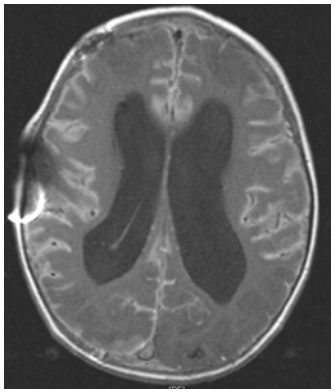
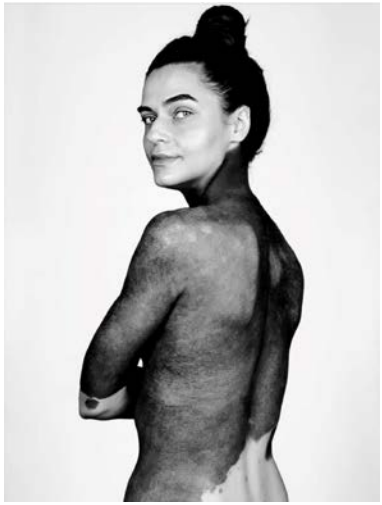
MSK Kids
Memorial Sloan Kettering



Neurologic conditions associated with large congenital melanocytic nevi

Yasmin Khakoo, MD
Child Neurology Director, MSK Kids
September 12, 2019



Nevus Outreach
The Association for Large Nevi & Related Disorders

Naevus
INTERNATIONAL

Disclosures

Nevus Outreach
The Association for Large Nevi & Related Disorders

Provides funding for MSK NCM database

Naevus
INTERNATIONAL

Reimburses for meeting/travel related expenses

Outline

Definition

History

Criteria

Incidence and epidemiology

Embryology

Mouse models/genetics

Neuropathology

Screening recommendations

Neurologic complications

Therapeutic targets

Photo cred: Brock Elbank and Caring Matters Now

Definition

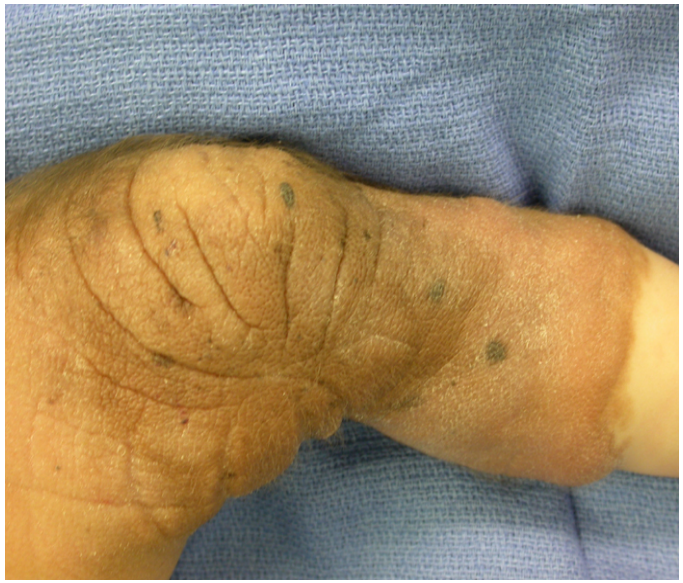
A rare neurocutaneous syndrome defined by the presence of large and/or multiple congenital cutaneous nevi and melanocytes in the CNS

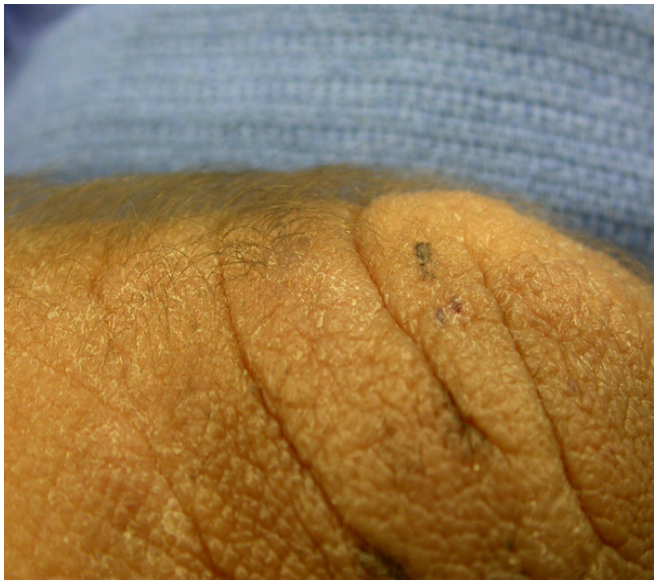
Pediatric Dermatology Vol. 26 No. 1 79–82, 2009

Large Congenital Melanotic Nevi in an Extremity with Neurocutaneous Melanocytosis

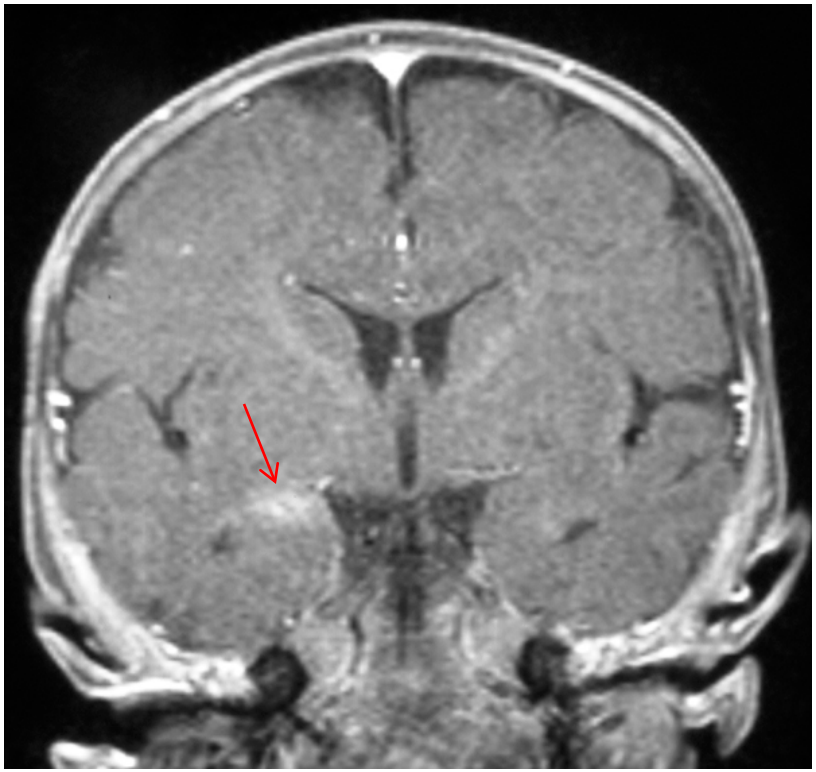
Oren J. Becher, M.D.,* Mark Souweidane, M.D.,† Ehud Lavi, M.D.,‡ Kim Kramer, M.D.,* Eric Lis, M.D.,§ Ashfaq A. Marghoob, M.D.,¶ and Yasmin Khakoo, M.D.,*

**Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, †Departments of Neurosurgery, and ‡Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, §Departments of Radiology, and ¶Dermatology, Memorial Sloan Kettering Cancer Center, New York*

