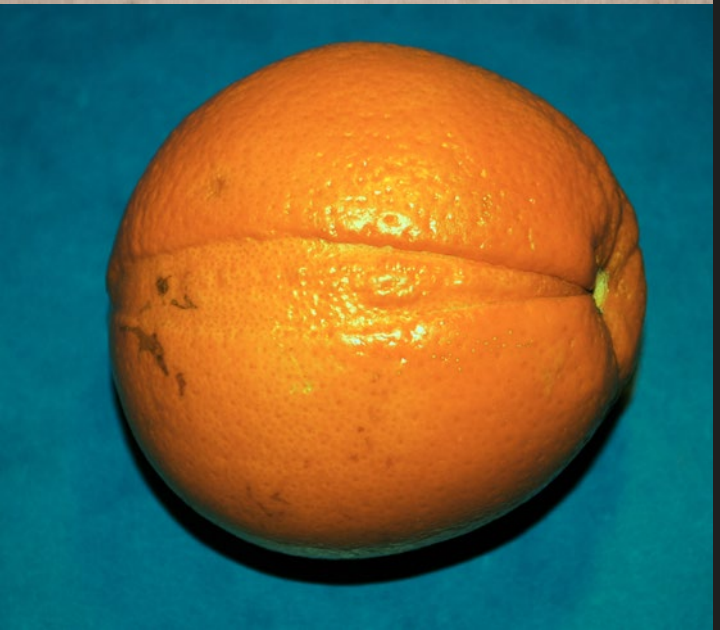
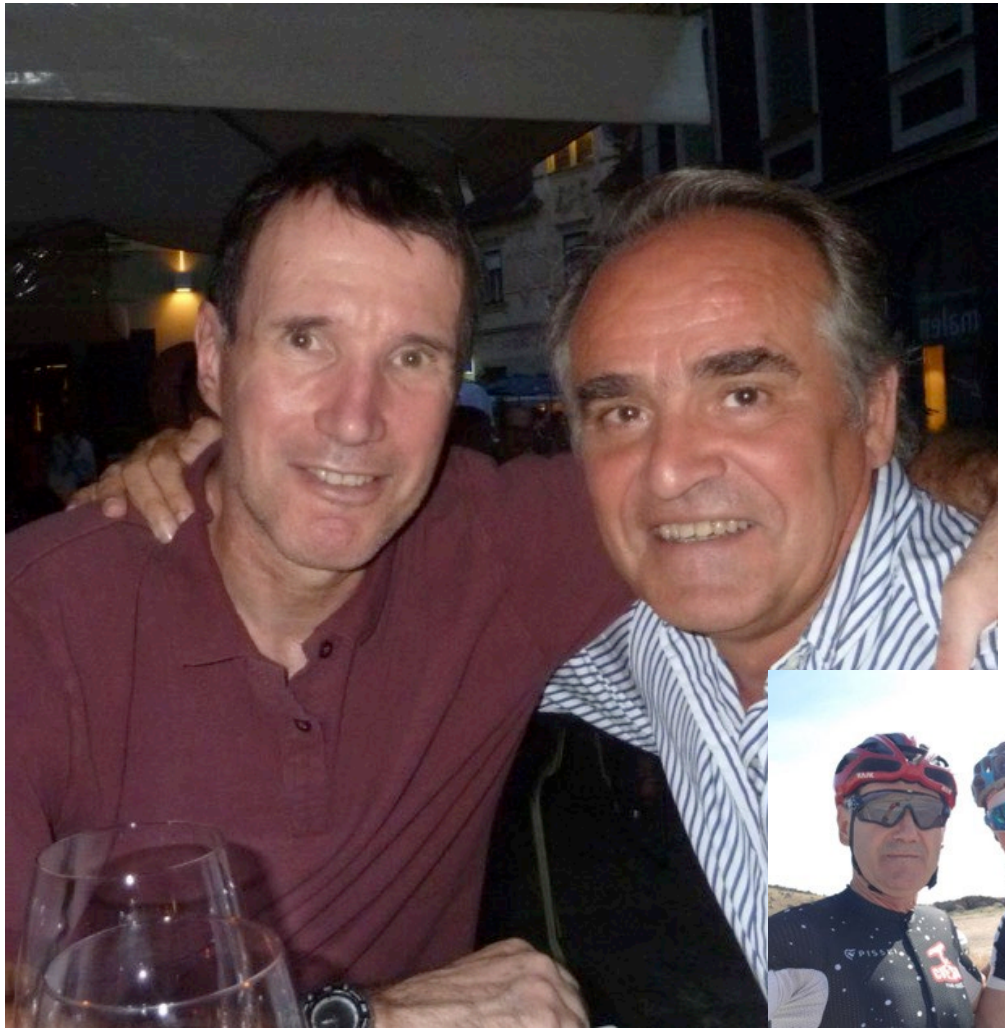
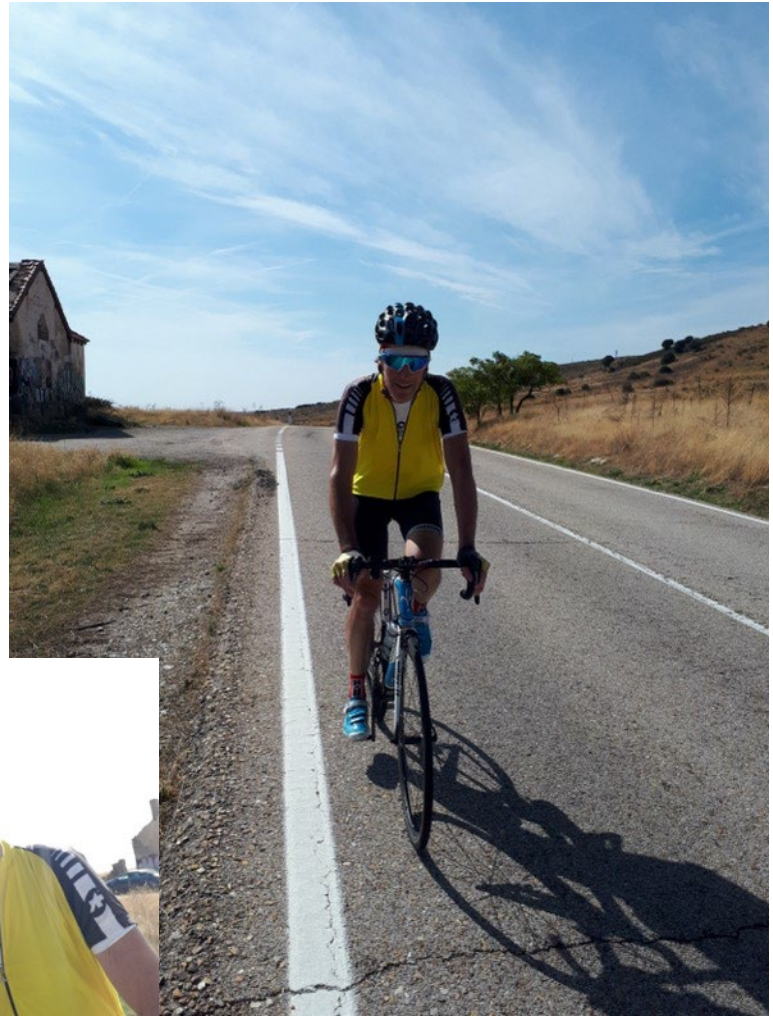


