

Pigmentflecken und -Mosaik

Nicole Knöpfel, MD PhD

Zentrum Kinderhaut, Dermatologie



Overview

1

Café-au-lait macules (CALMs)

2

Mosaic disorders affecting pigmentation

Practical Tips for Approach and Update

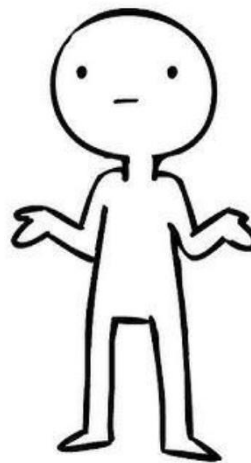


1

Café-au-lait macules (CALMs)



Parent self searching CALMs



1

Café-au-lait macules (CALMs)

Approach and Key Clues

Number of CALMs

CALM morphology: Typical vs Atypical

Patient Age

Family history


Other comorbidities; complete examination



Number of CALMs in children

Incidence of isolated CALMs

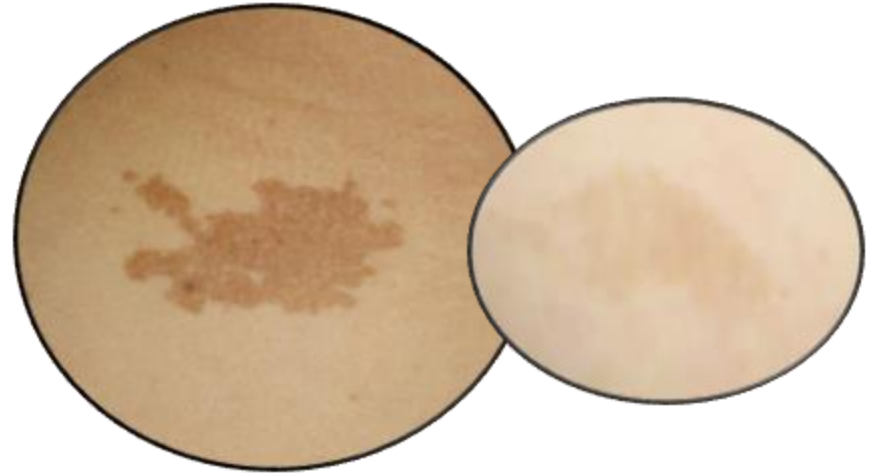
Between 1 and 3  36% of healthy children

More than 3  0.3% of healthy children
May indicate an underlying genetic disease

CALM morphology: Typical vs Atypical

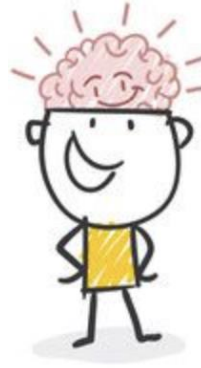


“Typical” CALM
smooth borders
homogeneous pigmentation



“Atypical” CALM
irregular borders – feathery
lightly pigmented – often in fair skin