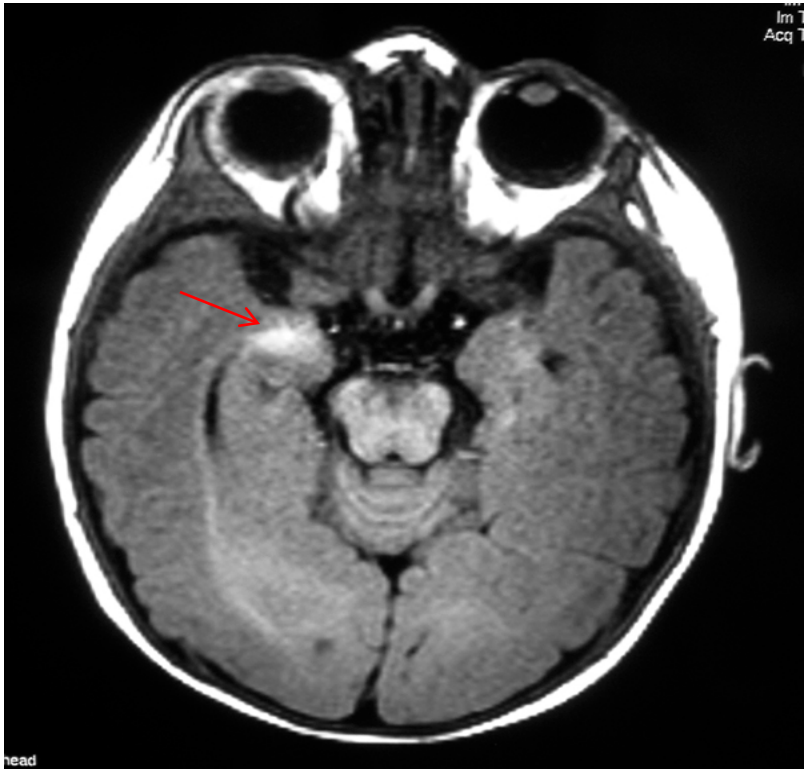




MRI brain



Coronal post contrast



Axial T1 FLAIR

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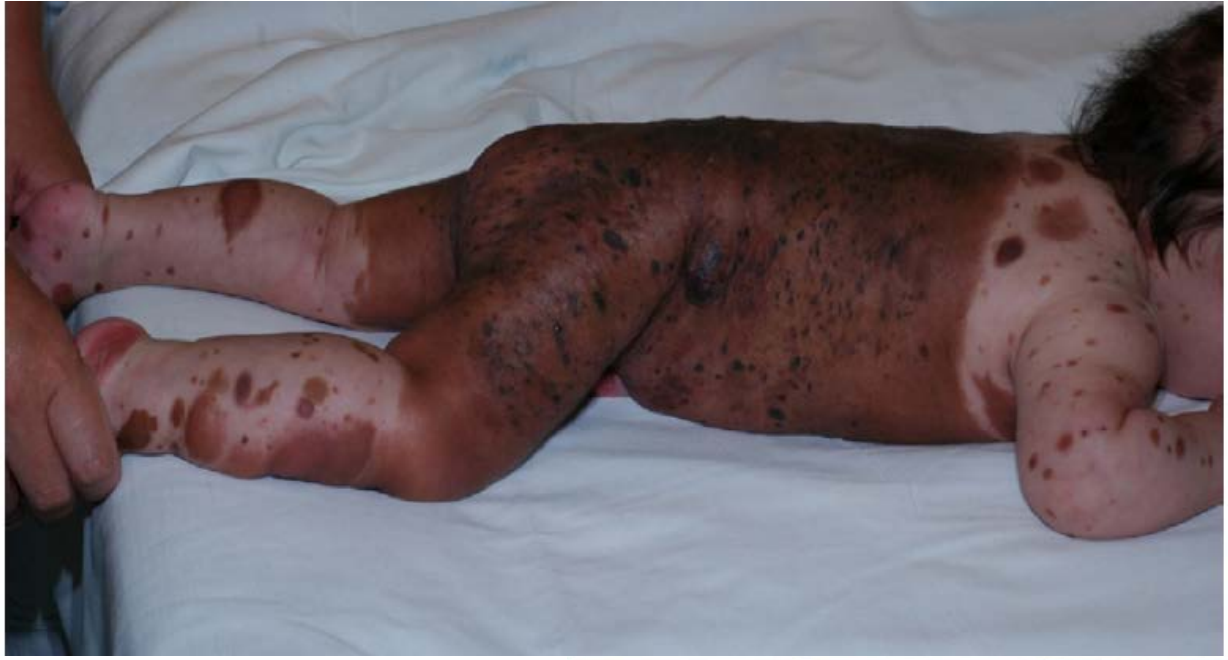

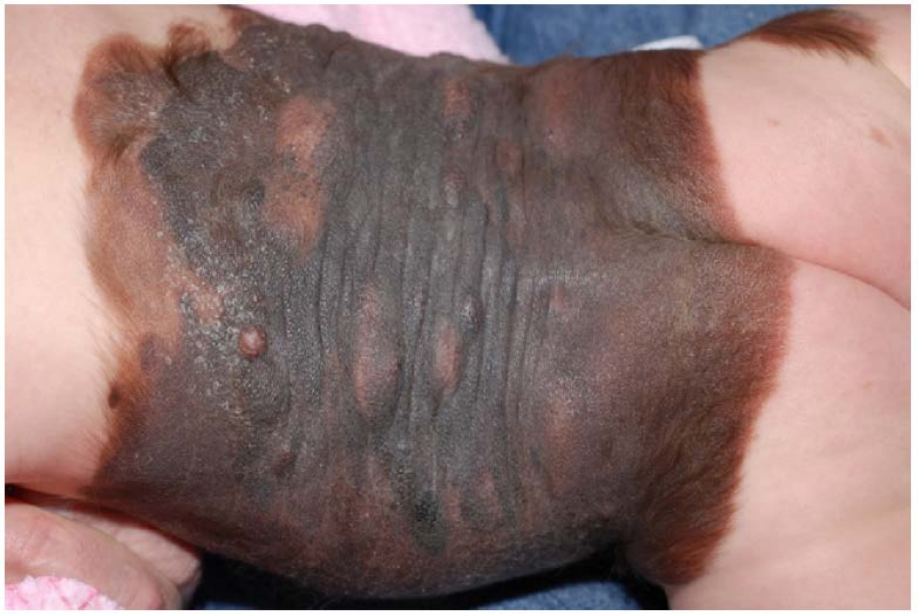

Slutsky et al, Semin Cut Med and Surg 2010

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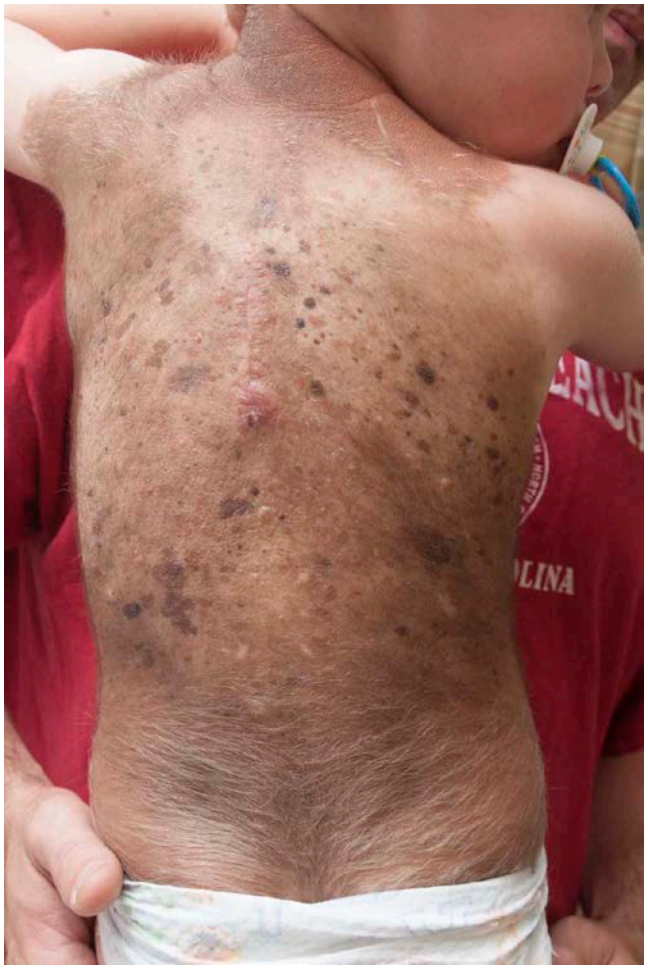
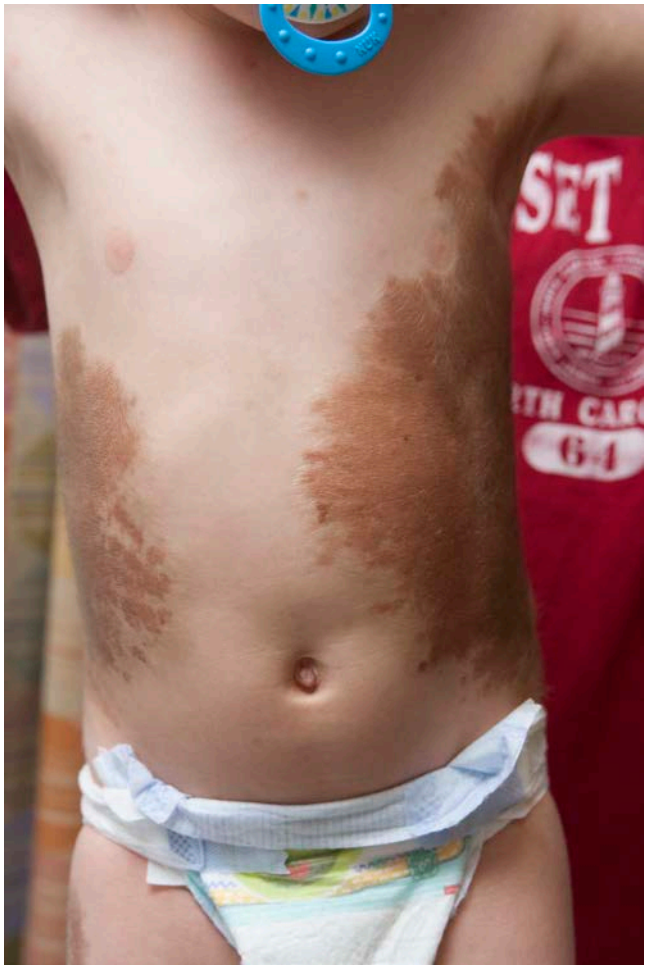
One of our recent patients





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History

1861: Viennese pathologist Karl Rokitansky

described autopsy findings of a 14 yo girl with developmental delay and nevi

Allgemeine Wiener

medizinische Zeitung.