Diagnostic insights into mosaic skin diseases

Summer Academy 2024, Graz

by Antonio Torrelo
Chair, Department of Dermatology
Hospital Infantil Niño Jesús
Madrid, Spain



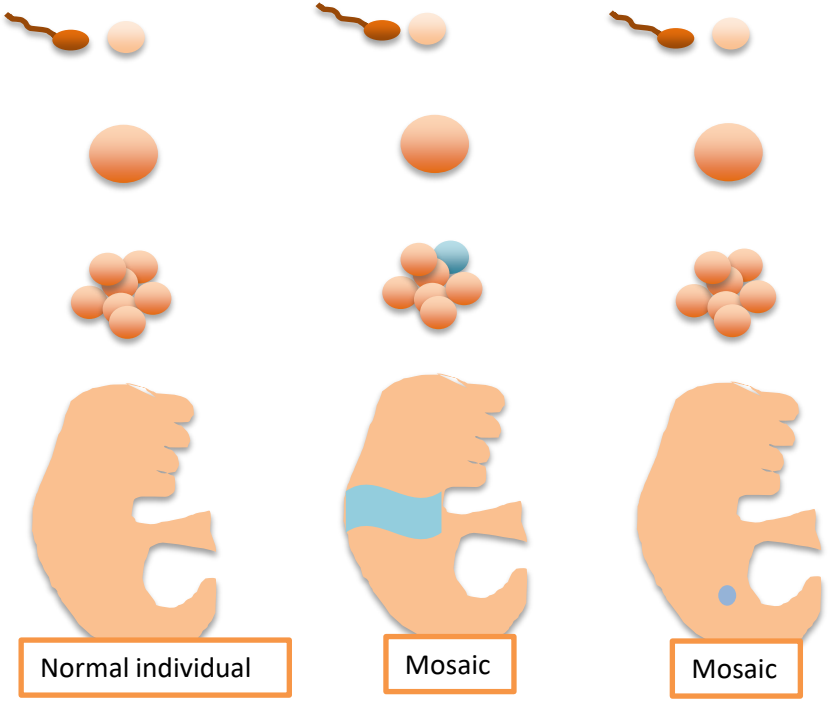


Part 1. The fundamentals of cutaneous mosaicism

Part 2. Diagnostic approach to cutaneous mosaicism