Multiple “Typical” CALMs
Very good predictor of NF1

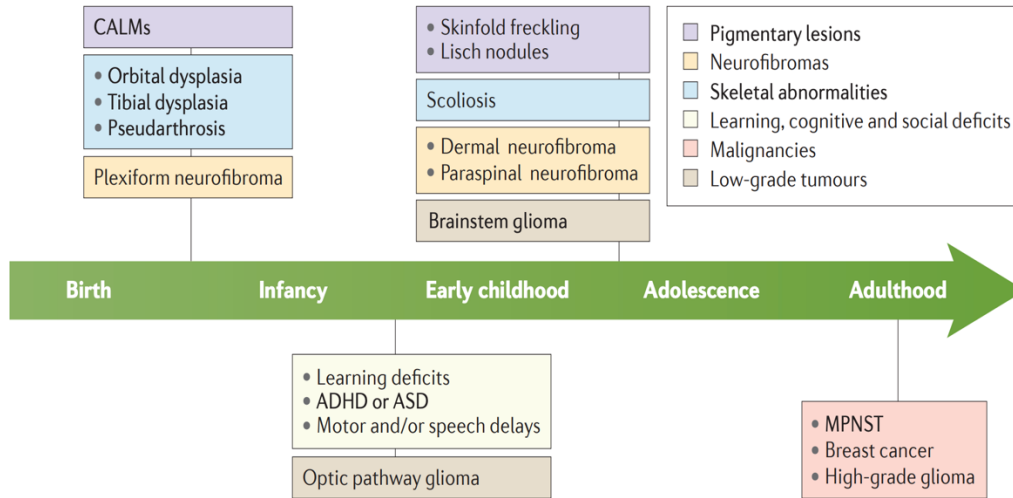


Multiple “Atypical” CALMs
Other conditions

NF1

PTPN11-related Noonan syndrome with lentigines

Patient Age



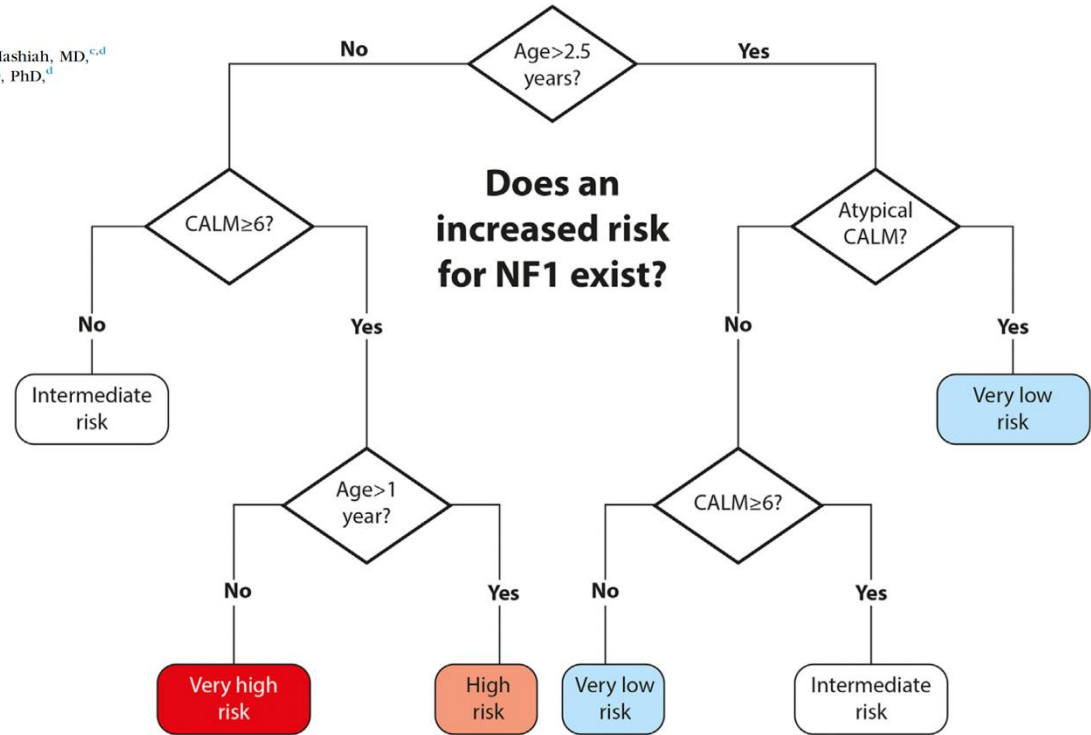
Clinical diagnostic criteria for NF1 fulfilled:

- 54% by age 1
- 95% by age 8
- 100% by age 20

NATURE REVIEWS | DISEASE PRIMERS

Predicting neurofibromatosis type 1 risk among children with isolated café-au-lait macules

Shay Ben-Shachar, MD,^{a,d} Tom Dubov, BSc,^d Hagit Toledano-Alhadeef, MD,^{a,b,d} Jacob Mashiah, MD,^{c,d}
Eli Sprecher, MD, PhD,^{c,d} Shlomi Constantini, MD, MSc,^{a,d} Moshe Leshno, MD, PhD,^d
and Ludwine M. Messiaen, PhD^c
Tel-Aviv, Israel, and Birmingham, Alabama



Very low risk	< 1%
Intermediate risk	10-30%
High risk	>80%

Table 1. Revised diagnostic criteria for neurofibromatosis type 1 (NF1).

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:

- Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals^a (Supplementary Fig. 6)
- Freckling in the axillary or inguinal region^a (Supplementary Fig. 7)
- Two or more neurofibromas of any type or one plexiform neurofibroma (Supplementary Fig. 8a, b)
- Optic pathway glioma (Supplementary Fig. 9)
- Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging (Supplementary Fig. 10a, b)
- A distinctive osseous lesion such as sphenoid dysplasia,^b anterolateral bowing of the tibia, or pseudarthrosis of a long bone (Supplementary Fig. 11)
- A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present



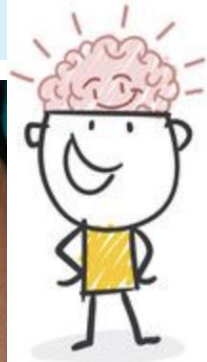
Helpful clues in predicting NF1



Nevus anaemicus

- Up to 51%
- Most common on neck and upper trunk
- Often noted in children < 2 years of age with only 1 sign of NF1

Rub the skin!



