



Manchester Rare
Conditions Centre

MANCHESTER ESHG

SYNDROMOLOGY AND
DYSMORPHOLOGY COURSE 2026

14-16 October 2026 • The Manchester Academic Health Science Centre, Manchester, M13 9PL



The European Society
of Human Genetics

Quiz!

Hair, nails, skin and teeth as a clue to syndrome diagnosis

Sofia Douzgou Houge

NORWEGIAN CENTRE FOR
RARE DISEASES

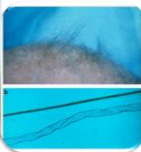
HELSE BERGEN

1

hair as a clue to
diagnosis

2

- which condition?
- what is the presenting clinical picture?
- what imaging studies you should look for/request?
- inheritance?



Tümer Z, Möller LB. Eur J Hum Genet. 2010;18:511

1

3

ATP7A variants - Menkes Disease (Kinky Hair)

- X-linked
- A clinical spectrum of disorders including
 - Menkes Disease
 - Occipital Horn Syndrome
 - Distal motor neuropathy
- Encodes a protein with the role of regulating copper levels in the body



Tümer Z, Möller LB.
Eur J Hum Genet. 2010;18:511

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Effects on Cu-Requiring Enzymes in Menkes Disease

- **Lysyl hydroxylase** - connective tissue features, skin and joint laxity, bladder diverticula, osteopenia, vascular tortuosity, premature rupture of membranes
- **Cytochrome -c-oxidase** – Leigh-like picture
- **Dopamine beta hydroxylase** – temp instability, ptosis, neurological effects
- **Tyrosinase** – Pale hair

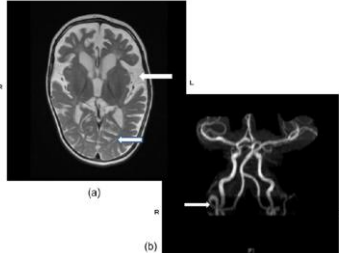
Biochemical findings					
Low copper	83.3% (75/90)	72.7% (8/11)	73.3% (22/30)	80.2% (105/131)	0.395
Low ceruloplasmin	96.6% (85/88)	63.6% (7/11)	80.0% (24/30)	89.9% (116/129)	<0.001 (0.009, 0.024, 1.000)

De Feyter S, Beyens A, Collewaert B. *Journal of Inherited Metabolic Disease.* 2023;46(2):163–173

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ATP7A-related disease (Kinky Arteries)

- delayed myelination
- white matter changes (may mimic a leukodystrophy)
- transient temporal lobe abnormalities
- global atrophy
- subdural hygromas
- tortuous cerebral blood vessels



(a) (b)

Magnetic Resonance of Myelination and Myelin Disorders.
MS van der Knaap, J Valk. 3rd ed. Springer

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INSR-Related Severe Insulin Resistance Syndromes

* 147670

INSULIN RECEPTOR; INSR

HGNC Approved Gene Symbol: [INSR](#)

Cytogenetic location: 19p13.2 Genomic coordinates (GRCh38): 19:7,112,265-7,294,414 (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Gene (clinical frequency)	Phenotype MIM number	Inheritance	Phenotype mapping key
Hyl3.2	Diabetic mellitus, insulin-resistant, with acanthosis nigricans		612401		3
	Diabetes syndrome		246200	AR	3
	Hypoadrenocorticism/hypoglycemia, familial, 5		609948	AD	3
	Polycystic ovaries with hyperandrogenism		261700	AD	2

*also, hyperkeratosis and acanthosis nigricans

Treatments under investigation

- Recombinant Human Insulin-like Growth Factor 1 (rhIGF-1)
- Recombinant Human Leptin (Metreleptin)

Gene Reviews, updated 2025

- Macrocephaly
- Which clinical follow-up you will request?



