Mosaic Disorders in Children

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Overview

- **What is a mosaic?**

Definition and types of mosaicism

- **Cutaneous mosaicism in children**

- **Approach to a suspected mosaic patient**


What is a mosaic?

Mosaicism - traditional definition

- The coexistence of cells with at least two genotypes, in an individual derived from a single zygote

Problems

- We all have mutations *in utero* all the time
- We all have mutations after birth all the time – naevi, cancer etc.

We are all mosaic by this definition

Kinsler V et al. Mosaic abnormalities of the skin: review and guidelines from the European Reference Network for rare skin diseases BJD 2020

Mosaicism – definition updated from genetic knowledge

Mosaic disorder

The coexistence of cells with at least two genotypes, **by the time of birth***, in an individual derived from a single zygote, where the postzygotic mutation has led to **the whole disease phenotype**.

* This does not mean that the phenotype has to be present at birth

Kinsler V et al. Mosaic abnormalities of the skin: review and guidelines from the European Reference Network for rare skin diseases BJD 2020

Classification of mosaicism according to..

Mechanism of origin

- Single-point mutation, loss of heterozygosity, recombination, non-disjunction

Organ involvement

- Somatic, gonadal, gonado-somatic

Pattern

- Segmental (with a pattern), non-segmental

Category

- Genomic or epigenetic

Timing

- Very early, early, late or postnatal

Direction

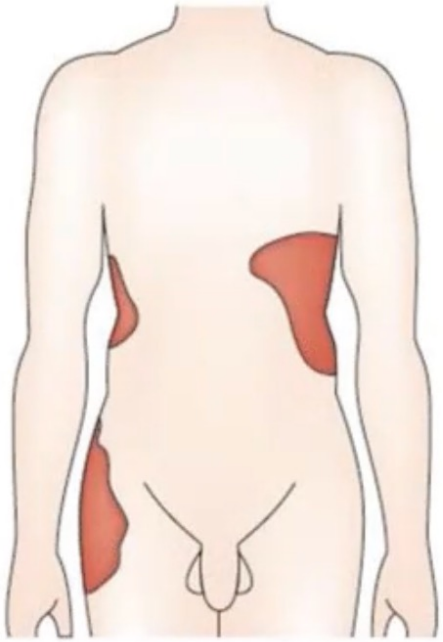
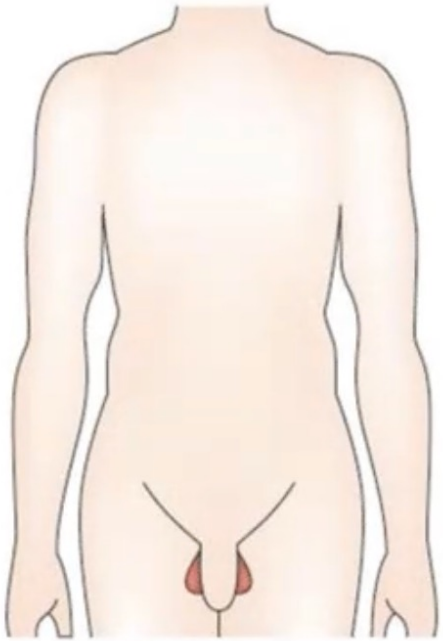
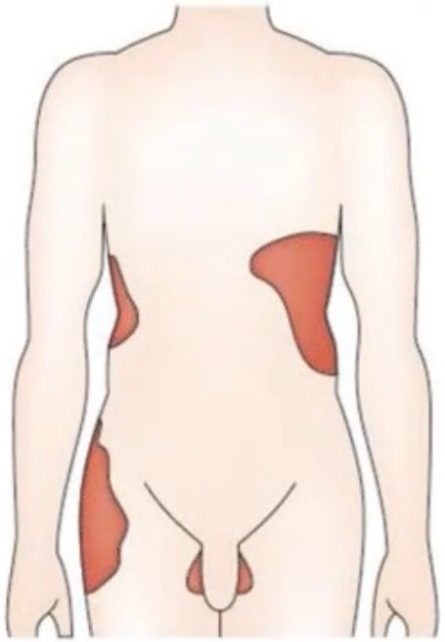
- Forward or backwards

Classification proposed by A Torrelo 2021

Classification of mosaicism according to..

Organ involvement

Classification proposed by A Torrelo 2021

Only somatic cells	Only gonadal cells (germinal)	Somatic and gonadal cells
		
Somatic Mosaicism	Gonadal Mosaicism	Gonado-somatic Mosaicism
Not passed on	Passed on	Passed on

Classification proposed by A Torrelo 2021

Classification of mosaicism according to..

