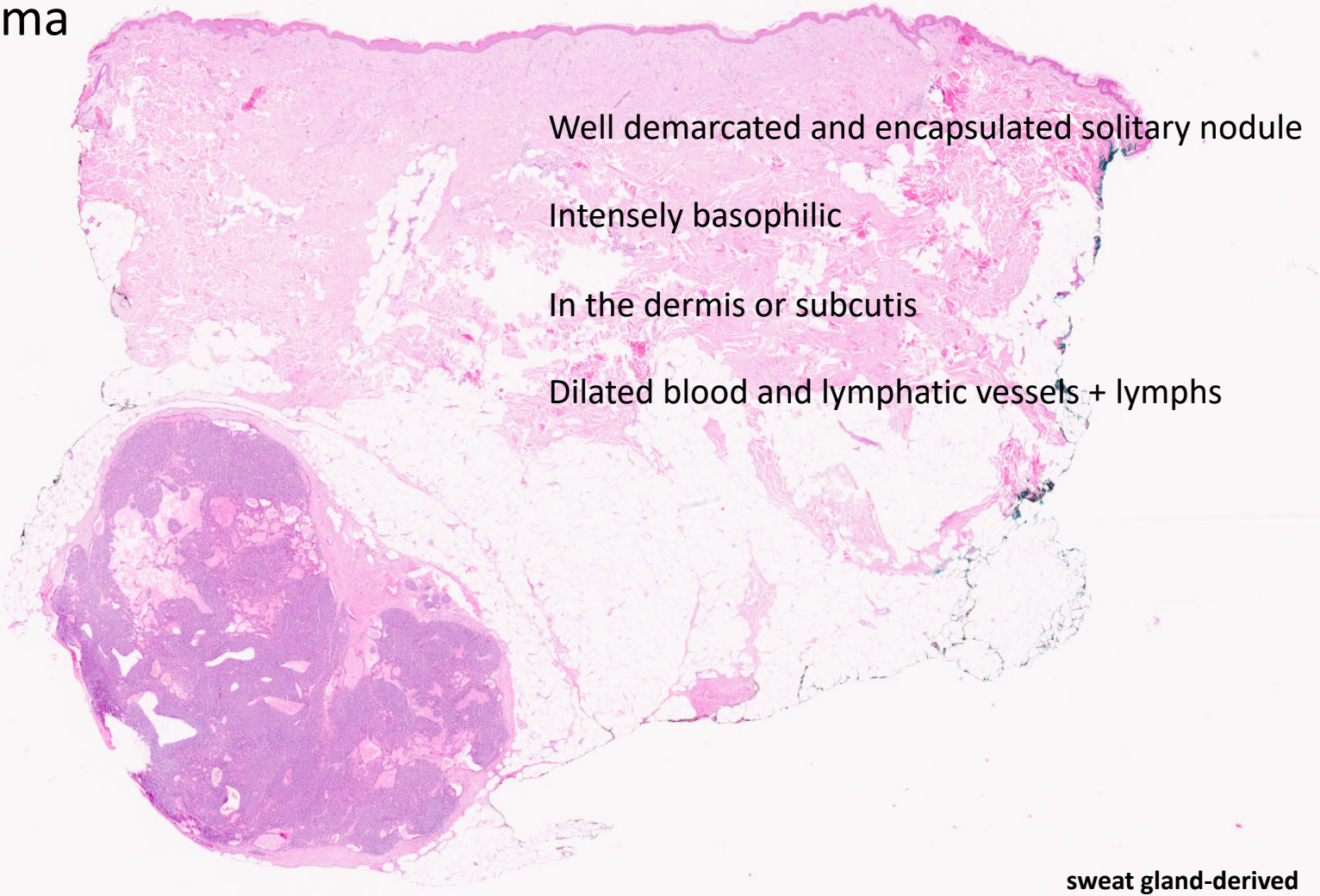


ALPK1 hotspot mutation as a driver of human spiradenoma and spiradenocarcinoma

Spiradenoma



Well demarcated and encapsulated solitary nodule

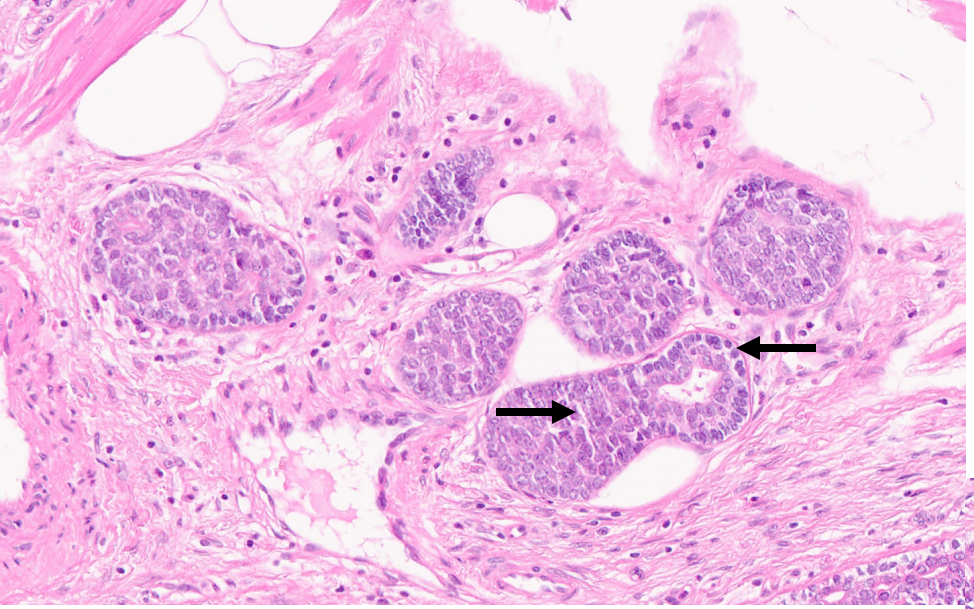
Intensely basophilic

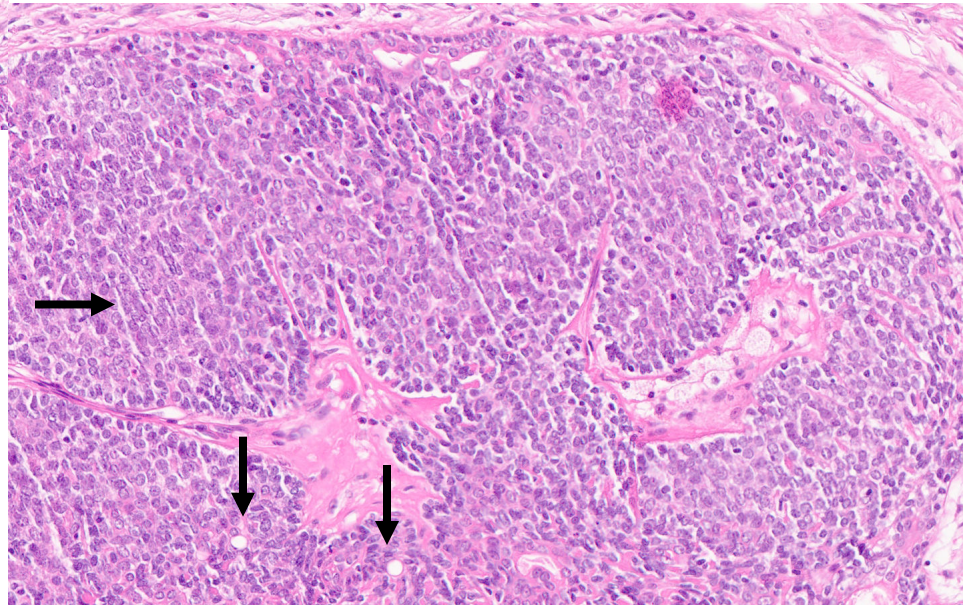
In the dermis or subcutis

Dilated blood and lymphatic vessels + lymphs

sweat gland-derived

Spiradenoma



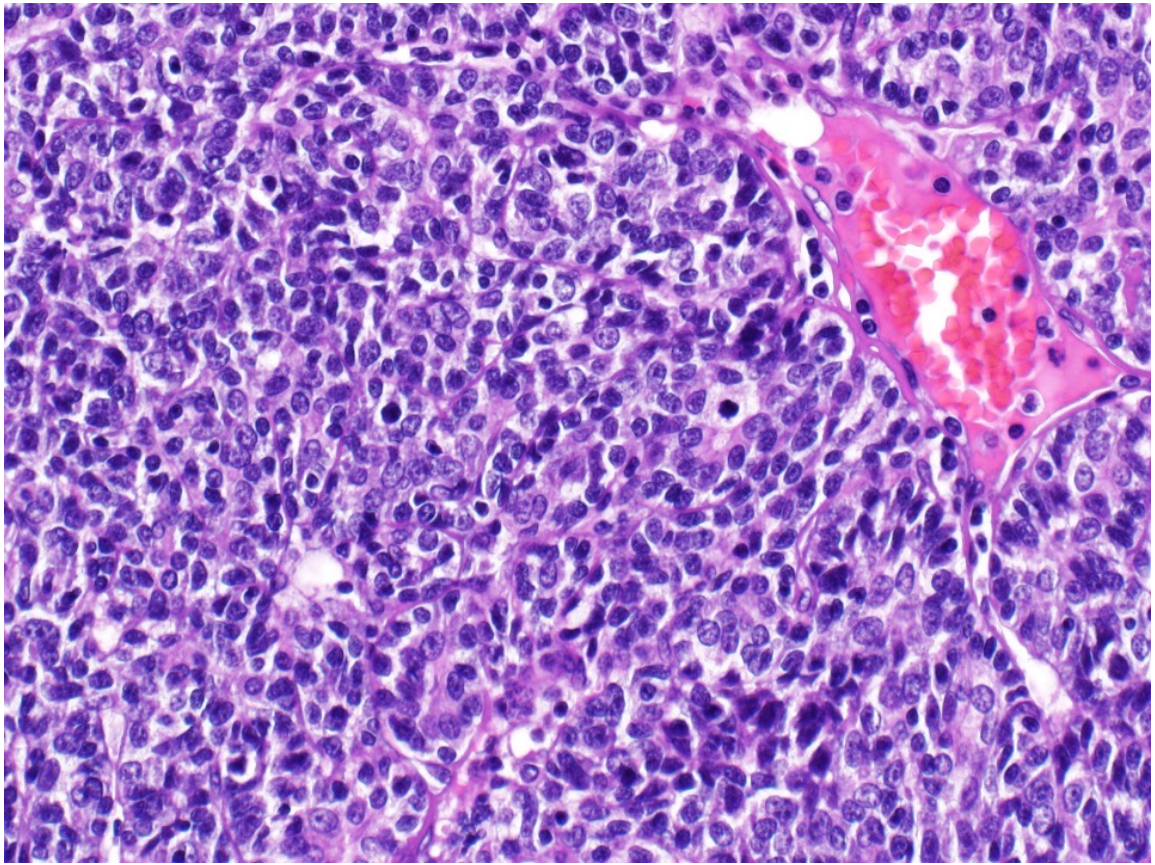


Two cell types – clear and dark

Clear cells (centre). Dark cells (peripheral)

Ductal differentiation

Low-grade spiradenocarcinoma



Easily mistaken for spiradenoma

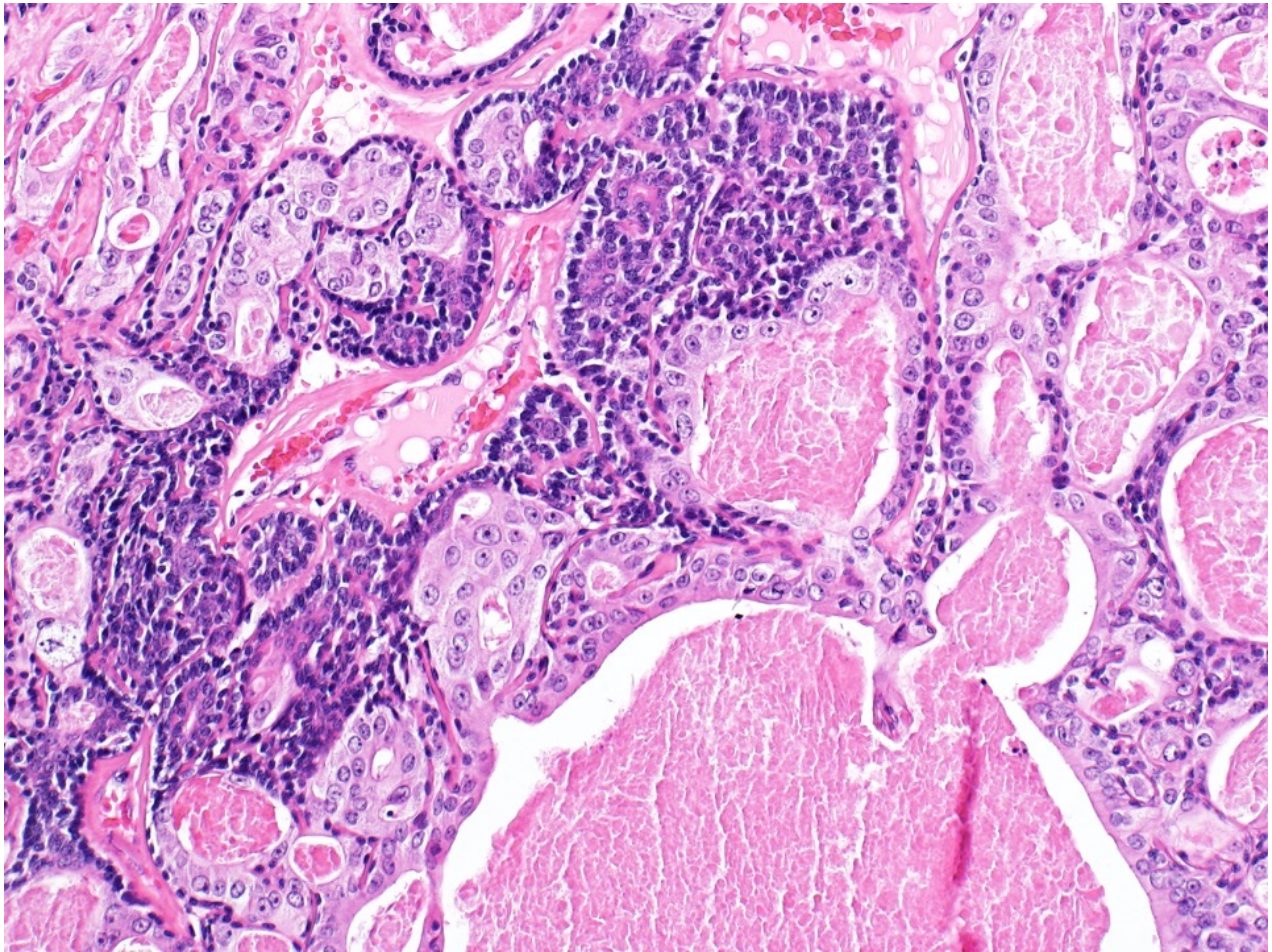
Loss of dual population

Monotonous epithelial cells

Mild-moderate atypia

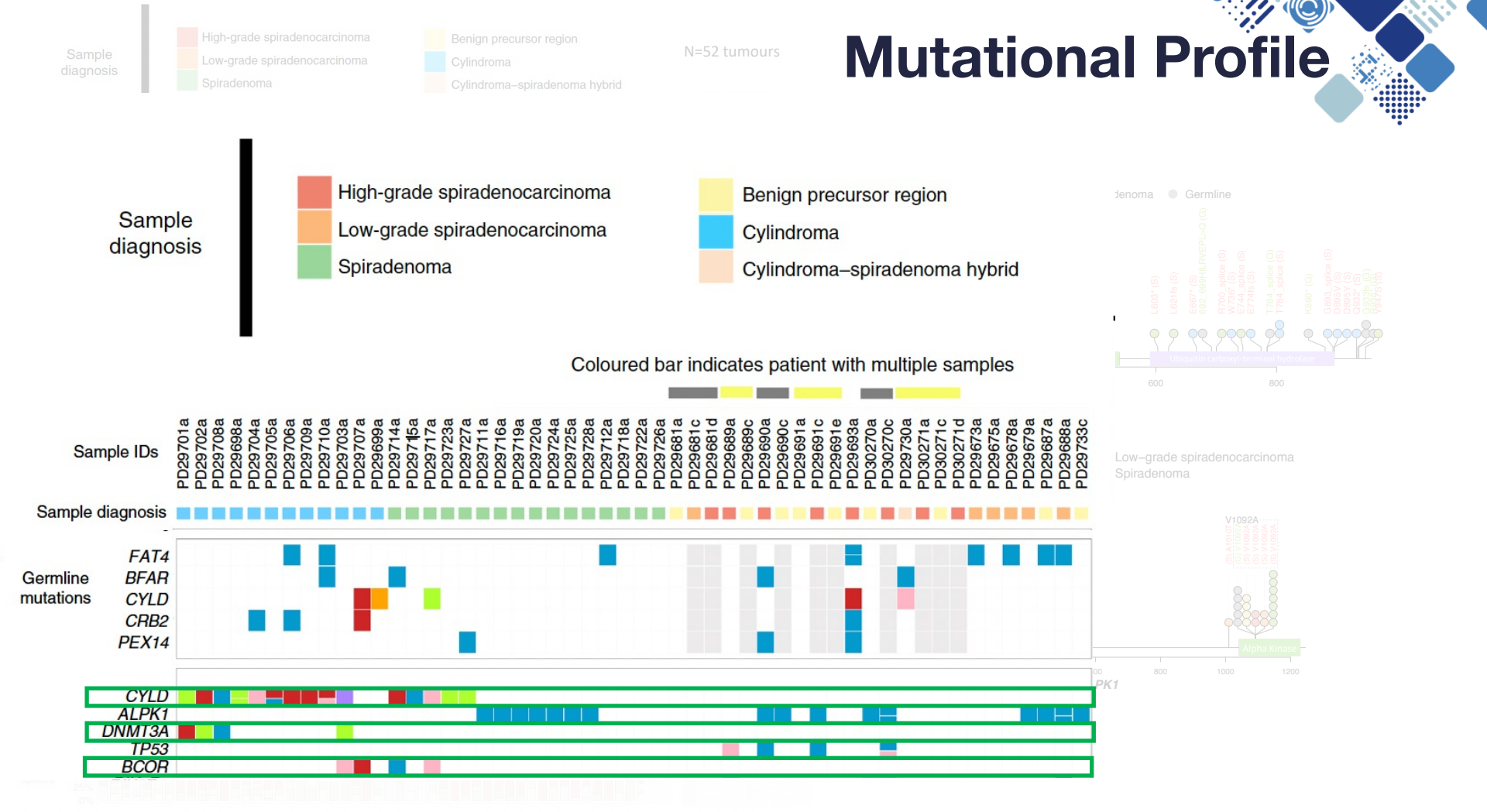
van der Horst M. *et al, Modern Pathology* 2015

High-grade spiradenocarcinoma



Cytological atypia

Mutational Profile

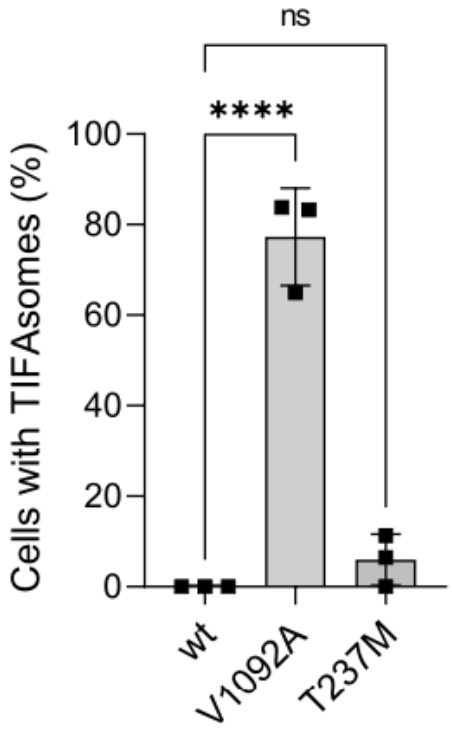


Check for updates

OPEN

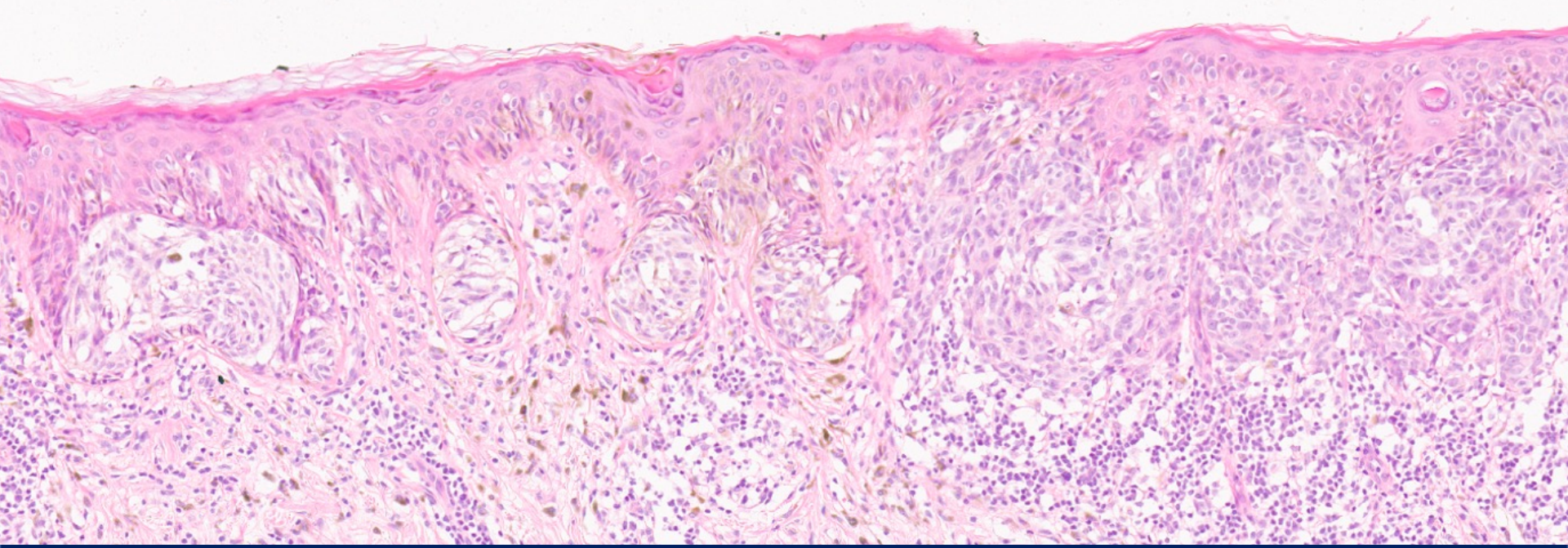
In vitro kinase assay reveals ADP-heptose-dependent ALPK1 autophosphorylation and altered kinase activity of disease-associated ALPK1 mutants