Helpful clues in predicting NF1



Juvenile Xanthogranuloma

- In around 10%
- Most multiple and spontaneous resolution
- Head and genital area

Association with chronic myelomonocytic leukemia
– debated

Silver-Russel syndrome

Fanconi Anaemia

RASopathies

CMMRD

Many conditions featuring CALMs

NF2

Ring chromosome syndromes

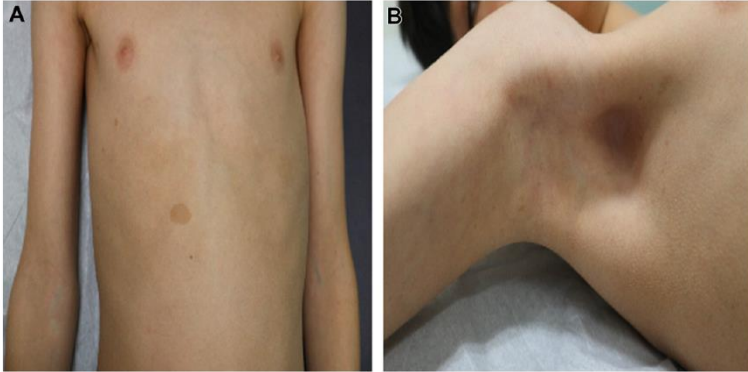
PTEN syndrome

Ataxia Telangiectasia

Bloom syndrome

And more!

Legius syndrome



Heterozygosity for loss-of-function variants in *LZTR1* is associated with isolated multiple café-au-lait macules

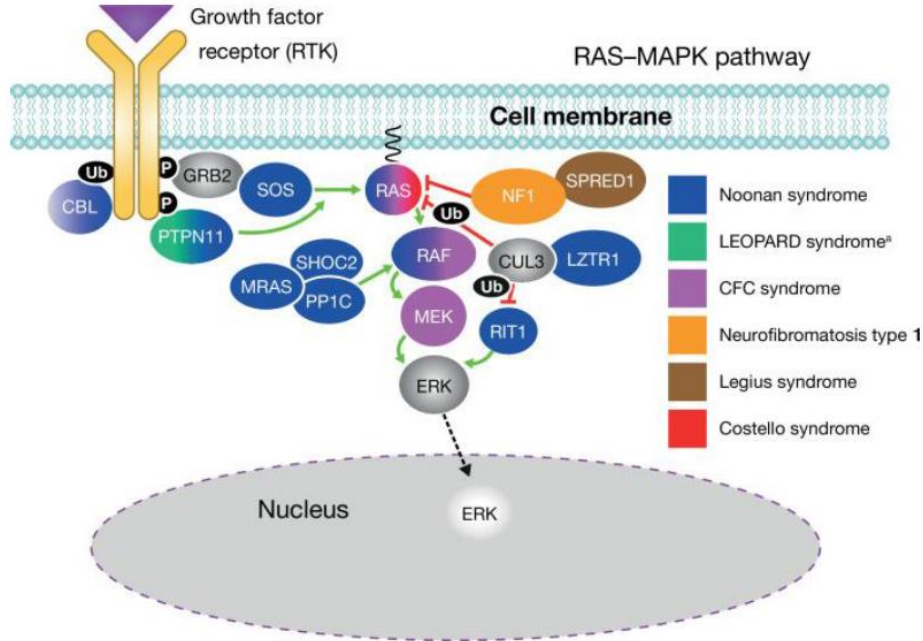
Mastromoro et al. 2024



CALMs in varying number
Mostly atypical
Freckling on the folds

Pathogenic variants in *LZTR1* known to cause schwannomatosis and dominant/recessive Noonan syndrome

CALMs – a common feature in RASopathies



Phenotype



Dysmorphic facies

Hair and other ectodermal abnormalities

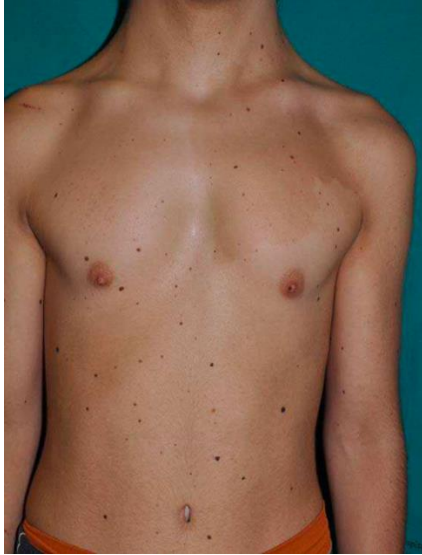
Increased melanocytic naevi; Lentigines

Heart defects

Pectus deformity

Other problems..

CALMs – a common feature in RASopathies



Noonan syndrome

- Large CALM
- Melanocytic naevi
- Pectus excavatum
- Pterigium colli



Noonan syndrome with lentigenes

- Café Noir macule
- Lentigenes

Syndromes	Skin Manifestations
Noonan	Café-au-lait spots Melanocytic nevus Lymphedema of the lower limbs
Noonan with lentigenes	Freckles Dark café-au-lait spots
Cardiofaciocutaneous	Short, thin, curly hair Ichthyosiform scaling Follicular keratosis Ulerythema ophryogenes Acquired multiple nevi Café-au-lait spots
Costello	Loose skin Hyperpigmentation Papillomatous lesions around the orifices Deep lines on the palms



Constitutional mismatch repair deficiency (CMMRD)

MMR genes (*MSH2*, *MSH6*, *MLH1*, *PMS2*)