Czeschik et al. 2013

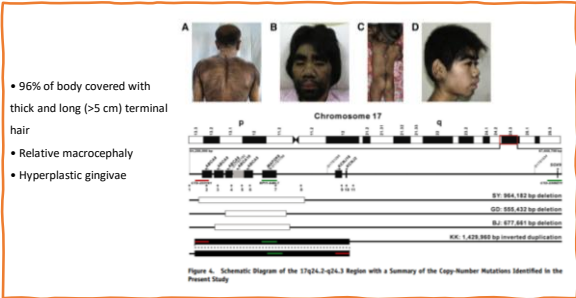
ABCC9-Related Cantu syndrome

TABLE I. Cardiac Manifestations in Cantu Syndrome

	Patient 1 4 years 0 months	Patient 2 31 years	Previously reported patients (n = 83 years [3.5 months to 50 years])
Age	—	—	—
Cardiomegaly	+	—	43/54 ^a
Pericardial effusion	—	—	9/51 ^a
Thoracic aortic aneurysm	—	+	0/53 ^a
Congenital heart defects	—	—	25/54 ^a
PLA	—	—	16/43 ^a
Cardiac hypertrophy	—	—	27/44 ^a
Cardiomegasy	—	—	7/44 ^a
Cardiac hypertrophy	—	—	20/44 ^a
Left ventricular hypertrophy	—	—	12/44 ^a
Biventricular hypertrophy	—	—	4/44 ^a
Right ventricular hypertrophy	—	—	2/44 ^a
Bilateral left ventricle	—	—	2/44 ^a
Hemodynamic abnormalities	+	—	21/33 ^a
Pulmonary hypertension	+	—	—
Tetralogy of Fallot/ventricular septal defect	—	—	7
Mitral regurgitation/mitral incompetence	—	—	5
Aortic regurgitation	—	—	3
Dyspnea on exertion	—	—	3
Orthopnea	—	—	1
Cardiac failure	—	—	6/8

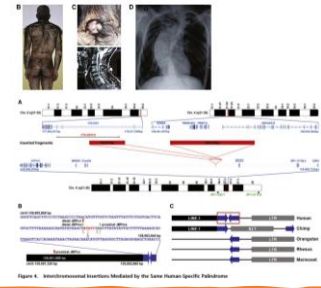
*also, headaches!

Hiraki et al., 2014



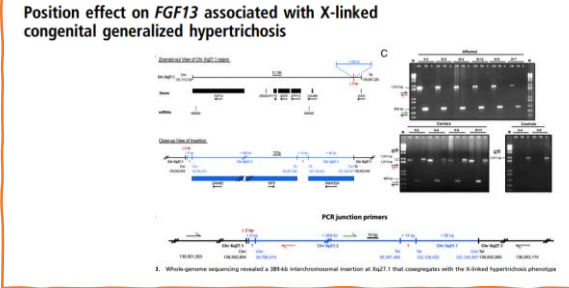
Sun et al, 2009

- 96% of body covered with thick and long (>5 cm) terminal hair
- Relative macrocephaly
- Hyperplastic gingivae



Zhu et al, 2011

- 96% of body covered with thick and long (>5 cm) terminal hair
- Scoliosis
- Spina bifida



De Stefano, PNAS, 2012

Position effect on *FGF13* associated with X-linked congenital generalized hypertrichosis

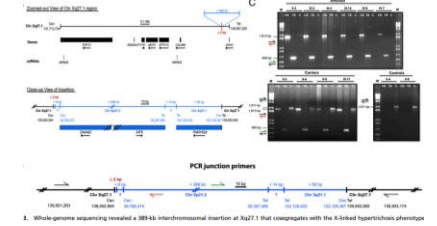


Figure 6. Position effect on FGF13 associated with X-linked congenital generalized hypertrichosis

Nails (and hair) as a clue to diagnosis

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• which condition?

- intellectual disability
- delayed growth
- hypoplastic, 5th digit nails and phalanges
- hirsutism



Gorlin RJ et al. 2001.
4th ed. Oxford University Press.

Santen et al., 2012

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Coffin-Siris syndrome

- 1970, Coffin and Siris, 3 children
- severe intellectual disability
 - delayed growth
 - hypoplastic, 5th digit nails and phalanges
 - other, minor skeletal findings

- hypotonia
- postnatal growth deficiency
- microcephaly
- lumbosacral hirsutism
- hearing loss
- CHD

- AD, mutations in genes (12 so far) encoding subunits of the SWI/SNF complex, also known as the BAF complex, which functions as a chromatin remodeling factor.