Verantwortliche Redacteure und Herausgeber: Dr. Kraus, Dr. Pichler.

INHALT: Ein ausgezeichneter Fall von Pigmentmal mit ausgebreiteter Pigmentirung der inneren Hirn- und Rückenmarkshäute; von Prof. Rokitansky. — Medizinische Klinik des Prof. Skoda: Beiträge zur Lehre vom Typhus. — Beitrag zur Lehre vom Harnröhrentripper des Weibes von Dr. Mathias Singer. — Beiträge zur Lehre von der Pneumonie; von Dr. M. Smoler. — Das Bezirkskrankenhaus Wieden. — Notizen. — Anzeigen.

Ein ausgezeichneter Fall von Pigment-Mal mit ausgebreiteter Pigmentirung der inneren Hirn- und Rückenmarkshäute.

Von Prof. Rokitansky.

(Translation: “A remarkable case of a pigmented nevus with extensive leptomeningeal pigmentation”)

History continued

1948: Van Bogaert named the syndrome neurocutaneous melanosis (NCM)

1991: Kadonaga and Frieden outlined criteria

2000: Nevus Outreach, Inc registry formed

2005: Marghoob: NCM in pts with LCMN: 7%

2007: Bauer: *NRAS* mutations in LCMN

2012: Shakhova: Mouse model

2012: Kinsler estimated 18% of LCMN have brain lesions

2013: Kinsler detects *NRAS* mutations in brain lesions

2018: Naevus International formed

Photo cred: Brock Elbank and Caring Matters Now

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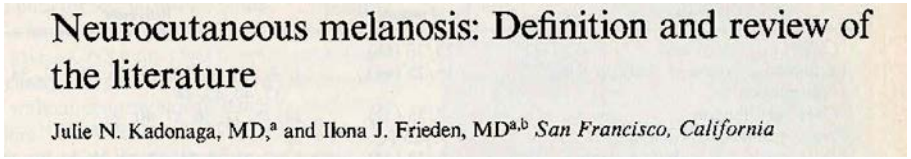
Criteria

- Presence of large (>20 cm) and/or multiple (>3) congenital melanocytic nevi (CMN) with meningeal melanosis or melanoma;
- Must distinguish between metastatic melanoma and primary


Neurocutaneous melanosis: Definition and review of the literature

Julie N. Kadonaga, MD,[a] and Ilona J. Frieden, MD[a,b] *San Francisco, California*

1991, J Am Acad Derm

Incidence/epidemiology

A mostly sporadic condition (one report of 2 siblings)

LCMN: 1/20,000 → brain 1/200,000

M=F

Age was ~ 3 but with MRI, earlier diagnosis

Majority of patients who will become symptomatic do so by 2 years; 70% by 5 yrs

Reports of patients who become symptomatic in 2nd or 3rd decade

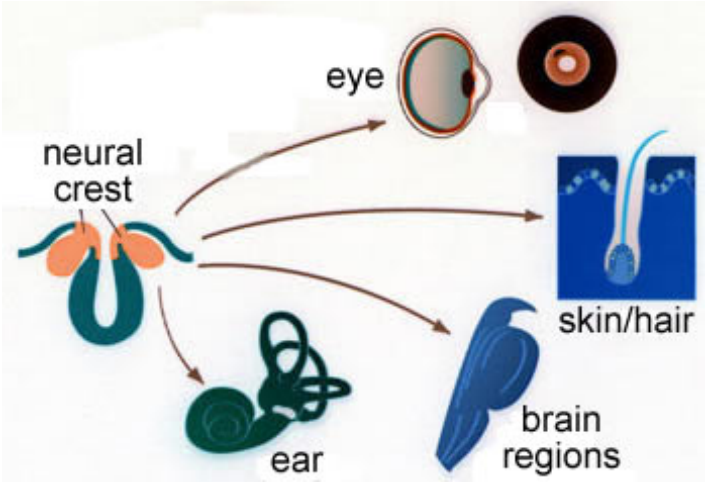
Use of MRI and other radiographic techniques may increase the number of patients identified

Embryology

Melanocytes develop from neural crest and migrate throughout the body including the covering of the brain (leptomeninges)

Nevi: melanocytes which arrest along the path

NCM may be a marker for abnormal neuronal migration



Wolff et al: E11.5 mouse LacZ staining for melanoblasts

Congenital Melanocytic Nevi Frequently Harbor *NRAS* Mutations but no *BRAF* Mutations

Jürgen Bauer[1,2], John A. Curtin[3], Dan Pinkel[3] and Boris C. Bastian[1,3,4]

2007, J Invest Dermat

Table 2. Frequencies of *BRAF* and *NRAS* mutations

	Congenital melanocytic nevi	Proliferating nodules in congenital melanocytic nevi	Congenital pattern nevi
BRAF mutations	0 (0%)	0 (0%)	20 (71.4%)
NRAS mutations	26 (81.3%)	7 (70.0%)	7 (25.0%)
No mutations	6 (18.8%)	3 (30.0%)	1 (3.6%)

Mutation found in codon 61 of the *NRAS* gene

Sox10 promotes the formation and maintenance of giant congenital naevi and melanoma

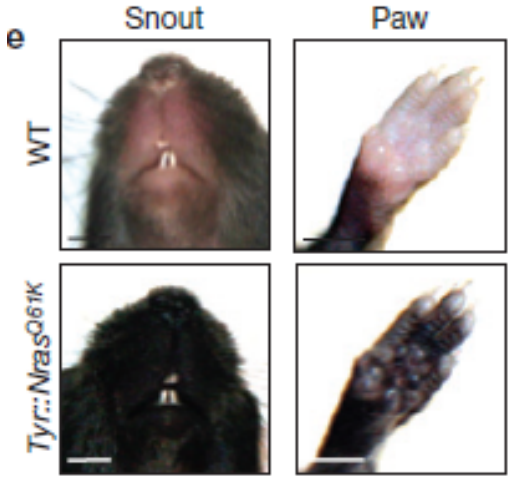
Olga Shakhova[1,10], Daniel Zingg[1], Simon M. Schaefer[1], Lisette Hari[1], Gianluca Civenni[1], Jacqueline Blunschi[1], Stéphanie Claudinot[2], Michal Okoniewski[3], Friedrich Beermann[4], Daniela Mihic-Probst[5], Holger Moch[5], Michael Wegner[6], Reinhard Dummer[7], Yann Barrandon[2], Paolo Cinelli[8,9] and Lukas Sommer[1,10]

2012 Nat Cell Biol

SOX10 important in neural crest development

SOX10 highly expressed in LCMN and melanoma

NRAS Q61 controls the expression of SOX10



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Multiple Congenital Melanocytic Nevi and Neurocutaneous Melanosis Are Caused by Postzygotic Mutations in Codon 61 of *NRAS*

Veronica A. Kinsler[1,2], Anna C. Thomas[2], Miho Ishida[2], Neil W. Bulstrode[3], Sam Loughlin[4], Sandra Hing[5], Jane Chalker[5], Kathryn McKenzie[6], Sayeda Abu-Amero[2], Olga Slater[7], Estelle Chanudet[8], Rodger Palmer[4], Deborah Morrogh[4], Philip Stanier[9], Eugene Healy[10], Neil J. Sebire[11,12] and Gudrun E. Moore[2]

2013 J Invest Derm

Twelve of 15 patients tested had *NRAS* mutations in affected skin and neural tissue