Biallelic germline mutations → CMMRD
(early life cancers)

Monoallelic germline mutations → Lynch
(adult onset cancers)

Early diagnosis is
crucial to start
surveillance protocol

→ Surveillance protocol for patients with CMMRD

Examination	Start age	Frequency	Tumors
MRI brain	At diagnosis	Q 6 months	Brain tumors
WBMRI	6 years	Once a year	All tumors
CBC	1 year	Q 6 months	Leukemia
Abdominal U/S	1 year	Q 6 months	Lymphoma
Upper gastrointestinal endoscopy; VCE, ileocolonoscopy	4 to 6 years	Once a year	Gastrointestinal tumors
GYN exam, transvaginal U/S, pipelle curettage, urine cytology, dipstick	20 years	Once a year	Genitourinary cancers

Abbreviations: GYN, gynecologic; Q, every; U/S, ultrasound; VCE, visual capsule endoscopy.

1

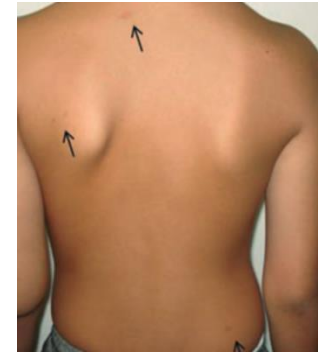
Café-au-lait macules (CALMs) – **and when they're not!**



Particularly in dark skin. Easily misdiagnosed



Also presenting with multiple lesions
Family member with similar lesions



CM-AVM syndrome

Caused by pathogenic variants in *RASA1* and *EPHB4*. AD inheritance



Multiple 1-3cm, round-oval, pinkish to red to brown
with **peripheral halo**
High-flow on US doppler

Table 1 Summary of data.

Clinical presentation	n
Reason for consultation	
Concern about lesions	46
Aesthetic reasons	1
Incidental finding	17
Cutaneous lesions	
Colour	
Pink	52
Red	22
Brown	36
Size, mm	
< 10	40
10–50	53
> 50	14
Morphology	
Oval	45
Round	35
Irregular	17
Whitish halo in:	
> 50% lesions	22
< 50% lesions	29



CM-AVM syndrome

Caused by pathogenic variants in *RASA1* and *EPHB4*. AD inheritance



Multiple 1-3cm, round-oval, pinkish to red to brown
with **peripheral halo**
High-flow on US doppler

After diascopy:
Brown background/network

RASA1 and *NF1* - both encode GTPase-activating proteins acting as RAS signalling suppressors
CM-AVM another RASopathy



CM-AVM syndrome

Brain and Spine AVMs

- Potentially serious

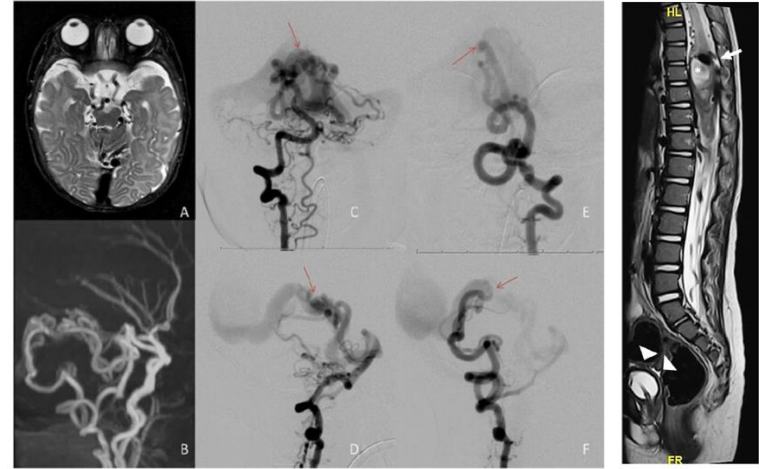
RASA1-related CM-AVM (10% risk)

EPBH4-related CM-AVM (3% risk)

Screening AngioMRI recommended

In a retrospective study:

50% of children presenting with cerebral hemorrhage due to intracranial AVMs had CM-AVM phenotype