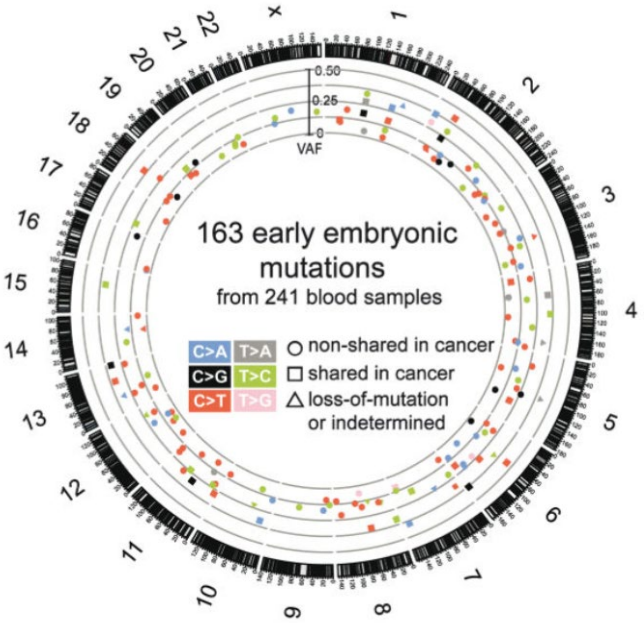
What is a Mosaic?

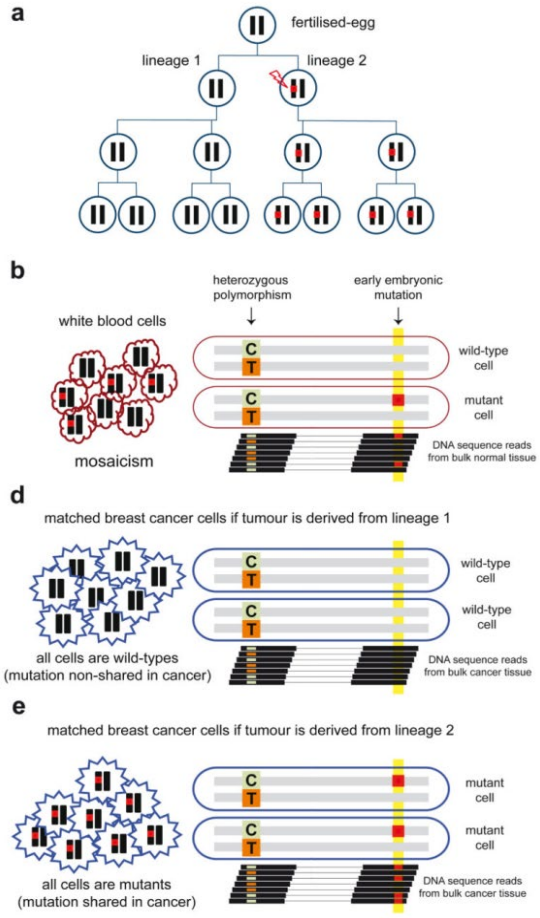
An individual with a heterogeneous genetic dotation originated from a genetically homogeneous zygote



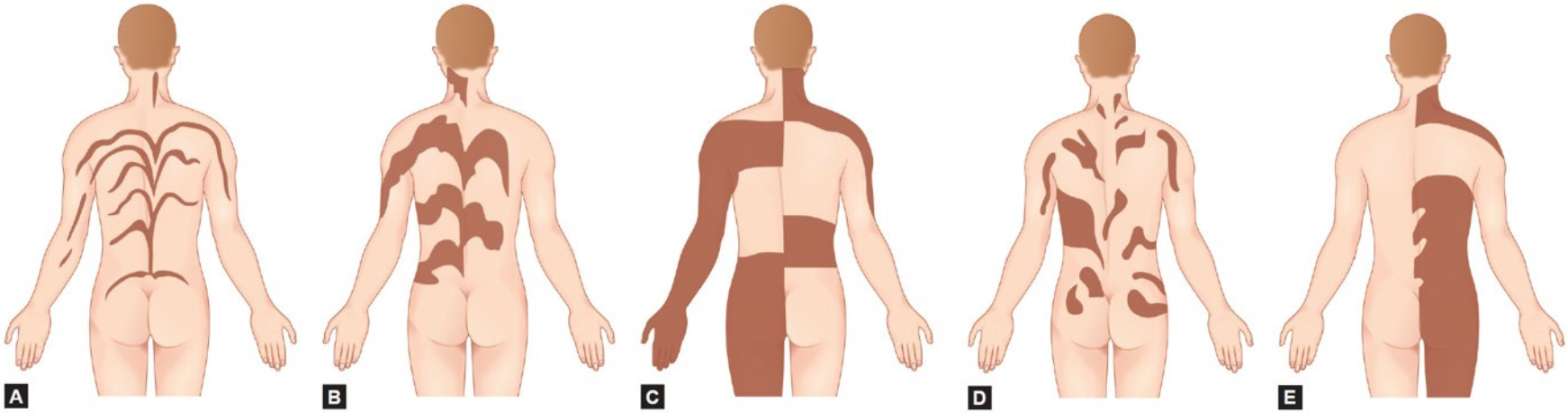
Somatic mutations reveal asymmetric cellular dynamics in the early human embryo