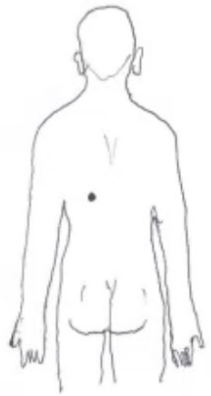
Patterns

Classification proposed by A Torrelo 2021

The Categories of Cutaneous Mosaicism: A Proposed Classification

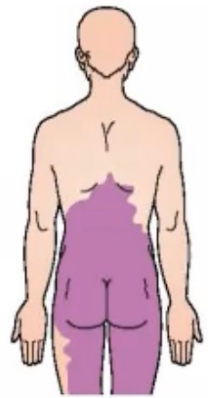
Rudolf Happle*

1. Non-segmental Mosaicism



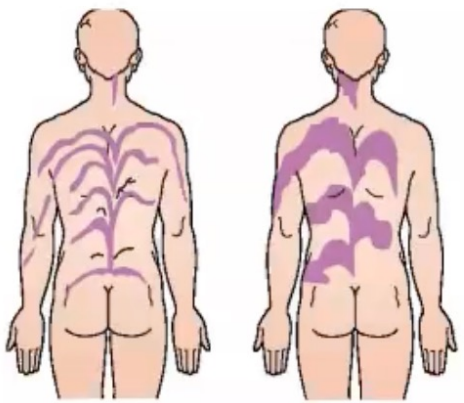
Single point mosaicism

Disseminated mosaicism

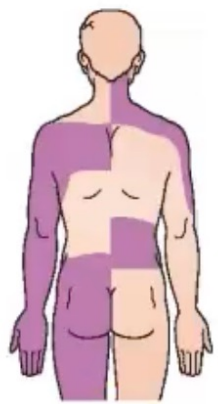


Patchy mosaicism without midline separation

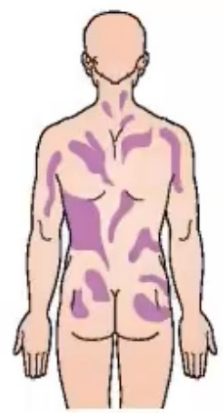
2. Segmental Mosaicism



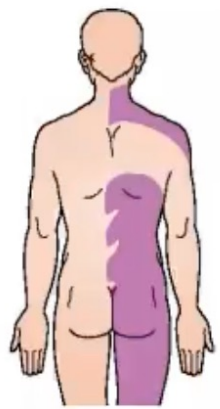
Lines of Blaschko



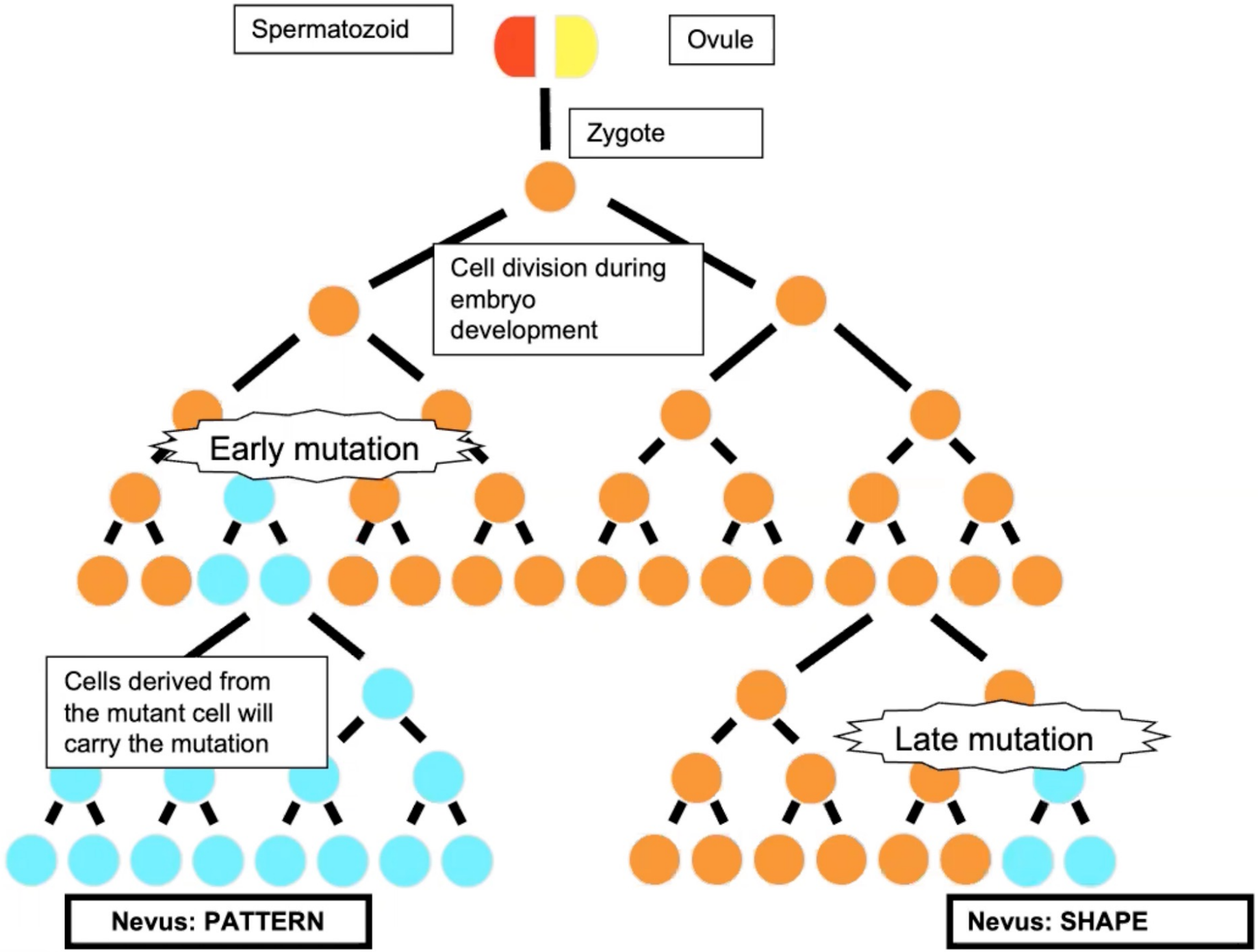
Block or flag-like pattern

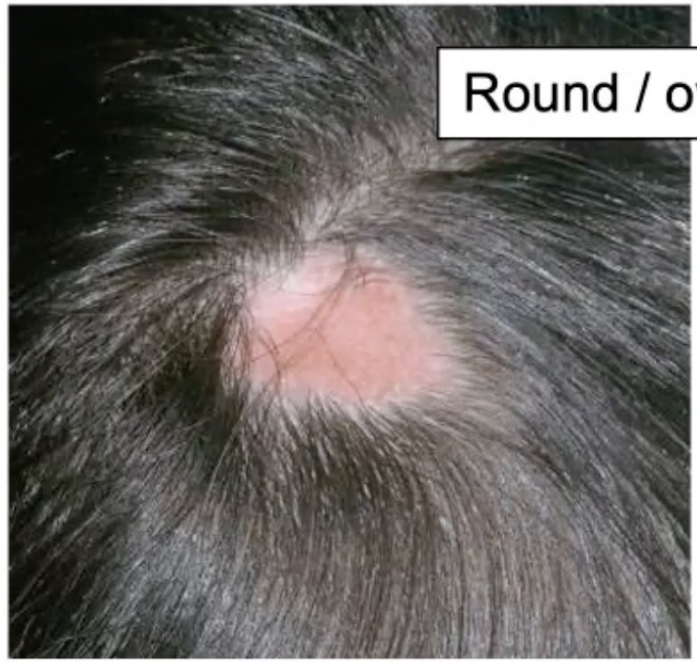


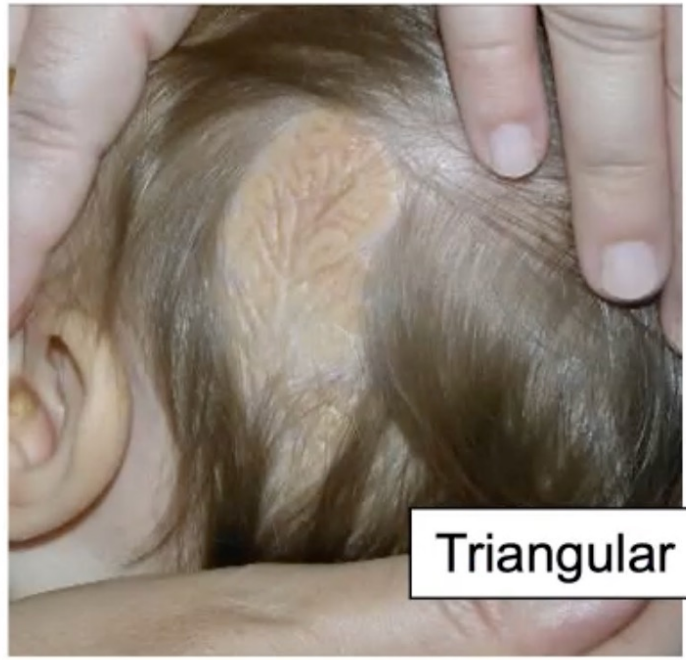
Phylloid pattern

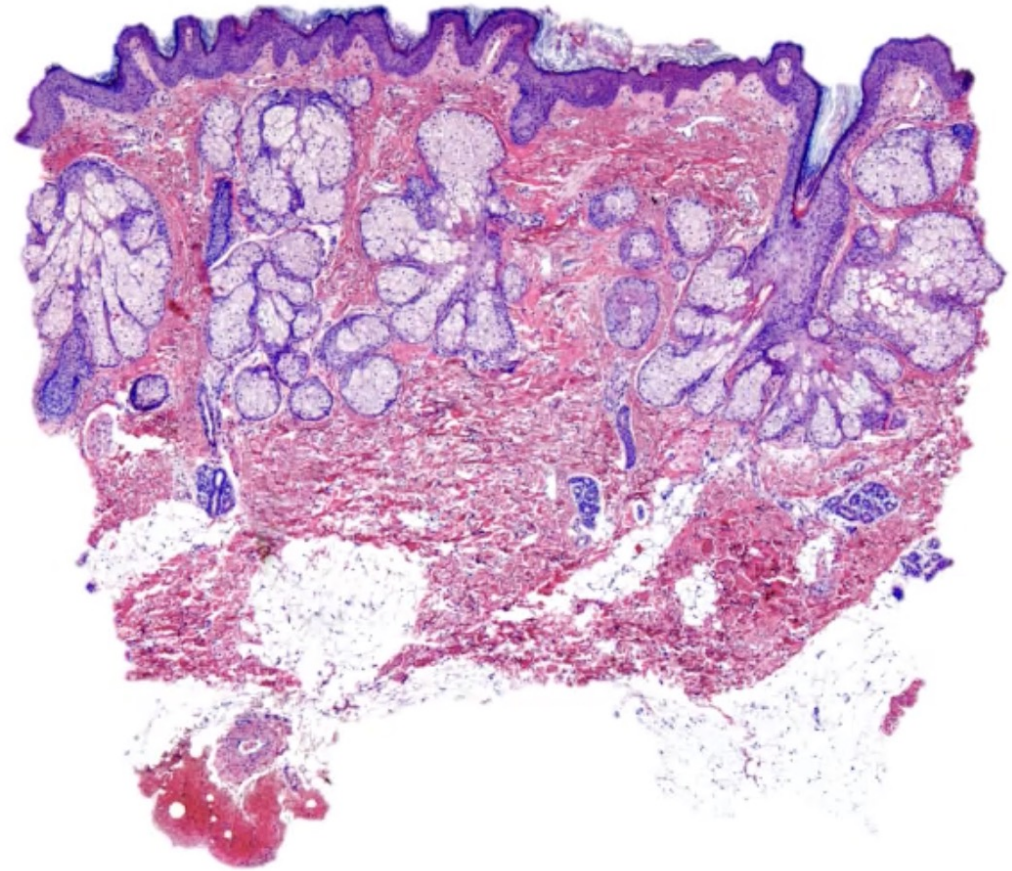


Lateralization pattern

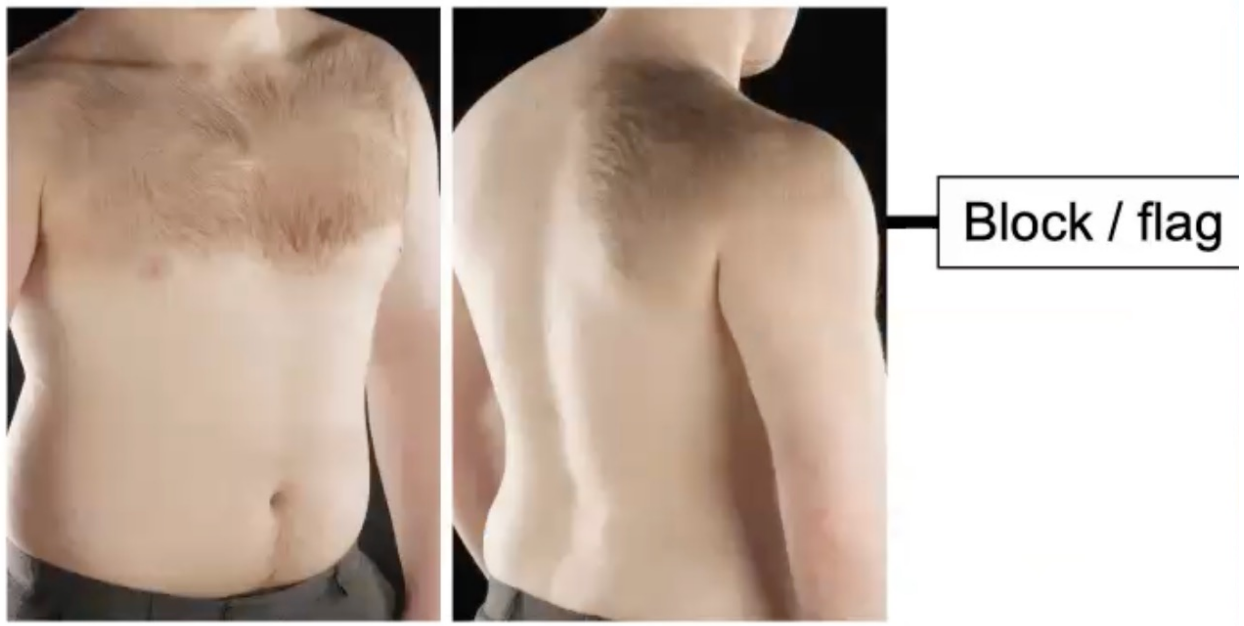

Spermatozoid
Ovule
Zygote
Cell division during embryo development
Early mutation
Cells derived from the mutant cell will carry the mutation
Late mutation
Nevus: PATTERN
Nevus: SHAPE


Round / oval


Triangular



Actb mosaicism



Block / flag

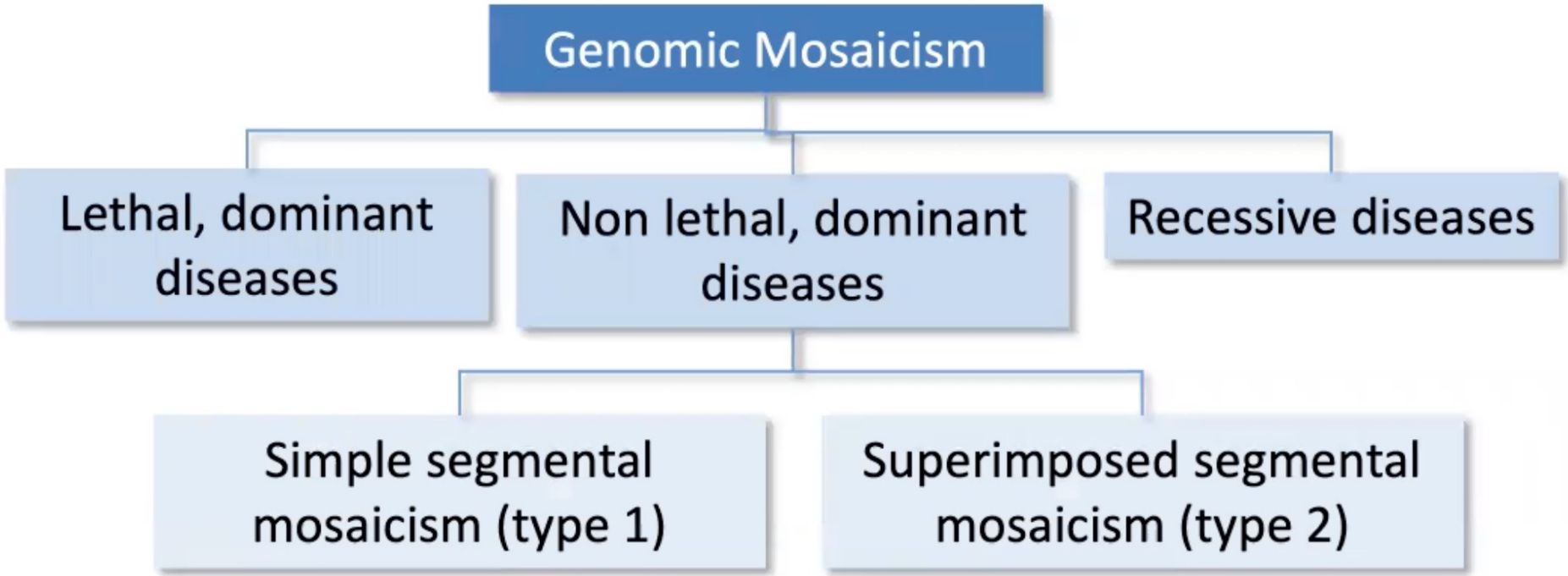
Becker’s naevus

Gnaq/11 mosaicism

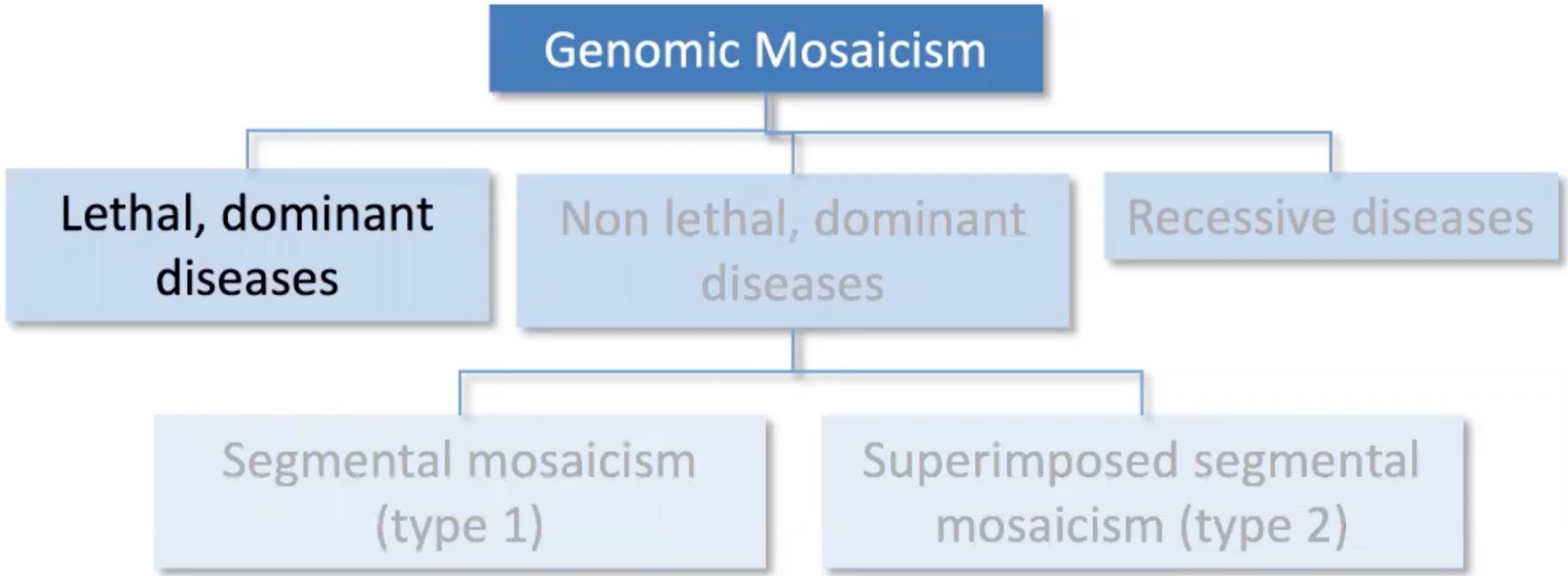
Classification of mosaicism according to..

Category

Classification proposed by A Torrelo 2021

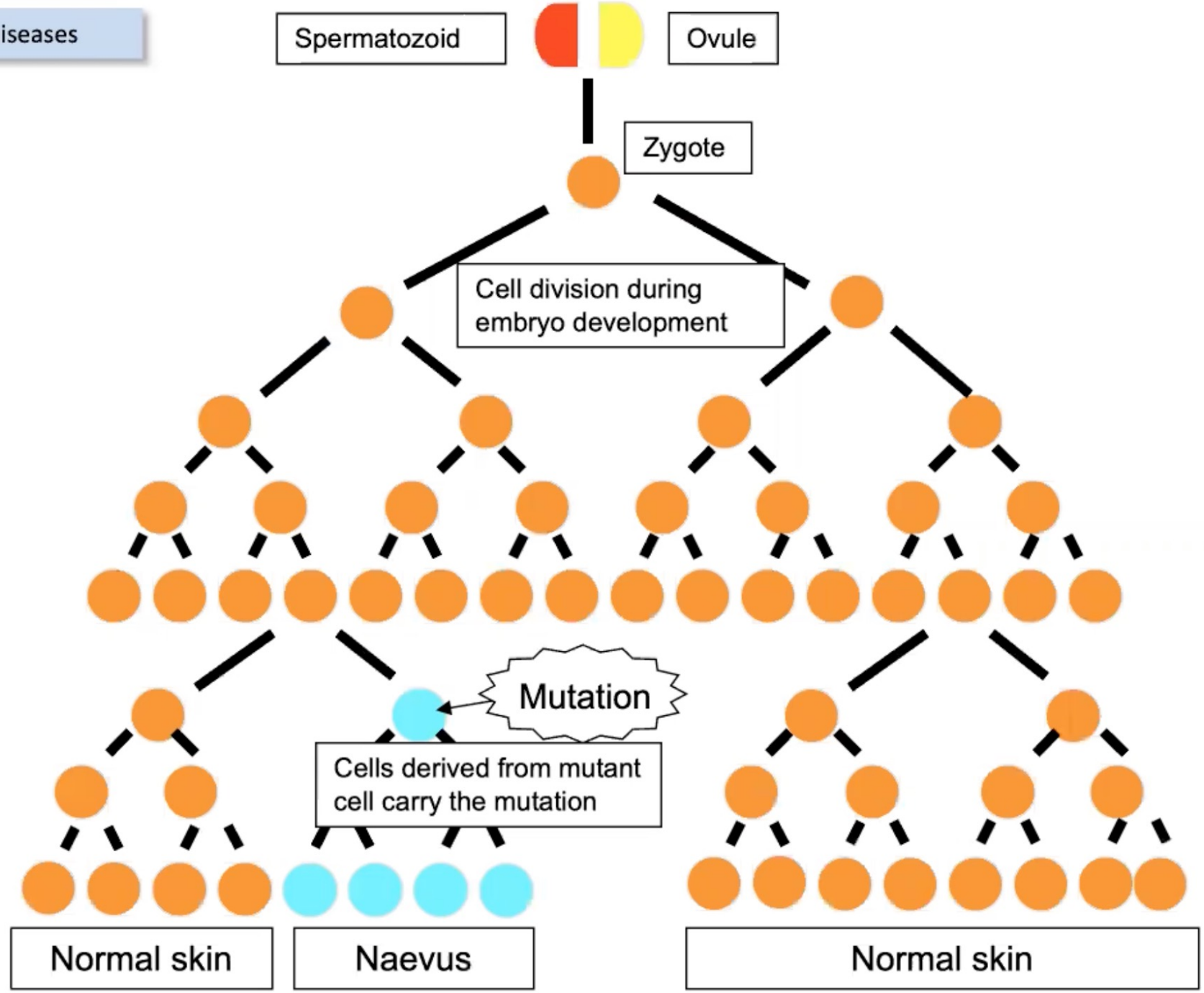


Classification proposed by A Torrelo 2021



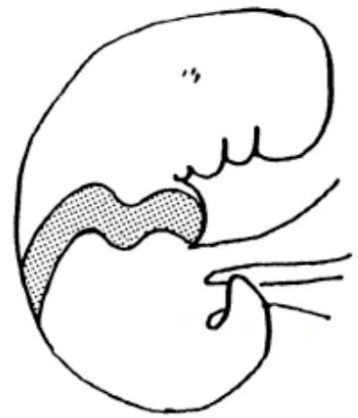
Classification proposed by A Torrelo 2021