Diego García-Weber[1,3], Anne-Sophie Dangeard[1,3], Veronica Teixeira[1], Martina Hauke[2], Alexis Carreaux[1], Christine Josenhans[2] & Cécile Arrieumerlou[1]✉



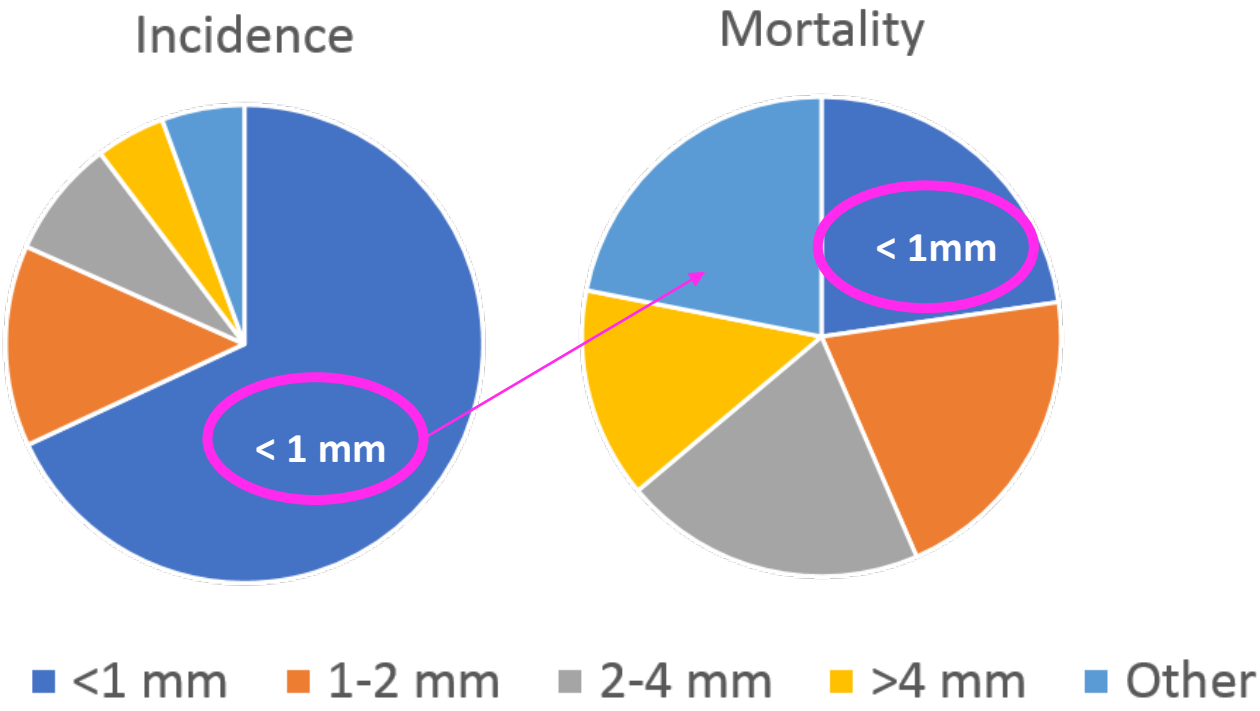
TIFAsome

NFkB activation

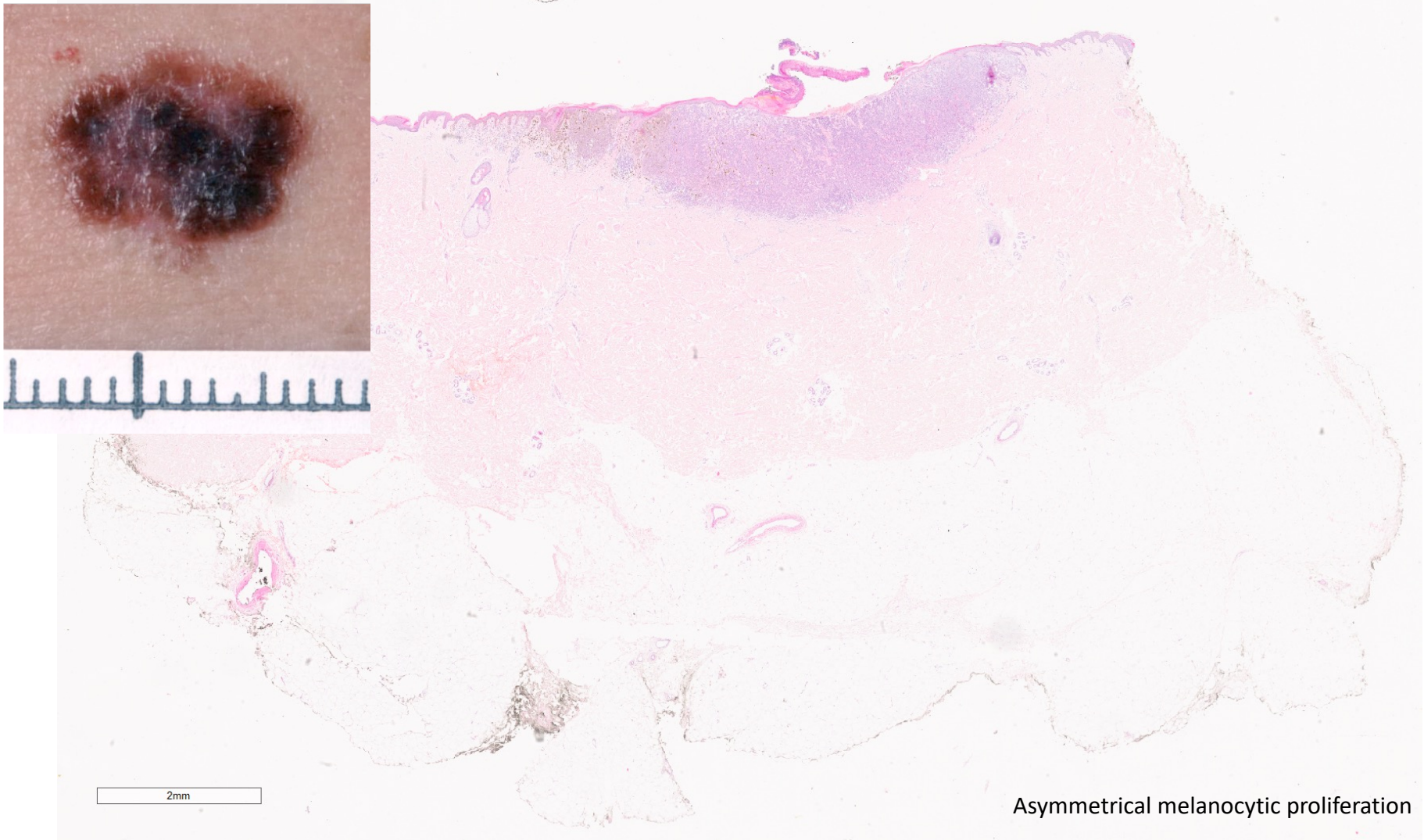


Mutually exclusive genetic interactions and gene essentiality shape the genomic landscape of primary melanoma