Check the skin to diagnose CM-AVM

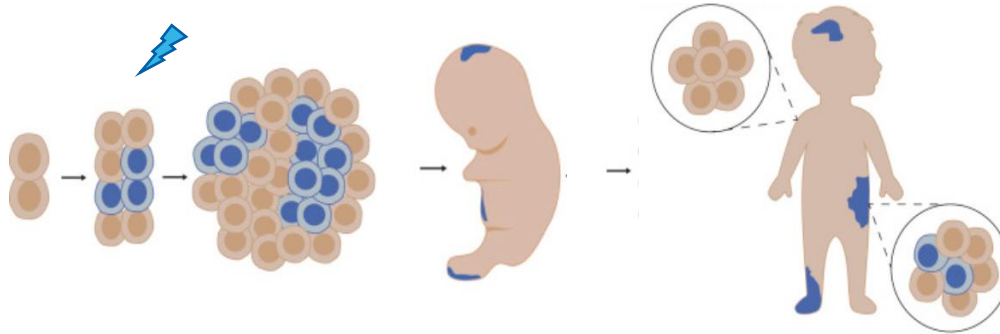


2

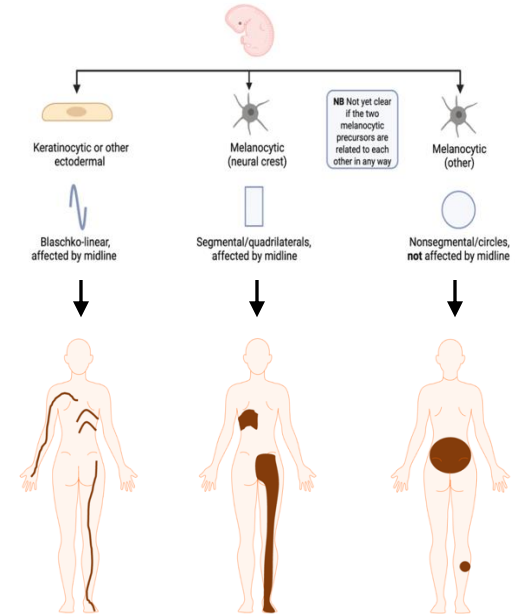
Mosaic disorders affecting pigmentation

2

Mosaic disorders affecting pigmentation



A mosaic disorder is caused by a disease-causing single cell mutation during embryonic or fetal development



**Blaschkolinear,
epidermal/keratinocytic**

**Isolated on the skin
or affecting other organs
(incl. CNS)**

Chromosomal mosaicism

Single gene mosaicism

Hyper –

*KITLG, IKBKG, PHF6,
POLA1, EDA, ATP7A*

Hypo –

*IKBKG, TP63, MTOR,
RHOA, GNA13..*

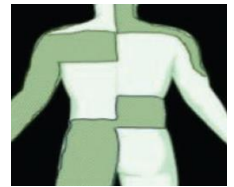
What's the pattern?



*Blaschkolinear,
broad bands*



Lateralization



*Checkerboard
blocklike*



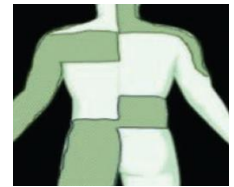
Segmental, melanocytic
affected by midline



*Blaschkolinear,
broad bands*



Lateralization



*Checkerboard
blocklike*



Distinct classical patterns reflect a same embryonic cell type
– Cluster all as **Segmental Pattern**

Very little known..

Incidence unknown

Varying terminology

Segmental Pigmentation Disorder, Metzker 1983

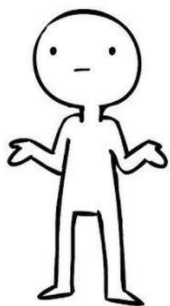
Segmental pigmentation anomaly

Pigmentary mosaicism, segmental CALMs ..

Varying inclusion criteria in few cohort studies

Majority of children apparently doing well





Does the child need any investigations?

Can this go with other medical problems in the future?

Segmental macular hyperpigmentation - a feature of McCune Albright Syndrome

Estimated prevalence: between 1/100,000 and 1/1,000,000

Caused by mosaic activating variants in *GNAS* at codons 201 and 227



Café-au-lait pigmentation

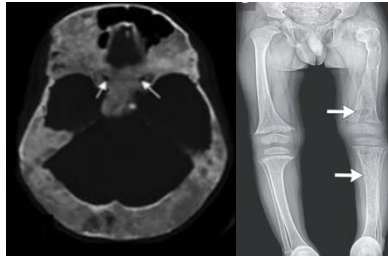
in 'broad bands', borders
resembling 'Coast of
Maine'. Oral mucosae can
be affected

Polyostotic fibrous dysplasia

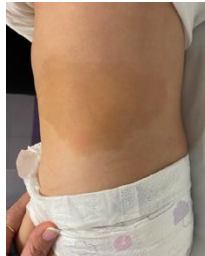
(craniofacial, axial or
appendicular- long bones)

Endocrine dysfunction

(precocious puberty,
hyperthyroidism, growth
hormone excess,
hypercortisolism)



with hypercortisolism



with GH excess

Segmental macular hyperpigmentation: new genes, new clinical implications

Veronica A Kinsler^{1,2,3}, Nicole Knöpfel^{1,2,3} and Satyamaanasa Polubothu^{1,2}