Lethal, dominant diseases



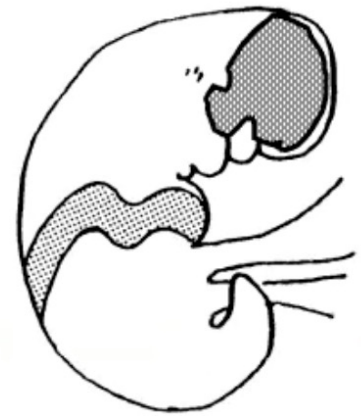
Genomic mosaicism of dominant lethal mutations

Normal individual



Segmental mosaicism

Naevus



Segmental mosaicism

Syndrome

The exact same mutation *GNAQ* p.R183Q

Isolated port wine stain

Sturge-Weber syndrome

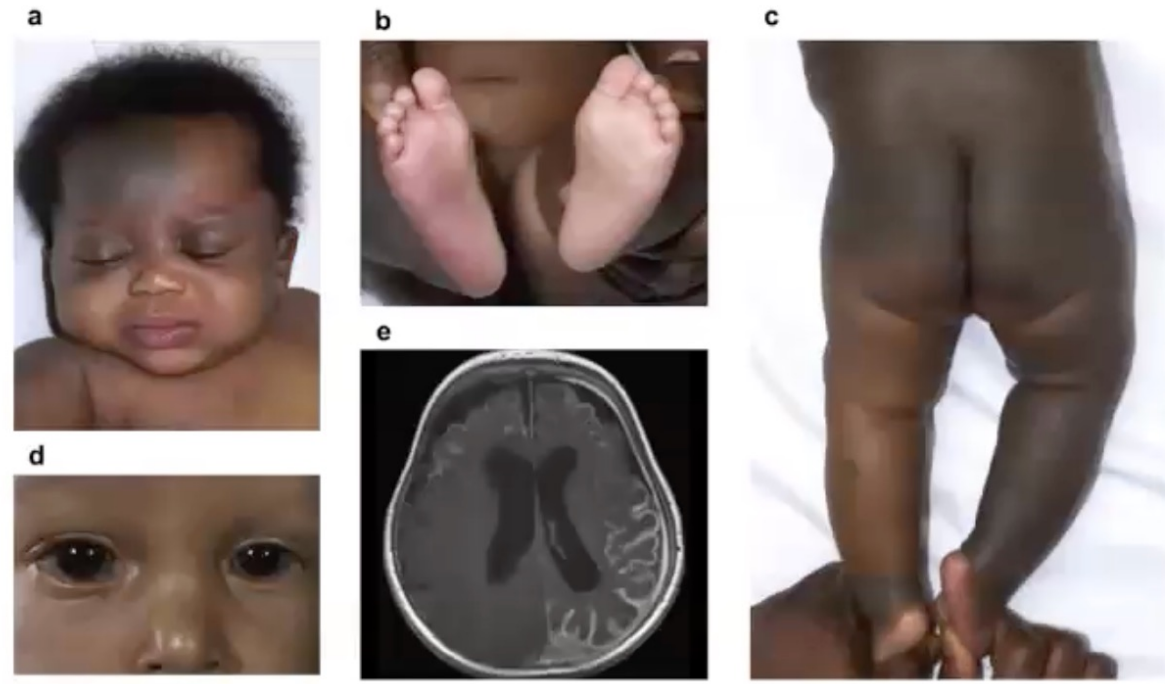
Shirley M et al. NEJM 2O13

GNAQ/GNA11 Mosaicism

JID 2016

Mosaic Activating Mutations in *GNA11* and *GNAQ* Are Associated with Phakomatosis Pigmentovascularis and Extensive Dermal Melanocytosis

Anna C. Thomas[1,18], Zhiqiang Zeng[2,18], Jean-Baptiste Rivière[3,18], Ryan O'Shaughnessy[4], Lara Al-Olabi[1], Judith St.-Onge[3], David J. Atherton[5], Hélène Aubert[6], Lorea Bagazgoitia[7], Sébastien Barbarot[6], Emmanuelle Bourrat[8,9], Christine Chiaverini[10], W. Kling Chong[11], Yannis Duffourd[3], Mary Glover[5], Leopold Groesser[12], Smail Hadj-Rabia[13], Henning Hamm[14], Rudolf Happle[15], Imran Mushtaq[16], Jean-Philippe Lacour[10], Regula Waelchli[5], Marion Wobser[14], Pierre Vabres[3,17,19], E. Elizabeth Patton[2,19] and Veronica A. Kinsler[1,5,19]



A single somatic mutation in GNA11 or GNAQ is responsible for both types of cutaneous lesion in PPV

Mosaicism of activating *FGFR3* mutations in human skin causes epidermal nevi

Christian Hafner,[1] Johanna M.M. van Oers,[2] Thomas Vogt,[1] Michael Landthaler,[1] Robert Stoehr, Hagen Blaszyk,[4] Ferdinand Hofstaedter,[5] Ellen C. Zwarthoff,[2] and Arndt Hartmann[5]

[1]Department of Dermatology, University of Regensburg, Regensburg, Germany. [2]Department of Pathology, Josephine Nefkens Institute, Erasmus MC, Rotterdam, The Netherlands. [3]Department of Urology, University of Regensburg, Regensburg, Germany. [4]Department of Pathology, University of Vermont College of Medicine, Burlington, Vermont, USA. [5]Institute of Pathology, University of Regensburg, Regensburg, Germany.

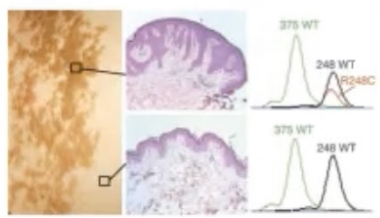
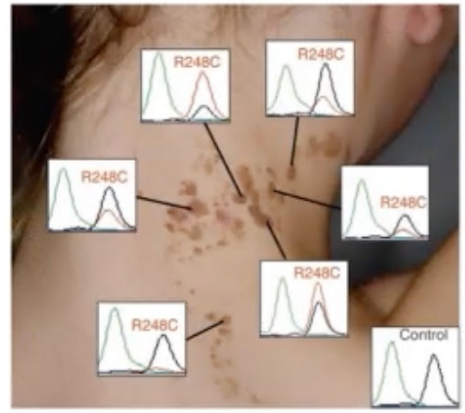


Figure 3
Patient 32 had a common soft-type epidermal nevus on his back. Two biopsies were taken from the epidermal nevus and the adjacent normal skin. The epidermal nevus histologically showed the typical acanthosis and papillomatosis (H&E staining; original magnification, ×40) and an R248C mutation in the SNaPshot analysis. In contrast, the clinically and histologically normal epidermis revealed a WT status for codon 248. This result suggests a strong genotype-phenotype correlation and the presence of a mosaicism of the *FGFR3* mutation in the epidermis of this patient.

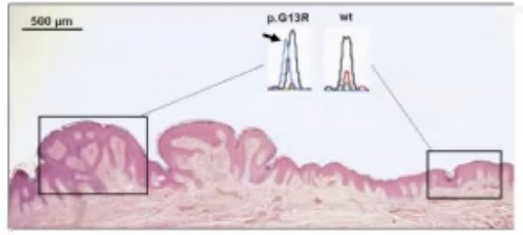


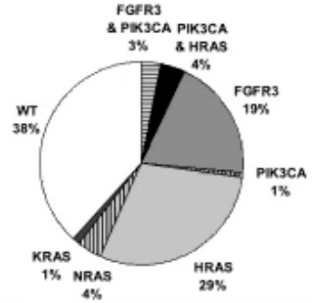
Somatic mosaicism

SHORT REPORT

Keratinocytic epidermal nevi are associated with mosaic *RAS* mutations

Christian Hafner,[1] Agusti Toll,[2] Susanne Gantner,[1] Andreas Mauerer,[1] Irene Lurkin,[3] Francesco Acquadro,[4] Alejandro Fernández-Casado,[2] Ellen C Zwarthoff,[3] Wolfgang Dietmaier,[5] Eulalia Baselga,[6] Elisabet Parera,[2] Asunción Vicente,[7] Ariel Casanova,[8] Juan Cigudosa,[4] Thomas Mentzel,[9] Ramon M Pujol,[2] Michael Landthaler,[1] Francisco X Real[8,10]





Journal of Investigative Dermatology

Available online 19 April 2016

In Press, Accepted Manuscript — Note to users

9591||

Somatic embryonic *FGFR2* mutations in keratinocytic epidermal nevi

Agustí Toll[1, *], Luis C. Fernández[2, *], Tirso Pons[3], Leopold Groesser[4], Ana Sagrera[2], Enrique Carrillo-de Santa Pau[2], Asunción Vicente[5], Eulàlia Baselga[6], Miguel Vázquez[3], Sergi Beltrán[7], David G. Pisano[8], Daniel Rueda[9], Marta Gut[7], Ramon M. Pujol[1], Christian Hafner[4], Ivo Gut[7], Alfonso Valencia[3], Francisco X. Real[1, 10]

Show more

Oncogenic *PIK3CA* mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern

Christian Hafner*, Elena López-Knowles†, Nuno M. Luis†, Agusti Toll‡, Eulàlia Baselga§, Alex Fernández-Casado‡, Silvia Hernández¶, Adriana Ribé‖, Thomas Mentzel**, Robert Stoehr††, Ferdinand Hofstaedter‡‡, Michael Landthaler*, Thomas Vogt*, Ramón M. Pujol‡, Arndt Hartmann‡‡§§, and Francisco X. Real†¶.¶¶

Departments of *Dermatology and ††Urology and ‡‡Institute of Pathology, University of Regensburg, 93042 Regensburg, Germany; †Unitat de Biologia Cellular i Molecular, Institut Municipal d'Investigació Mèdica, Carrer del Dr. Aiguader 88, 08003 Barcelona, Spain; ‡Servei de Dermatologia, Hospital del Mar, Universitat Antònoma de Barcelona, Passeig Marítim 25, 08003 Barcelona, Spain; §Servei d'Anatomia Patològica and ¶Servei de Dermatologia, Hospital de Sant Pau, Universitat Autònoma de Barcelona, 08025 Barcelona, Spain; ‖Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra, Carrer del Dr. Aiguader 88, 08003 Barcelona, Spain; **Department of Dermatopathology, 88048 Friedrichshafen, Germany; and §§Department of Pathology, University of Erlangen–Nürnberg, 91054 Erlangen, Germany

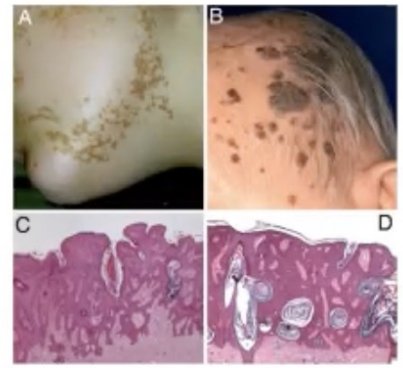


Fig. 1. Morphological similarities of linear lesions of congenital EN from a child following Blaschko's lines (*A*) and SK from an elderly patient (*B*). At the microscopic level, both lesions are characterized by acanthosis, papillomatosis, and variable degrees of hyperkeratosis and hyperpigmentation (*C*, EN; *D*, SK).

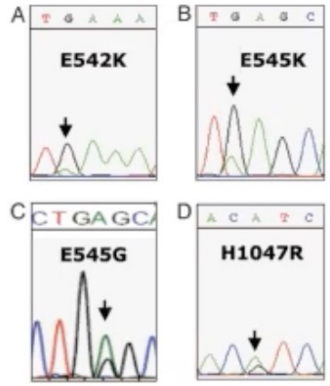
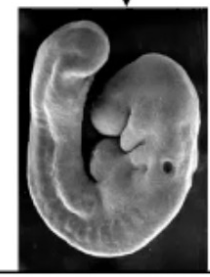


Fig. 2. Mutational analysis of EN and SK. In all cases, the mutant sequence was accompanied by the presence of the WT allele, indicating heterozygosity.