Primary Melanoma



Whiteman DC *et al*, *J Invest Dermatol* 2015

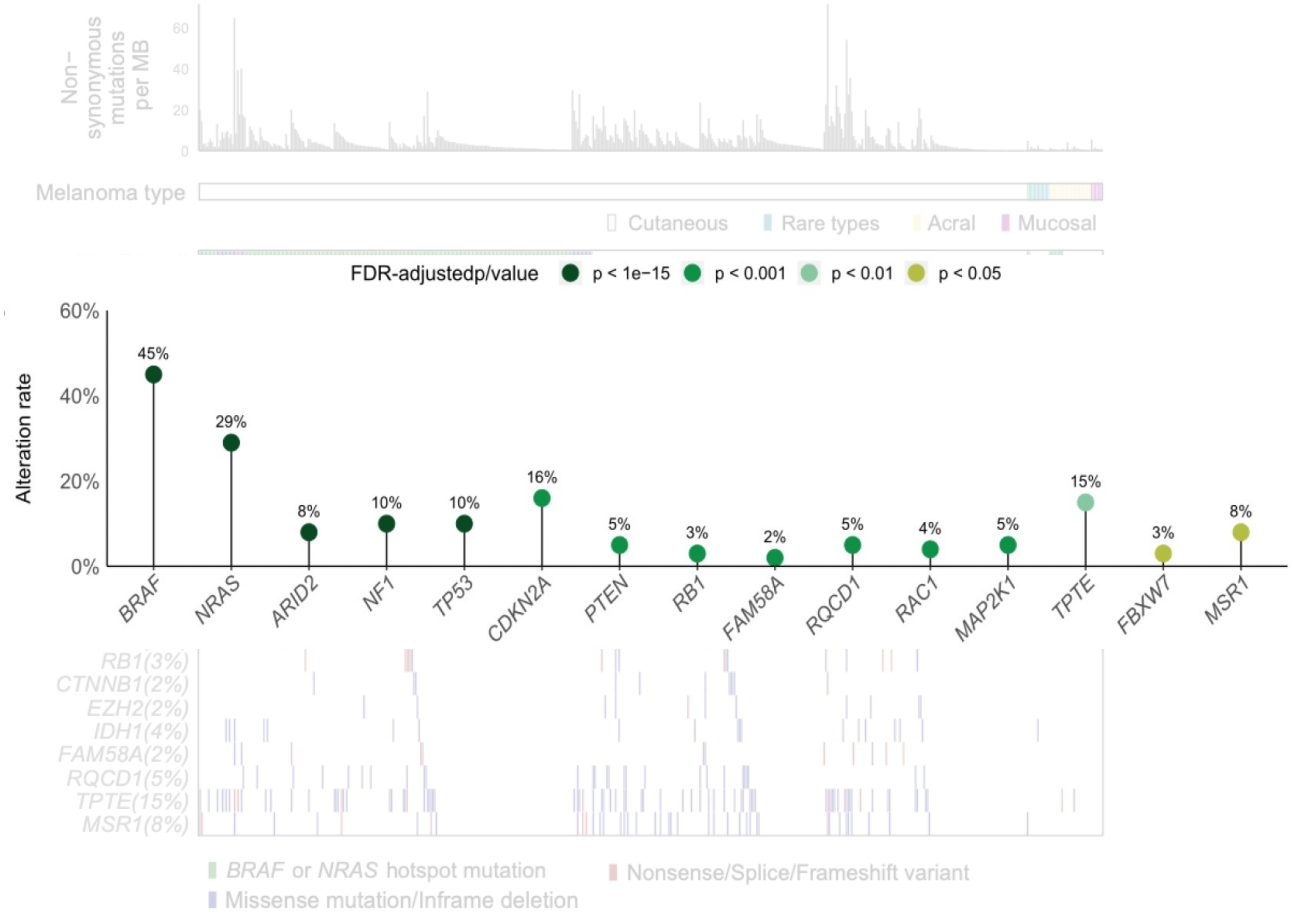


Asymmetrical melanocytic proliferation

Vertical growth phase
200um

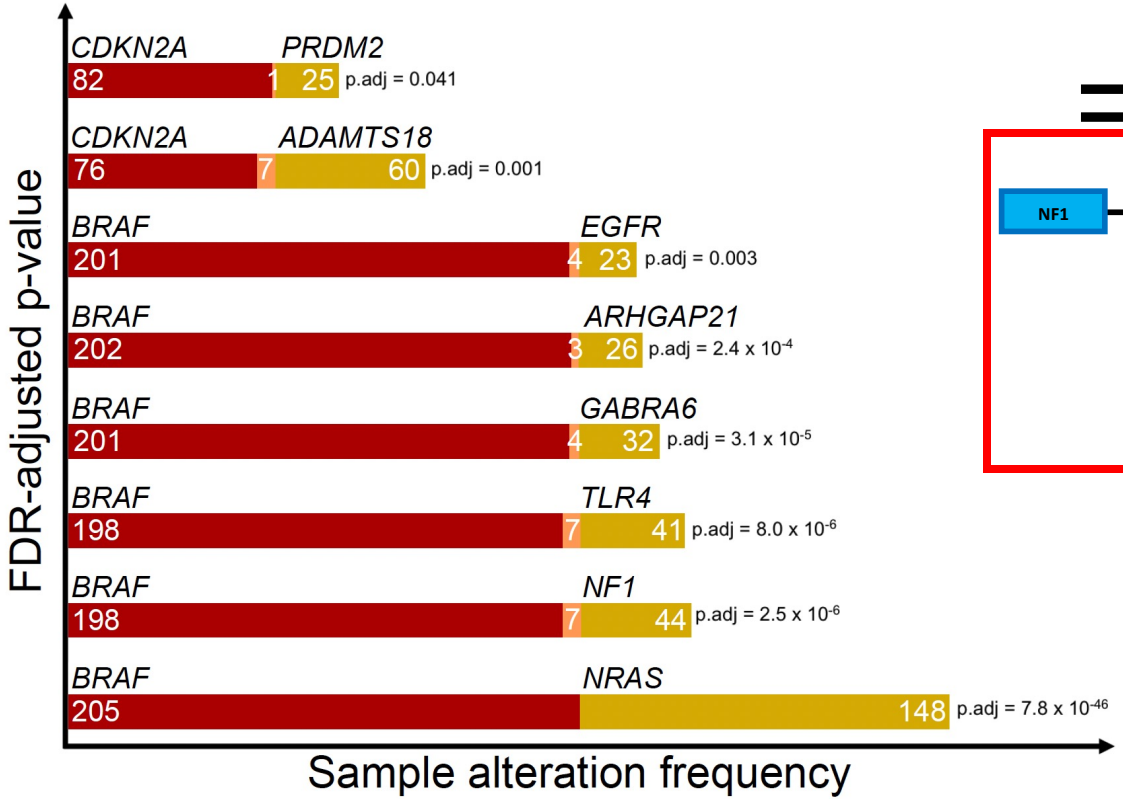
Mutational Profile

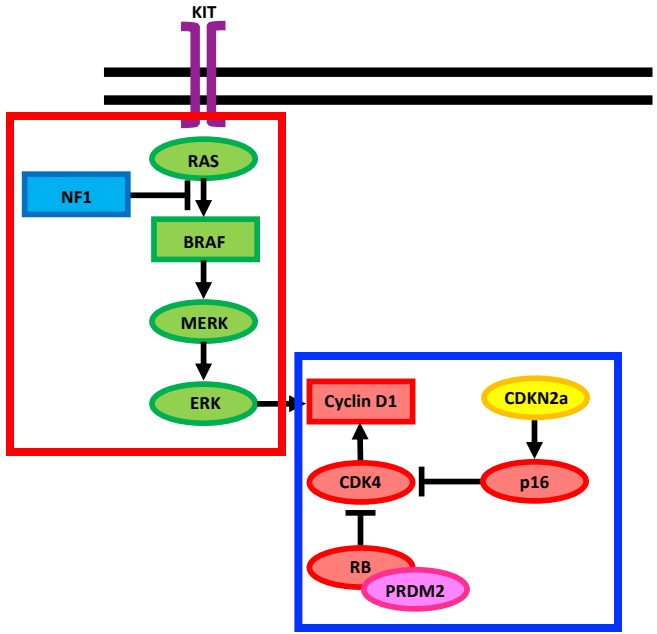
dN/dScv



Mutual exclusive genetic interaction

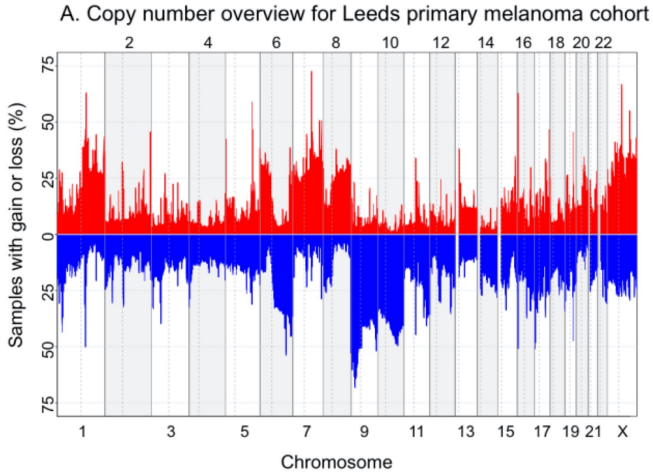
DISCOVER ANALYSIS

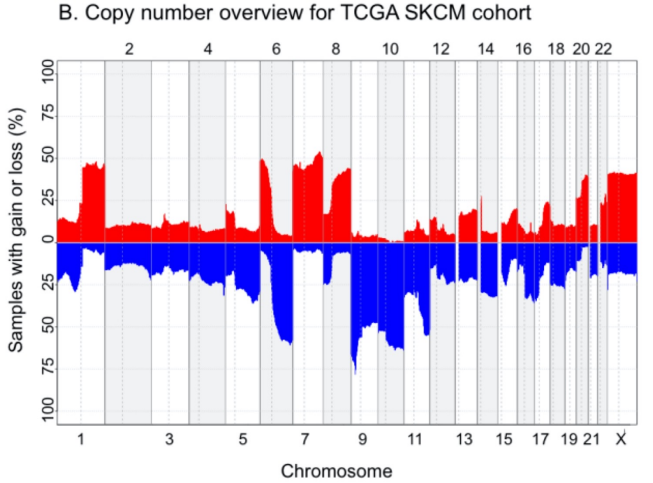


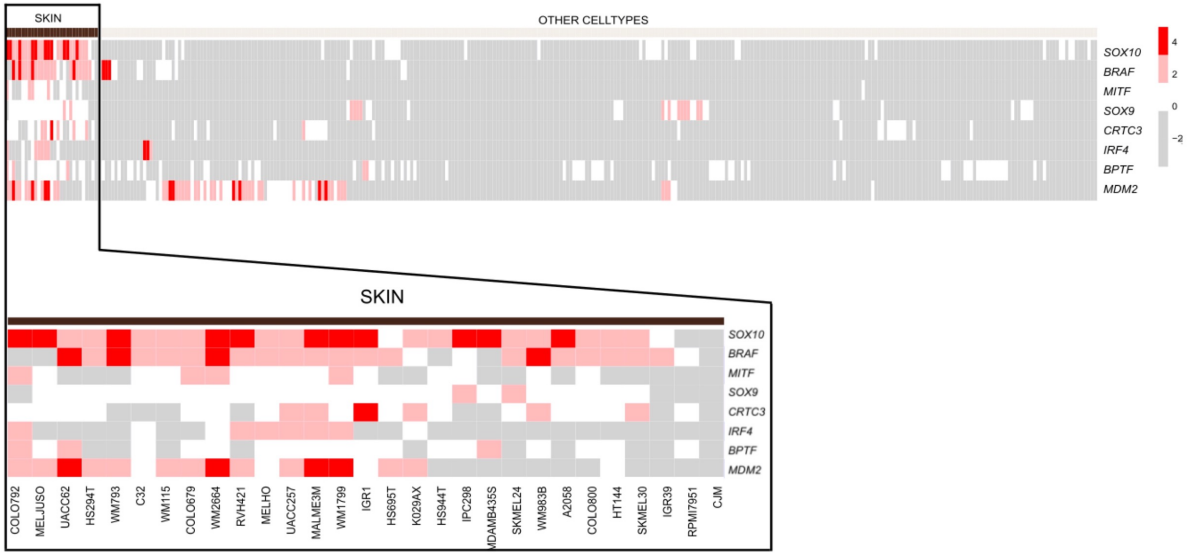


Canisius et al., *Genome Biology*. 2016

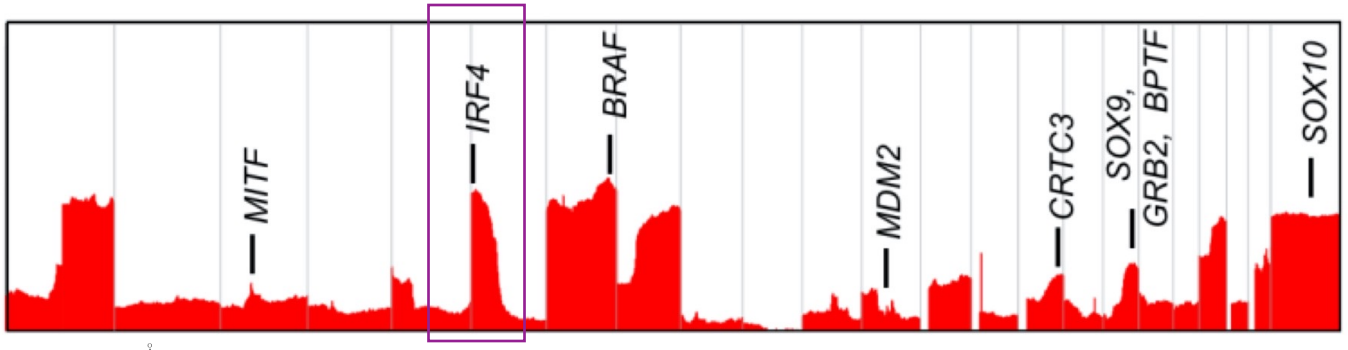
Genome-wide CRISPR Screening

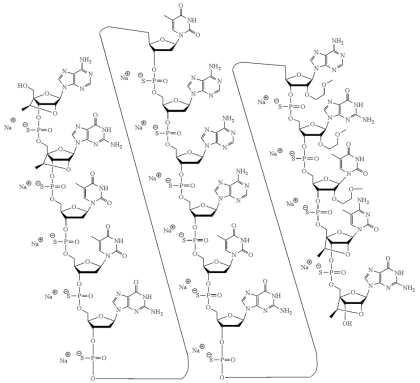




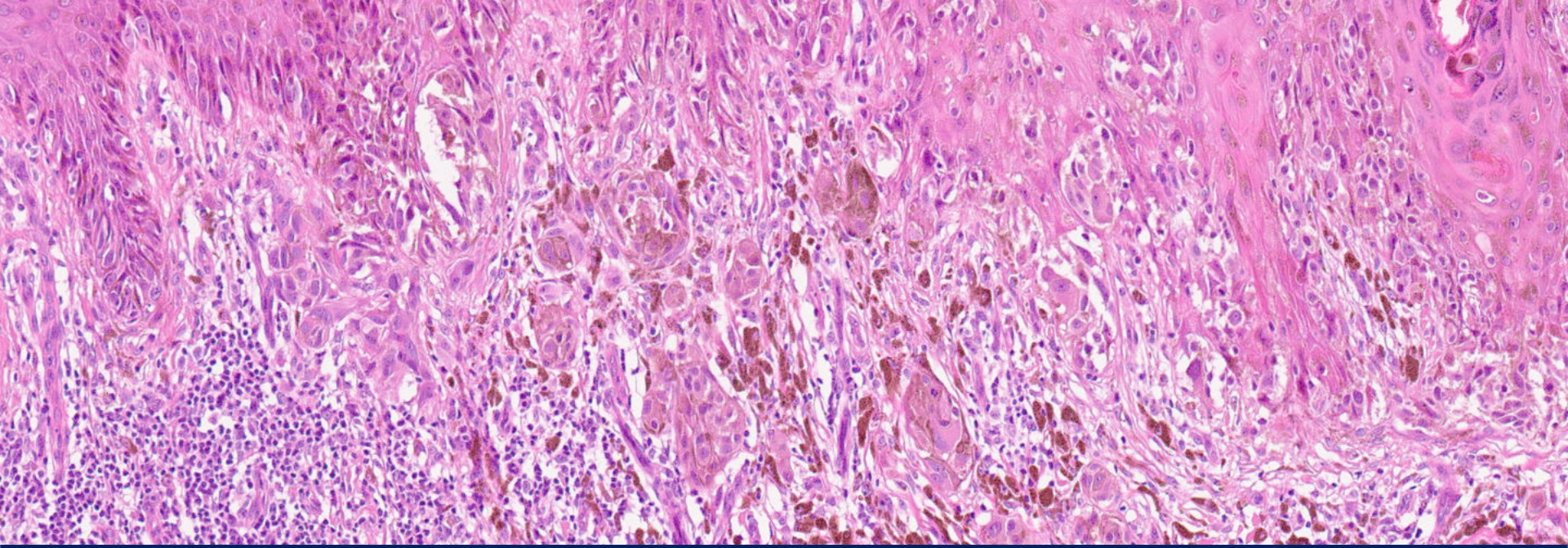


Melanoma essential genes in copy number amplified regions



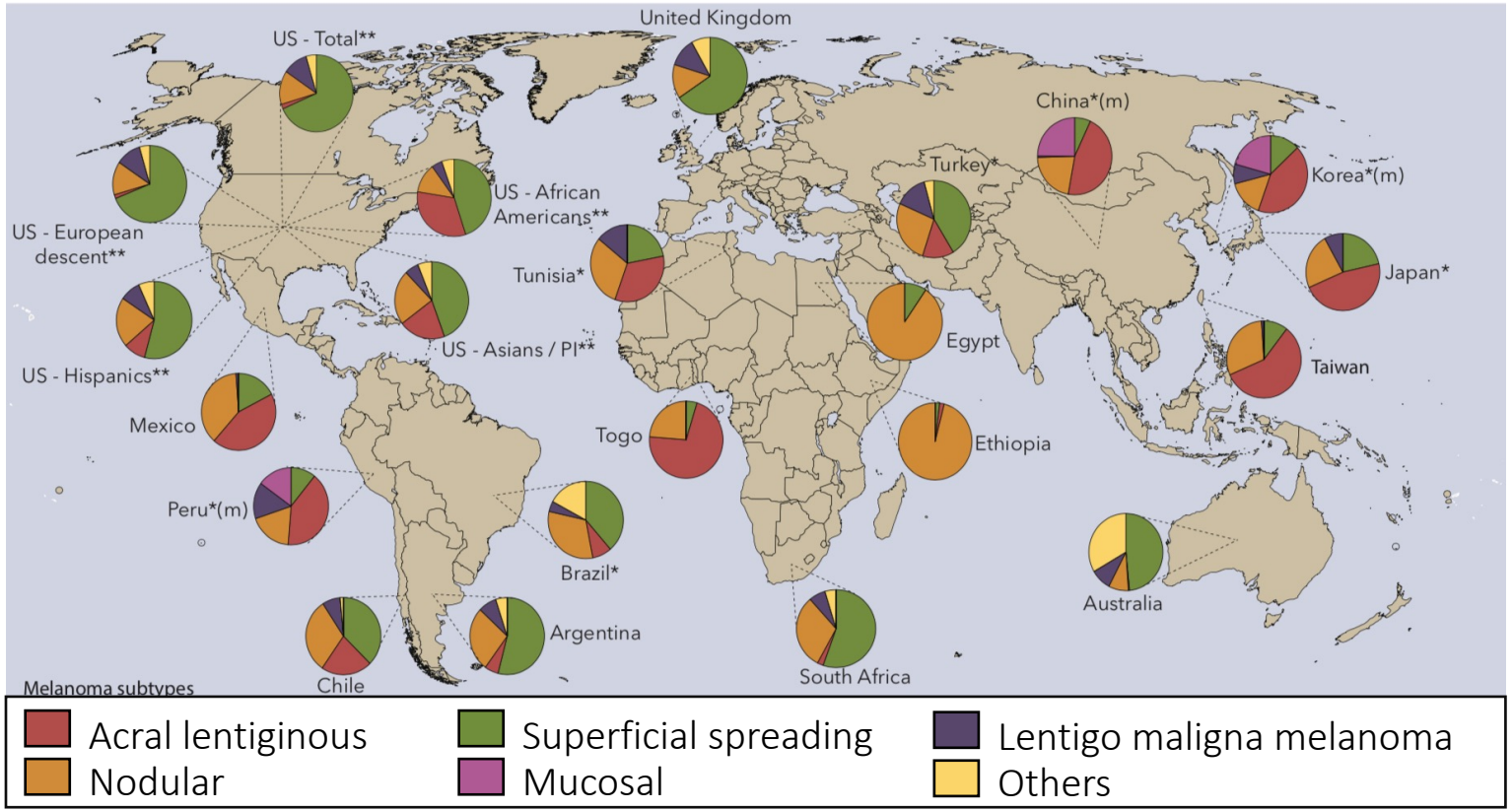


IRF4 inhibitor in use in myeloma



Molecular profiling of acral lentiginous melanoma in Mexican patients

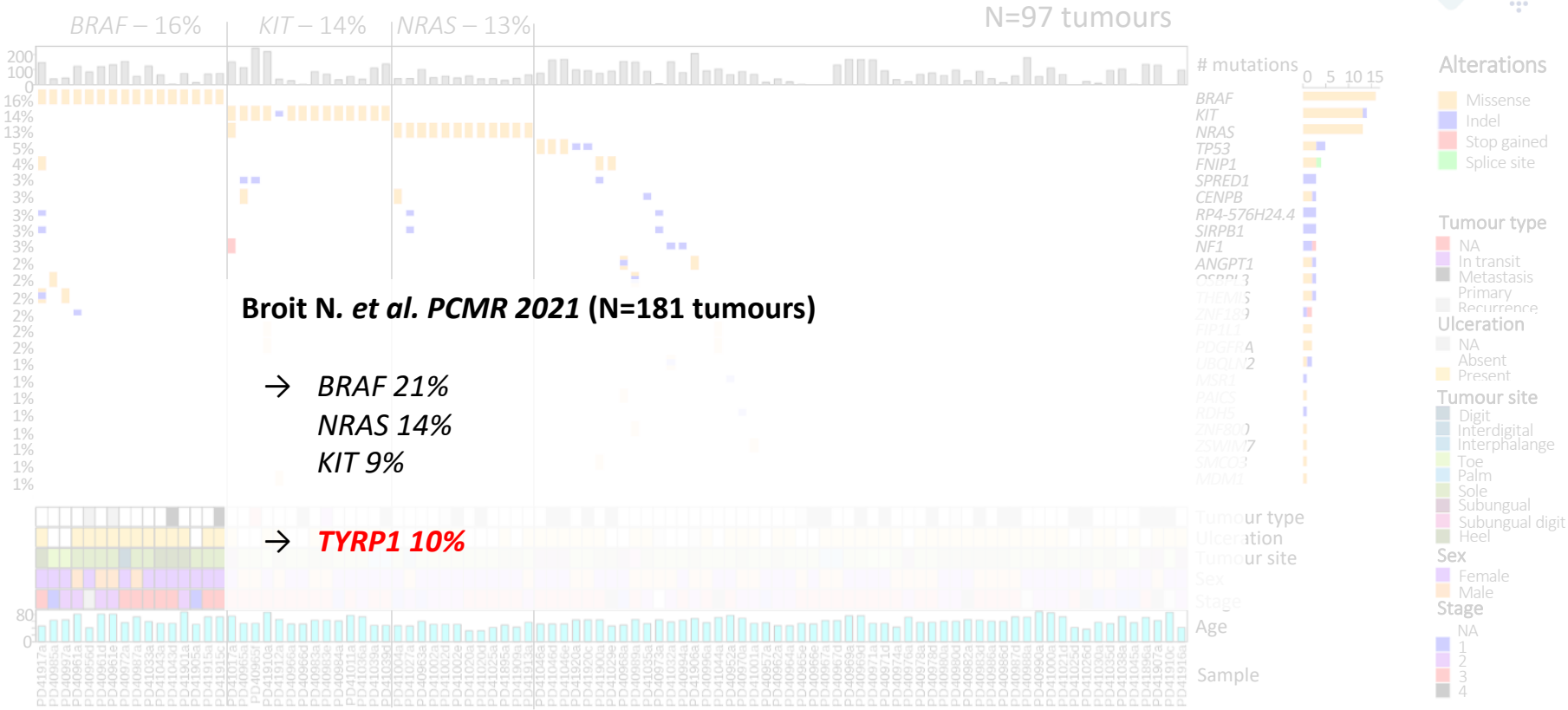
Incidence of melanoma subtypes



Ossio R *et al, Nature Reviews Cancer* 2017

Acral in the nail apparatus

Mutational Profile



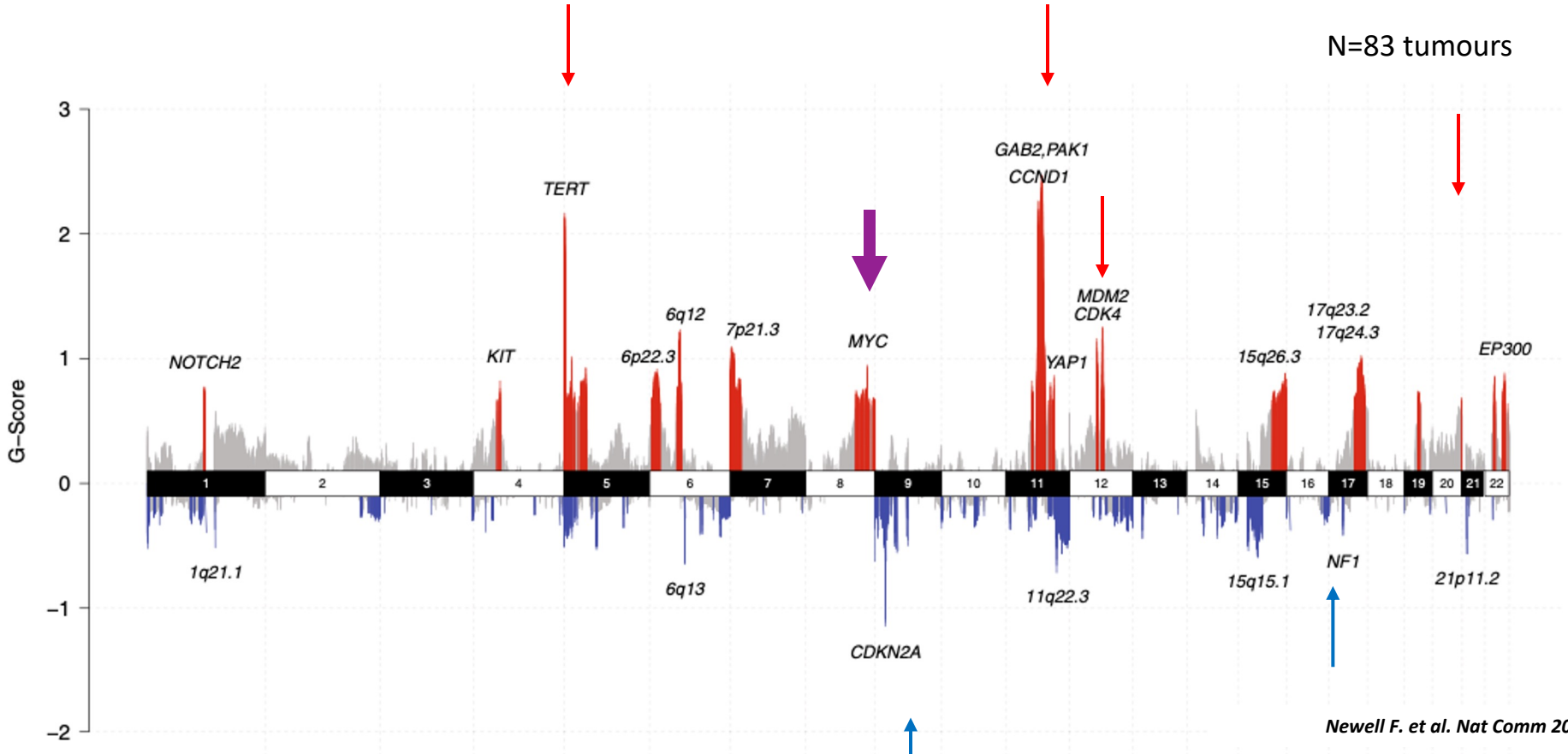
Broit N. *et al. PCMR 2021* (N=181 tumours)