Young Seok Ju[1,2], Inigo Martincorena[1], Moritz Gerstung[1,3], Mia Petljak[1], Ludmil B Alexandrov[1,4], Raheleh Rahbari[5], David C Wedge[1,6], Helen R Davies[1], Manasa Ramakrishna[1], Anthony Fullam[1], Sancha Martin[1], Christopher Alder[1], Nikita Patel[1], Steve Gamble[1], Sarah O'Meara[1], Dilip D Giri[7], Torril Sauer[8], Sarah E Pinder[9], Colin A Purdie[10], Åke Borg[11,12,13], Henk Stunnenberg[14], Marc van de Vijver[15], Benita K.T. Tan[16], Carlos Caldas[17], Andrew Tutt[18,19], Naoto T Ueno[20], Laura J van't Veer[21], John W. M. Martens[22], Christos Sotiriou[23], Stian Knappskog[24,25], Paul N. Span[26], Sunil R. Lakhani[27,28,29], Jórunn Erla Eyfjörd[30], Anne-Lise Børresen-Dale[31,32], Andrea Richardson[33], Alastair M. Thompson[34], Alain Viari[35], Matthew E Hurles[5], Serena Nik-Zainal[1], Peter J Campbell[1], and Michael R Stratton[1,‡]





Segmental mosaicism



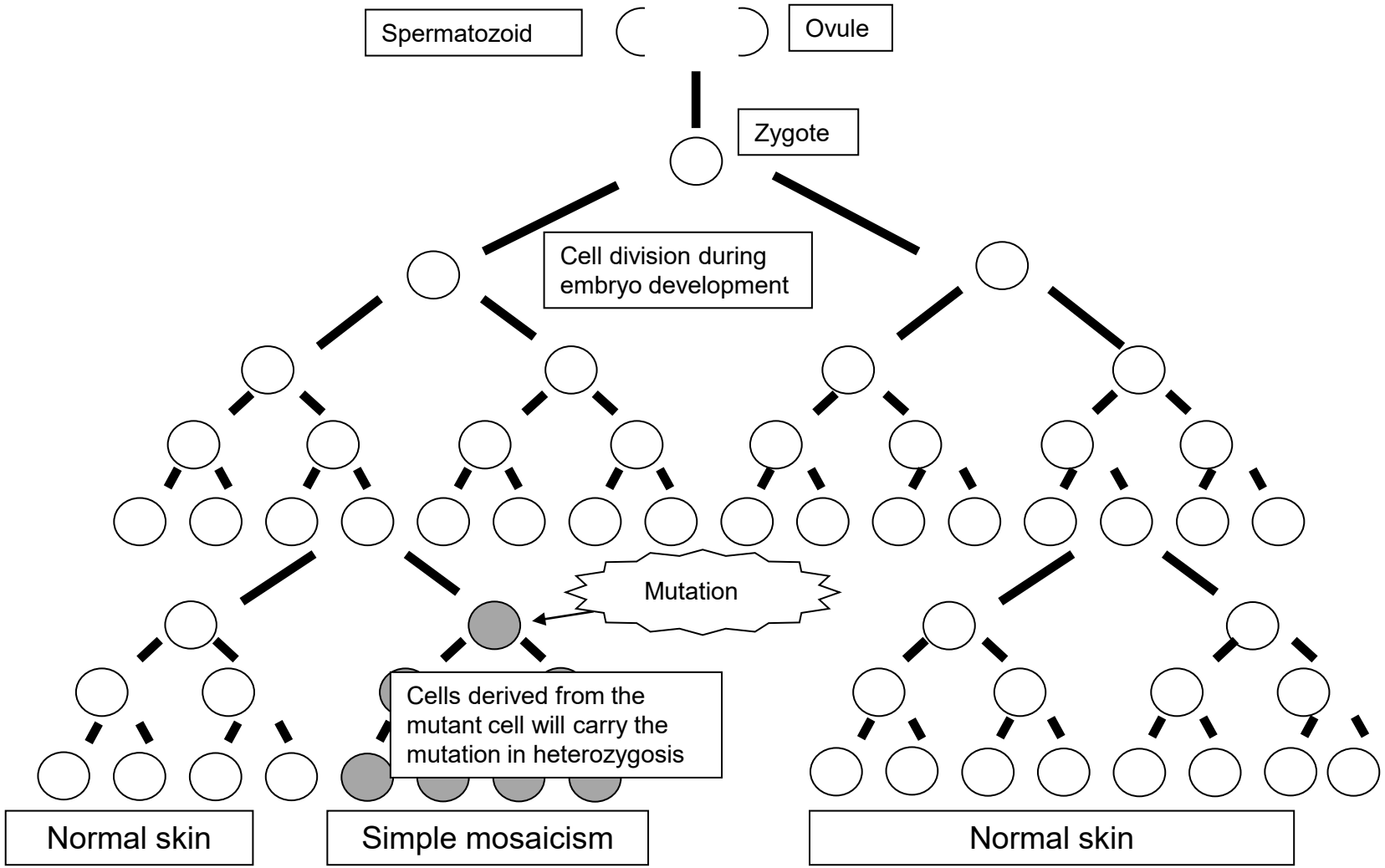
Lines of Blaschko

Blocks

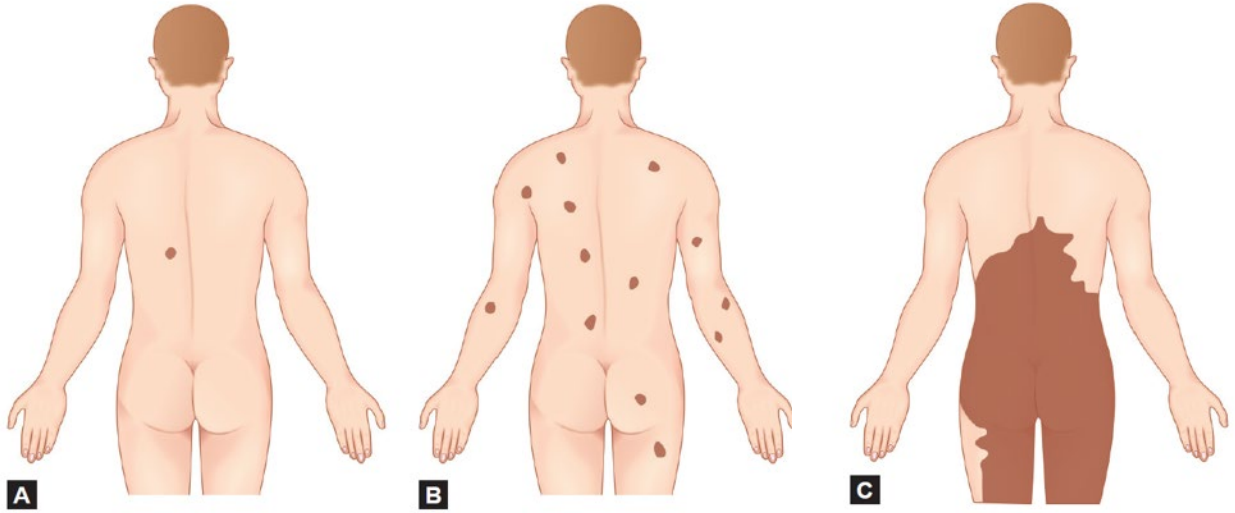
Phylloid

Lateralization

Mutation in embryo


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

Non-segmental mosaicism

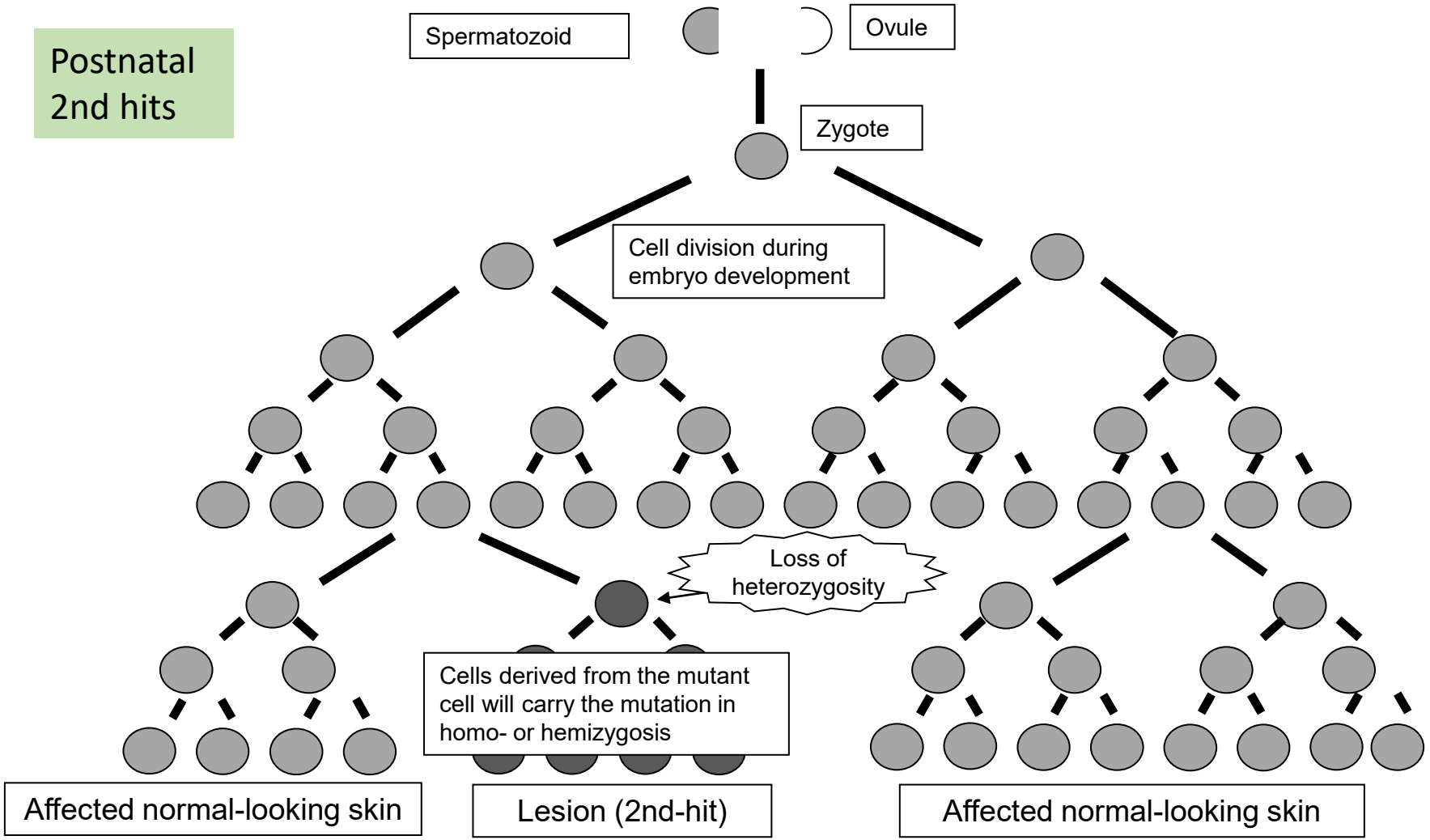