Gorlin RJ et al. 2001.
5th ed. Oxford University Press.

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- which condition?
- intellectual disability
- epilepsy
- broad thumbs
- Great toes anonychia (absent nails)



Sanfey et al., 2012

LETTERS

nature genetics

Mutations in the voltage-gated potassium channel gene *KCNH1* cause Temple-Baraitser syndrome and epilepsy

Cao Simona^{1,2,3,4}, Lachlan D Rush^{1,2,3}, Joanne Crawford¹, Linda Mei¹, Ben G Kellie¹, Gregory J Baillie¹, Yasmina Alame¹, Adeline Jacques¹, Franck Alain Verheul^{1,2}, Joseph Sheu¹, Glenda Young¹, Sarah Gales¹, Adam Yekta¹, Sean M Grimmond^{1,2}, Julie McGaughey^{1,2,3}, Glenn F King^{1,2}, Michael T

- intellectual disability
- epilepsy
- dysmorphic facial features
- broad thumbs
- great toes with absent/hypoplastic nails

➤ two women with epileptic seizures and children with TMBTS were shown to have low-level mosaicism of the familial *KCNH1* mutations (Simons et al. 2015) demonstrating that mosaic mutations in *KCNH1* can lead to epileptic seizures in otherwise unaffected individuals.





Case from Dyscrne

Key Details

18 year old male with moderate learning disability (non-verbal IQ 55) and short stature. Coarse facial features, thick lips and gums, hypertrichosis and absent distal phalanges and nails of toes, 4th fingers and 1. index finger. Scoliosis, hypermetropia and R hearing loss. CF shows normal atrophy. Diagnoses considered are Coffin-Löscher, Zimmerman Laband and DOOR. Normal organic acids. Array showed 23Mb del 22q13.33 inherited from father.

Distinctive Features

- hypertrichosis
- hypoplasia of distal phalanges
- thick lip
- coarse face
- mental retardation
- absence of nails
- hypotrophy of auditory canal
- gingival hyperplasia
- scoliosis
- low implanted hair

Zimmerman-Laband Syndrome

- ID
- Ano/hyponychia
- Gingival fibromatosis and dental defects
- Hypertrichosis



Garlin RJ et al. 2001.
5th ed. Oxford University Press.
Bazopoulou-Kyrkanidou et al. 1990

Syndromic disorders caused by gain-of-function variants in *KCNH1*, *KCNK4*, and *KCNN3*
—a subgroup of K⁺ channelopathies



Gripp K et al, EJHG, 2021

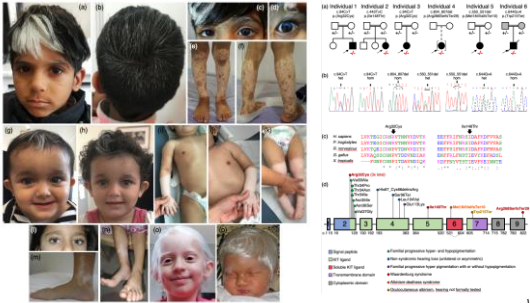
Gene	<i>KCNH1</i>	<i>KCNK4</i>	<i>KCNN3</i>			
Total number of patients	270	47	7			
Neurodevelopment						
Mild-moderate ID	150	19%	44	100%	13	17%
Severe ID	1821	80%	104	100	23	80%
Mild-moderate ID	123	4%	33	100%	13	17%
Severe ID	2323	90%	102	100	23	80%
Hypotonia	1527	90%	48	67%	23	80%
Neuroimaging	1427	89%	103	100	23	80%
Muscular abnormalities						
Hypokalemic periodic paralysis or none at all	1317	76%	65	100%	ND	ND
Finger and/or toe	1124	80%	16	17%	ND	ND
Brachial dimple and/or toe	1418	79%	16	17%	ND	ND
Peroneal placement and long thumb	1524	63%	26	10%	ND	ND
Long great toe	1427	79%	58	87%	10%	10%
Nails						
Absence or hypoplasia of thumb nail	1427	89%	68	100%	10%	10%
Absence or hypoplasia of great toe nail	1427	89%	68	100%	10%	10%
Absence or hypoplasia of other fingers and/or toe nails	1420	80%	68	100%	10%	10%
Other findings						
Clinical enlargement	1519	79%	48	67%	23	100%
Hypertrichosis	1516	19%	58	80%	23	100%