→ *BRAF 21%*
NRAS 14%
KIT 9%

→ ***TYRP1 10%***

Copy Number Profile

N=83 tumours

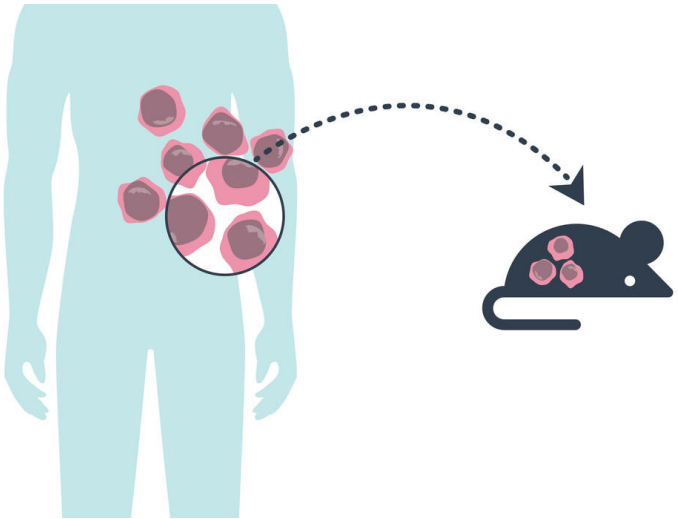


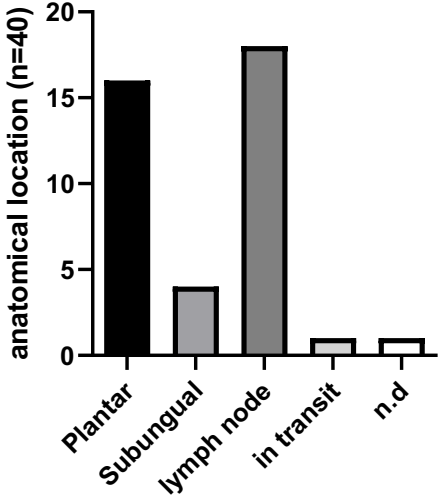
Newell F. et al. Nat Comm 2020

PDX cohort

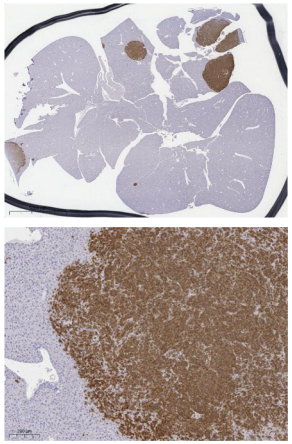
n=61 patients

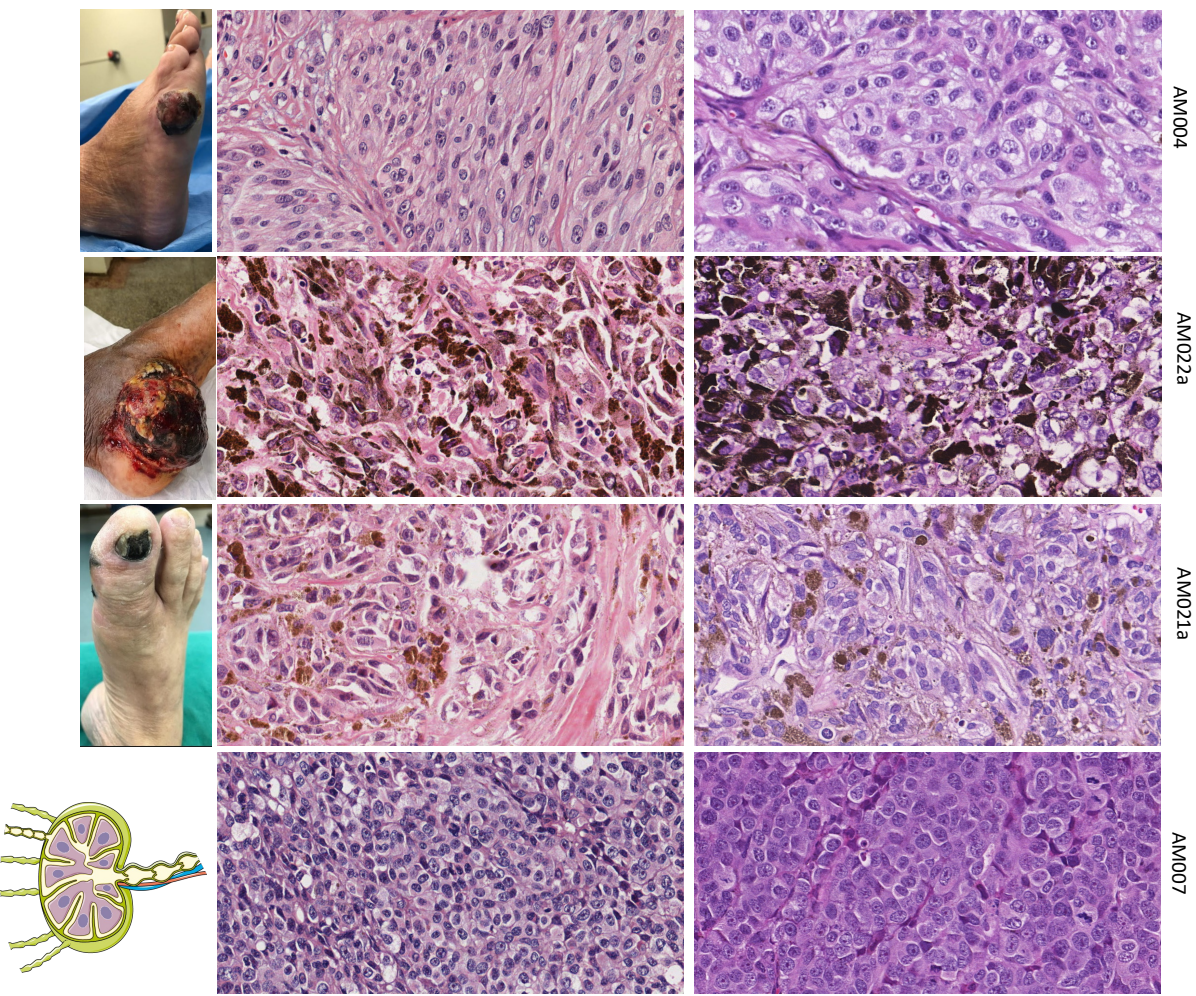
n=73 samples
66 BR + 7 MX





Melan A





CRISPR Screen

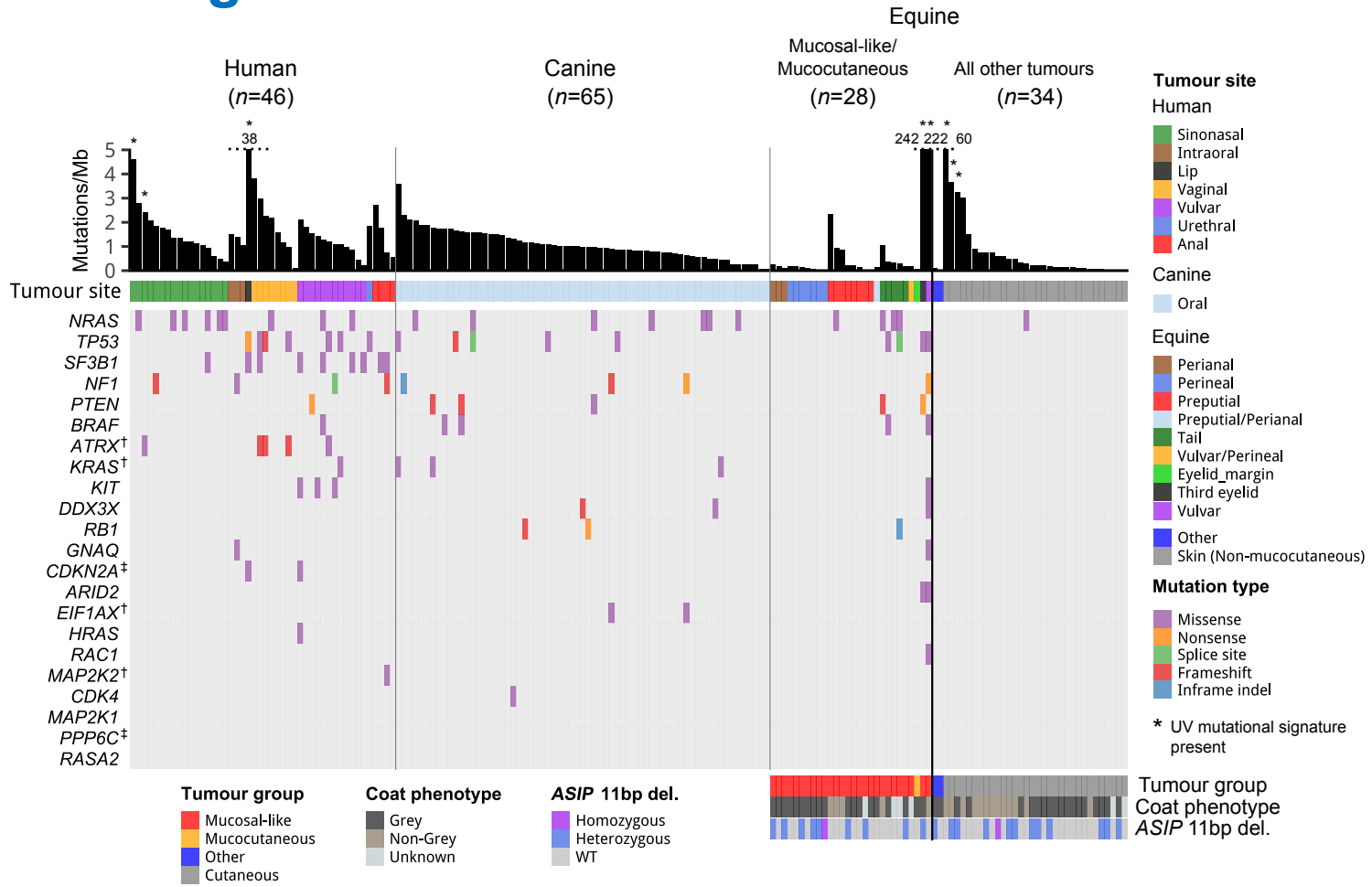
Drug Screen

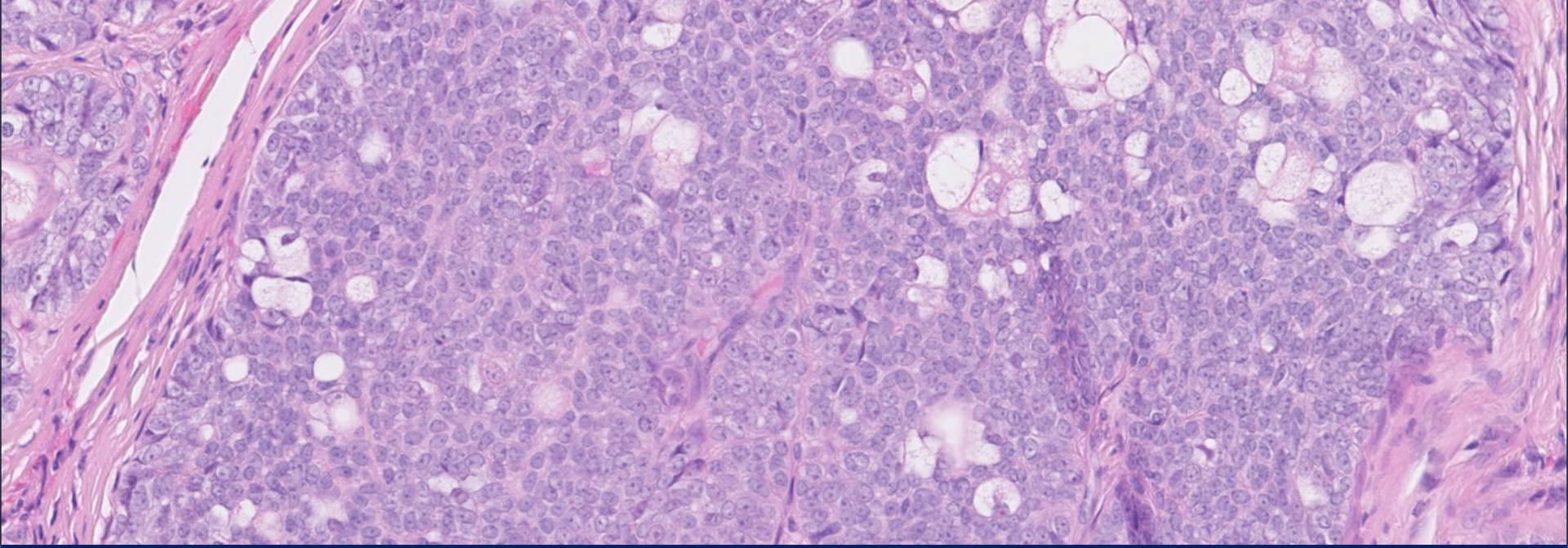
-> in vivo modelling

Mucosal melanoma

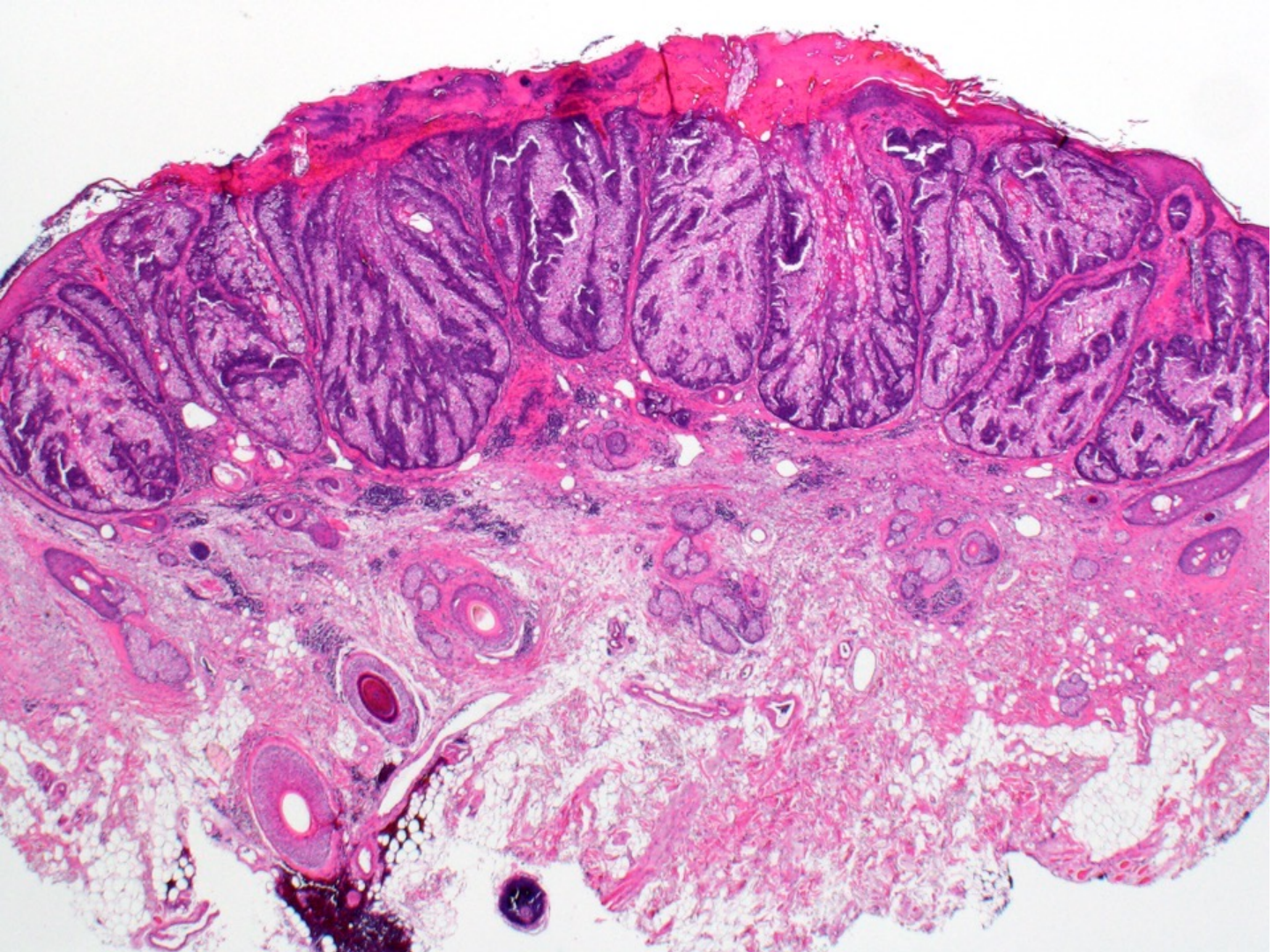
Can we use cross-species approaches to define new drivers/ explore the biology of the disease?

Comparative genomics of mucosal melanoma





Mutational landscape of sebaceous tumours

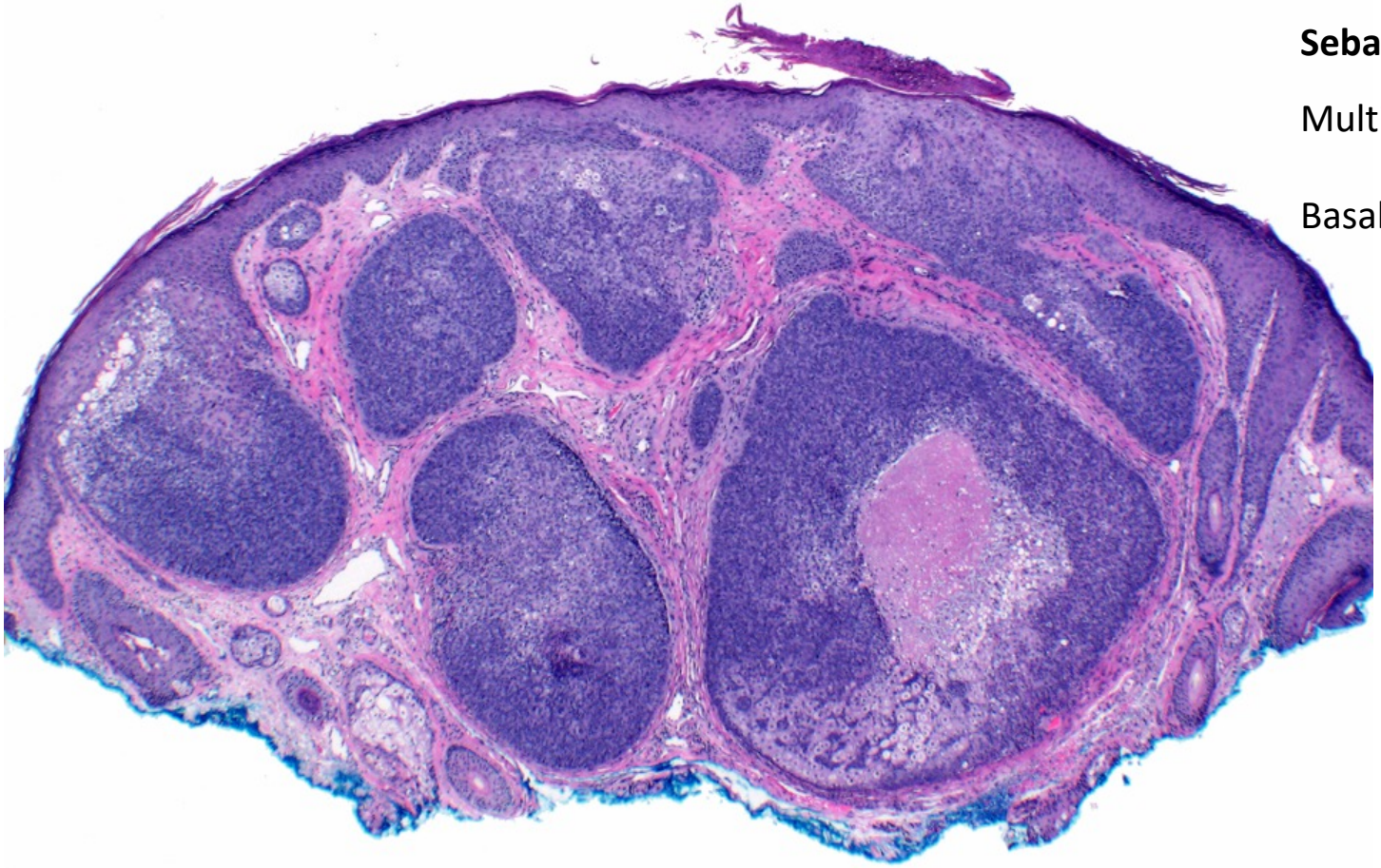


Sebaceous Adenoma

Well circumscribed, Symmetrical

Multifocal epidermal connections

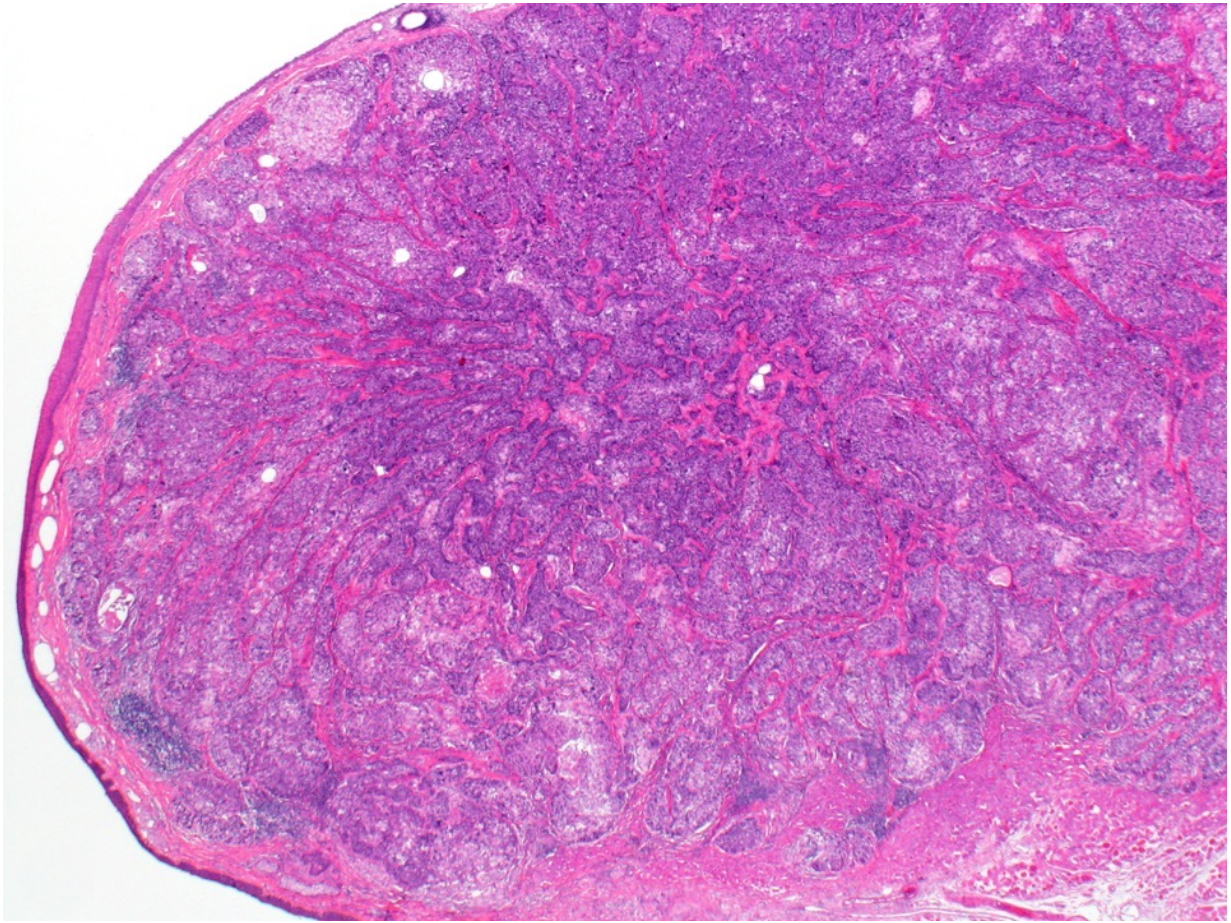
By courtesy **Dr D. Franck**



Sebaceoma

Multi-nodular

Basaloid



Sebaceous carcinoma

Extra-ocular &

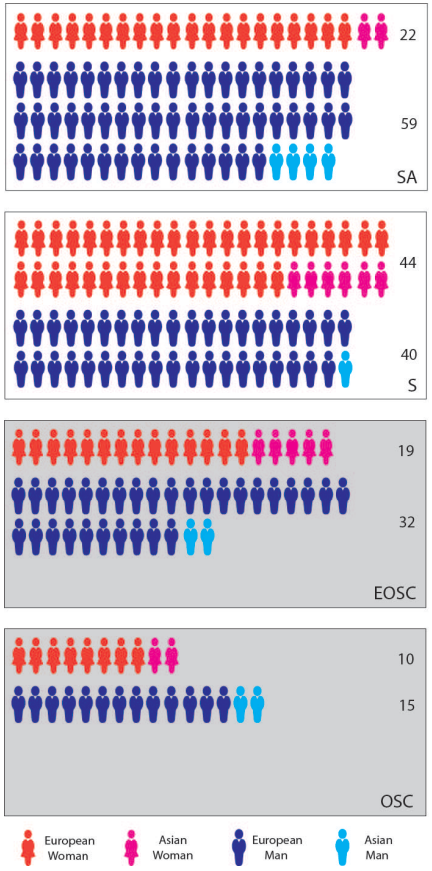
Peri-ocular.