Mutational spectrum in FGFR3

Germinal

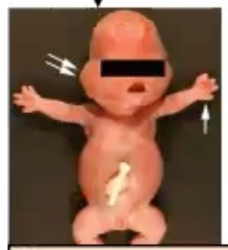
Early embryo

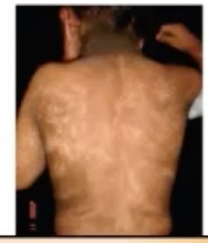


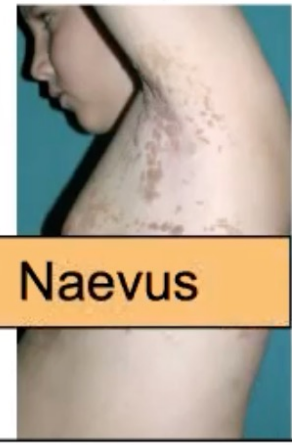
Late embryo

Adult life

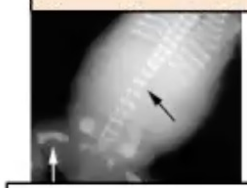
Adult life



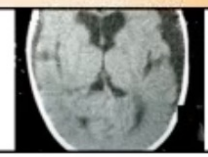




Development Anomaly — Naevus

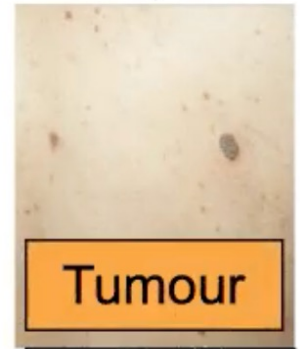


Tanatophoric dysplasia



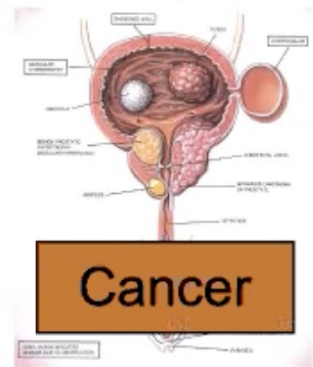
Epidermal Naevus syndrome

Common epidermal naevus



Tumour

Seborrheic queratosis



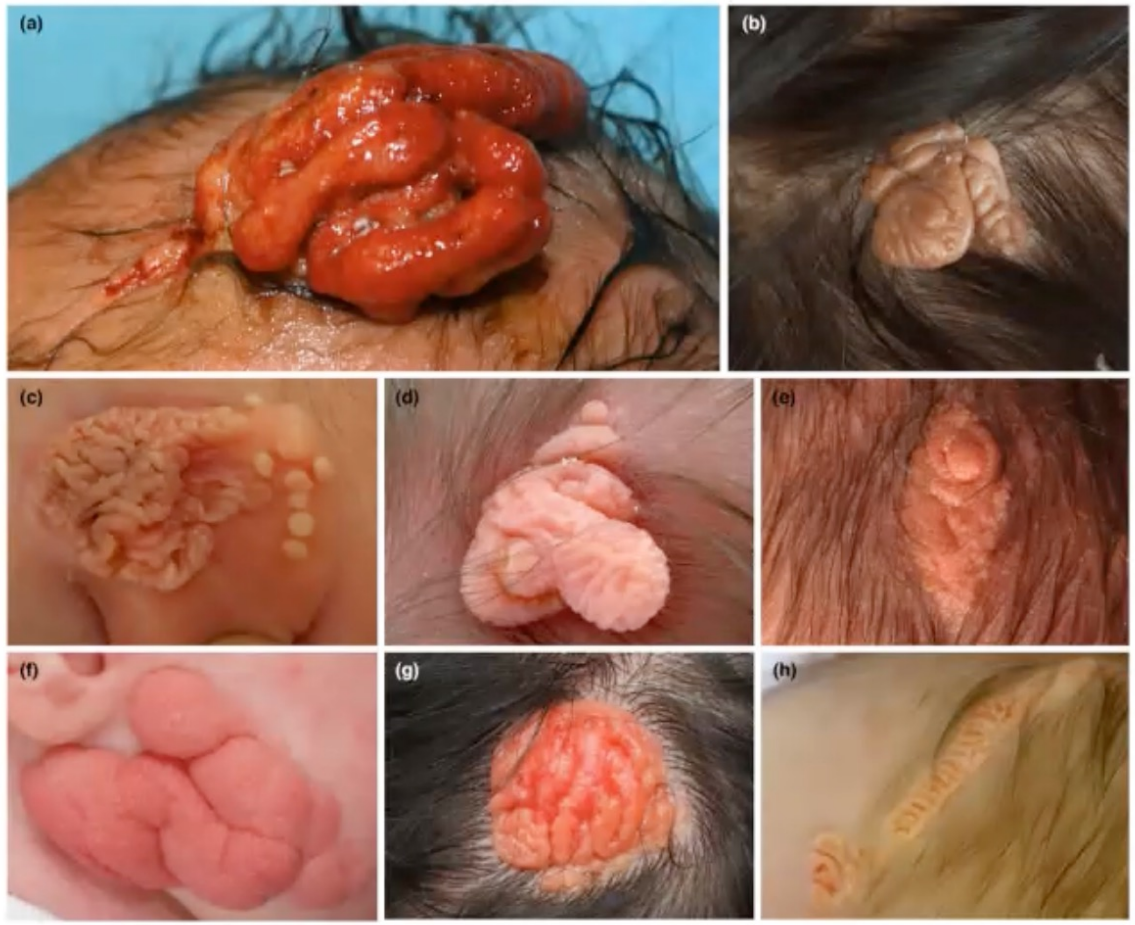
Cancer

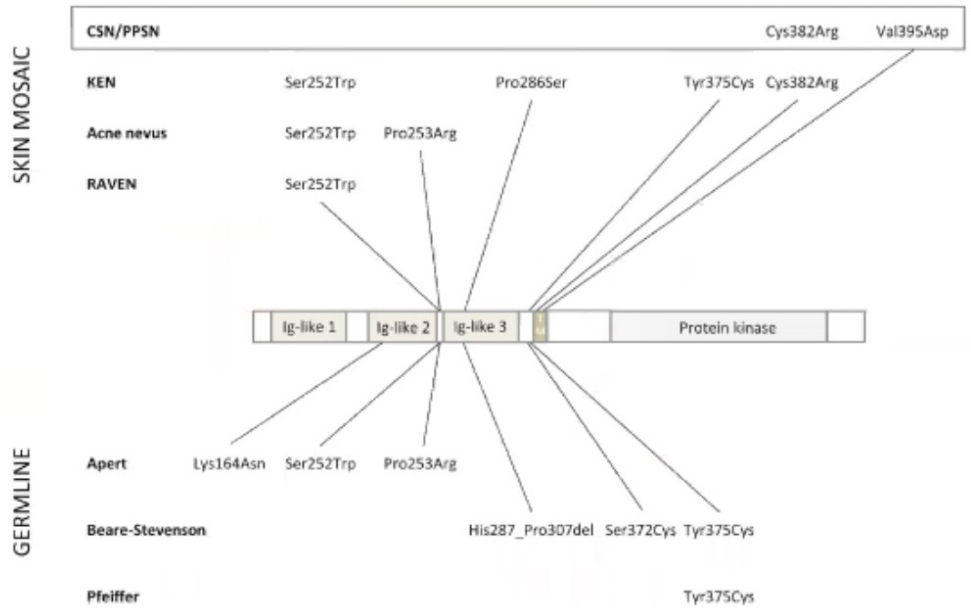
Bladder cancer

Cerebriform sebaceous nevus: a subtype of organoid nevus due to specific postzygotic FGFR2 mutations

JEADV 2021

M. Theiler,[1,*] L. Weibel,[1] S. Christen-Zaech,[2] V. Carmignac,[3] A. Sorlin,[3,4] K. Neuhaus,[5] M. Chevarin,[3] C. Thauvin-Robinet,[3,4,6] C. Philippe,[3,6] L. Faivre,[3,4,6] P. Vabres,[36,7,†], P. Kuentz[3,6,8,†]

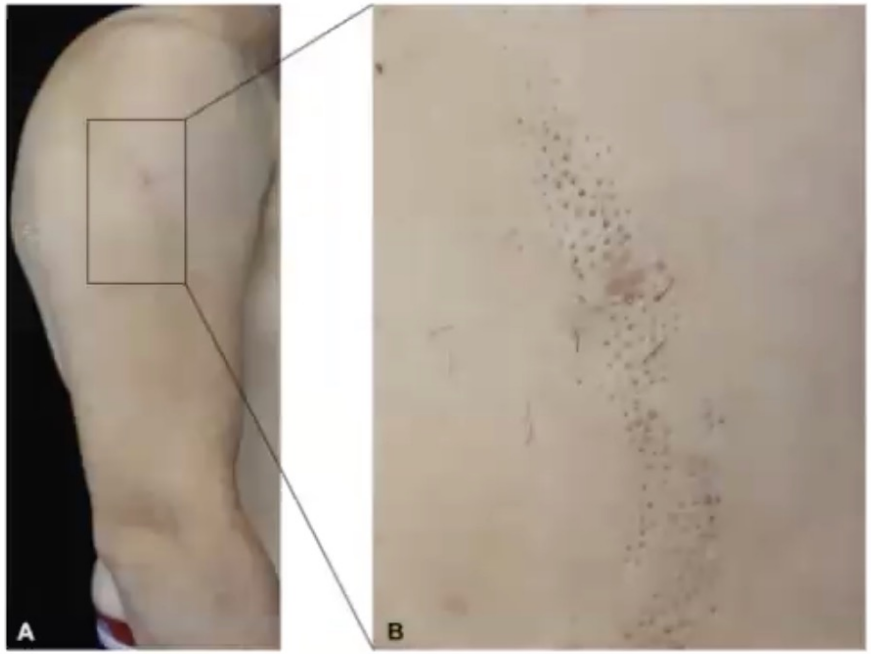




Three novel pathogenic *NEK9* variants in patients with nevus comedonicus: A case series

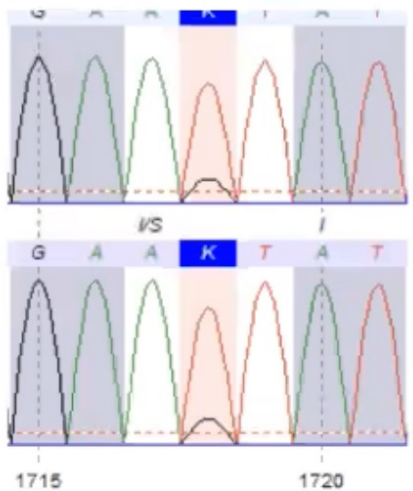
JAAD 2021

Hazem A. Juratli MD [a], Sabine Jägle PhD [b], Martin Theiler MD [c], Dario Didona MD [a], Rudolf Happle MD [d], Nicole Knöpfel MD [c], Lisa Weibel MD [c], Judith Fischer MD, PhD [b]



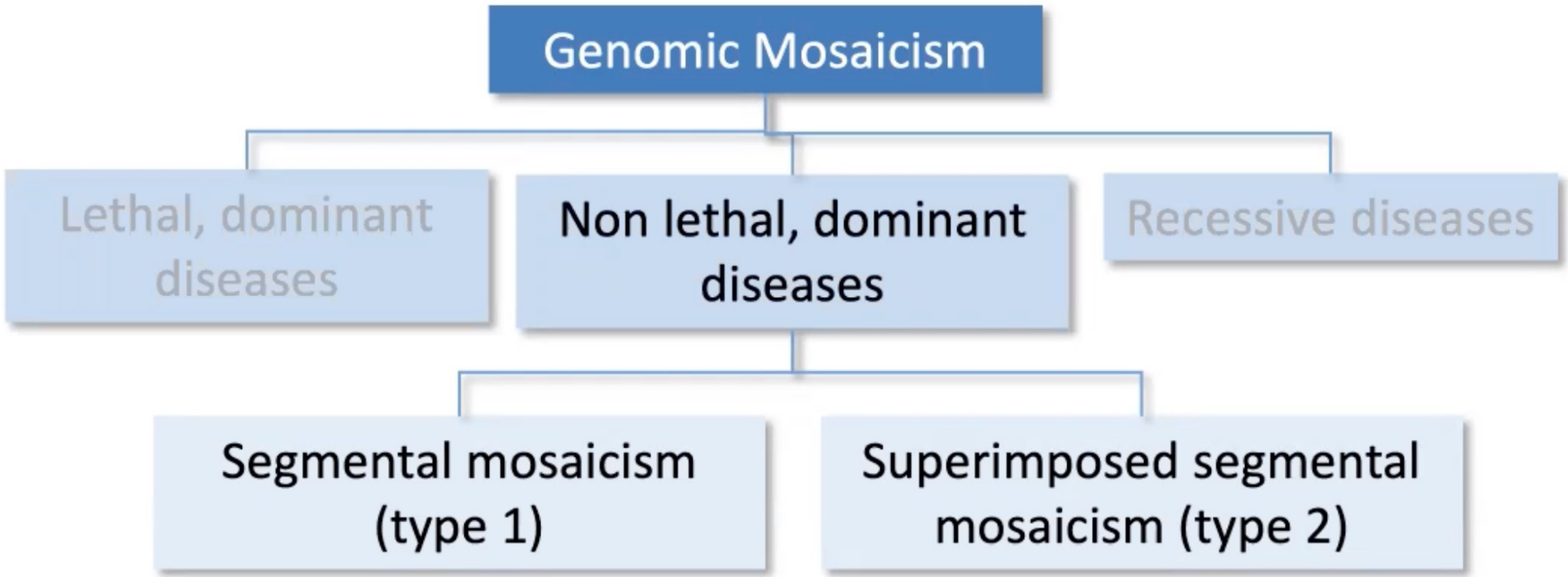
Patient	Nucleotide change*	Protein change	Variant type	Exon	Coverage	Reads alternative allele	Mosaic percentage	Associated figure
P1	c.1756_1758del	p.(Thr586del)	In frame deletion	15	1090–1105x	74-75	6.6%	Supplemental Figure 2, A
P2	c.1738_1752del	p.(His580_Tyr584del)	In frame deletion	15	1042–1302x	69-70	5.9%	Supplemental Figure 2, B
P3	c.373_375delinsATT	p.(Leu125Ile)	Indel/missense	2	1136–1144x	87	7.6%	Supplemental Figure 2, C
P4	c.1718T>G	p.(Ile573Ser)	Missense	14	1272x	212	16.7%	Supplemental Figure 2, D