Postnatal mutation

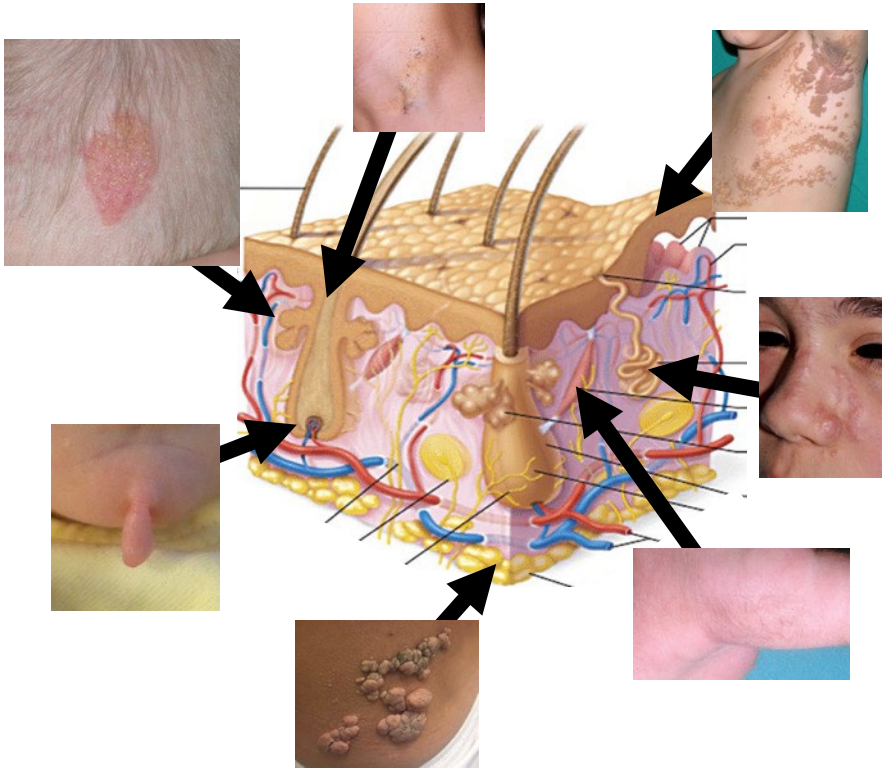
Postnatal 2nd hits

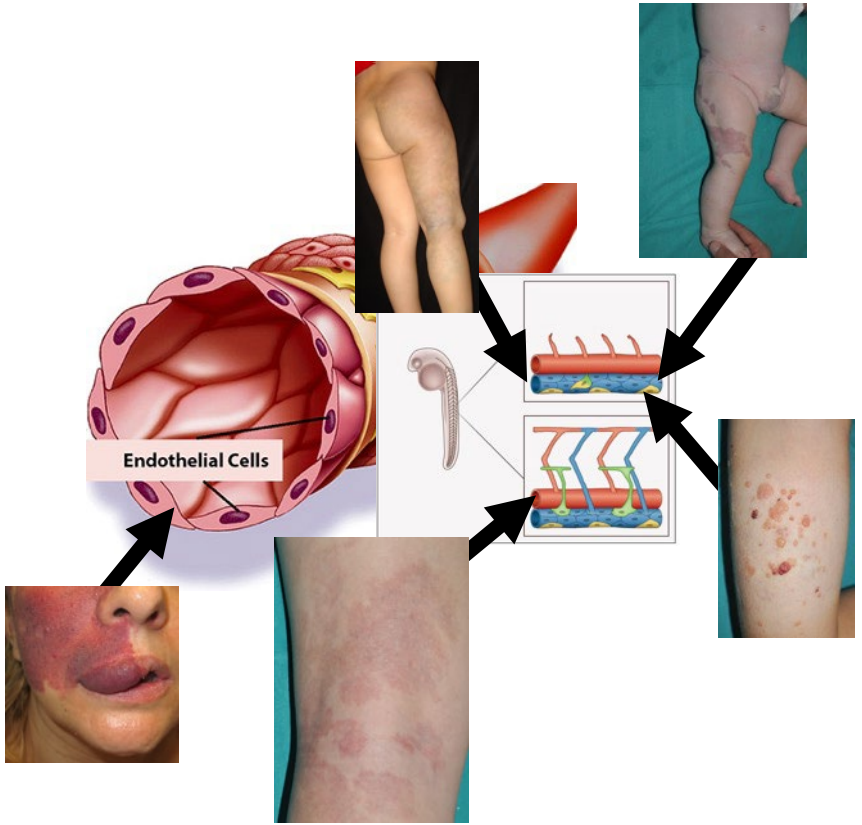
Migration pattern

Postnatal
2nd hits



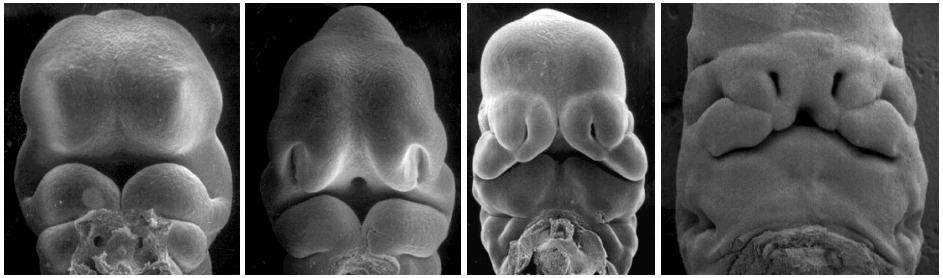
Who carries mosaic mutations?

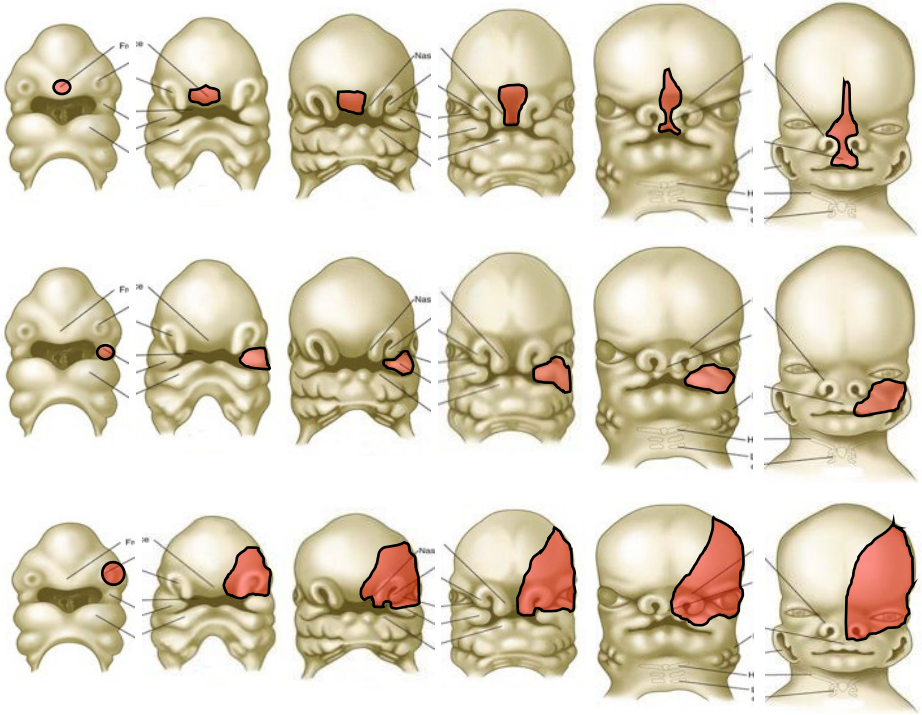


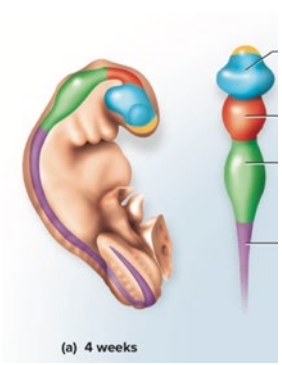


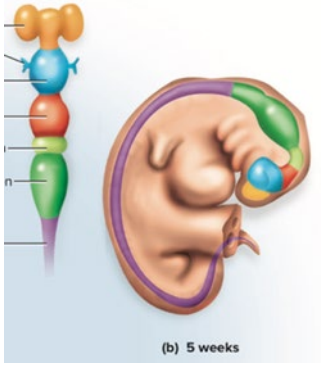
Who carries mosaic mutations?