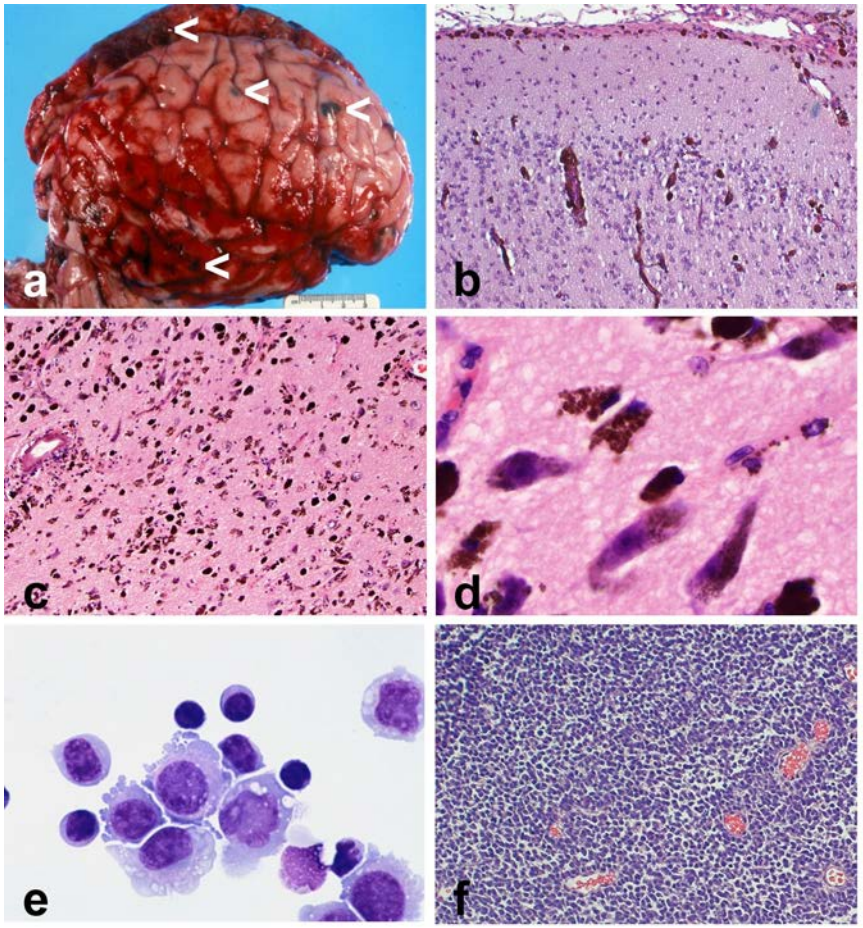
Normal tissue and blood were normal

Ten had a Q61K mutation while 2 had Q61R

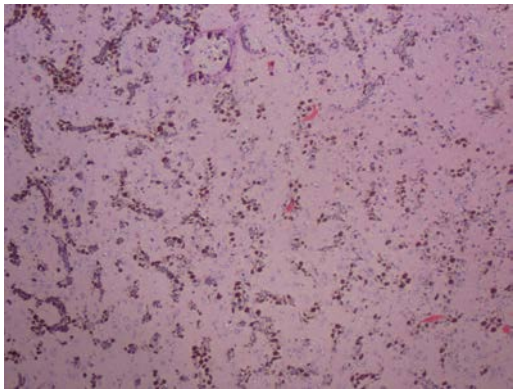
LOH was seen in 2 patients who developed cutaneous melanoma

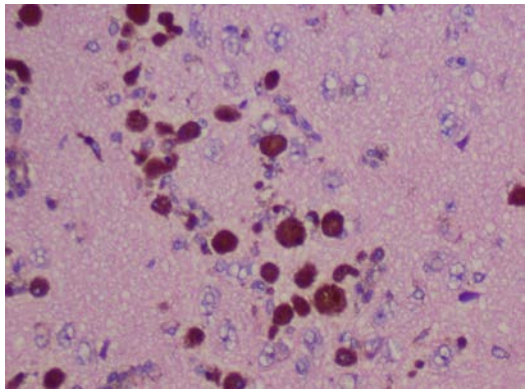
We identified same mutations in 2 patients

Neuropathology: Gross

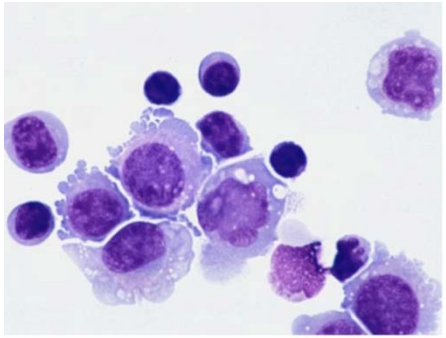


Neuropathology: microscopic

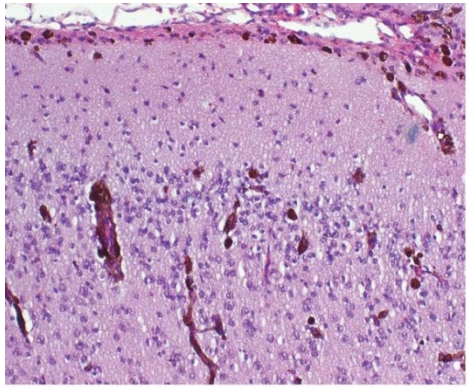




Low and high power views of the cortex infiltrated with pigmented cells



CSF with nevo-melanocytes

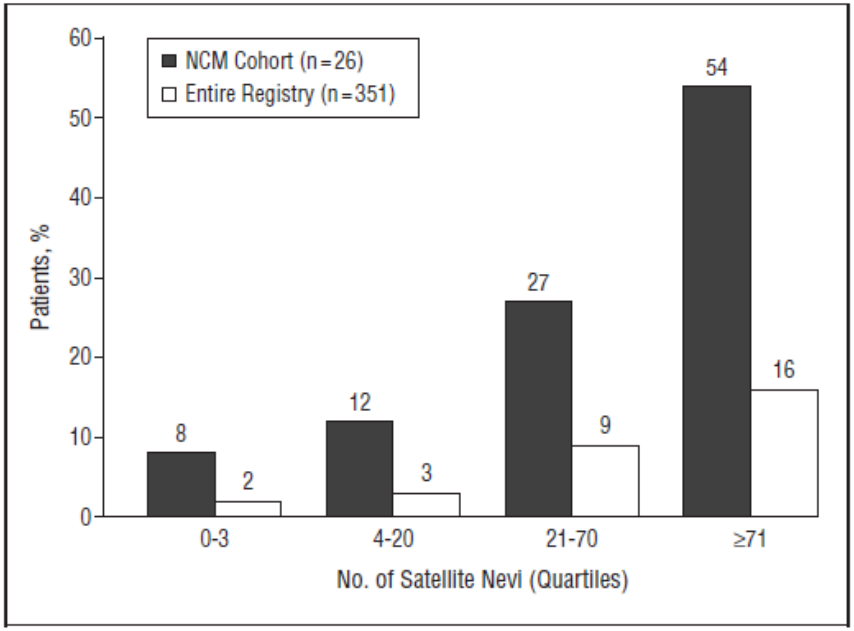


Leptomeningeal and sulcal melanocytosis *(courtesy M. Reyes-Mugica)*

Number of Satellite Nevi as a Correlate for Neurocutaneous Melanocytosis in Patients With Large Congenital Melanocytic Nevi

Ashfaq A. Marghoob, MD; Stephen Dusza, MPH; Susan Oliveria, ScD, MPH; Allan C. Halpern, MD, MS *(Arch Dermat 2004)*

Patients with 20 or more satellite nevi are at high risk



Patients with posterior midline LCMN had moderate risk

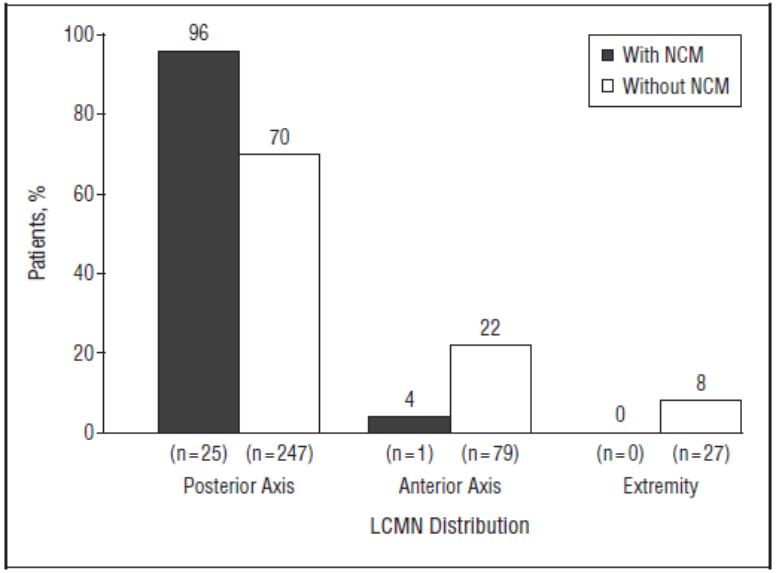


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Photo cred: Brock Elbank and Caring Matters Now