Skin as a clue to diagnosis



- 3rd child of healthy, remotely consanguineous couple
- Mild gross motor delay; Frequent falls after achieving late ambulation
- Left sensorineural hearing loss (complete)

Biallelic *KITLG* variants lead to a distinct spectrum of hypomelanosis and sensorineural hearing loss



Vona et al., JEADV, 2022

Global developmental delay
Feeding and nutritional difficulties
Sleep difficulties
Relative macrocephaly

Balance and coordination difficulties
Oromotor difficulties:
Unclear speech, drooling and feeding difficulties
Impaired eye coordination



NF1
Global developmental delay
Feeding and nutritional difficulties
Sleep difficulties
Relative macrocephaly

**ATM
comp heterozygous**
Balance and coordination difficulties
Oromotor difficulties:
Unclear speech, drooling and feeding difficulties
Impaired eye coordination

TSC1



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Consensus clinical diagnostic criteria for **tuberous sclerosis complex** ([Northrup et al 2021](#)): TSC **possible** with either

- one major clinical feature or
- two or more minor features

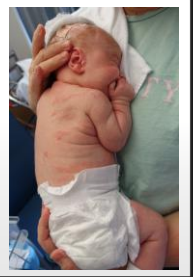
Major features

- Angiofibromas (≥3) or fibrous cephalic plaque
- Cardiac rhabdomyoma
- Multiple cortical tubers and/or radial migration lines
- Hypomelanotic macules (≥3 macules that are at least 5 mm in diameter)
- Lymphangioleiomyomatosis (LAM) (See [Clinical Diagnosis](#), *Note.)
- Multiple retinal nodular hamartomas
- Renal angiomyolipoma (≥2) (See [Clinical Diagnosis](#), *Note.)
- Shagreen patch
- Subependymal giant cell astrocytoma (SEGA)
- Subependymal nodules (SENs) (≥2)
- Ungual fibromas (≥2)

Minor features

- Sclerotic bone lesions
- "Café-au-lait" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs)
- Dental enamel pits (≥3)
- Intraoral fibromas (≥2)
- Multiple renal cysts

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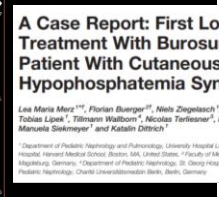
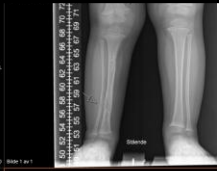
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Linear sebaceous nevus with mosaic RAS/MAPK pathway gene mutations

Nat Genet. 2012 10;44(7):783-7

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A Case Report: First Long-Term Treatment With Burosumab in a Patient With Cutaneous-Skeletal Hypophosphatemia Syndrome

Lee Maria Mura^{1,2,3}, Florian Burger^{1,2}, Nils Zingelbach¹, Martin Zanker¹, Ilse Wieland¹, Tobias Liska¹, Tillmann Wallborn¹, Nicolas Terheiden¹, Frank Prenzler¹, Manuela Sienkmeier¹ and Katrin Dittsch¹

¹Department of Pediatric Nephrology and Pulmonology, University Hospital Leipzig, Leipzig, Germany; ²Boston Children's Hospital, Harvard Medical School, Boston, MA, United States; ³Faculty of Medicine, University Hospital Magdeburg, Magdeburg, Germany; ⁴Department of Pediatric Nephrology, St. Georg Hospital, Leipzig, Germany; ⁵Department of Pediatric Nephrology, Charité Universitätsmedizin Berlin, Berlin, Germany

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Proposed tumour surveillance in mosaic HRAS-related RASopathy

2024 SYSTEMATIC REVIEW	69 reported patients	17% developed cancer	7 / 7 RMS were urgent	IR 800 RMS vs general population
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1 RHABDOMYOSARCOMA (RMS)

Complete ultrasound of the pelvis and lower abdomen

Perform with a full bladder when feasible to improve tissue visualisation.