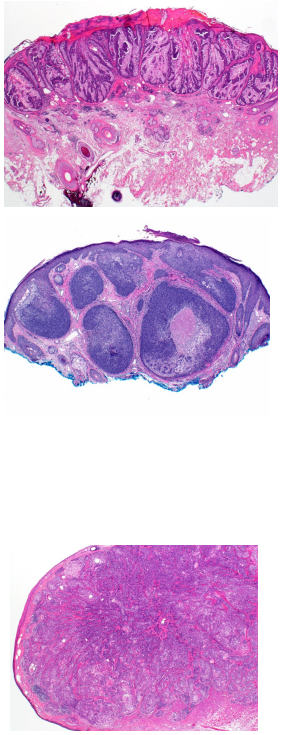
By courtesy **Dr A. Leonard**

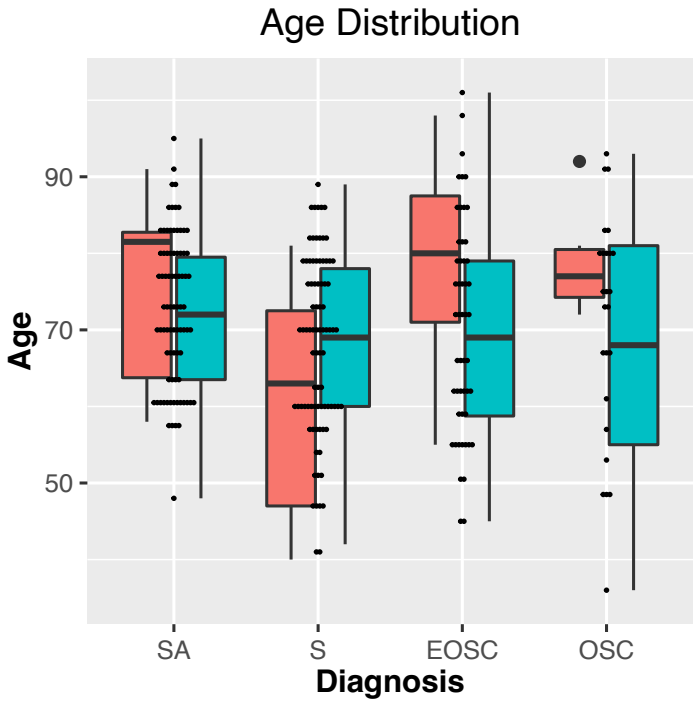
Clinical details

Benign

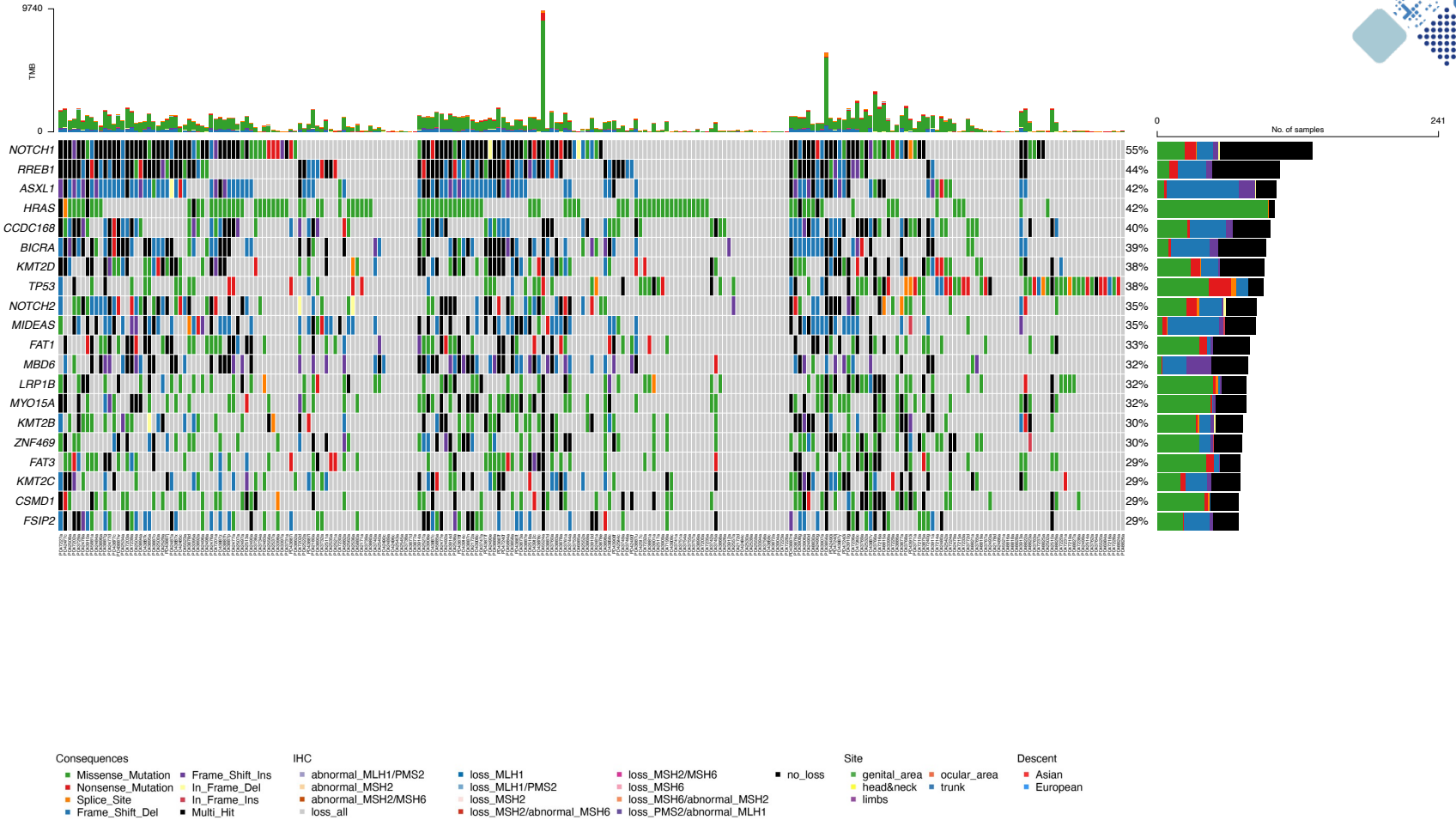
Malignant



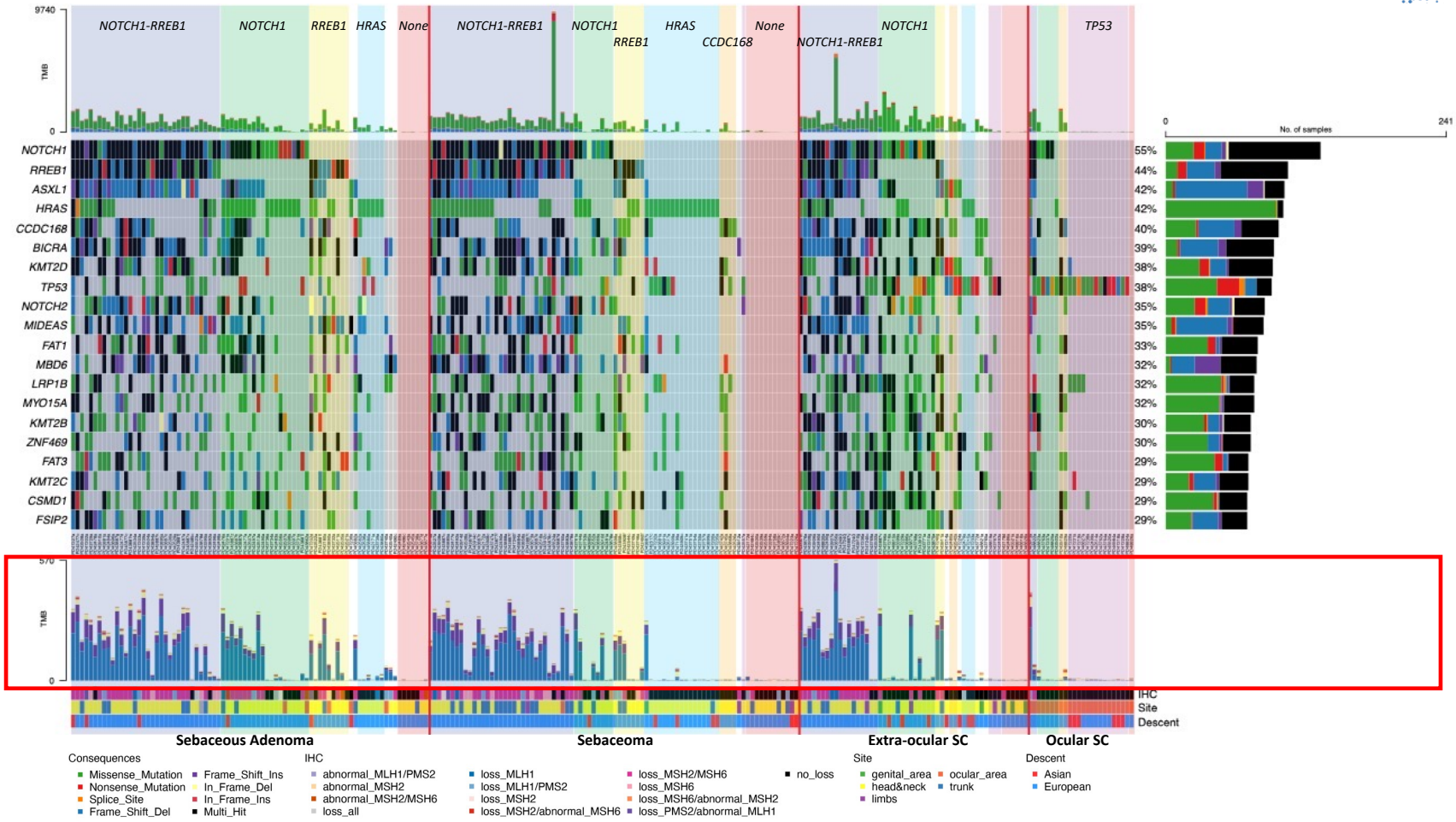




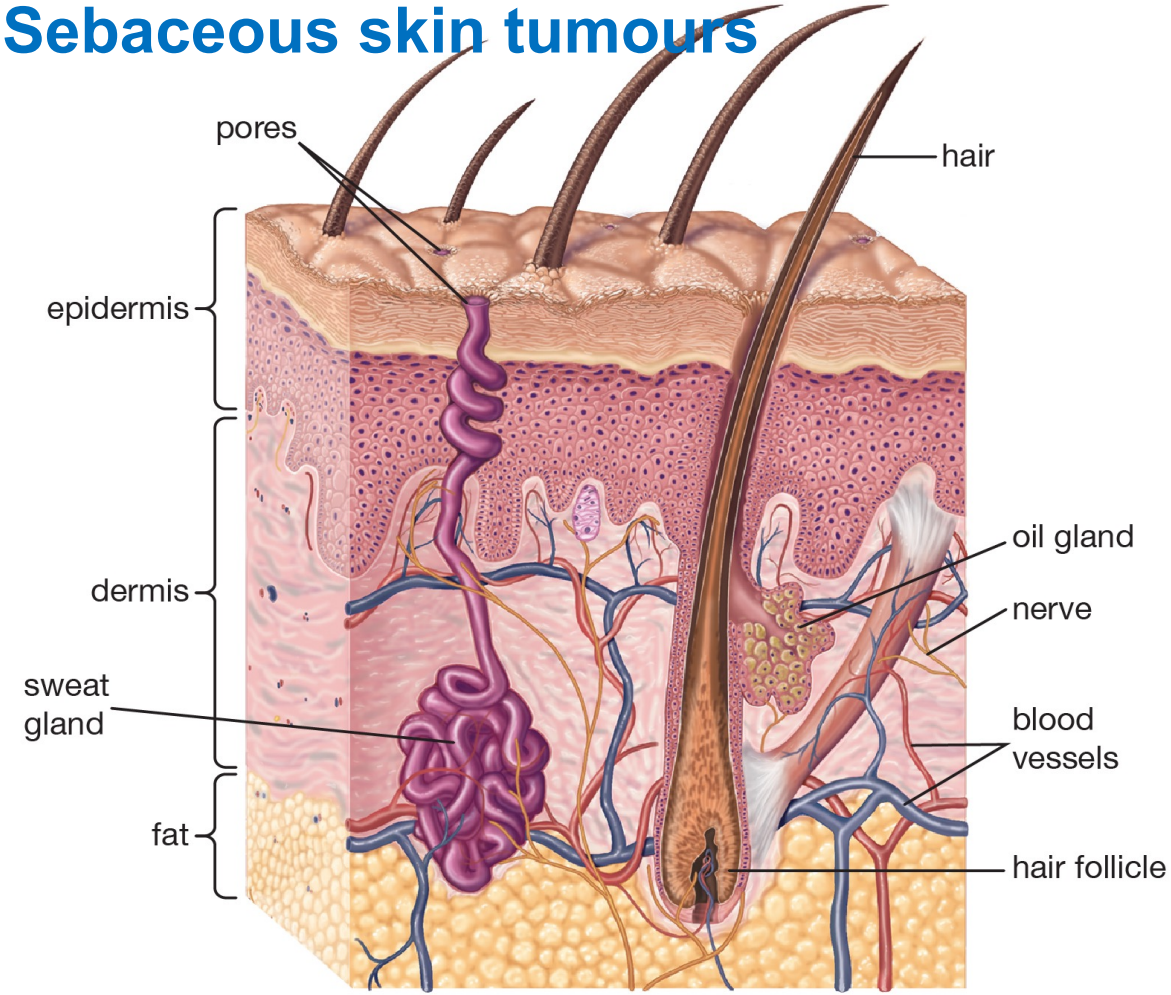
Somatic mutations



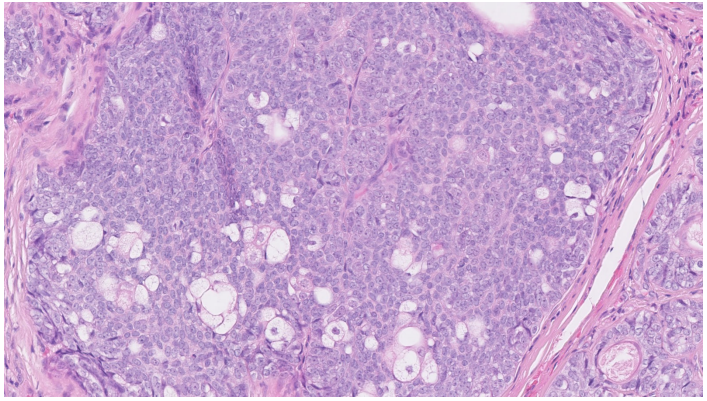
Somatic mutations

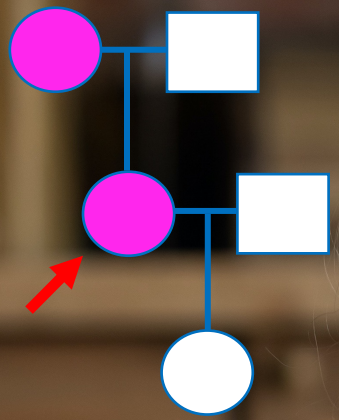


Sebaceous skin tumours



Oil gland



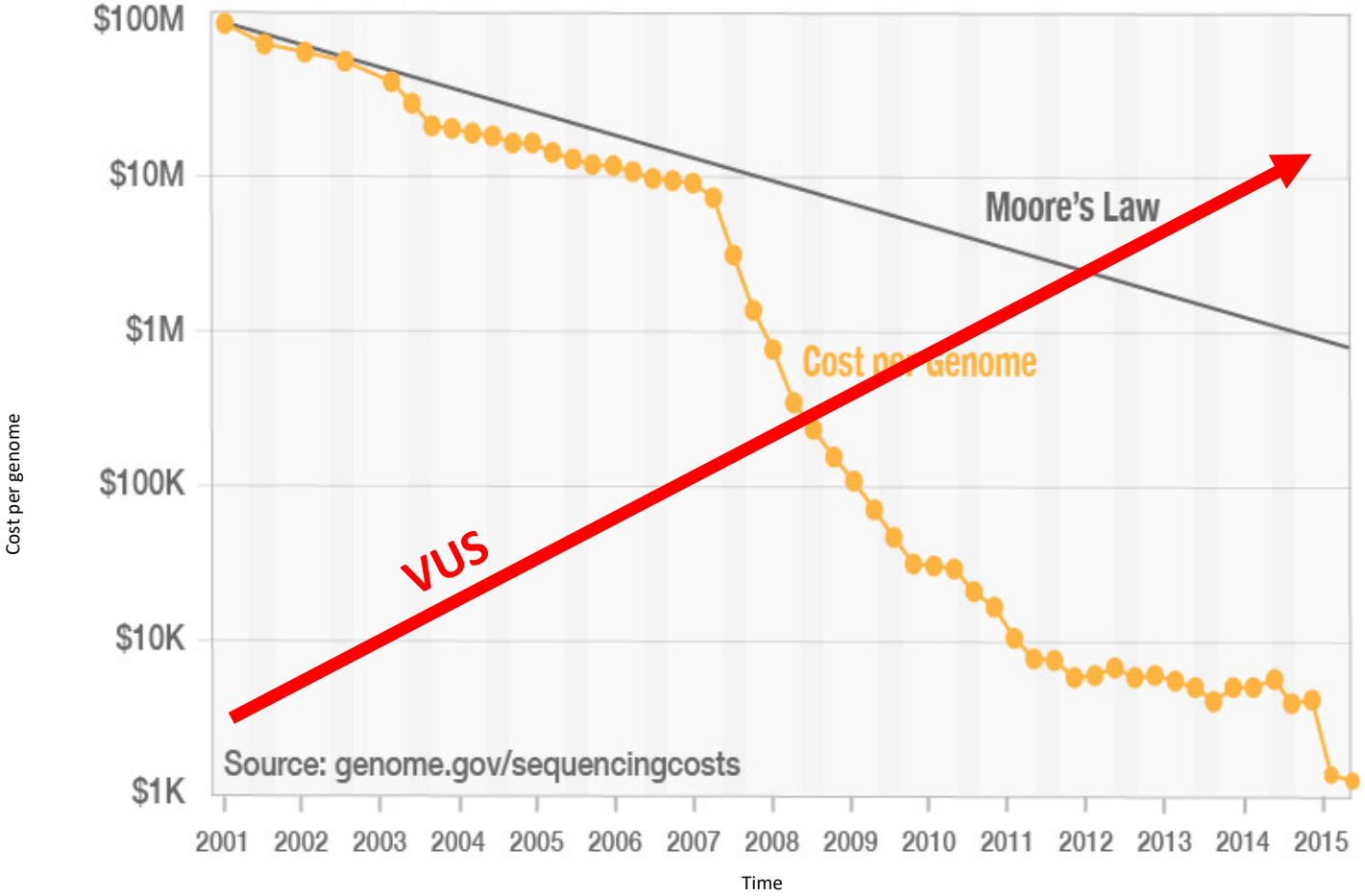


No variants in *CDKN2A*

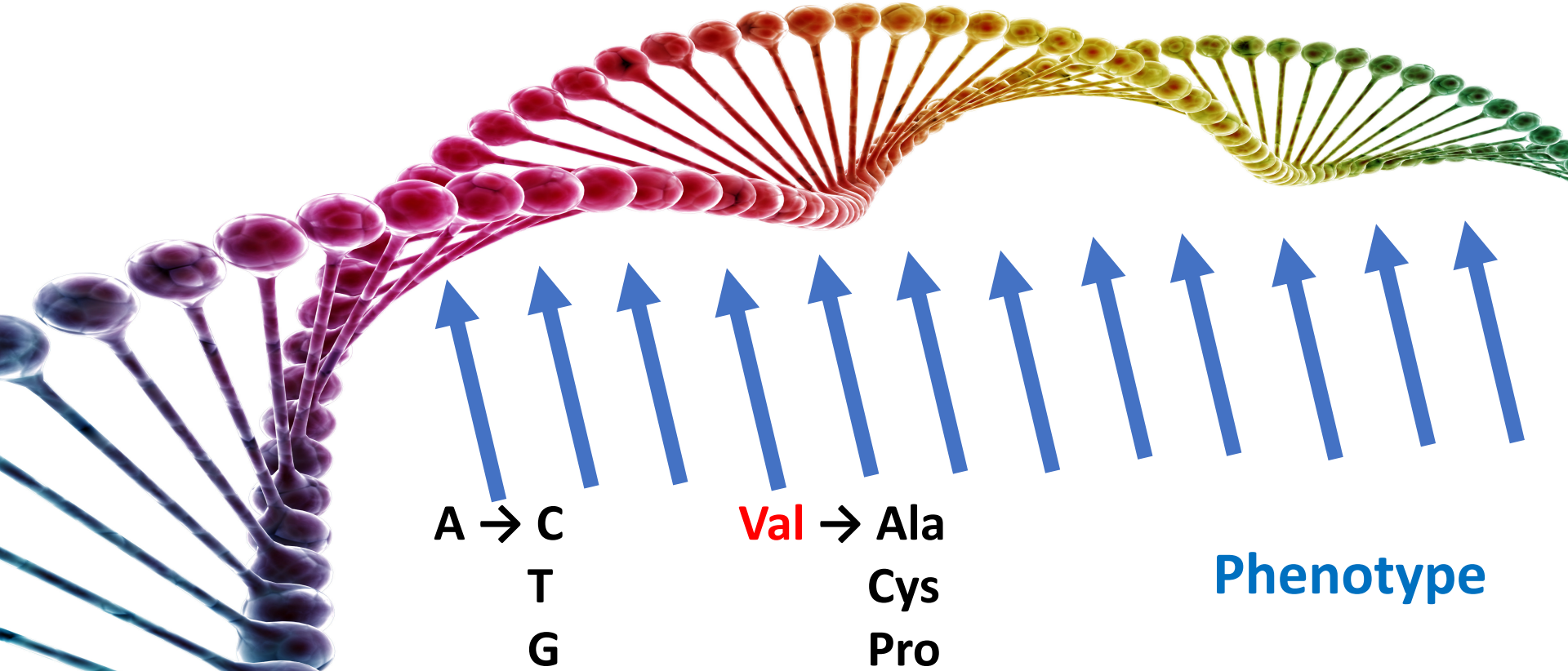
Variant of uncertain significance (VUS) in *CDK4*

How do you respond?

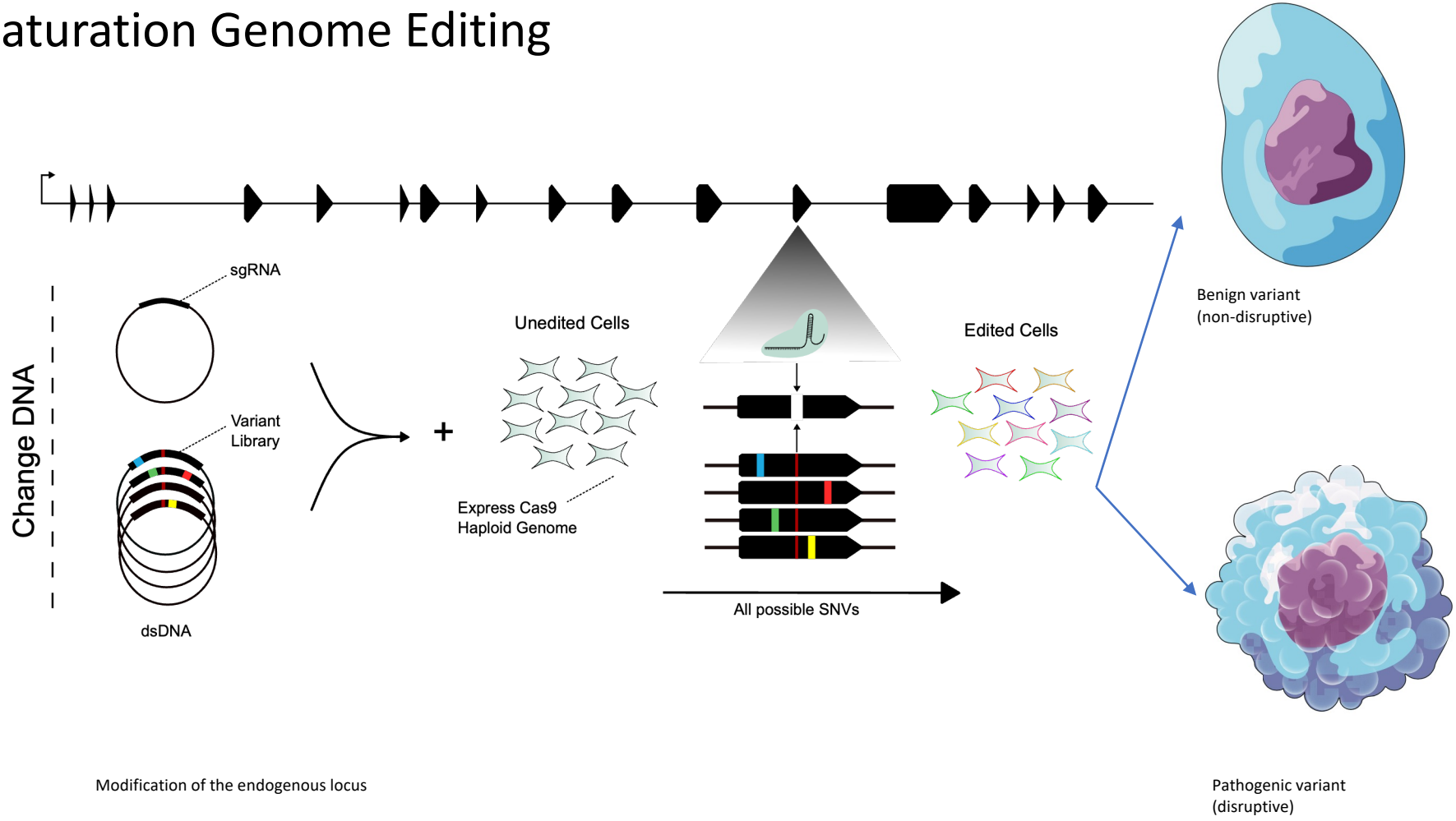
Variants of Uncertain Significance (VUS)