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Neurologic complications

Some children with brain lesions have NO neurologic complications

Conversely, some patients with LCMN and normal MRI have neurologic complications

Hydrocephalus

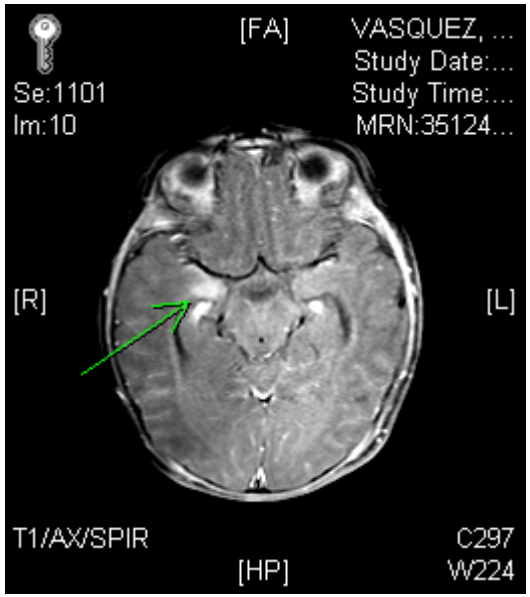
Seizures

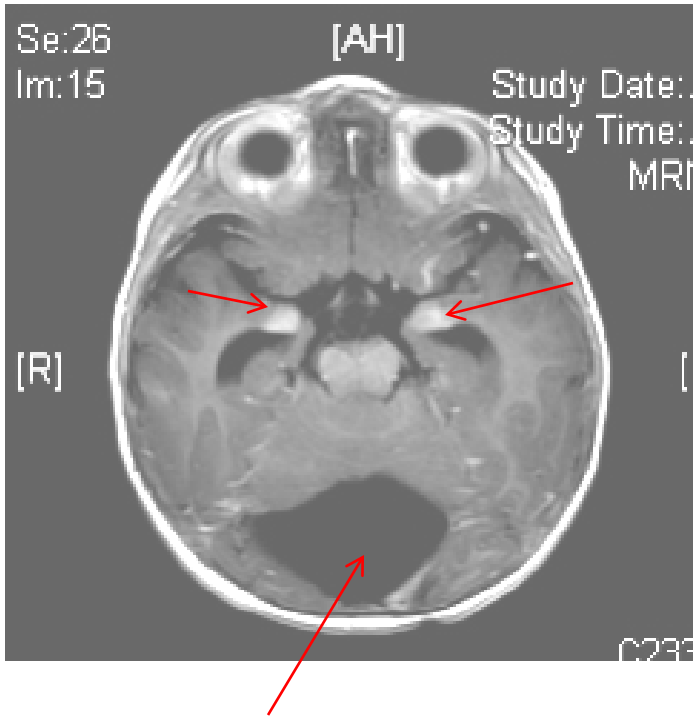
Cranial/spinal nerve dysfunction

Developmental delay

Spinal cord compression/tethered cord

Temporal lobe melanocytosis and Dandy-Walker cyst





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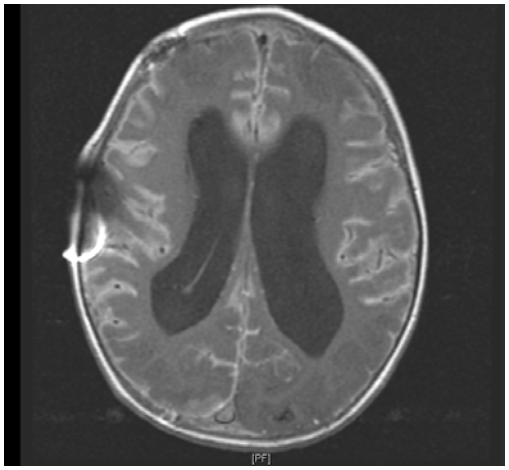
Hydrocephalus

Decreased outflow either communicating or obstructive



Axial T1 post contrast MRI: diffuse leptomeningeal enhancement

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Hydrocephalus: treatment

Either a ventriculo-peritoneal (VP) shunt or endoscopic third ventriculostomy (ETV)

If protein or cells in spinal fluid is high, shunt obstruction may occur

New programmable shunts may improve outcome in NCM pts

Hydrocephalus: signs and symptoms

Headaches (irritability, head banging in pre-verbal child)

Enlarging head circumference

Morning nausea and vomiting

Limited upgaze (Sun setting eyes)

Diplopia (CN VI palsy)

Lower extremity spasticity

Seizures

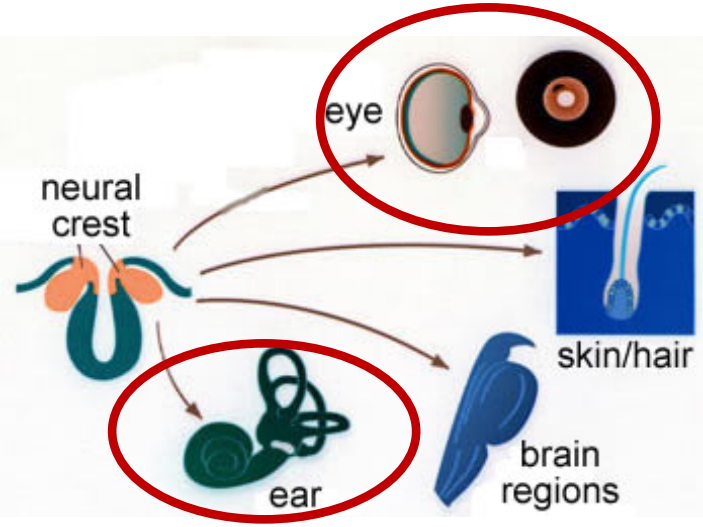
- Causes of seizures in patients with LCMN
    - **Abnormal neuronal migration**
- Typically have partial seizures;
    - 2 infants presented with infantile spasms
- Treatment
    - Anticonvulsants
    - Surgery if a focus can be identified

Cranial nerve symptoms/signs

May have diminished hearing because of melanocytic deposits on auditory nerves

- Screening audiogram recommended for all patients
- Sign language

All patients should have baseline eye exam



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Developmental/behavioral issues

May result from chronic neurologic conditions

May also be due to psychological effects of

Early intervention for all children <3 yrs

May need resource room as child gets older

Certain anticonvulsants may be helpful for treating behavioral issues as well

Spinal nerve root and cord compression

Cord compression from nodules or tethered cord

Delayed motor milestones or toe walking (myelopathy)