**NEK9* reference sequence NM_033116.5 (GRCh37.p13).



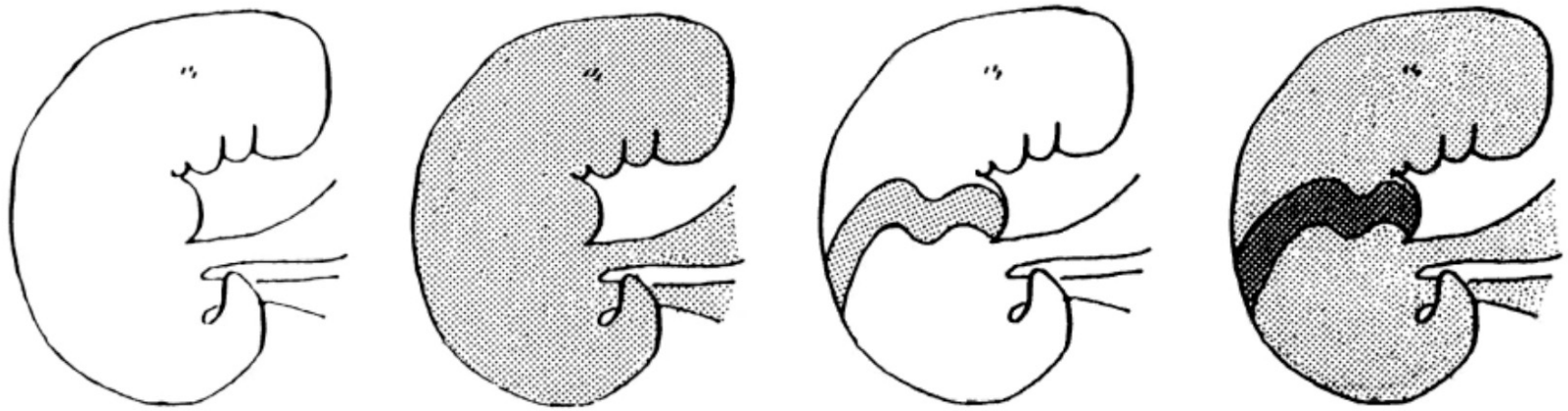
Genomic mosaicism of dominant lethal mutations

- Sturge-Weber syndrome (GNAQ/GNA11)
- Epidermal naevus and epidermal naevus syndrome (FGFR3, FGFR2, HRAS, PIK3CA)
- Sebaceous naevus and sebaceous naevus syndrome (KRAS, HRAS, FGFR2)
- PROS spectrum (PIK3CA)
- Proteus syndrome (AKT1)
- Spilus naevus and related (HRAS, PTPN11)
- McCune-Albright syndrome (GNAS)
- Maffucci syndrome (IDH1, IDH2)
- Congenital melanocytic naevus and CMN syndrome (NRAS)
- Becker naevus and Becker naevus syndrome (ACTB)
- Naevus comedonicus and naevus comedonicus syndrome (NEK9)
- Encephalocraneocutaneous syndrome (FGFR1)
- Vabres syndrome (RhoA)



Classification proposed by A Torrelo 2021

Genomic mosaicism of non-lethal, dominant mutations



Normal individual

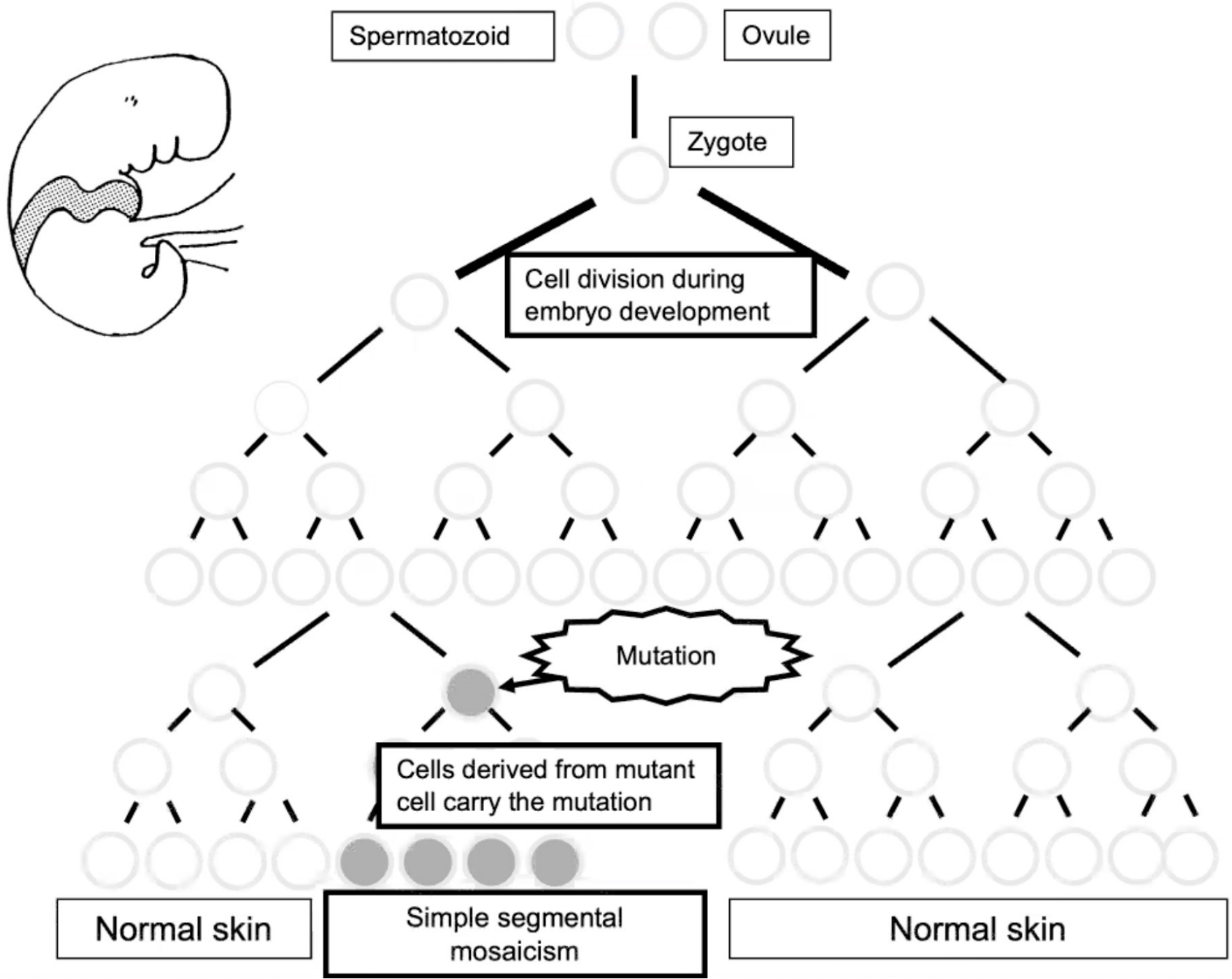
Affected individual

Mosaicism type 1

Mosaicism type 2

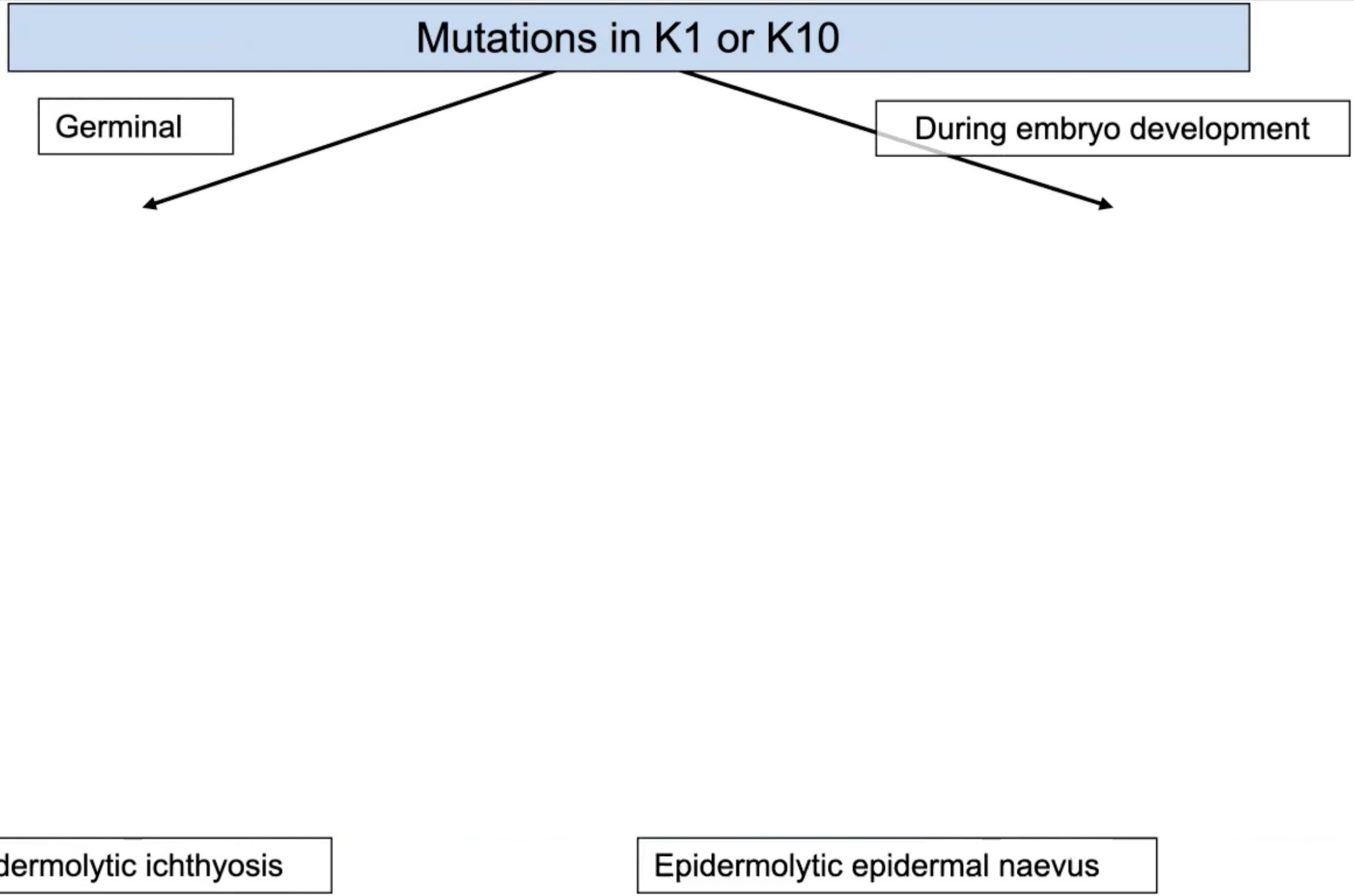
Simple segmental mosaicism of dominant non-lethal diseases

Superimposed segmental mosaicism of dominant non-lethal diseases

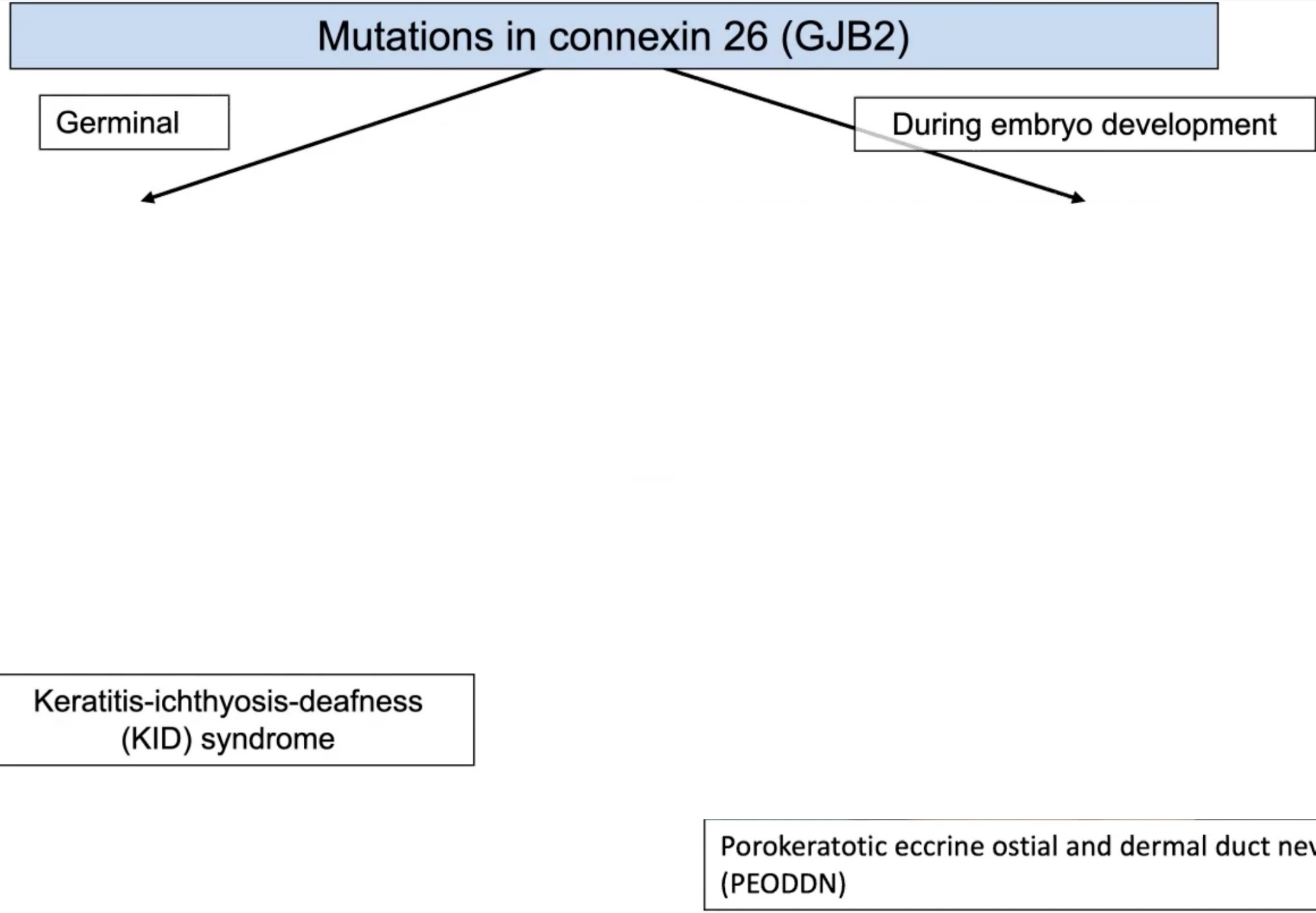

Spermatozoid
Ovule
Zygote
Cell division during embryo development
Mutation
Cells derived from mutant cell carry the mutation
Normal skin
Simple segmental mosaicism
Normal skin