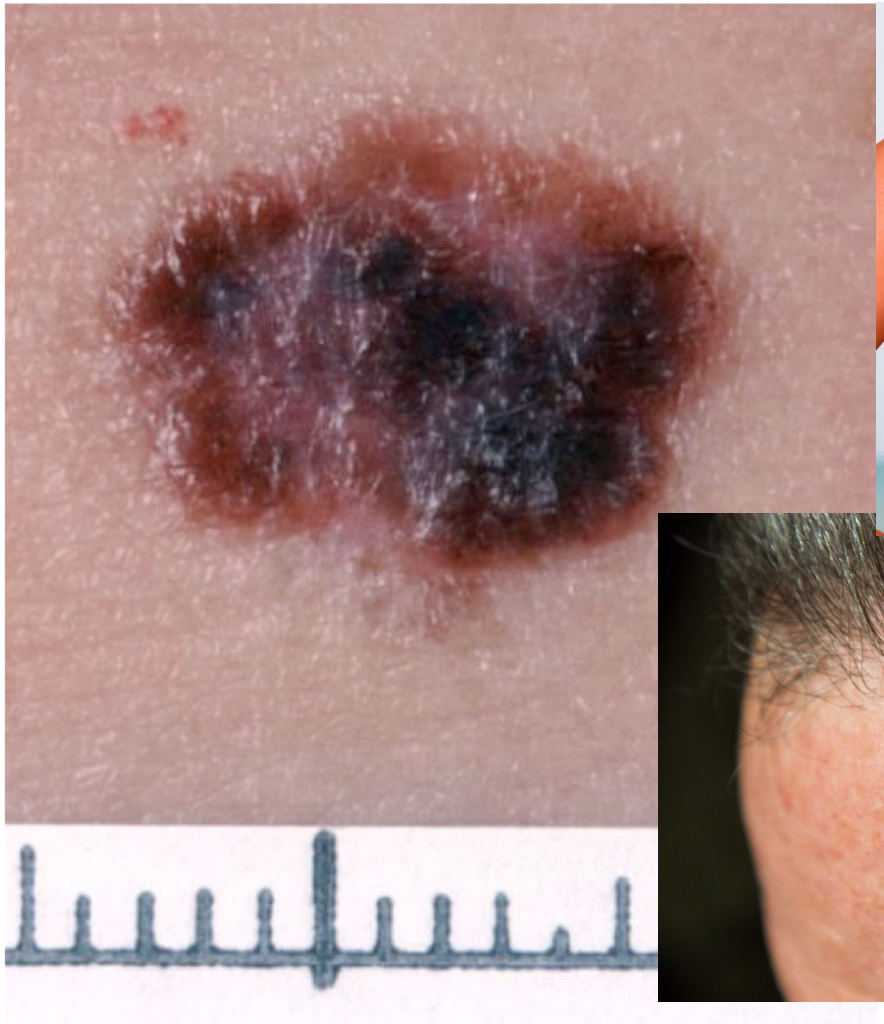
MAVE: Multiplex Assay of Variant Effect



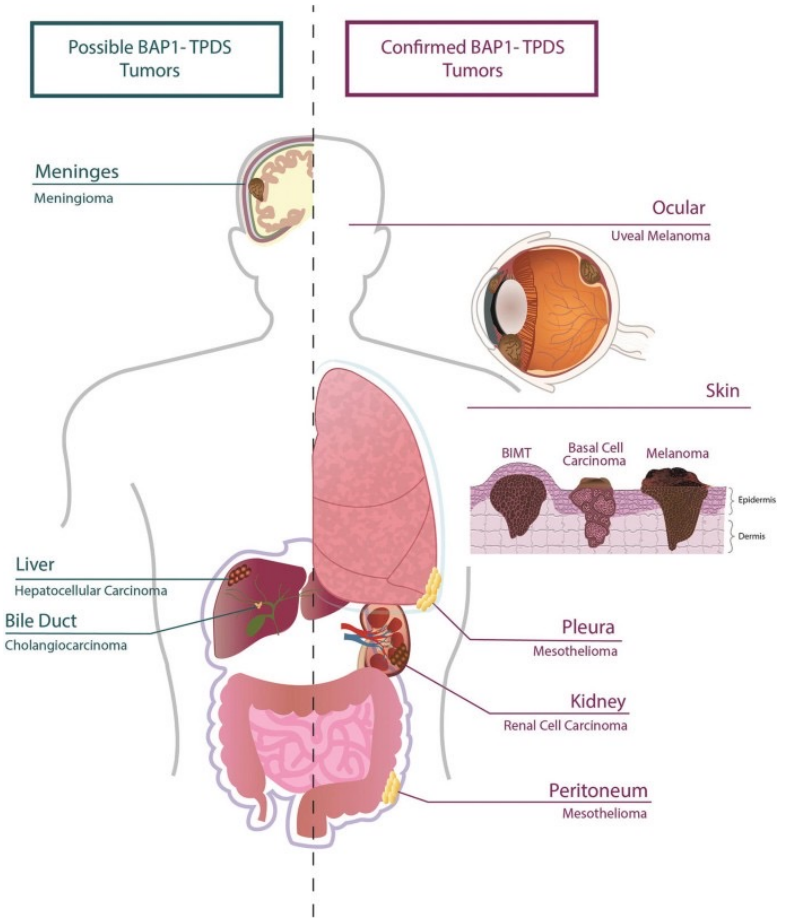
Saturation Genome Editing

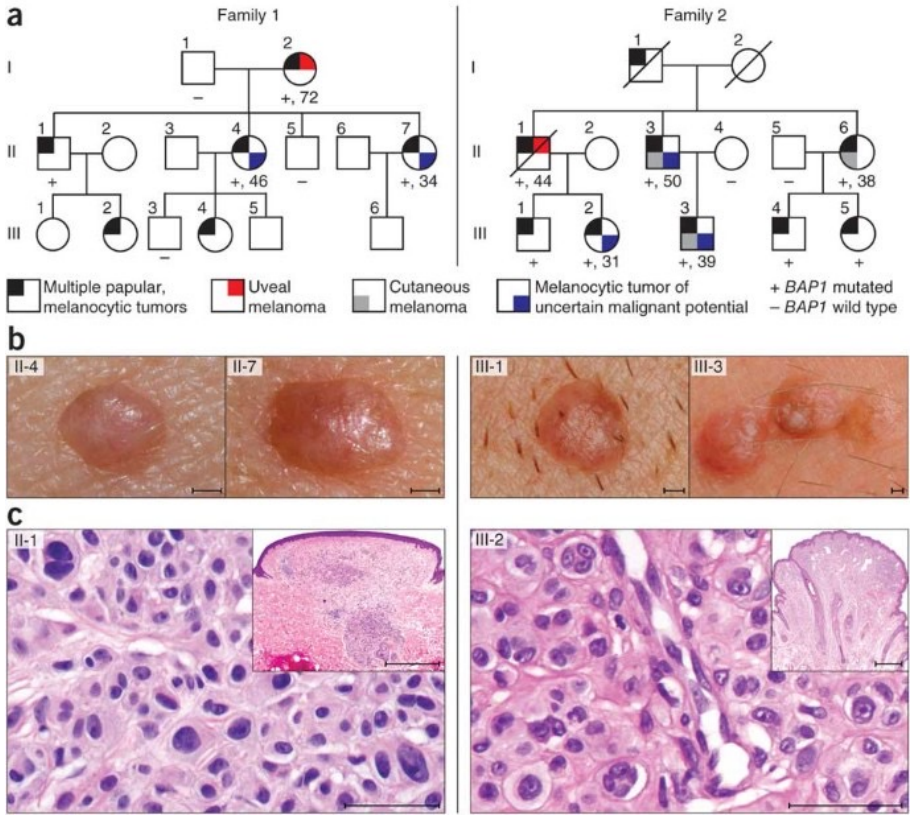


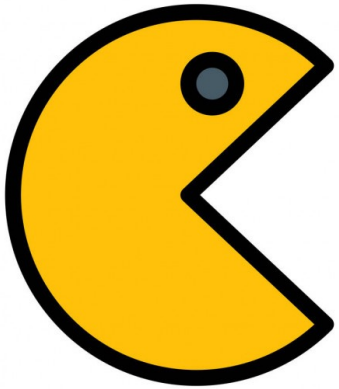
Modification of the endogenous locus



BAP1: BRCA-associated Protein-1



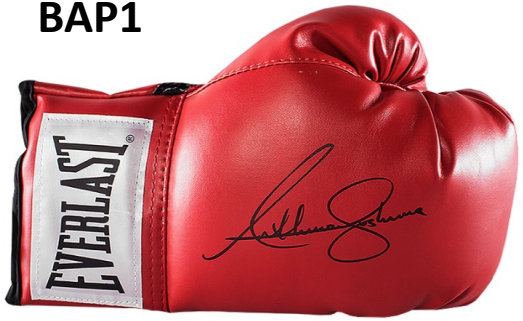


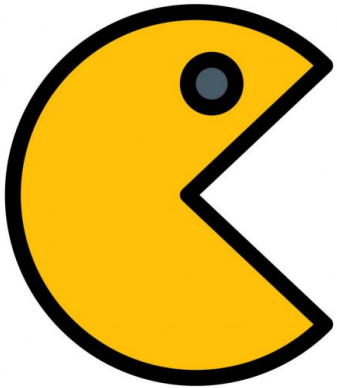


Ubiquitin

Proteins

BAP1

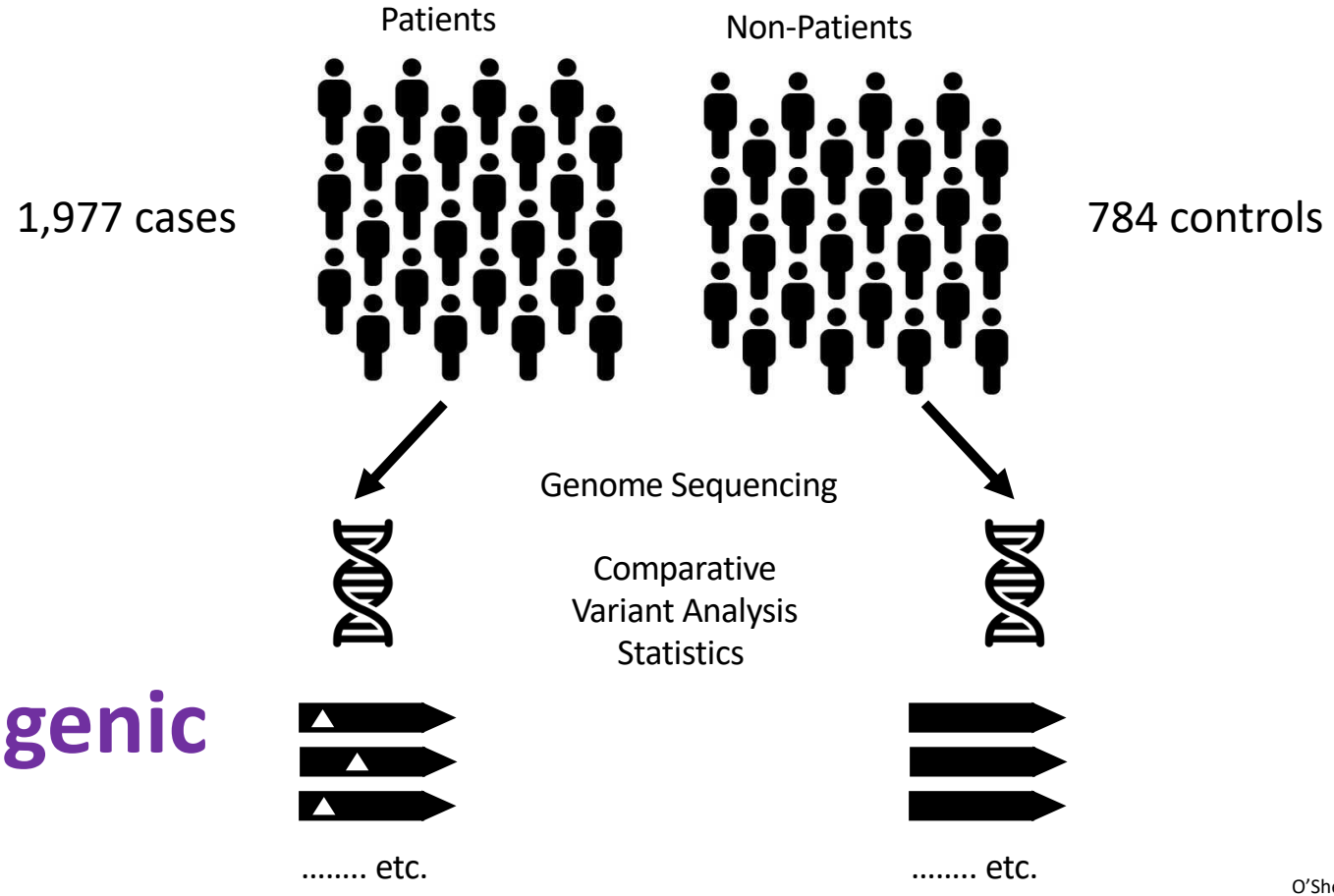




Ubiquitin

Proteins

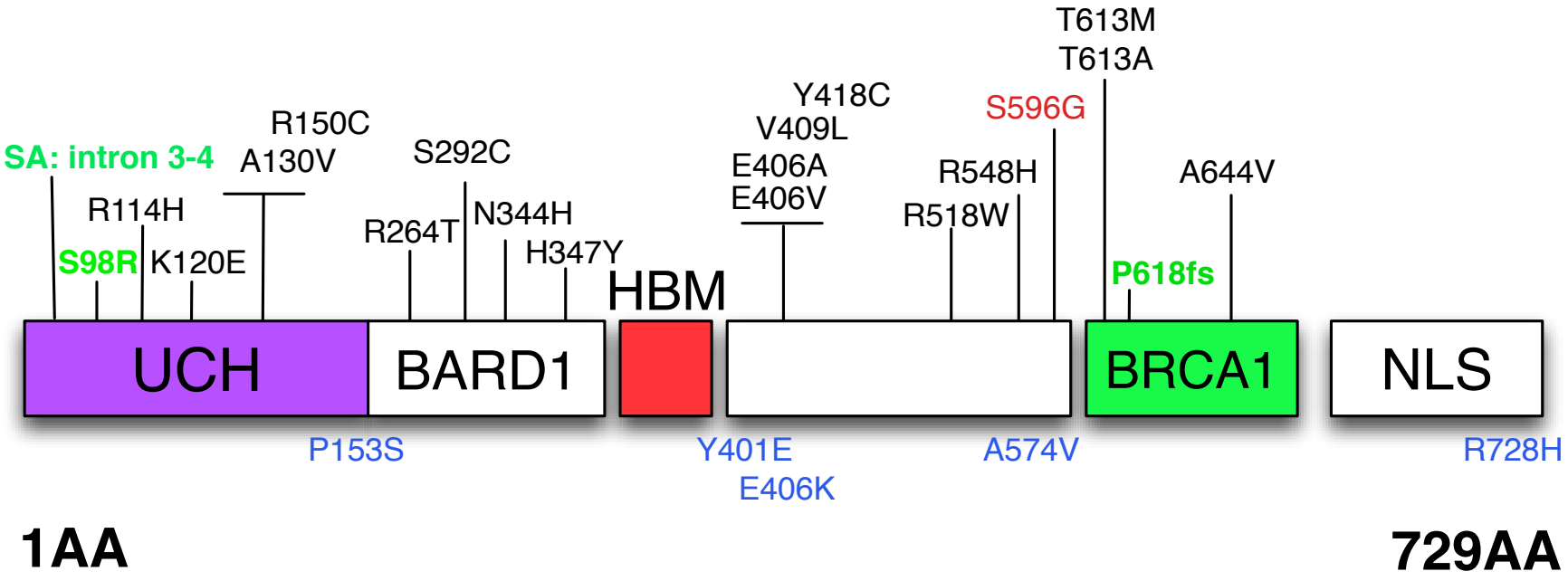
Melanoma case-control



O'Shea & Robles-Espinoza *et al.*, 2017

Analysis of *BAP1* in a population ascertained cohort

A total of 30 variants were identified



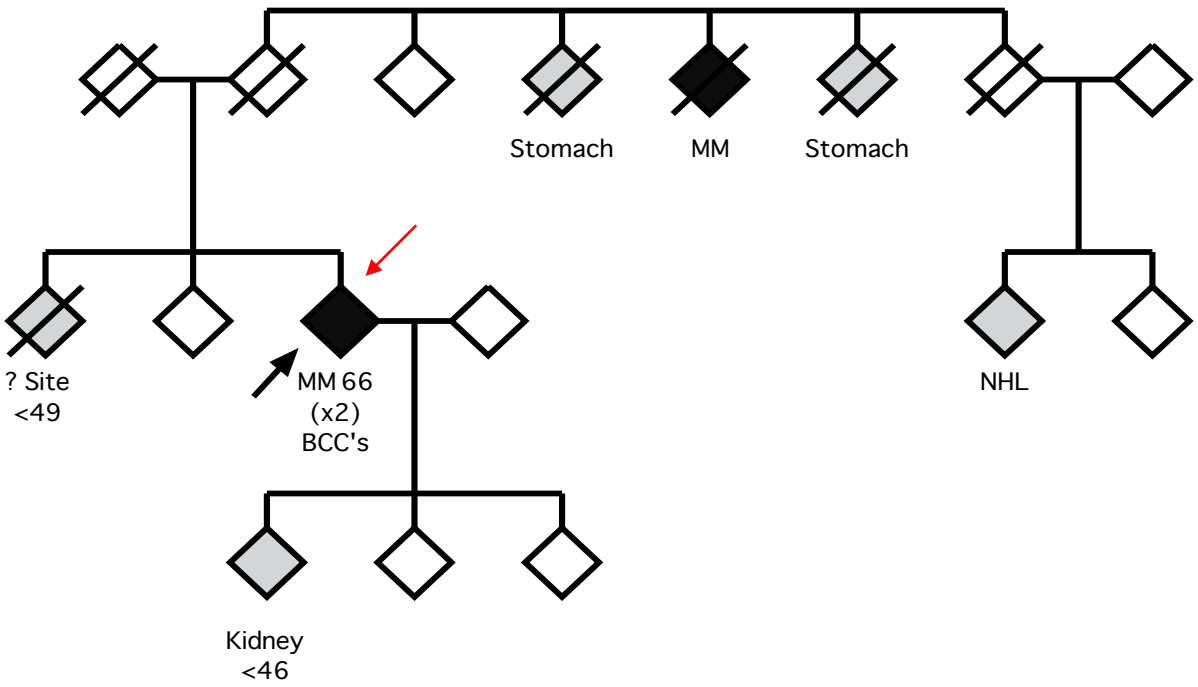
Downloaded Oct22

NIH *ClinVar*

Conflicting interpretations	69
Benign	45
Likely benign	632
Uncertain significance	868
Likely pathogenic	53
Pathogenic	173

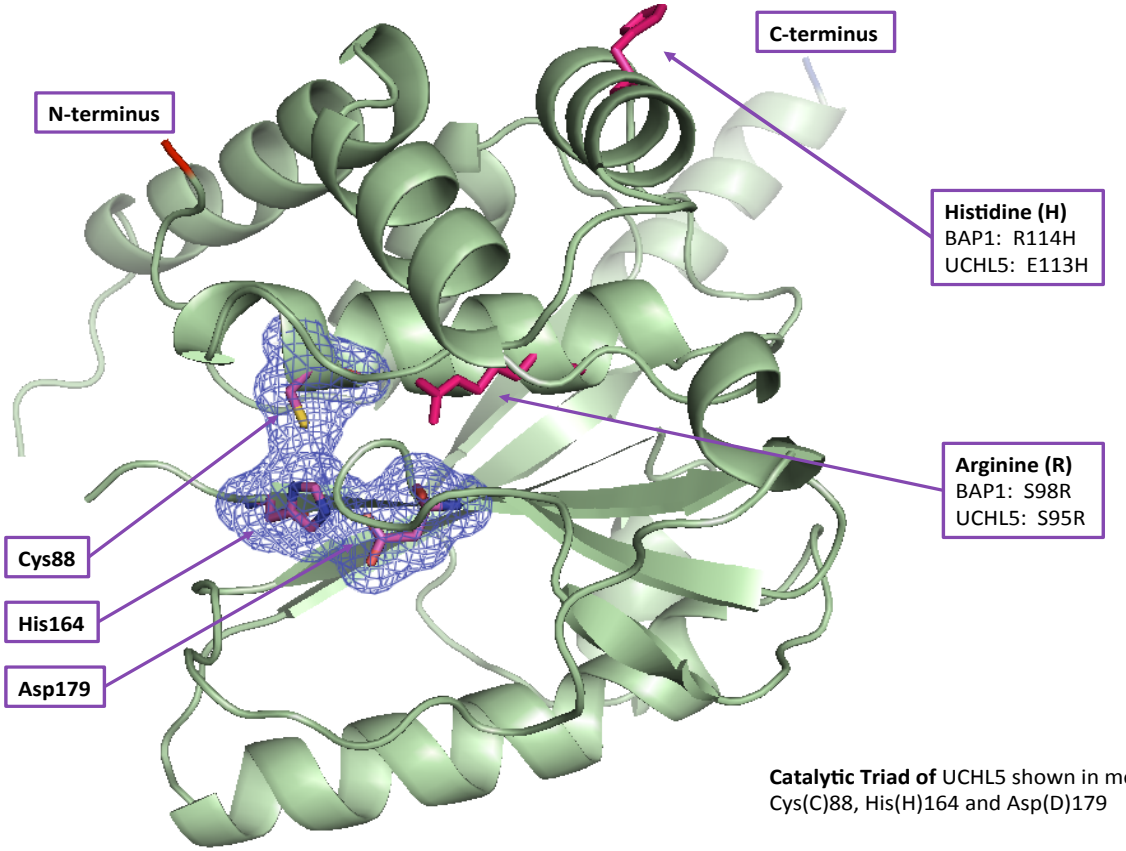
Enormous challenge for clinical management