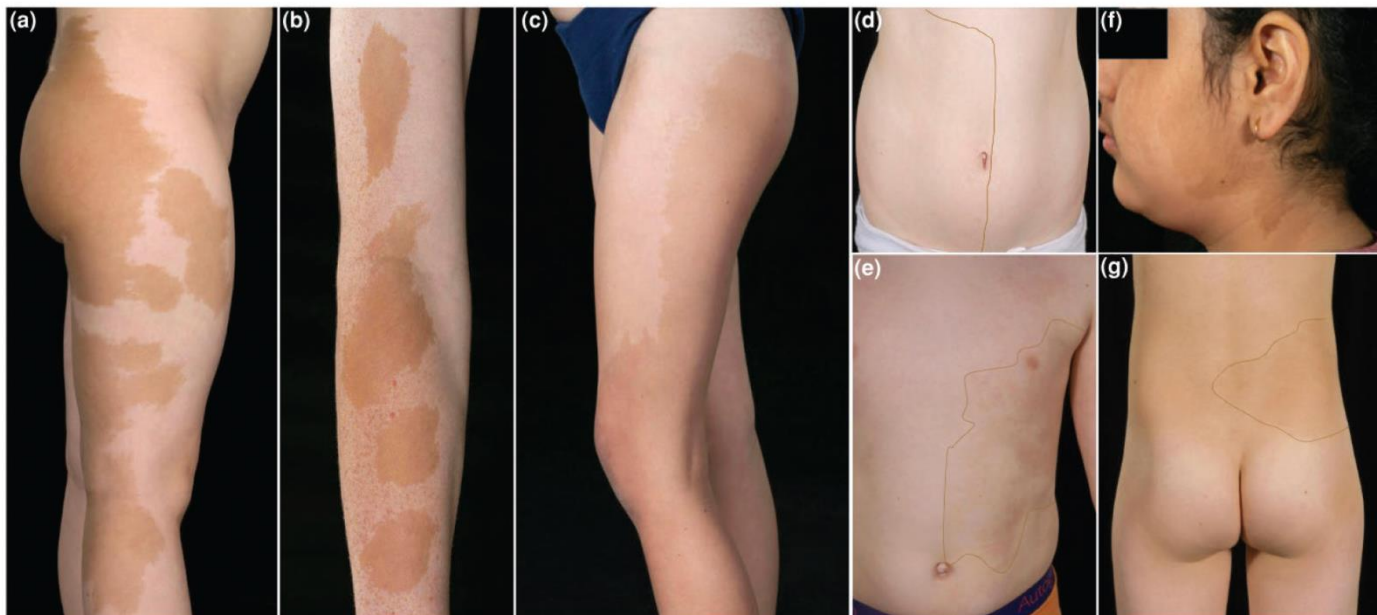
¹NHS England Rare Disease Collaborative Network for Mosaic Disorders, Paediatric Dermatology, Great Ormond Street Hospital for Children, London, UK

²Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health, London, UK

³Mosaicism and Precision Medicine Laboratory, The Francis Crick Institute, London, UK

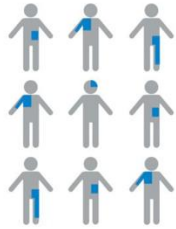
Correspondence: Veronica A. Kinsler. Email: v.kinsler@ucl.ac.uk

V.A.K., N.K. and S.P. contributed equally to this work.



Segmental macular hyperpigmentation (SMH)

Study Design



50 patients
with SMH



Complete examination and
medical history



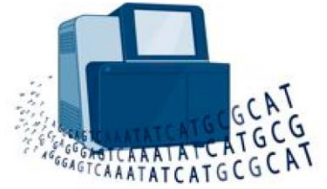
Imaging studies directed by the
presence of symptoms and referral
to designated specialty



Biopsy from
affected skin



Blood DNA



DNA sequencing
Targeted NGS mosaic
panel
GNAS hotspot
sequencing

***GNAS* mosaicism in 7%**



GNAS c.601C>T p.(Arg201Cys)
0.3% VAF



GNAS c.602G>A p.(Arg201His) 1% VAF



GNAS c.602G>A p.(Arg201His)
0.4% VAF

Variant allele load extremely low

Follow-up: *GNAS* mosaicism diagnosis from skin

Sex	Age, years	Genotype	Follow-up / Outcome
F	0.6	<i>GNAS</i> c.601C>T p.(Arg201Cys) 0.3% VAF	Hyperthyroidism requiring treatment at age 12 years
M	17.1	<i>GNAS</i> c.602G>A p.(Arg201His) 1% VAF	History of hip pain. XR pelvis and long bones normal
F	1.4	<i>GNAS</i> c.602G>A p.(Arg201His) 0.4% VAF	Lost to follow-up

- ✨ Opportunity for early diagnosis and alert patients/families on future related complications
- ✨ Consider retesting with the newer improved NGS in patients who previously tested negative