Q3M

Every 3 months

Use the same imaging interval throughout surveillance.

D-5

Start immediately at diagnosis

Continue through age 5

MRI

Escalate to regional MRI

If haematuria or complete urinary retention develops.

2 WILMS TUMOUR (RENAL)

Wilms tumour was uncommon in the mosaic HRAS/KRAS cohort (1/69)

Renal ultrasound with retroperitoneal Doppler

Q3M

Every 3 months

Combine with the pelvic/low abdominal ultrasound.

5T

Continue through age 7

Routine renal surveillance may stop after the seventh birthday.

ADAPT

Extrapolated surveillance

Based on protocols for established paediatric Wilms predisposition.

One coordinated ultrasound appointment every 3 months: pelvis + lower abdomen + kidneys

Windrich et al., Clin Cancer Res 2024

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Teeth as a clue to diagnosis

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Which condition?

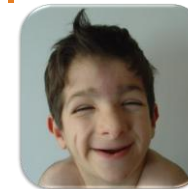
- Intellectual disability
- Dysmorphic features
- Cheloids
- Accessory cusps on the lingual side of incisors



Deepthi DA, et al. *J Clin Diagn Res.* 2017;11(5):ZJ05–ZJ06. Figure 3.

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Consensus group: 52 participants • 41 institutions • 11 countries • 6 patient advocacy groups representatives



- Talon cusps are accessory cusps on the lingual side of incisors
- 27% of primary incisors and 70–92% of permanent ones
- *CREBBP*, *EP300* are strongly expressed in both incisors and molars

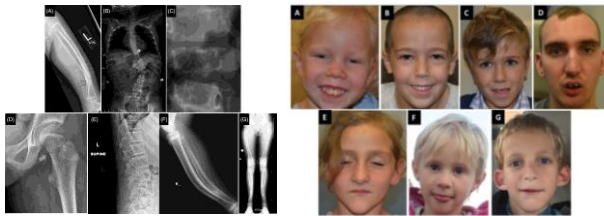
Intraoral characteristics

- R39**
In every newborn or child with RTT the palate should be closely examined at diagnosis by inspection and palpation.
Strength of recommendation: A++
- R40**
Specific attention should be paid to talon cusps in everyone with RTT, especially in the permanent dentition. Treatment is indicated if interfering with occlusion, mouth closure or causing caries.
Strength of recommendation: A++
- R41**
Prescribing daily oral hygiene is strongly recommended in individuals with RTT. Regular professional dental assessment should take place periodically by a specialist dental service. Detailed dental assessment and treatment may be facilitated if performed under sedation or anesthesia.
Strength of recommendation: A++

Lacombe et al. *J Med Genet* 2024

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Glass syndrome – *SATB2* - AD



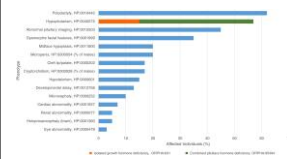
Clinical Genetics, 2017, DOI: (10.1111/cge.13121)

Gene Reviews

Culler Jones syndrome

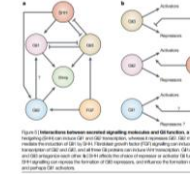


Truncating and zinc-finger variants in *GLI2* are associated with hypopituitarism



Corder et al, 2022

- SHH protein acts as a crucial factor that patterns the ventral forebrain and is required for the division of the primordial eye field and brain into 2 distinct halves.
- Occasional pituitary hypoplasia and/or holoprosencephaly also seen in patients with Pallister-Hall syndrome caused by *GLI3* mutations



	Investigation date (2007)	2016	Interviewer	Richardson, Genna
Step 1	1/10/2016- 3/12/2016	Participants in study of <i>Salmonella</i> infections	Dr. Genna Richardson	Richardson, Genna

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of Human Genetics

Thank you !



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