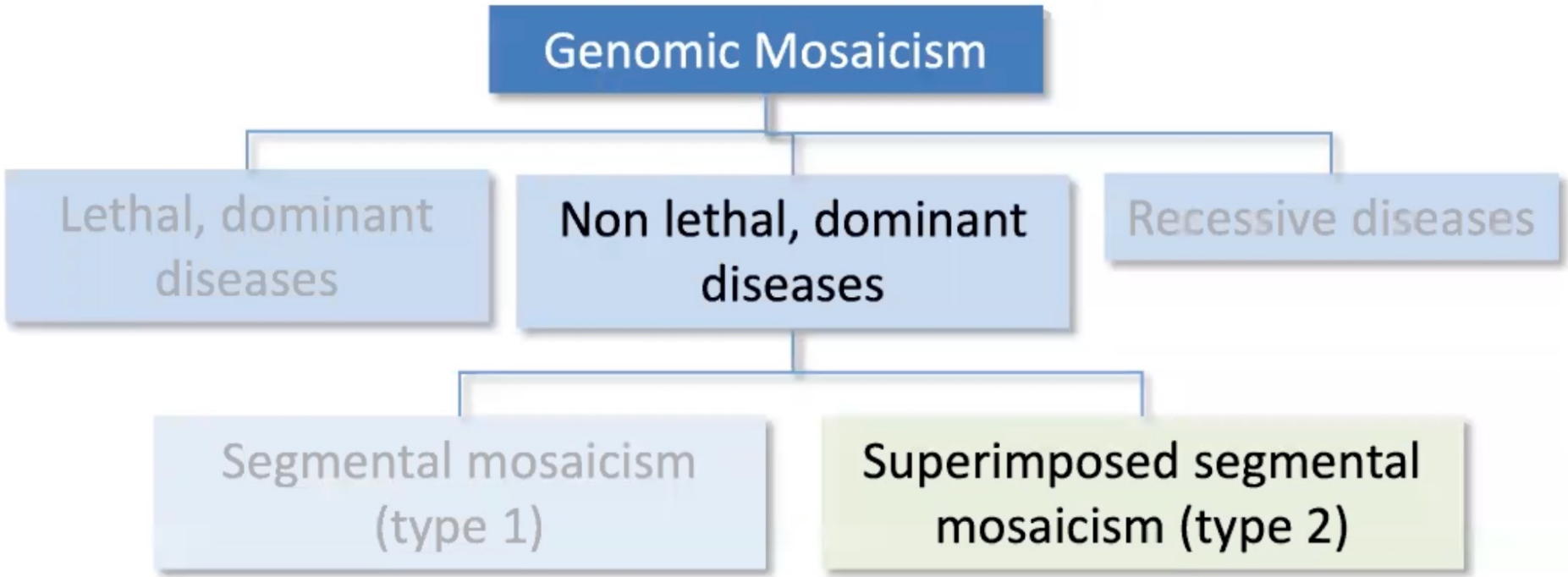
Simple segmental mosaicism of dominant, non-lethal diseases (confirmed by genetic analysis)

- Neurofibromatosis 1 (NF1)
- Gorlin syndrome (PTCH1, PTCH2, SUFU)
- Glomangiomatosis, GVM (GLML)
- Familial leiomyomatosis with kidney cancer (FH)
- Tuberous sclerosis complex (TSC1, TSC2)
- Epidermolytic ichthyosis Brocq (KRT1, KRT10)
- Superficial epidermolytic ichthyosis Siemens (K2)
- Darier disease (ATP2A2)
- Hailey-Hailey disease (ATP2C1)
- Pachyonychia congenita (KRT16)
- Dowling-Degos disease, Galli-Galli variant (KRT5)
- Keratitis-ichthyosis-deafness syndrome, KID (GJB24)

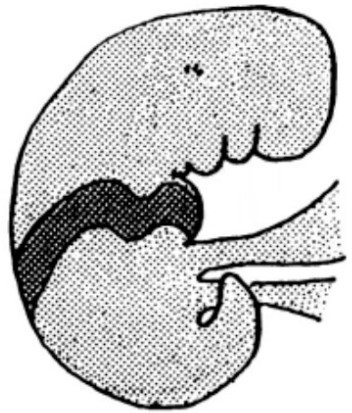

Mutations in K1 or K10
Germinal
During embryo development
Epidermolytic ichthyosis
Epidermolytic epidermal naevus

A Torrelo


Mutations in connexin 26 (GJB2)
Germinal
During embryo development
Keratitis-ichthyosis-deafness (KID) syndrome
Porokeratotic eccrine ostial and dermal duct nevus (PEODDN)



Classification proposed by A Torrelo 2021



Spermatozoid
Ovule
Zygote
Cell division during
embryo development
Loss of
heterozygosity
Cells derived from mutant
Cells carry the mutation
Involved skin
Superimposed mosaicism
Involved skin

Superimposed mosaicism in AD non-lethal diseases (confirmed by genetic analysis)

- Darier disease
- Gorlin syndrome
- Hailey-Hailey disease
- Osteomatosis cutis hereditaria
- Legius syndrome
- Neurofibromatosis 1
- Disseminated superficial actinic porokeratosis
- PTEN hamartoma syndrome
- CM-AVM syndrome

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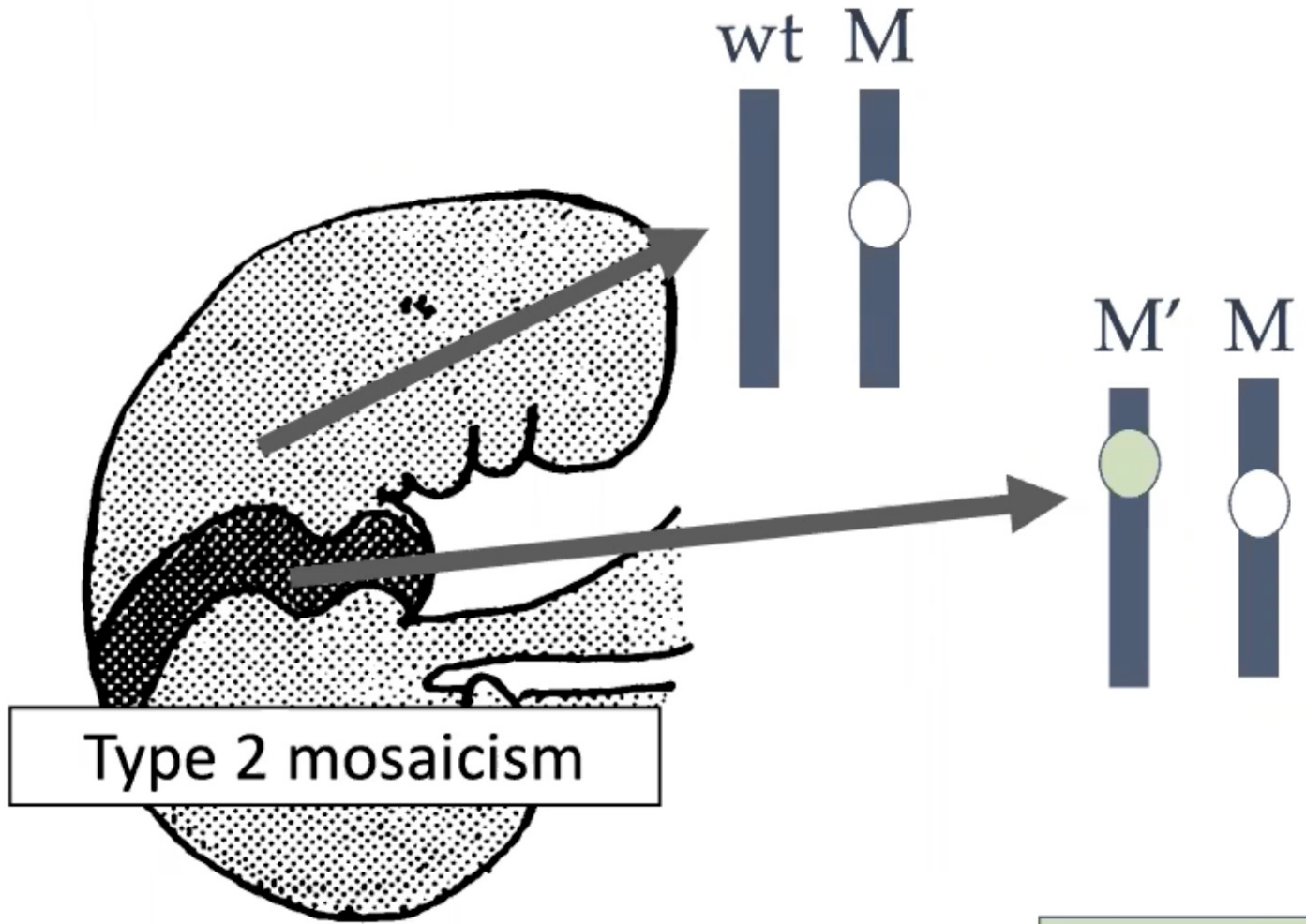
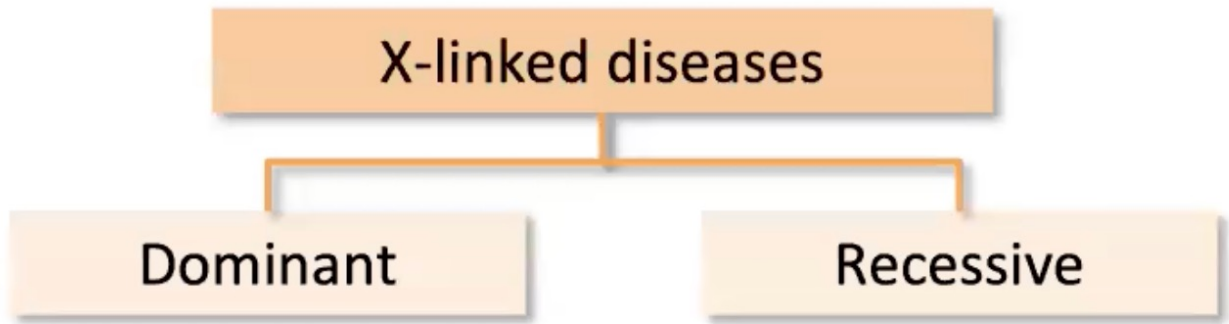
PTCH1



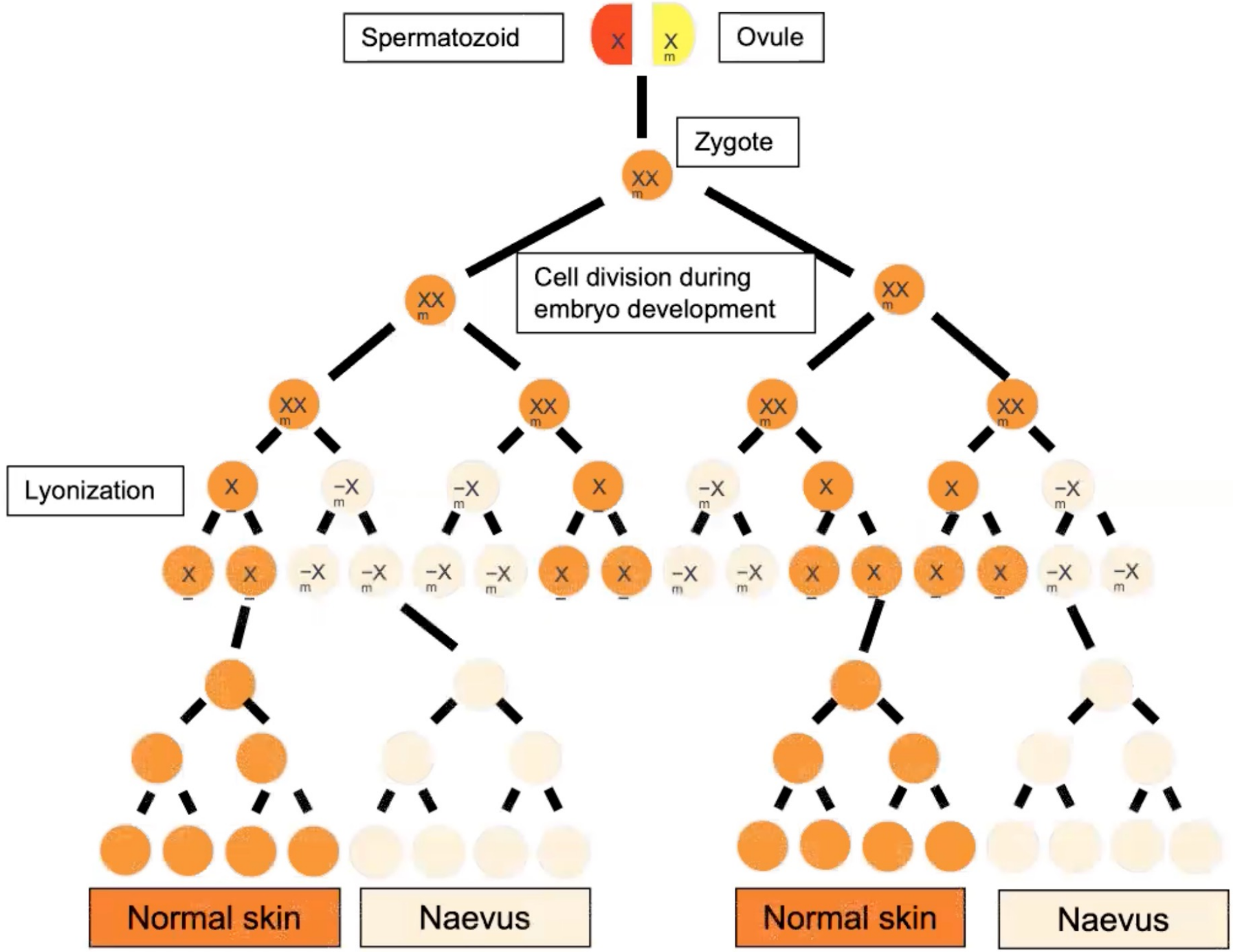
Gorlin syndrome + Segmental increased severity

Classification of mosaicism according to..