Unknown genotype after NGS panel

Still cannot rule out extremely low *GNAS* mosaicism



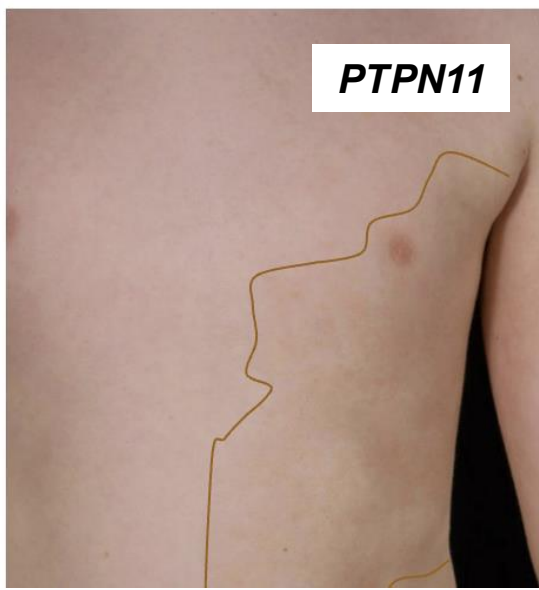
NRAS



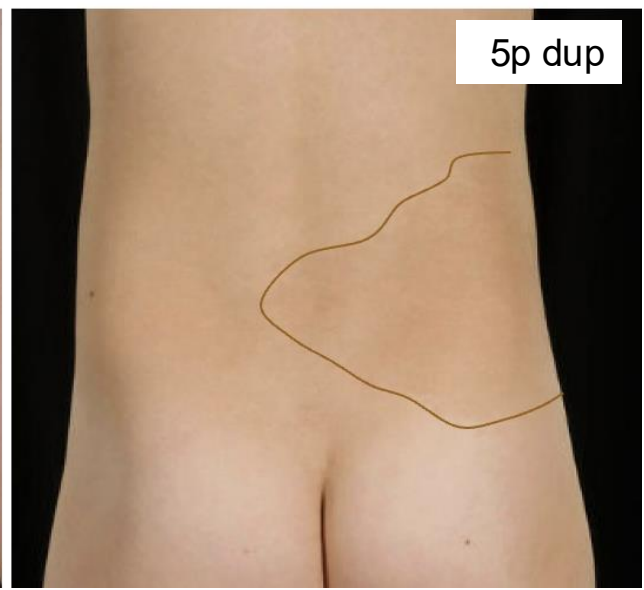
NRAS



BRAF



PTPN11



5p dup

New genetic causes of SMH

– *PTPN11* mosaicism



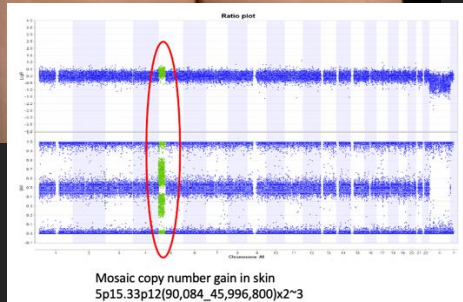
PTPN11 c.1282G>C p.(Val428Leu) 8% VAF

No evidence of spilus/
speckled component,
age 15 years

PTPN11 Mosaicism Causes a Spectrum of
Pigmentary and Vascular Neurocutaneous
Disorders and Predisposes to Melanoma



Chromosomal mosaicism in Segmental Pigmentation



46,XX / 47,XX +dic(15)(q13q15)

F Browne et al. BJD 2010

Extra-cutaneous features in our cohort

50 patients, 31 (62%) female

Mean and median age at first visit 4.9 years (range 0.2 -17.1) and 3.7

Neurological problems 16%

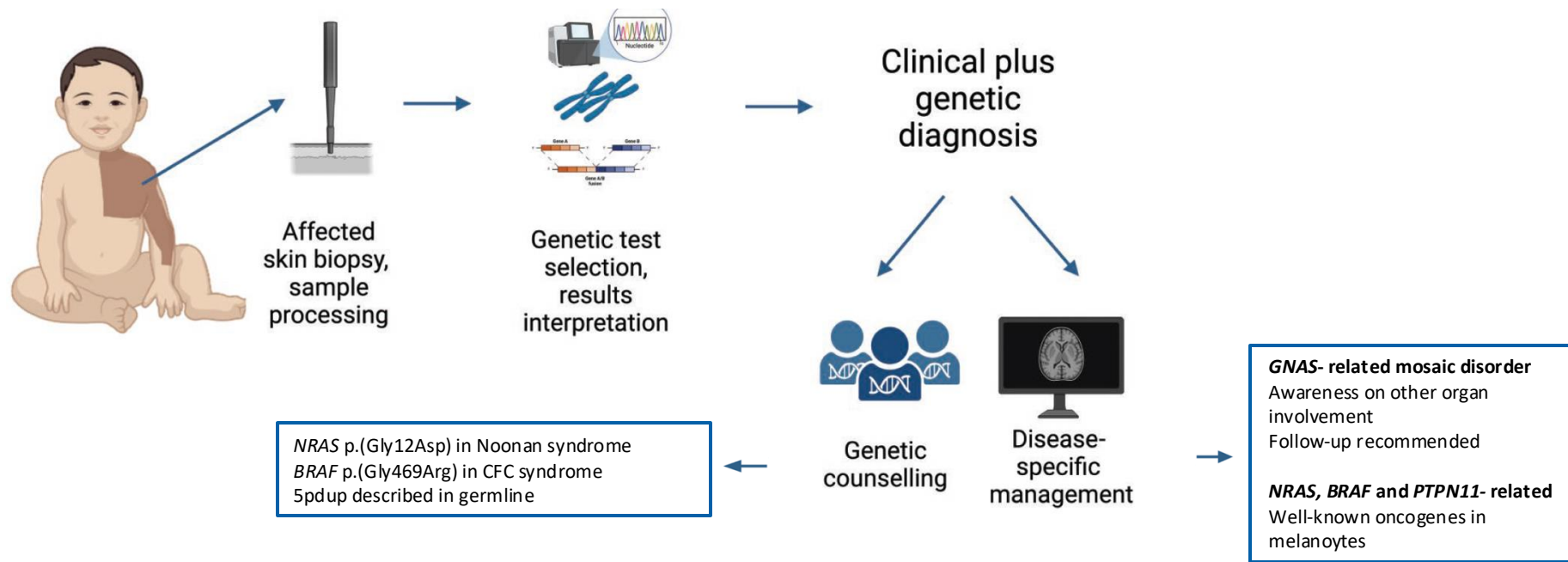
ADHD (2)	Brain MRI in 5 patients with normal findings
ASD (2)	
Speech delay (2)	
Dyspraxia (1)	
Dyslexia (1)	
Epilepsy due to carnitine deficiency (1)	