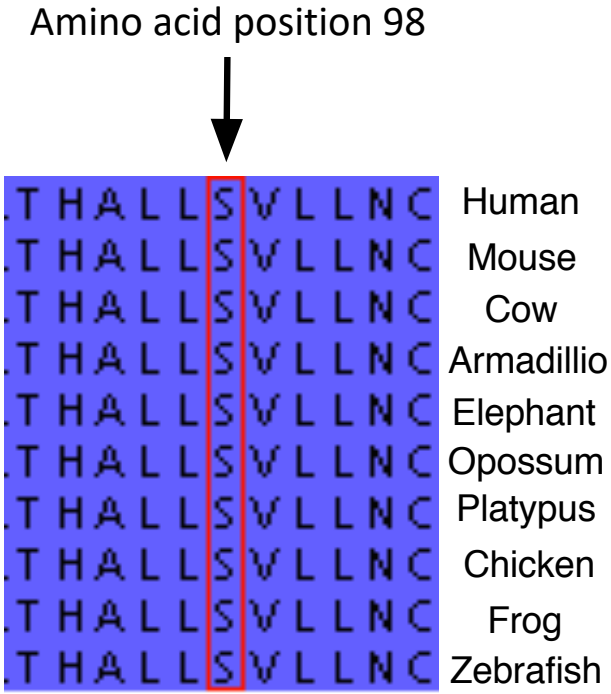
BAP1: S98R. A clinical example



Family with Serine 98 to Arginine (S98R) variant

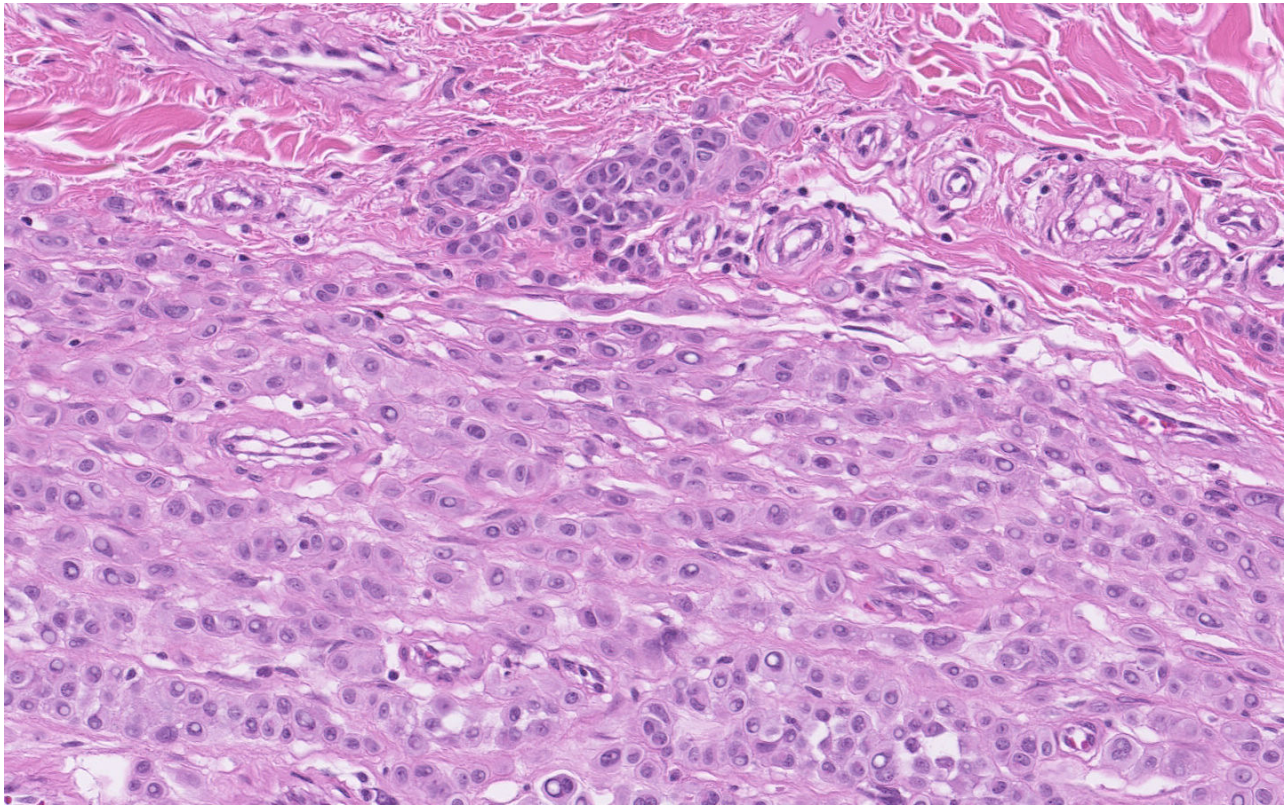
BAP1: S98R. A clinical example





Catalytic Triad of UCHL5 shown in mesh:
Cys(C)88, His(H)164 and Asp(D)179

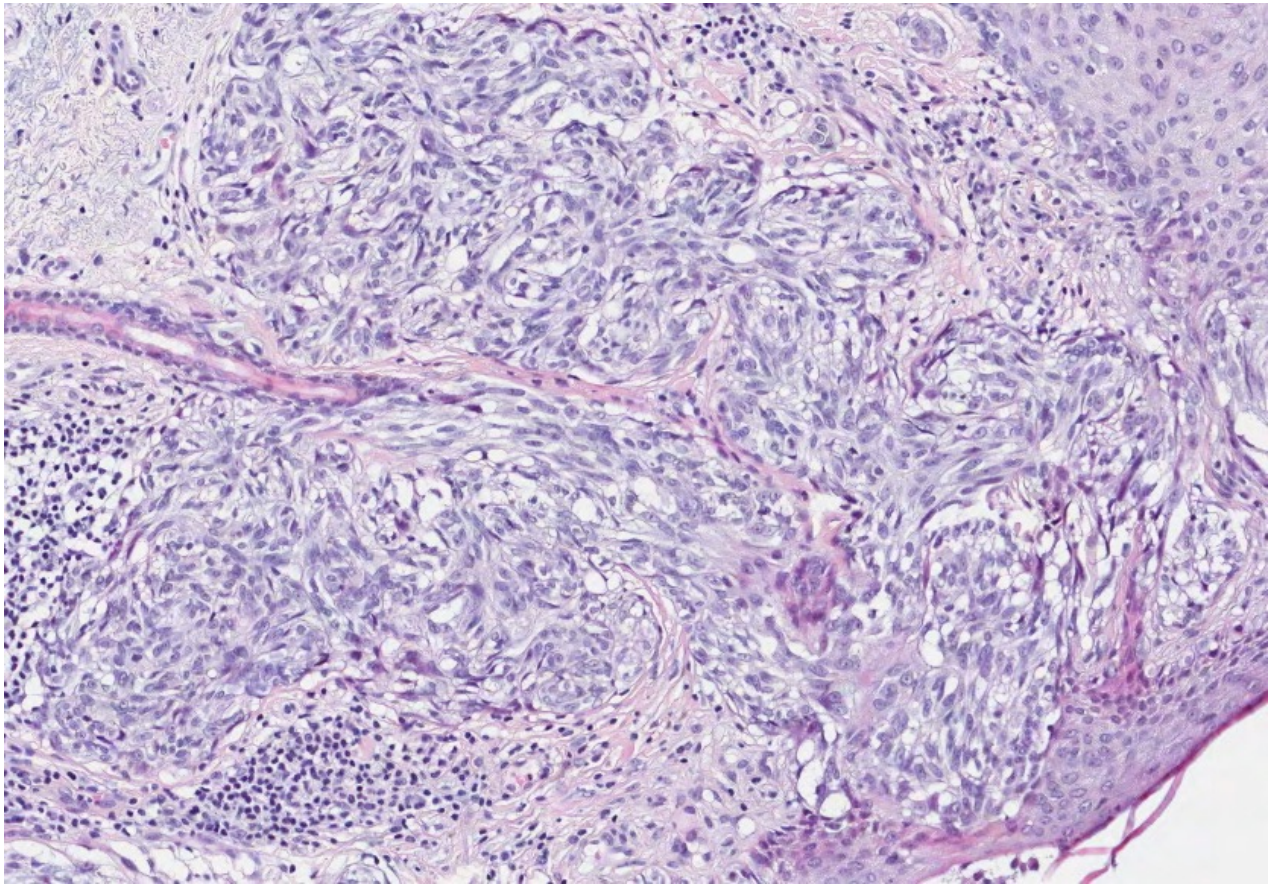
BAP1-associated histopathology



Multi-nucleated melanocytes

Intranuclear pseudoinclusions

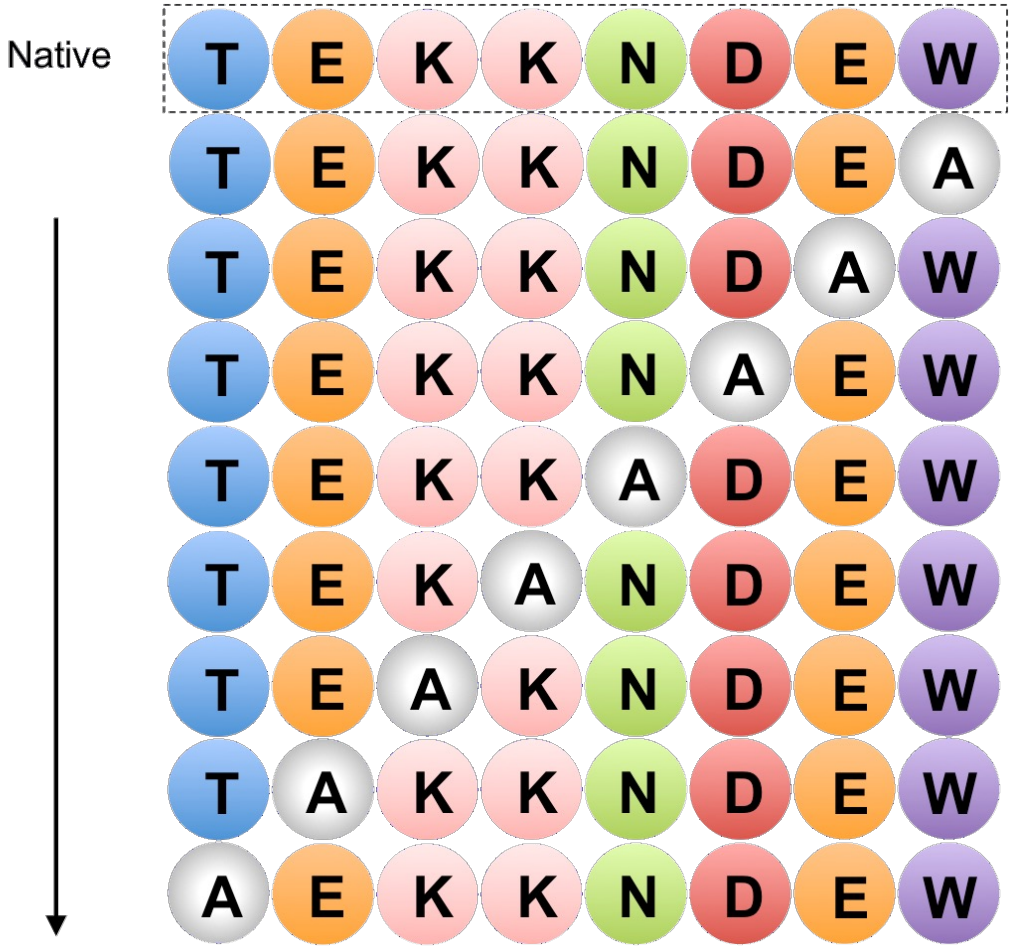
BAP1: S98R. A clinical example



No:
Multi-nucleated melanocytes

No:
Intranuclear pseudoinclusions

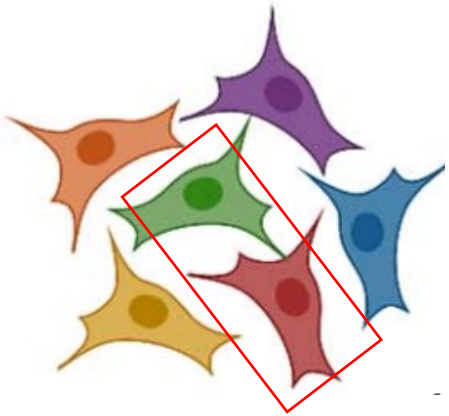
Function base-by-base



Results

SGE of *BAP1*

Day 4

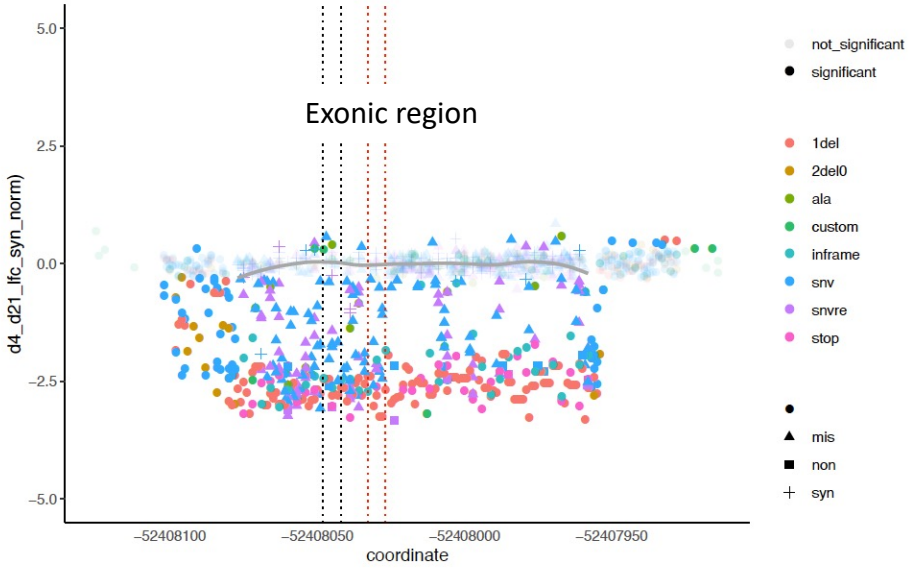


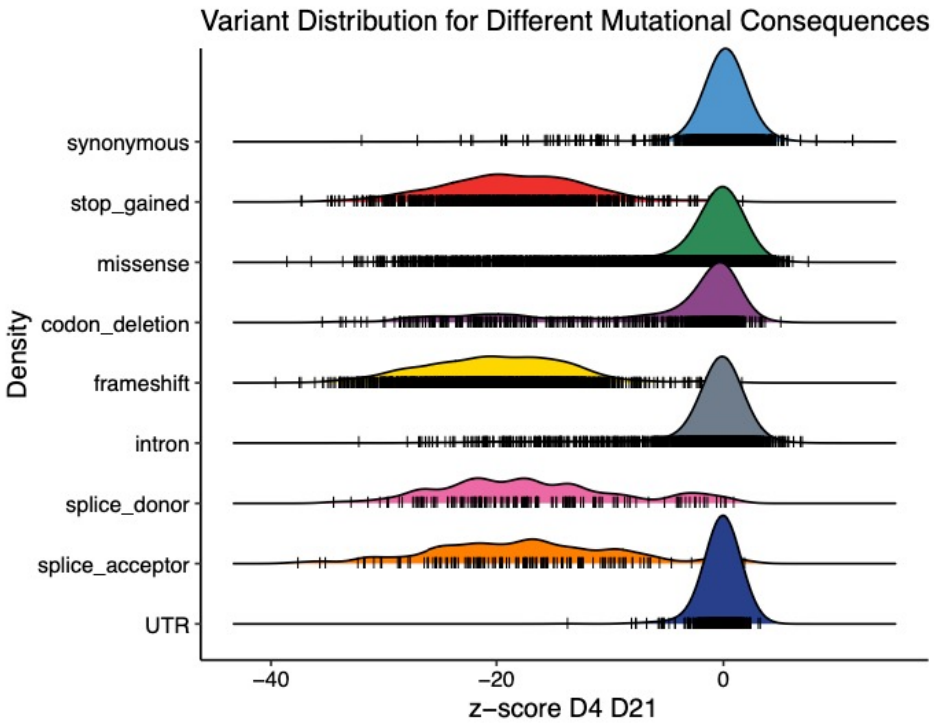
Benign

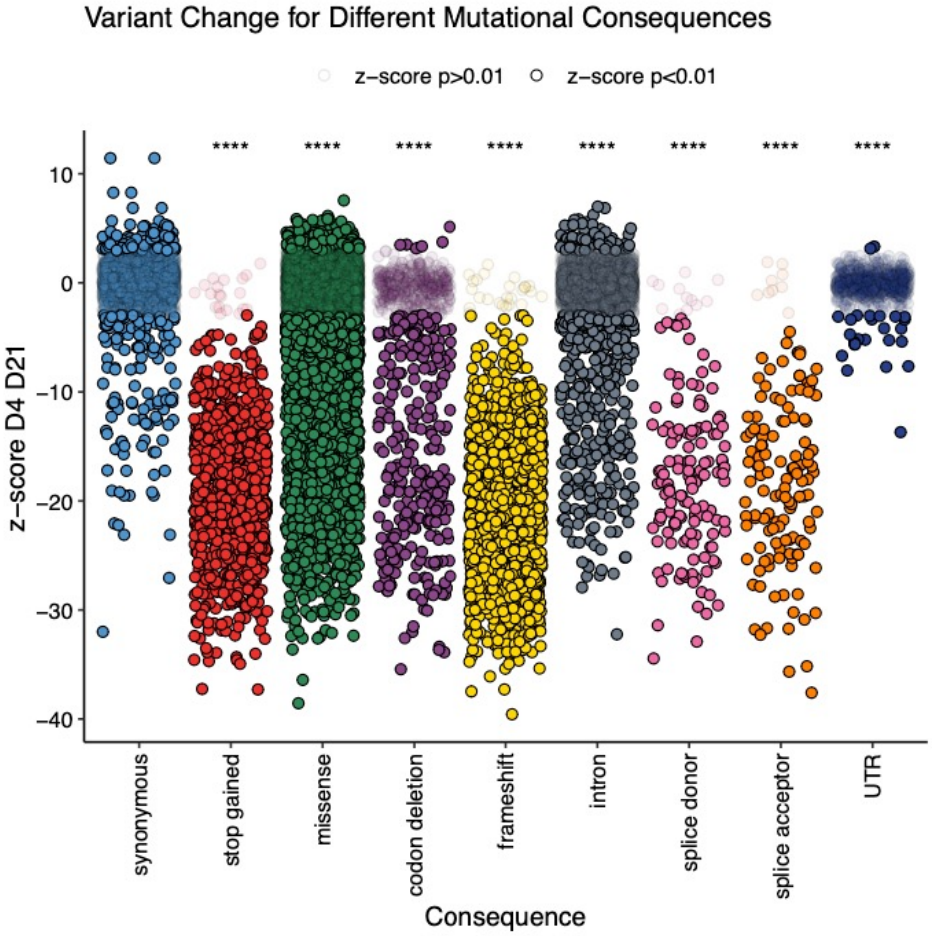
Disruptive

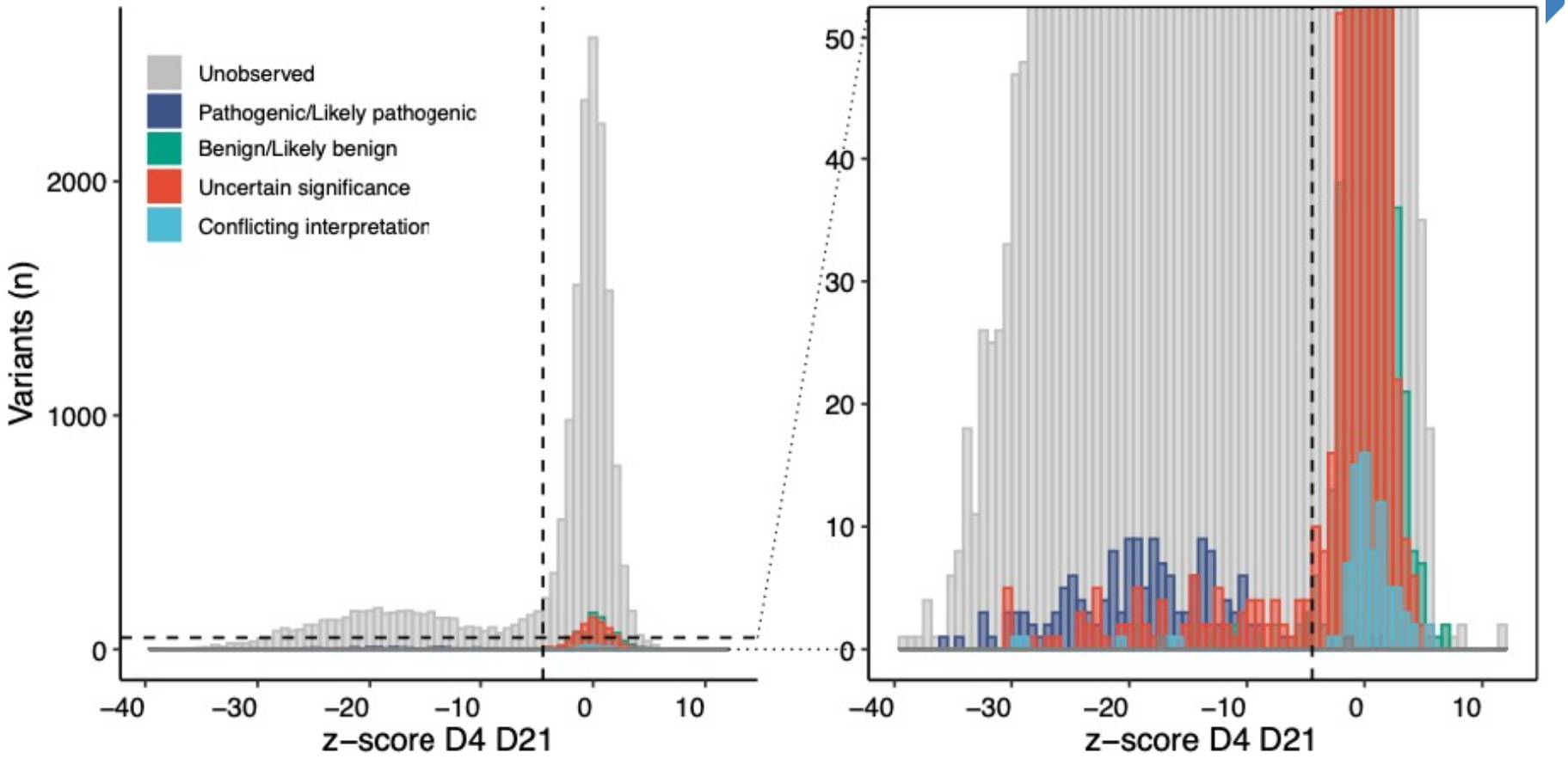
Day 21

Variant change between Day 4 and Day 21



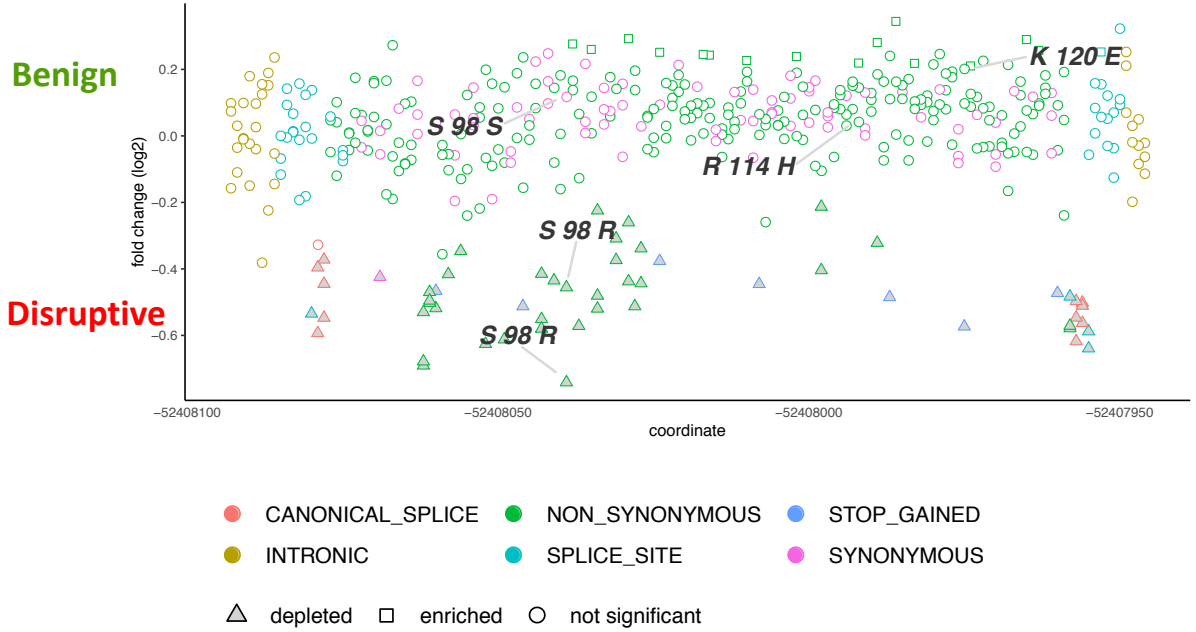

Variant Distribution for Different Mutational Consequences
synonymous
stop_gained
missense
codon_deletion
frameshift
intron
splice_donor
splice_acceptor
UTR
Density
−40
−20
0
z−score D4 D21