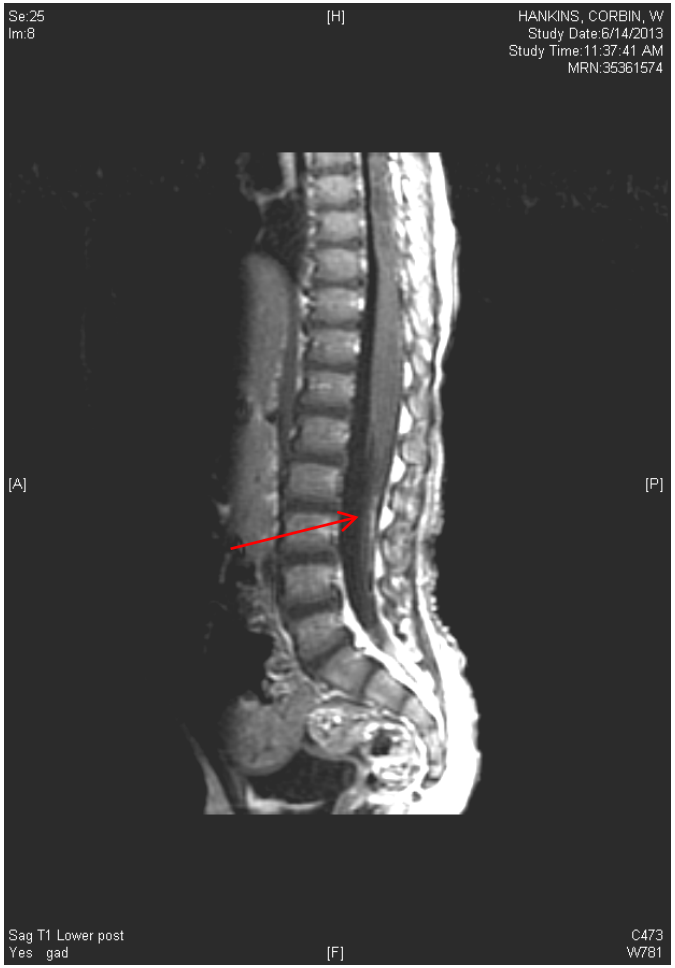
Delay in toilet training

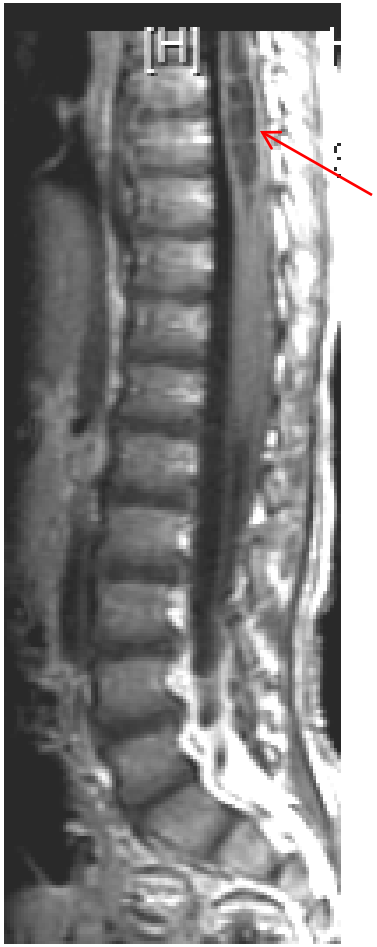
Back pain

Treatment of tethered cord: surgical release

Cord compression: symptomatic: steroids, surgical decompression

Tethered cord with associated syrinx





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Spinal arachnoid cyst

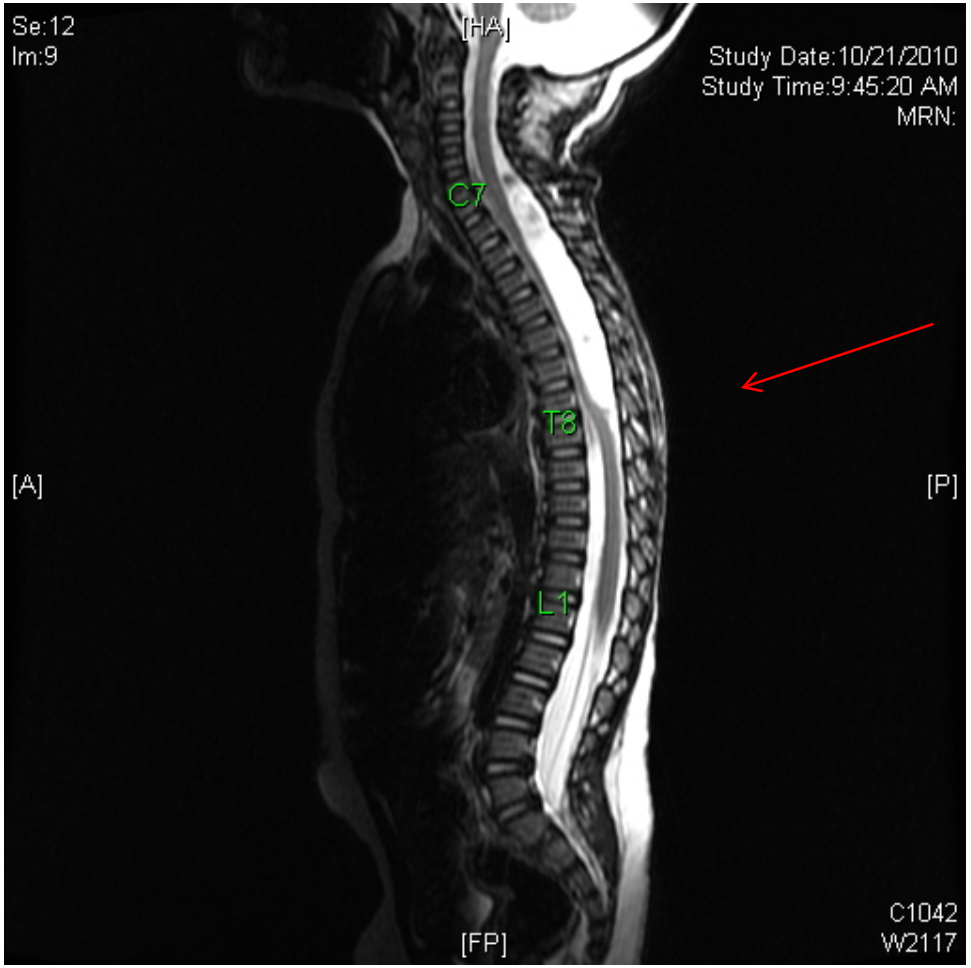

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Photo cred: Brock Elbank and Caring Matters Now

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Spectrum of central nervous system abnormalities in neurocutaneous melanocytosis

VIJAY RAMASWAMY[1] | HOLLY DELANEY[2] | SOFIA HAQUE[2] | ASHFAQ MARGHOOB[3] | YASMIN KHAKOO[1,4]

2012 Dev Med Child

IRB approved

Methods: Chart review 2003-2010

Results

- 14 patients LCMN/NCM identified
- All had MRI brain, spine
- 8/14 patients alive at a median age of 3 years
- 6 had diffuse leptomeningeal enhancement
- 3 had spinal arachnoid cysts
- 1 had a benign cervical spindle cell tumor

Results

5/14: Asymptomatic median age 48 mos

7/14: Seizures; 5 had sz as initial neurologic symptom

11 were normal or had mild developmental delay

- 3 had moderate –severe developmental delay
  - 2 had diffuse leptomeningeal enhancement

2/14 had symptomatic hydrocephalus

- Median age 16.2 mos (birth-8yrs)

4/5 with diffuse leptomeningeal enhancement had primary CNS melanoma

Neurologic summary

Children with mild to moderate NCM can live with some neurologic deficits

Presence of diffuse leptomeningeal disease portends poor prognosis

High incidence of spinal cystic malformations

Imaging of the entire neuraxis should be performed in all children with large congenital melanocytic nevi, ideally before 4 months of age

Screening recommendations

Patients with >20 satellite nevi and/or LCMN >20 especially 40c cm baseline MRI of the brain and spine with and without contrast before age 4 months

Risk of anesthesia needs to be considered

How many MRIs?

If initial MRI normal and child neurologically normal, no further imaging needed

If initial MRI positive for brain lesions child should be followed closely by child neurologist

If child continues to be neurologically asymptomatic, repeat MRI not indicated

If any clinical change MRI should be repeated

Food for thought

One patient had “disappearance” of brain lesions

Isolated reports of patients developing vitiligo who then have regression of brain lesions

Photo cred: Brock Elbank and Caring Matters Now

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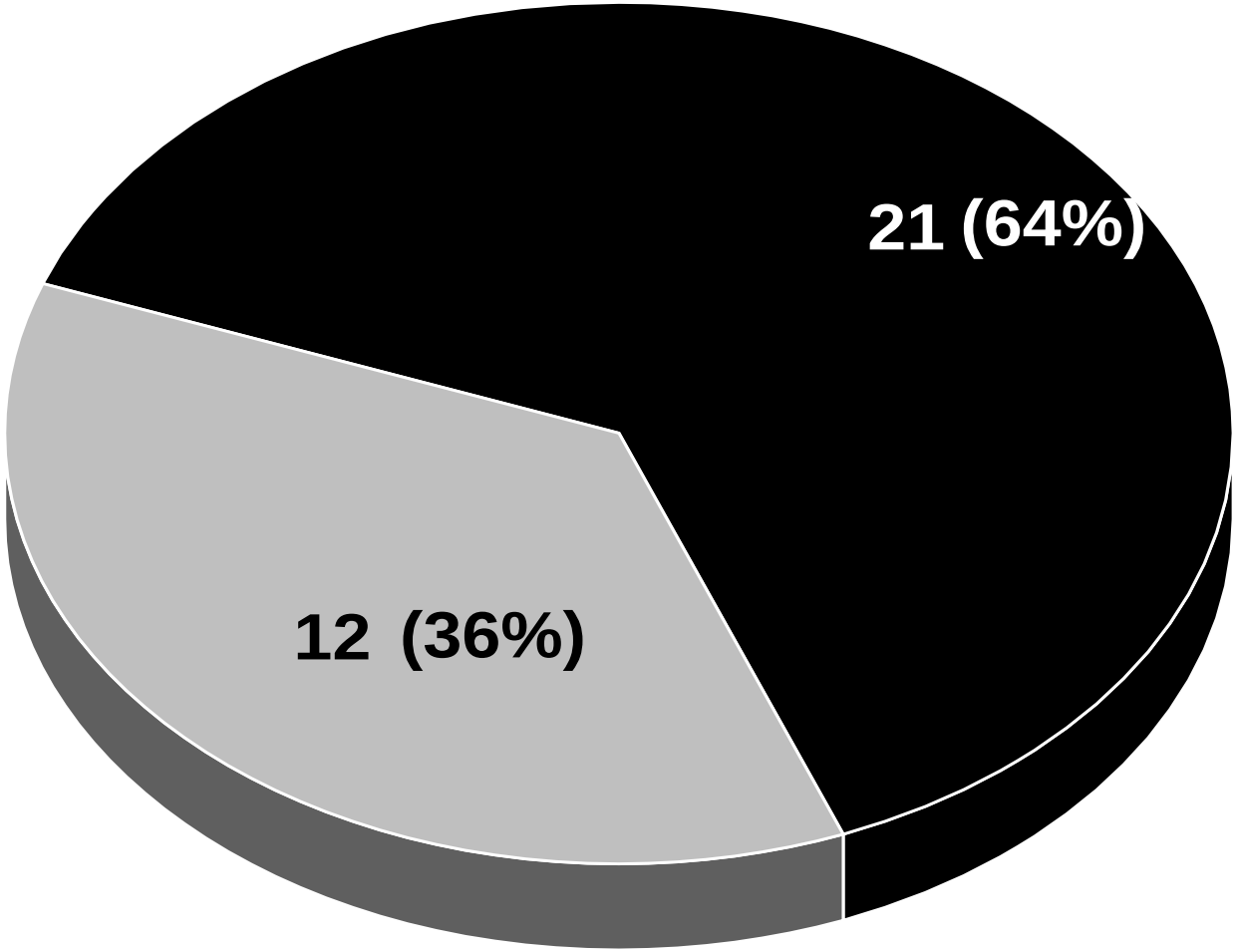
NCM→Melanoma?
Symptomatic NCM: 33 cases reviewed