Ophthalmological problems 6%

Scleral naevus (1)
Scleral melanocytosis (1)
Nystagmus (1)

None with segmental pigmentation
around the eye

Proposed Approach



2

Segmental hyperpigmentation

Take away Tips in your daily practice

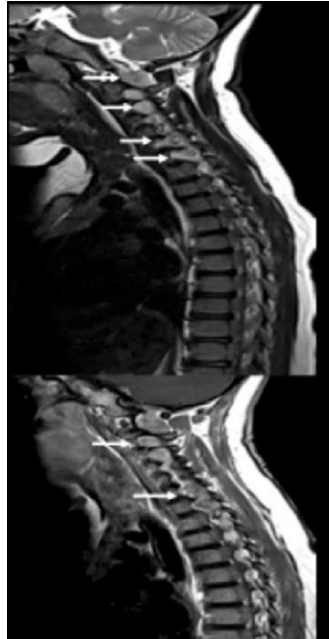
- Full body examination and medical history
- Developmental milestones
- Refer to appropriate specialist and order imaging depending on symptoms
- Genetic investigation: in clinical setting covered by the presence of comorbidities



Clinical and genetic diagnosis

To improve our understanding of disease

Pigmented Birthmarks and Spinal Neurofibromas in *KRAS* Mosaicism—Not to Be Confused With NF1



Other reported cases of *KRAS* mosaicism presenting with neurofibromas

Patient	1 (Farschtschi et al. 2015)	2 (Dionysou M et al. 2024)	Our patient
Age/Sex	17Y, M	7Y, F	9Y, F
Cutaneous	Blaschkolinear keratinocytic epidermal nevus right upper back. Large areas of macular hyperpigmentation on upper trunk and both arms.	Blaschkolinear keratinocytic epidermal nevus left posterior neck, upper back and left flank. Epidermal nevus on scalp.	Blaschkolinear sebaceous epidermal nevus right posterior parietal scalp. Uvular epidermal nevus. Blaschkolinear keratinocytic epidermal nevus right posterior neck and upper back. Two large patches of macular hyperpigmentation on the shoulders bilaterally.
Neurological	Delayed motor development. Normal MRI brain. Cervical and thoracic tumor (C3-T1) with histological findings of Schwann cell proliferation resembling onion bulb formation. Intraspinal lipoma C5-C7. Transversal spinal cord syndrome with spasticity, paraparesis and pain. Proximal neuropathy. Thoracolumbar scoliosis	Diffuse spinal nerve hypertrophy involving left C1-C7 bilateral T1-T2, L3, L4 and sacral plexus with progressive growth causing cervical spinal cord compression. Partial complex epilepsy, well controlled. Speech delay otherwise normal neurodevelopment.	Bilateral cervical neurofibromas from C2-C6
Ocular	Bilateral impaired vision (50%) and astigmatism		Right coloboma
Other	Thoracolumbar scoliosis. Generalized osteopenia.	Congenital heart disease (ectopic atrial tachycardia, PDA, coarctation of the aorta), Polycystic kidney disease, benign pelvic ganglioneuroma. Mild facial asymmetry ($R>L$)	Subtle facial asymmetry ($R>L$)
<i>KRAS</i> variant	c.35G>A p.(Gly12Asp) VAF 44% (skin) 49% (perineuroma) and 56% (lipoma)	c.35G>A p.(Gly12Asp) VAF not reported	c.35G>A p.(Gly12Asp) VAF 39%
Tissue samples tested	Skin, intraneural perineuroma, and lipoma	Epidermal nevus	Epidermal nevus

Vielen Dank für die Aufmerksamkeit!



nicole.knoepfel@kispi.uzh.ch