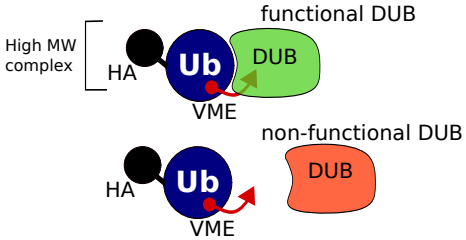

Variant Change for Different Mutational Consequences
z−score p>0.01
z−score p<0.01
****
10
0
−10
−20
−30
−40
z−score D4 D21
synonymous
stop gained
missense
codon deletion
frameshift
intron
splice donor
splice acceptor
UTR
Consequence

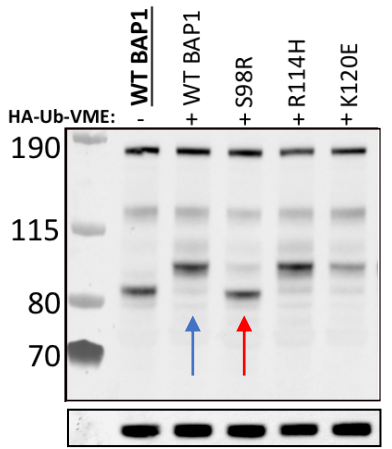

Unobserved
Pathogenic/Likely pathogenic
Benign/Likely benign
Uncertain significance
Conflicting interpretation
Variants (n)
2000
1000
0
−40
−30
−20
−10
0
10
z−score D4 D21
50
40
30
20
10
0
−40
−30
−20
−10
0
10
z−score D4 D21

BAP1: A clinical example

S98R is depleted in SGE assay, consistent with HA-Ub-VME assay







- AGC[S98]> AGA[R] & AGC[S98]> AGG[R] show strong depletion – concordant missense change
- synonymous change of AGC[S98] > AGT[S] does not deplete significantly

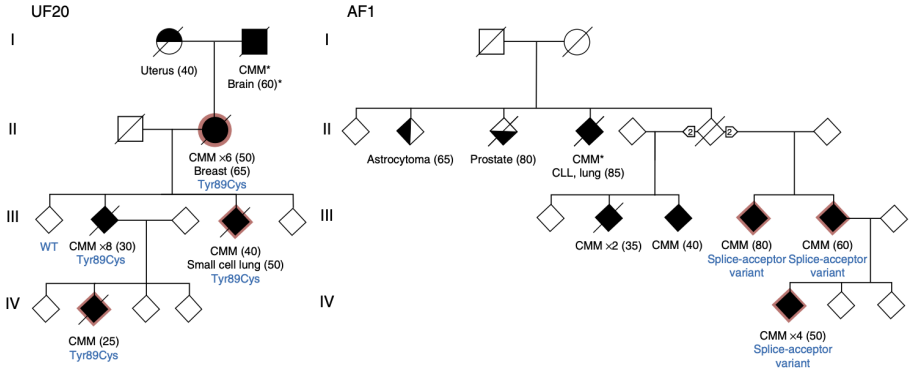
BAP1 enzyme activity (HA-Ub-VME) seems directly linked to viability (SGE assay)

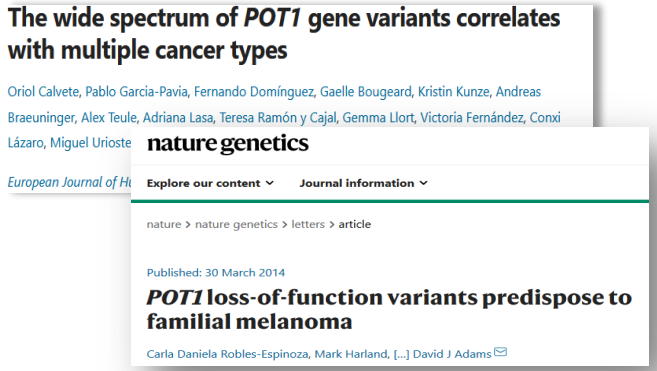
Familial melanoma

- 10-15% (1 in 20 patients) of all melanoma patients have familial melanoma

- Melanoma predisposition genes
  - <10 **predisposition genes** known
  - Patients & relatives at risk may lack indication for genetic counselling

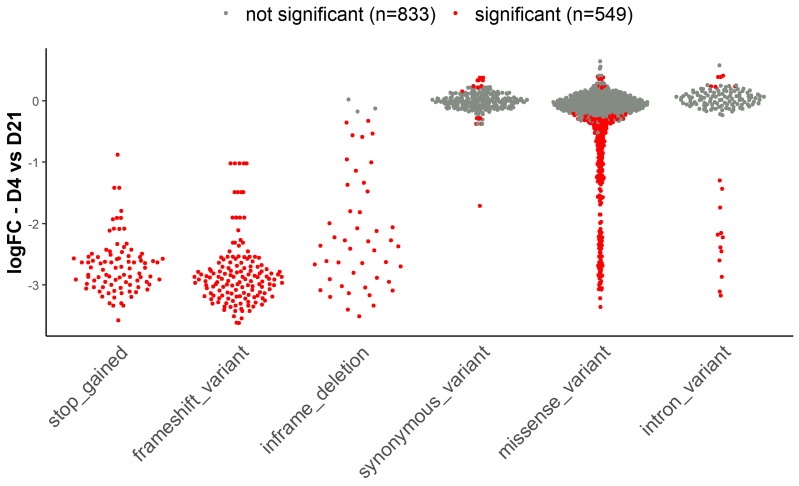
- ***POT1***-associated germline mutations → increased risk for familial melanoma

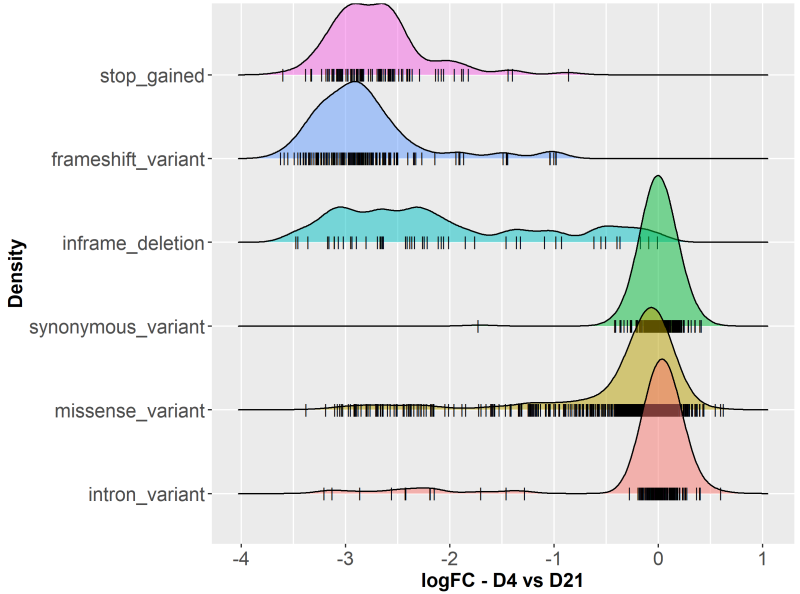




Potrony, M. *et.al.* (2015) Ann Transl Med.
Wong, K. *et al.* (2019) JAMA dermatology.
Image: Rogers, H.W. *et al.* (2006) Arch

SGE - Dropout of different variant types





SGE Data Exon 4 (OB2 domain) – Change in cell death day 4 vs day 21

Published: 30 March 2014

***POT1* loss-of-function variants predispose to familial melanoma**

Carla Daniela Robles-Espinoza, Mark Harland, ... David J Adams + Show authors

Nature Genetics **46**, 478–481 (2014) | Cite this article

Investigation of conformational dynamics of Tyr89Cys mutation in protection of telomeres 1 gene associated with familial melanoma

Mohd. Amir, Shahzaib Ahamad, Taj Mohammad, Deeba Shamim Jairajpuri, Gulam Mustafa Hasan, Ravins Dohare, Asimul Islam, Faizan Ahmad & Md. Imtaiyaz Hassan ...show less

Pages 35-44 | Received 22 Nov 2019, Accepted 05 Dec 2019, Accepted author version posted online: 17 Dec 2019, Published online: 27 Dec 2019

Research Articles

Impact of Gln94Glu mutation on the structure and function of protection of telomere 1, a cause of cutaneous familial melanoma

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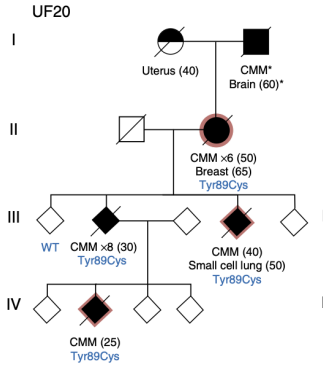

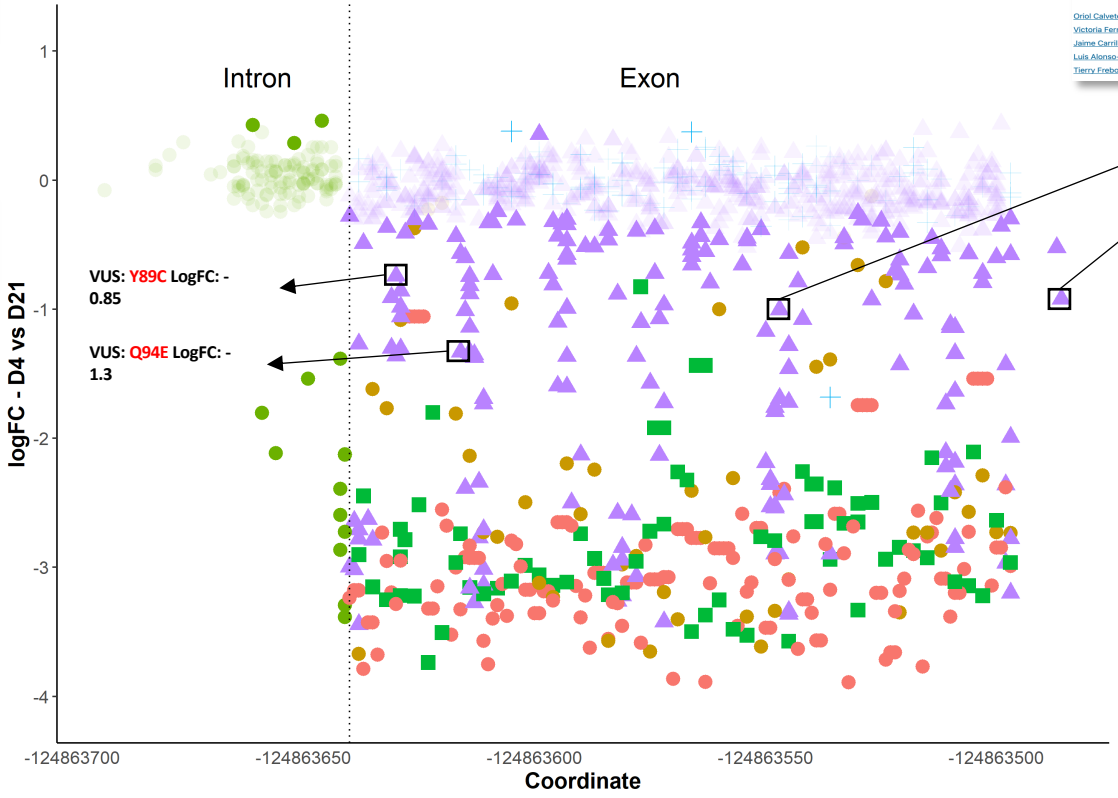

Open Access | Published: 25 September 2015

A mutation in the *POT1* gene is responsible for cardiac angiosarcoma in *TP53*-negative Li–Fraumeni-like families

Oriol Calvete, Paula Martinez, Pablo Garcia-Pavia, Carlos Benitez-Buelga, Beatriz Paumard-Hernández, Victoria Fernandez, Fernando Dominguez, Clara Salas, Nuria Romero-Laorden, Jesus Garcia-Donas, Jaime Carrillo, Rosario Perona, Juan Carlos Triviño, Raquel Andrés, Juana María Cano, Bárbara Rivera, Luis Alonso-Pulpon, Fernando Setien, Manel Esteller, Sandra Rodriguez-Perales, Gaelle Bougeard, Tierry Frebourg, Miguel Urioste & Maria A. Blasco & Javier Benitez

Leiden University Medical Center

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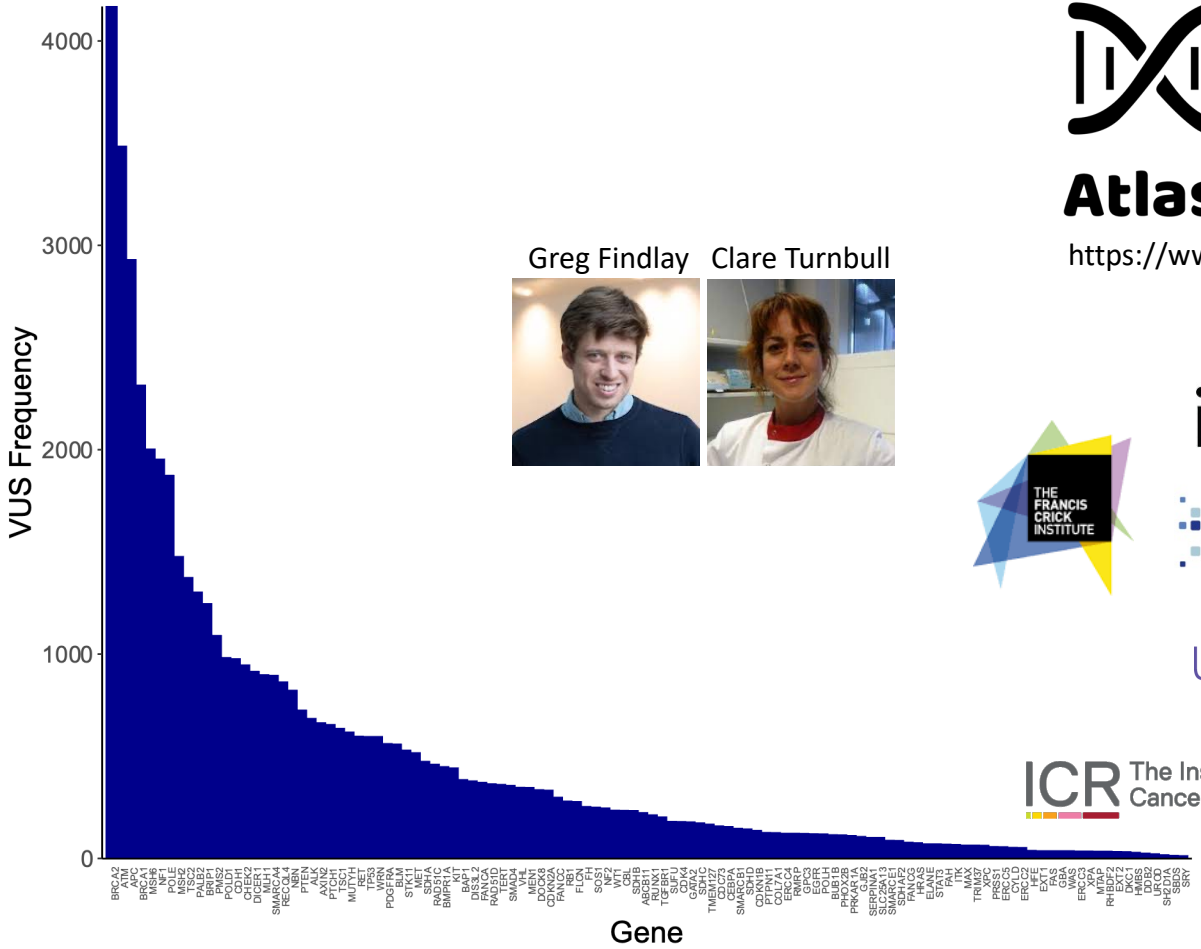
The VUS problem across cancer predisposition genes



Greg Findlay Clare Turnbull

Atlas of Variant Effects

https://www.varianteffect.org/

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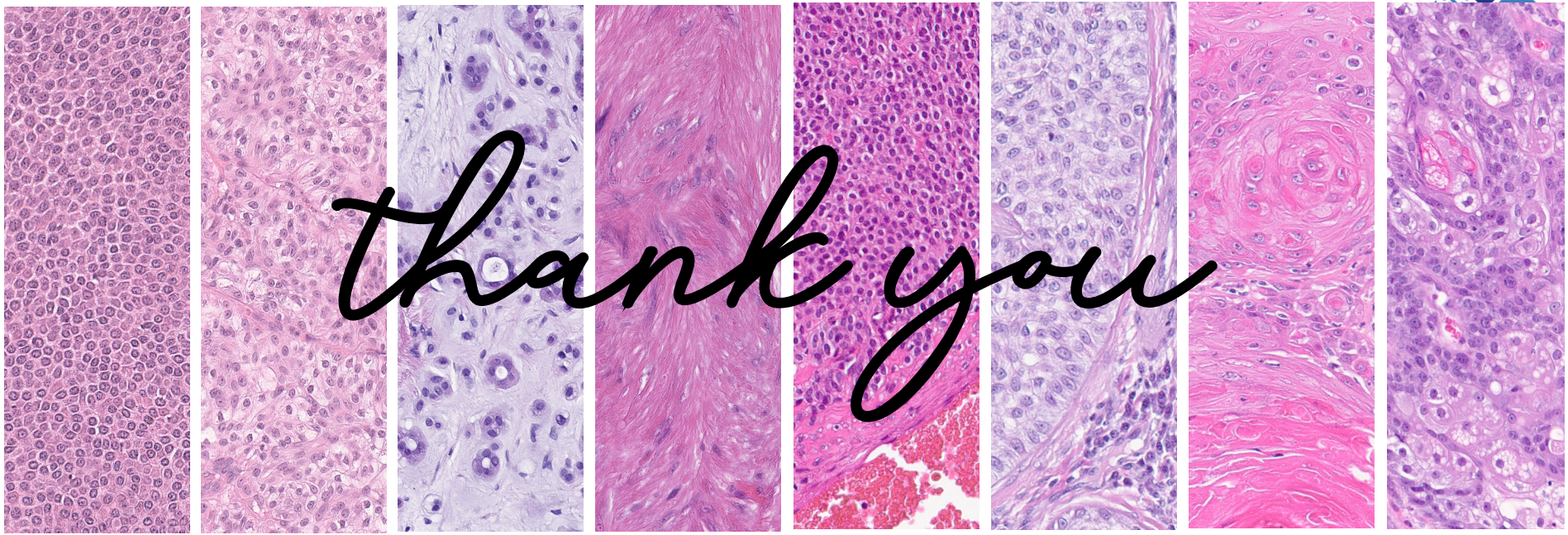
BROAD INSTITUTE

UW GS

WEHI brighter together

ICR The Institute of Cancer Research



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Kim Wong
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Collaborators
Patients

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CANCER RESEARCH UK

GenoMEL

The Melanoma Genetics Consortium

@David_J_Adams

da1@sanger.ac.uk