Category



Classification proposed by A Torrelo 2021


Spermatozoid
X
X m
Ovule
Zygote
XX m
Cell division during embryo development
Lyonization
Normal skin
Naevus
Normal skin
Naevus

Mosaicism of X-linked genes

Dominant: Females affected, lethal in males

- Incontinentia pigmenti (NEMO)
- Focal dermal hypolasia (PORCN)
- Conradi-Hünermann-Happle syndrome (EBP)
- CHILD syndrome (NSDHL)
- MIDAS syndrome / MLS (COX7B)
- Oro-facio-digital syndrome (CXORF5)

Recessive: Males affected, females carriers (healthy or mosaic)

- Hypohidrotic ectodermal displasia, X-linked (EDA)
- Diskeratosis congenita, X-linked (DKC1)
- Menkes syndrome (ATP7A9)
- IFAP syndrome: Follicular ichthyosis, atrichuia and photophobia (MBTPS2)
- Reticulated pigmented anomaly of Partington (POLA1)
- Borjesson-Forssman-Lehman syndrome (PHF6)

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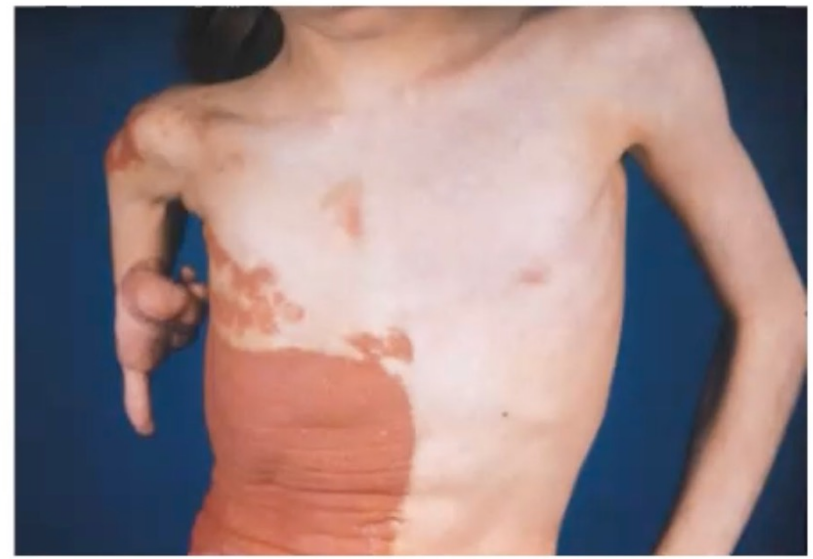
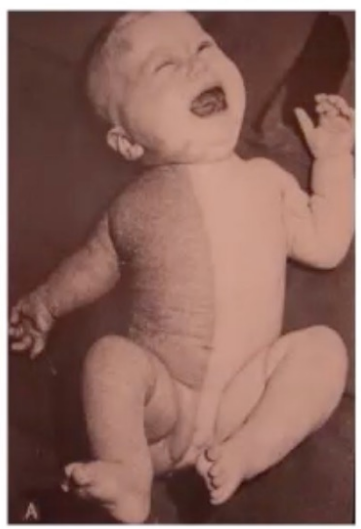
CHILD

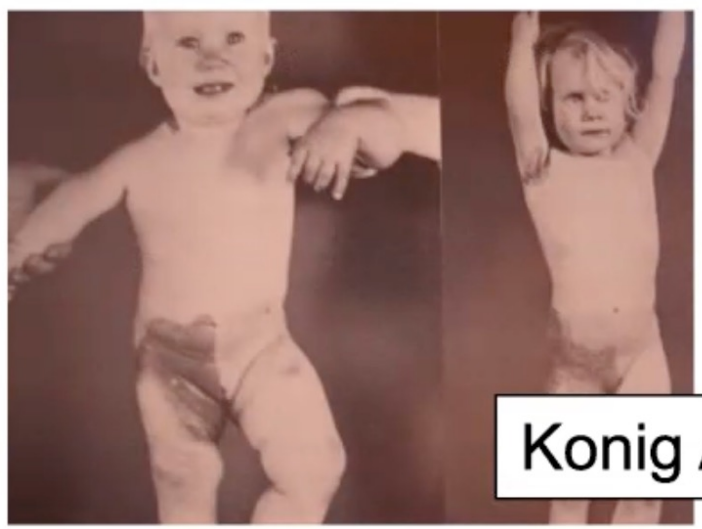
- *C*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects
- Mutations in *NSDHL* (NAD steroid deshydrogenase)
- X-linked dominant

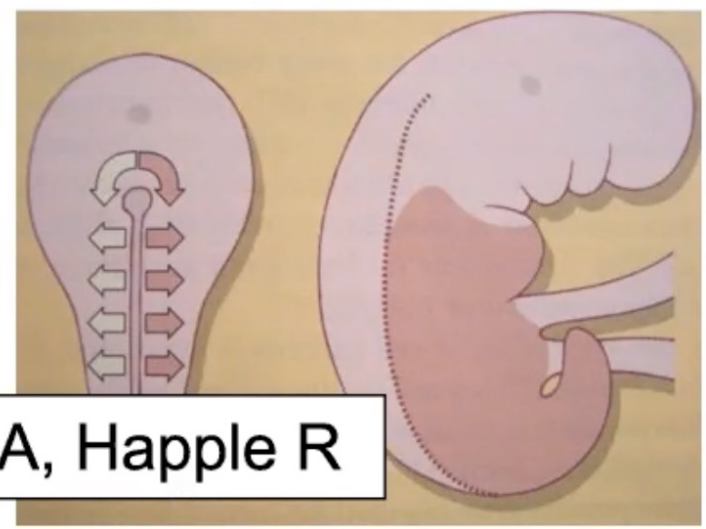
Table 1. Summary of Mutations Described in CHILD Syndrome

Serial No.	Source	No. of Cases	Mutation	Exon
1	Konig et al[8]	1	R88X	3
2	Konig et al[8]	3	A105V	4
3	Konig et al[8]	1	G205S	6
4	Konig et al[8]	1	Q210X	6
5	Konig et al[9]	1	A182P	6
6	Hummel et al[10]	1	E151X	5
7	Murata et al[11]	1	Y349C	8

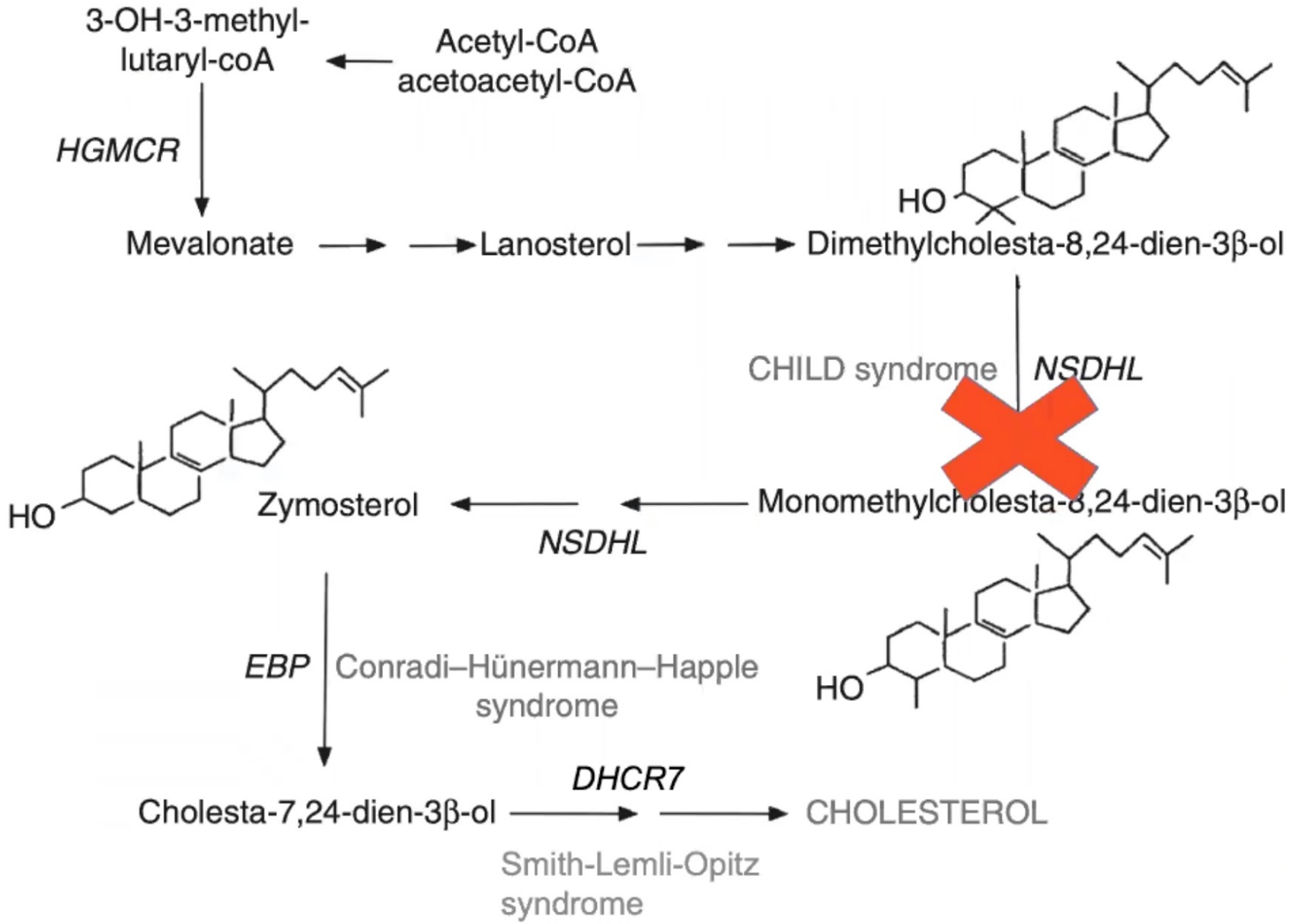








Konig A, Happle R


3-OH-3-methyl-
lutaryl-coA
Acetyl-CoA
acetoacetyl-CoA
HGMCR
Mevalonate
Lanosterol
HO
Dimethylcholesta-8,24-dien-3β-ol
CHILD syndrome
NSDHL
HO
Zymosterol
NSDHL
Monomethylcholesta-8,24-dien-3β-ol
HO
EBP
Conradi–Hünermann–Happle
syndrome
DHCR7
Cholesta-7,24-dien-3β-ol
CHOLESTEROL
Smith-Lemli-Opitz
syndrome

Targeting epidermal lipids for treatment of Mendelian disorders of cornification

Dimitra Kiritsi[1], Franziska Schauer[1], Ute Wölfle[1], Manthoula Valari[2], Leena Bruckner-Tuderman[1], Cristina Has[1*] and Rudolf Happle[1]

Abstract

Background: Inherited ichthyoses or Mendelian disorders of cornification (MeDOC) are clinically heterogeneous disorders with high unmet therapeutic needs, which are characterized by skin hyperkeratosis and scaling. Some MeDOC types are associated with defects of the epidermal lipid metabolism, resulting in perturbed barrier permeability and subsequent epidermal hyperplasia, hyperkeratosis and inflammation. An example is the CHILD (congenital hemidysplasia with ichthyosiform nevus and limb defects) syndrome, an X-linked dominant multisystem MeDOC caused by mutations in the *NSDHL* (NAD(P)H steroid dehydrogenase-like protein) gene, which is involved in the distal cholesterol biosynthetic pathway. The skin manifestations of the CHILD syndrome have been attributed to two major mechanisms: deficiency of cholesterol, probably influencing the proper corneocyte membrane formation, and toxic accumulation of aberrant steroid precursors.

Methods: Here we addressed the efficacy of an ointment containing cholesterol and simvastatin, an agent inhibiting endogenous ch[illegible]nts with CHILD syndrome. To test the spe[illegible]eatment to two patients with other types [illegible]

Results: The therapy with [illegible]y the CHILD syndrome patients; only lesions in the[illegible]as noted in the patients with other types of MeDO[illegible]

Conclusions: This therapy [illegible]because both simvastatin and cholesterol are available worldwide. Our data provide initial evidence of the specificity of the therapeutic effect of the simvastatin-cholesterol ointment in CHILD syndrome in comparison to other types of MeDOC.

Simvastatin 2 %
Cholesterol 2 %

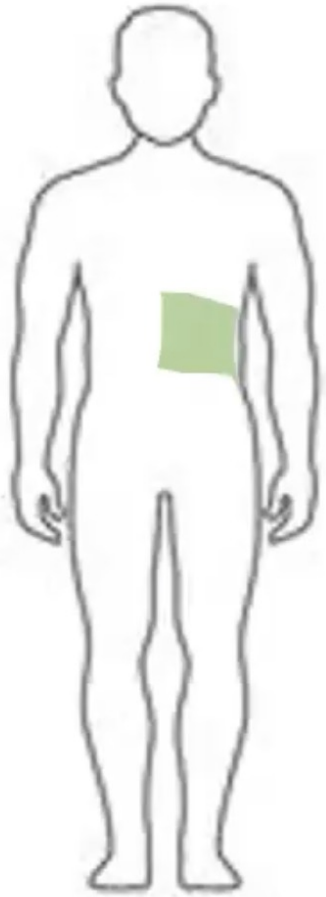
Keywords: Cholesterol, Mosaicism, Ichthyosis, Simvastatin, CHILD nevus, *NSDHL* mutations

Classification of mosaicism according to..