Courtesy Ashfaq Marghoob

CNS melanoma treatment options

Interferon alpha and IL-2 have not been effective

Temozolomide oral chemotherapy may help prolong survival

Platinum based IV chemotherapy may also prolong survival

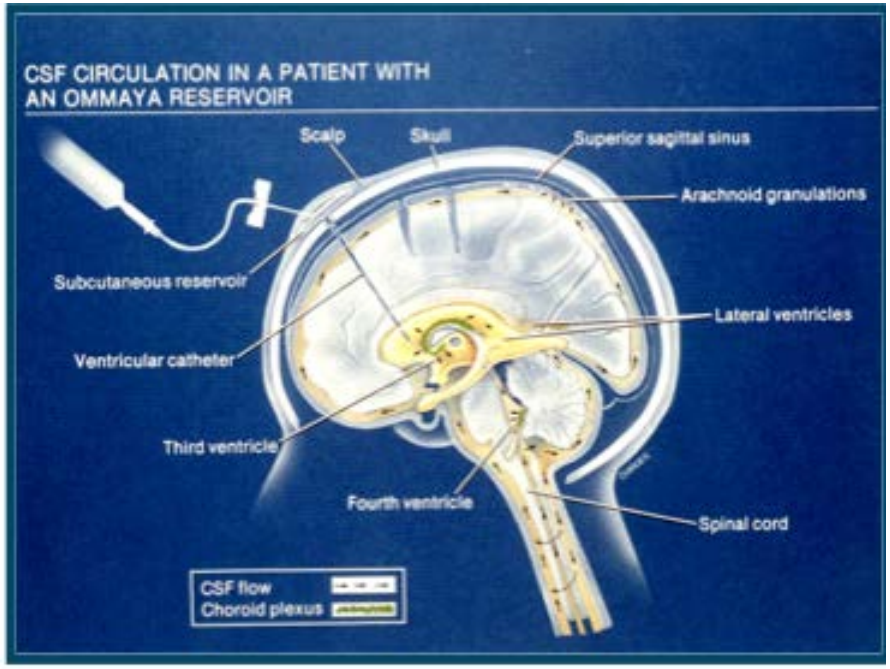
Ipilumimab

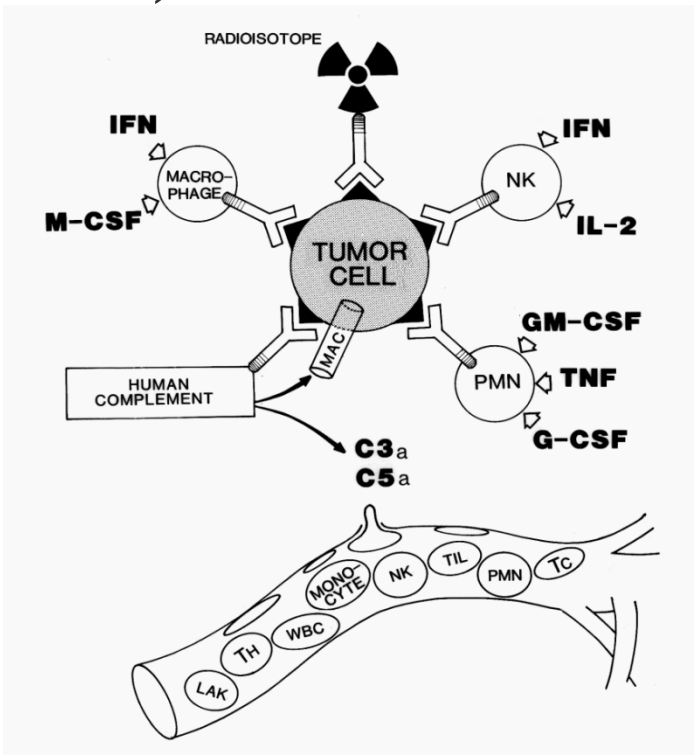
Intrathecal radio-immunotherapy may be more specific

- Non malignant brain lesions: no binding to 3F8 or 8H9
- Poor CSF flow when LMD is widespread

IT radiolabeled antibody: how does it work?

3F8 or 8H9 antibody selectively binds to tumor cells of neural crest origin (e.g. melanoma, medulloblastoma, neuroblastoma)





Courtesy of Dr. Kim Kramer

MSK Kids

Other targets : NRAS pathway

Somatic NRAS mutations identified in patients with LCMN *(Papp et al, 1999)*

Brain lesions also contains NRAS mutations *(Kinsler et al, 2013)*

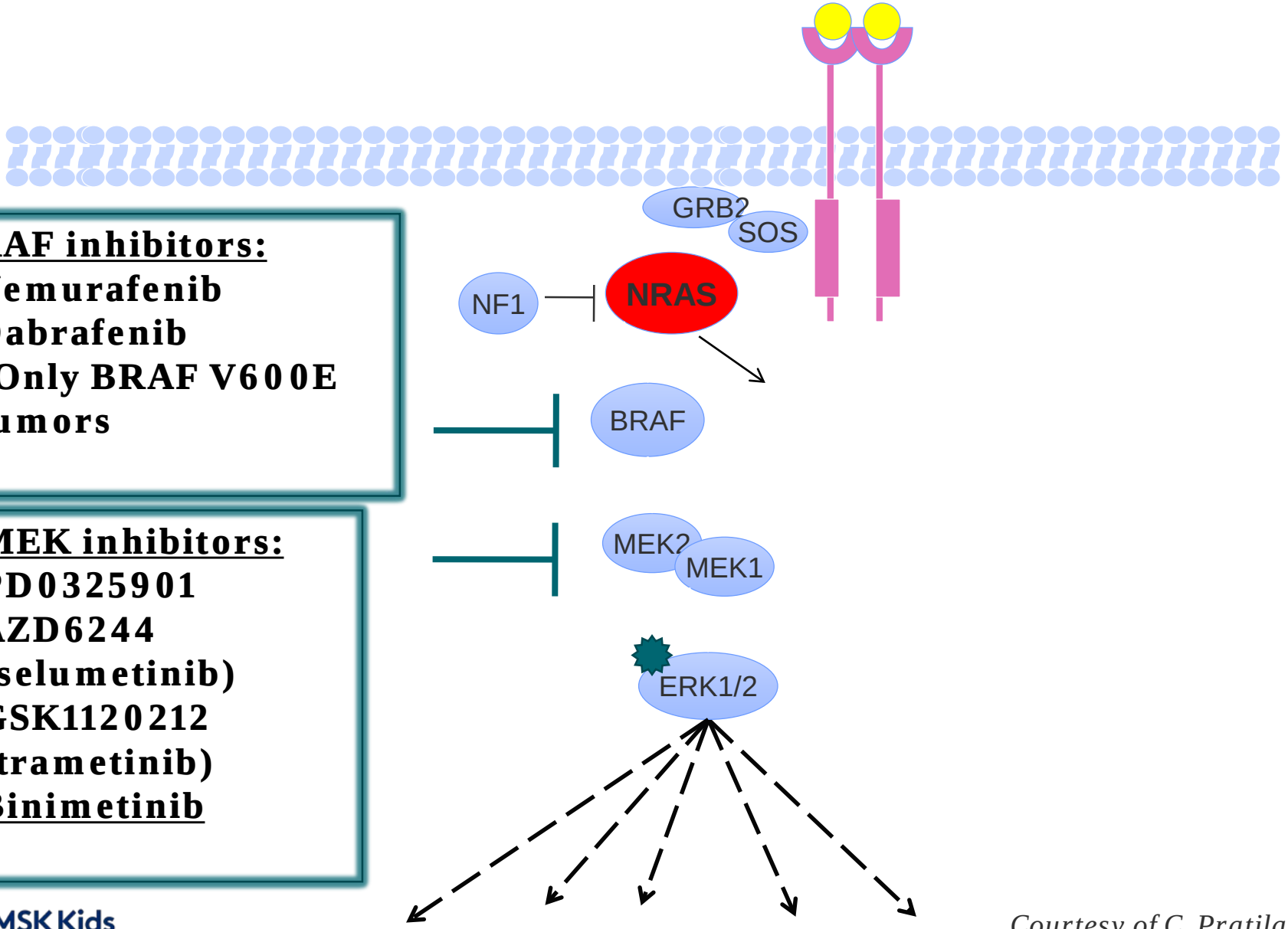
LCMN and brain lesions (esp with nodular features) may also contain BRAF mutations (*Salgado et al, 2015)*

We tested CNS tissue from two patients (one temporal lobe and one SC) and found same mutation

Pharmacologic inhibition of ERK signaling

RAF inhibitors:
Vemurafenib
Dabrafenib
***Only BRAF V600E tumors**

MEK inhibitors:
PD0325901
AZD6244 (selumetinib)
GSK1120212 (trametinib)
Binimetinib



MSK Kids

Courtesy of C. Pratilas

MEK inhibition appears to improve symptom control in primary *NRAS*-driven CNS melanoma in children

Veronica A Kinsler[*,1,2], Patricia O'Hare[3], Thomas Jacques[4], Darren Hargrave[3,5] and Olga Slater[3]

British Journal of Cancer (2017) 116, 990–993

Results: All four had an improvement in symptoms and objectively in signs. These varied from mild improvement for 1 month, to a sustained symptom-free period of 9 months in one case. In all cases there was eventual disease progression through treatment, followed by rapid death after discontinuation. There were no clinically-significant side effects.

Skin of Patients with Large/Giant Congenital Melanocytic Nevi Shows Increased Mast Cells

Cláudia M. Salgado,[1] Randi B. Silver,[2] Bruce S. Bauer,[3] Dipanjan Basu,[1] Lori Schmitt,[1] Yasmin Khakoo,[4] and Miguel Reyes-Múgica[1*]

2014 Ped Dev Pathol

Randi Silver PhD at Weill Cornell studies wound healing

Patients with LCMN have increased numbers of mast cells in tissue

We tested 2 CNS samples but did not detect presence of mast cells

Nevospheres from neurocutaneous melanocytosis cells show reduced viability when treated with specific inhibitors of *NRAS* signaling pathway

Dipanjan Basu†, Cláudia M. Salgado†, Bruce S. Bauer†, Donald Johnson, Veronica Rundell, Marina Nikiforova, Yasmin Khakoo, Lorelei J. Gunwaldt, Ashok Panigrahy, and Miguel Reyes-Múgica

2015 Neuro-Oncology

Nevospheres were isolated from skin, brain and spinal cord of patients with LCMN and brain lesions

All tissues harbored *NRAS* mutations

Vemurafenib (BRAF inhibitor) was not effective

MEK inhibitor only partially inhibited

PI3K and mTOR inhibitors seemed to work better

Pediatric Radiology
https://doi.org/10.1007/s00247-018-4205-x

ORIGINAL ARTICLE

New insights into neurocutaneous melanosis

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Abstract

Background Neurocutaneous melanosis is a rare disorder in which children with large cutaneous melanotic nevi have associated melanosis in the brain. Although many affected children have structurally normal brains, some have associated developmental disorders or brain anomalies.

Objectives To determine the range of extent of brain melanosis as assessed by magnetic resonance imaging (MRI) and to investigate the frequency and types of associated brain anomalies.

Materials and methods We retrospectively reviewed brain and spine MRIs of 80 patients with congenital melanocytic nevi (range: 1 day to 22 years of age) affiliated with Nevus Outreach Inc. from 1998 to 2017. Central nervous system (CNS) melanosis was diagnosed when a mass with abnormal parenchymal T1 hyperintensity was seen. The locations of abnormal signal, associated malformations, the presence of contrast enhancement and, in patients with more than one MRI, changes over time were recorded. Associations among findings were analyzed using chi-square test or Fisher exact test.

Results Brain abnormalities were identified in 33 patients. The most common finding was melanosis in the amygdala, which was found in 31 patients (an isolated finding in 14 patients). Nineteen patients had melanosis in the brainstem, cerebellum, cerebral cortex or thalamus. Cerebral and/or spinal leptomeningeal enhancement was uncommon (five patients). Hindbrain melanosis was associated with cerebellar and pontine hypoplasia (P=0.012). Brain melanosis was most easily seen on T1 images prior to myelination; reduced/loss of visibility was noted as the CNS matured.

Conclusion Brain melanosis is a common manifestation in children with large cutaneous melanotic nevi, most commonly found

CASE REPORT

Malignant transformation of neurocutaneous melanosis (NCM) following immunosuppression

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Genetic Abnormalities in Large to Giant Congenital Nevi: Beyond *NRAS* Mutations

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Table 2. Molecular Status of the CMN

Patient Number	Sex	CMN Subgroup	Krengel Classification	*NRAS* Status	*BRAF* Status	Other Alterations
1	F	Classic	G2 C1 R1 N0 H2 S3	$NRAS^{Q61R}$	WT	$PIK3CA^{R524K}$[3]
2	F	Classic	G1 C1 R2 N2 H1 S3	WT	WT	
3	M	Classic	G1 C2 R1 N2 H0 S3	WT	WT	*ZEB2-ALK*[4]
4	M	Classic	G2 C2 R1 N0 H2 S3	WT	WT	*SOX5-RAF1*[4]
5	F	Classic	G2 C2 R2 N2 H0 S2	$NRAS^{Q61K}$	WT	
6	F	Classic	G2 C0 R2 N2 H0 S3	WT	WT	
7	F	Classic	G2 C0 R0 N2 H0 S3	$NRAS^{Q61R}$	WT	*GGNBP2-MYO19*[3]
8	F	Classic	G1 C2 R1 N1 H1 S3	$NRAS^{Q61K}$	WT	
9	M	Classic	G2 C2 R1 N1 H0 S3	$NRAS^{Q61K}$	WT	
10	F	Classic	G2 C2 R1 N1 H1 S3	$NRAS^{Q61R}$	WT	
11	F	Classic	L1 C1 R0 N2 H1 S3	WT	WT	
12	F	Classic	L1 C1 R1 N0 H2 S0	$NRAS^{Q61K}$	WT	
13	M	Spilus like	G2 C0 R0 N0 H0 S2	WT	WT	$KRAS^{G174S}$
14	M	Spilus like	G1 C1 R0 N0 H0 S1	$NRAS^{Q61L}$	WT	
15	F	Spilus like	G1 C2 R0 N0 H0 S3	$NRAS^{G13R}$	WT	
16[1]	F	Spilus like	L1 C1 R1 N1 H0 S0	WT	$BRAF^{G464E}$ $BRAF^{L584F}$	
17[2]	M	Spilus like	L1 C1 R0 N0 H0 S1	WT	WT	$GNAQ^{I190I}$/APC^{P1268L}/MET^{S290} MET^{E1232K}/$EGFR^{L760L}$

Memorial Sloan Kettering Cancer Center

Characteristics of patients with neurocutaneous melanosis: the Memorial Sloan Kettering Cancer Center experience from 2003-2018

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Results

Patient characteristics

Median age at diagnosis = 5 months (range: 10 days – 25 years)

48 patients referred for NCM assessment (30 male)

- 34 (71%) had neurologic symptoms and abnormal imaging
- 6 (12.5%) were neurologically normal despite radiographically identified NCM
- 5 (10%) patients were neurologically normal and had normal imaging
- 3 (6%) had neurologic symptoms with a normal MRI

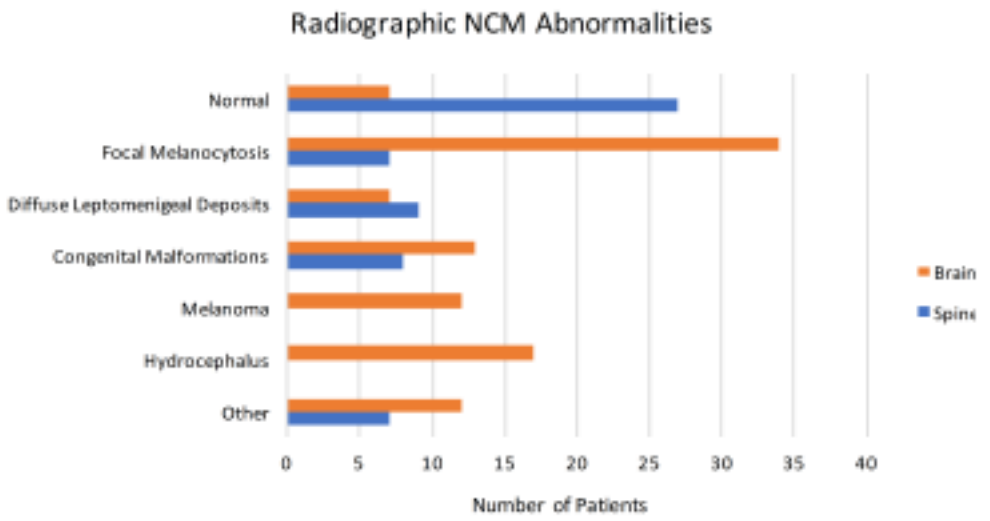

Photo cred: Brock Elbank and Caring Matters Now

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Future directions

Targeted therapy

Mast cell targets

PD1: nivo/ipi

Better characterizing NCM radiographically and clinically

Predicting which patients will develop CNS melanoma

Raising awareness in the medical community

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Patients and families

MSK Kids
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MSK Kids

Nevus Outreach
The Association for Large Nevi & Related Disorders

Naevus INTERNATIONAL