Direction

- Forwards or backwards

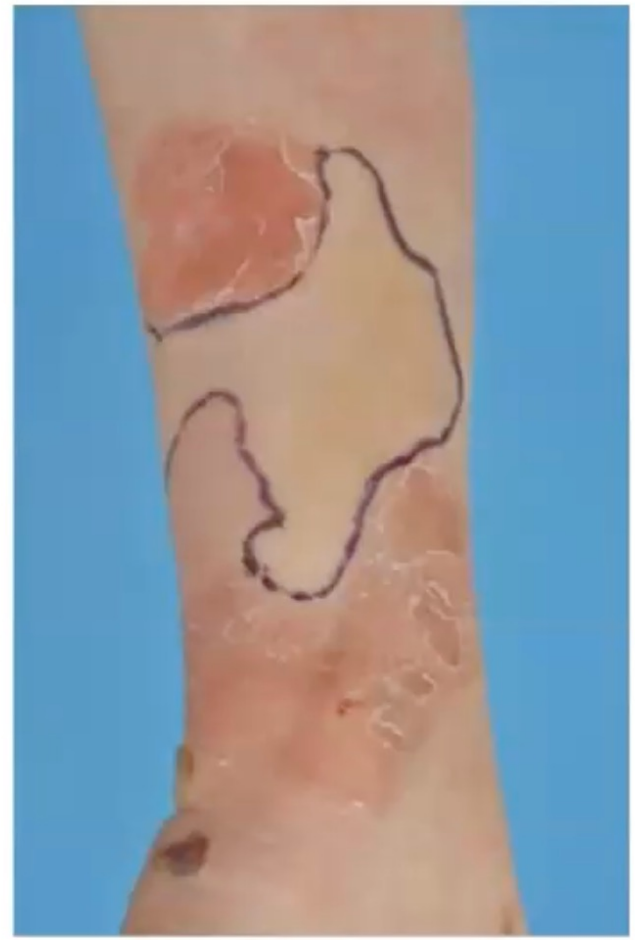
Classification proposed by A Torrelo 2021



Revertant mosaicism

Forwards
→ pathogenic mutation

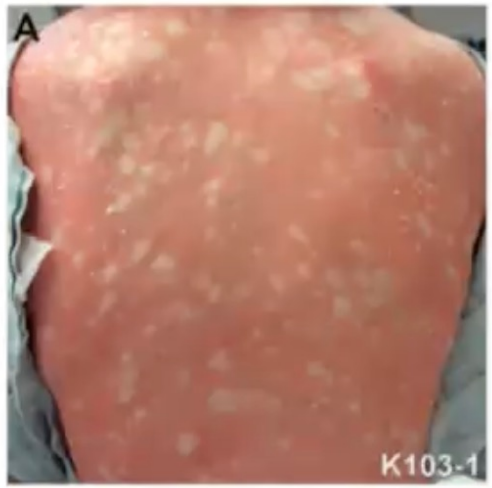
Reverse
pathogenic → Normal genotype

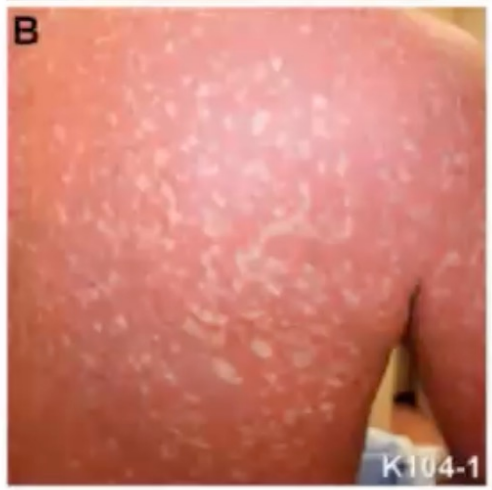


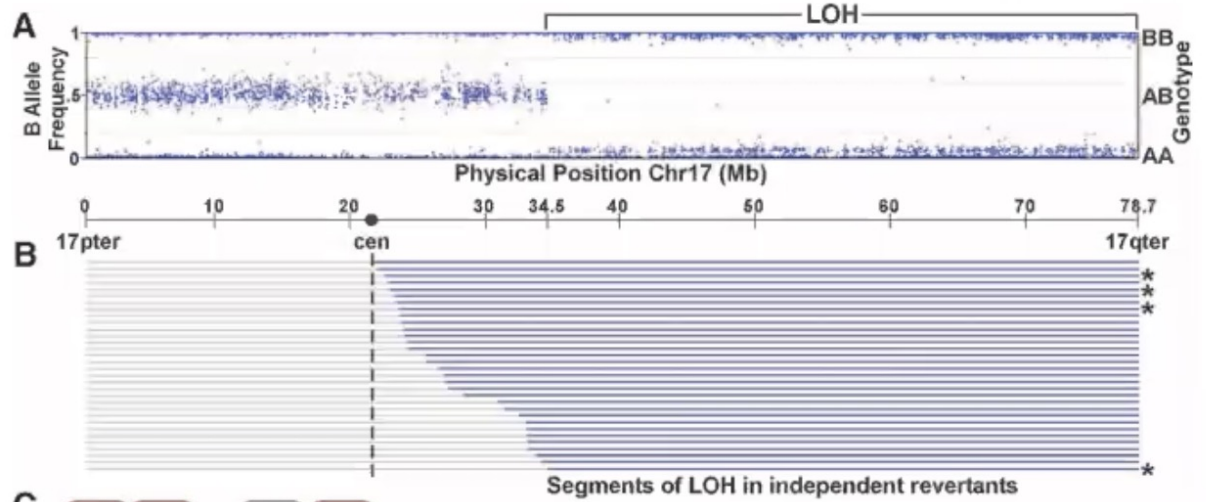
Revertant mosaicism or ‘natural gene therapy’, a phenomenon in which germline mutations are corrected by somatic events

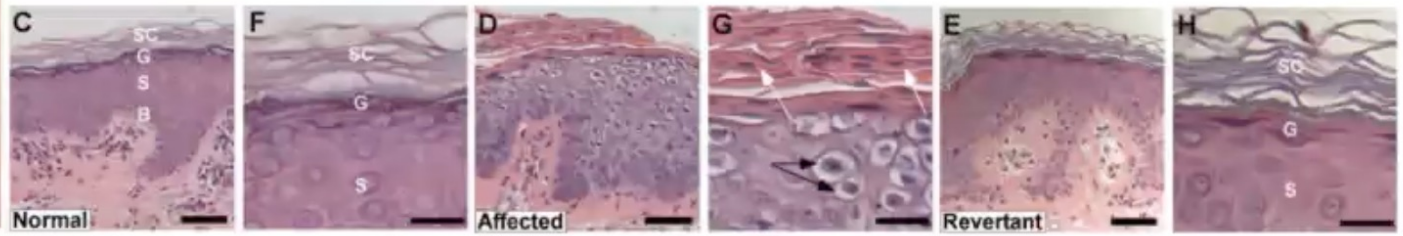
Mitotic Recombination in Patients with Ichthyosis Causes Reversion of Dominant Mutations in *KRT10*

Keith A. Choate[1,2], **Yin Lu**[2], **Jing Zhou**[1], **Murim Choi**[2], **Peter M. Elias**[3], **Anita Farhi**[2], **Carol Nelson-Williams**[2], **Debra Crumrine**[3], **Mary L. Williams**[3], **Amy J. Nopper**[4], **Alanna Bree**[5], **Leonard M. Milstone**[1], and **Richard P. Lifton**[2,‡]





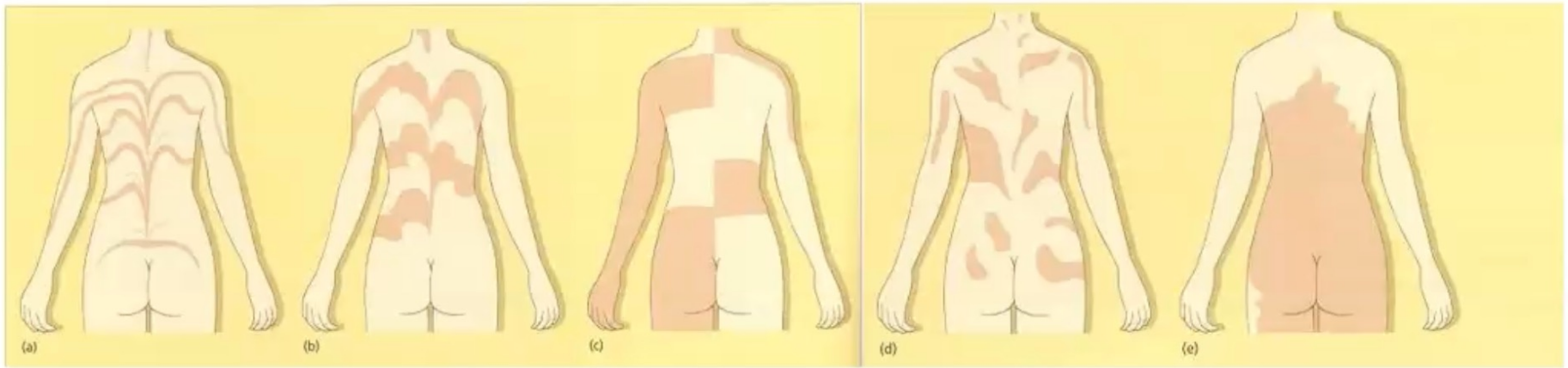




Our approach to mosaic disorders

Our approach to mosaic disorders

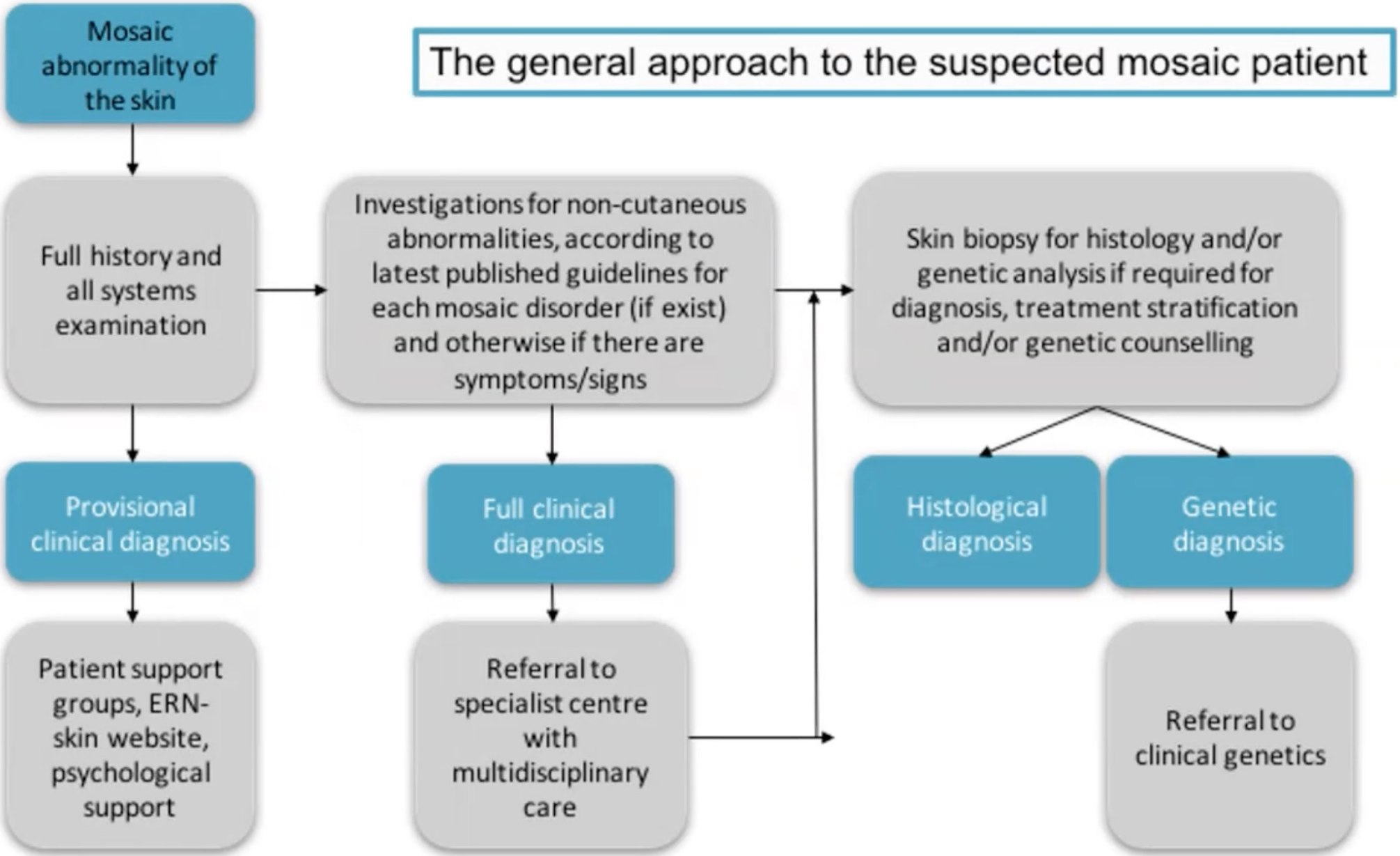
1 – Identify a mosaic disorder



PATTERNS

2 – Full history and systems exam; Family history

3 – Investigations: histology and genetics



Kinsler V et al. Mosaic abnormalities of the skin: review and guidelines from the European Reference Network for rare skin diseases BJD 2020

Check for updates

REVIEW ARTICLE

BJD
British Journal of Dermatology

Mosaic abnormalities of the skin: review and guidelines from the European Reference Network for rare skin diseases*

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Accepted for publication
19 March 2019

Funding sources
None.

Conflicts of interest
None declared.

*Plain language summary available online

DOI 10.1111/bjd.17924

Summary

Background Cutaneous mosaicism is an area of dermatology in which there has been an explosion of knowledge within the current decade. This has led to fundamental changes in the understanding of the conditions in this field, and to an ongoing paradigm shift in the approach to management of mosaic skin disorders.
Objectives To lay out the general principles of mosaicism as they are currently understood, summarize the known cutaneous mosaic abnormalities of the skin with associated phenotypic and genotypic information, review the latest trials on targeted therapies and propose guidelines for the general approach to a patient with suspected mosaicism.
Methods This was a consensus expert review as part of the European Reference Network project (ERN-Skin).
Conclusions This study provides clinicians with a practical approach to the patient with suspected mosaicism, redefines mosaicism for the modern genetic era, and proposes a new classification system based on genetic mechanism.

What's already known about this topic?

- Cutaneous mosaicism is a complex field of dermatology that encompasses most birthmarks, and many rare syndromes.
- Some cutaneous patterns are known to be seen in mosaicism.
- Very few treatment options are available for most mosaic abnormalities of the skin.
- Recent high-sensitivity genetic techniques have led to an explosion of knowledge about genotype and phenotype in the literature.

What does this study add?

- Expert consensus from the European Reference Network project.
- Review of knowledge of confirmed mosaic abnormalities of the skin, including cutaneous phenotype, extracutaneous associated features and genotype.
- Proposed new classification of mosaic abnormalities of the skin by genetic mechanism and therefore inheritance potential.
- Practical tips on correct sample collection and genetic investigation.
- Review of trials of targeted therapies.
- Guidelines for a practical clinical approach to the patient with suspected mosaicism.

If you want to explore more on mosaicism