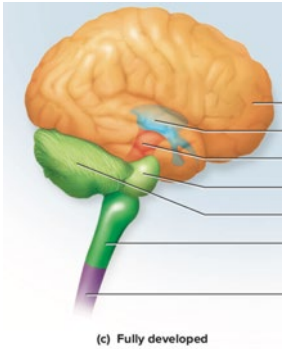
- A differentiated cell (a pure nevus)
- A stem cell (non-differentiated)
  - A multisystemic disease (a syndrome)
  - A multicomponent nevus (e.g., organoid nevus, combined vascular anomaly)
  - A pseudodidymosis

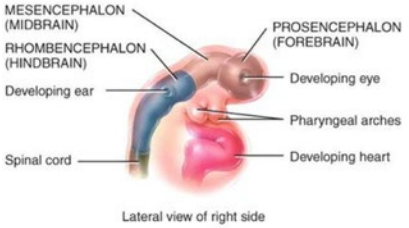




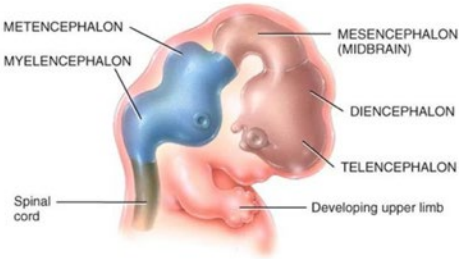




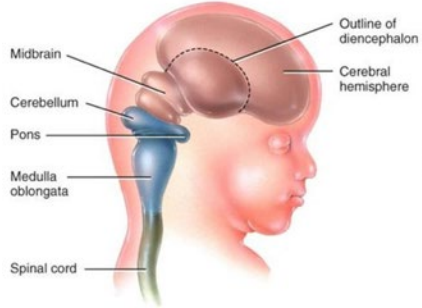




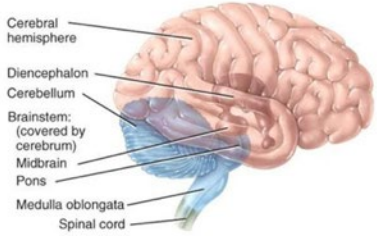
(a) Three- to four-week embryo showing primary brain vesicles



(b) Seven-week embryo showing secondary brain vesicles

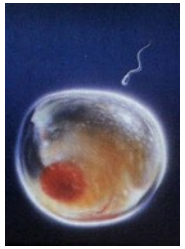


(c) Eleven-week fetus showing expanding cerebral hemispheres overgrowing the diencephalon



(d) Brain at birth (diencephalon and superior portion of brain stem projected to surface)

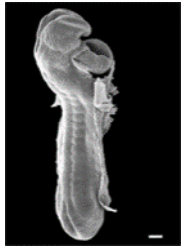
When do Mosaic mutations occur?



Germ line

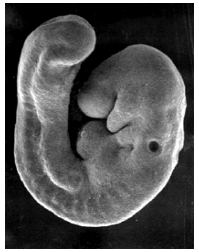
GNAQ/11

Not viable



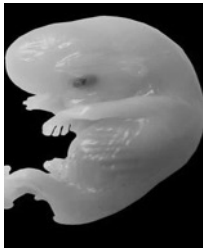
Early embryo

A syndrome



Late embryo

A segmental nevus



Embryo-fetal

A patch nevus

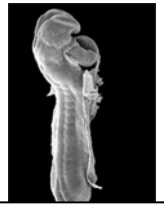
Adult life

A ‘tumor’

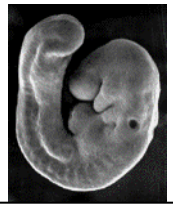
When do Mosaic mutations occur?

Germinal

FGFR3

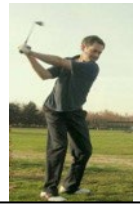


Early embryo



Late embryo

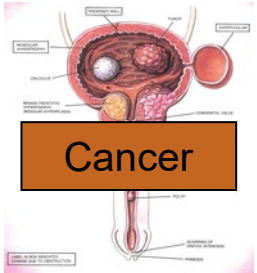
Developmental anomaly — Nevus



Adult life

Tumor

Adult life



Cancer

Thanatophoric dysplasia

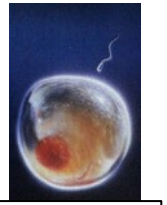
Epidermal nevus syndrome

Segmental epidermal nevus

Seborrheic keratosis

Bladder cancer

When do Mosaic mutations occur?



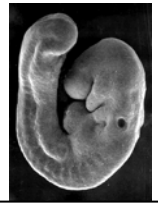
Germ line

HRAS (G12S)

Costello syndrome

Early embryo

Sebaceous nevus syndrome



Late embryo

Sebaceous nevus

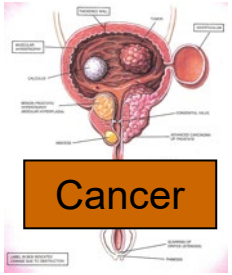
Abnormal development — Nevus

Adult life

Tumor

Sebaceous gland hyperplasia

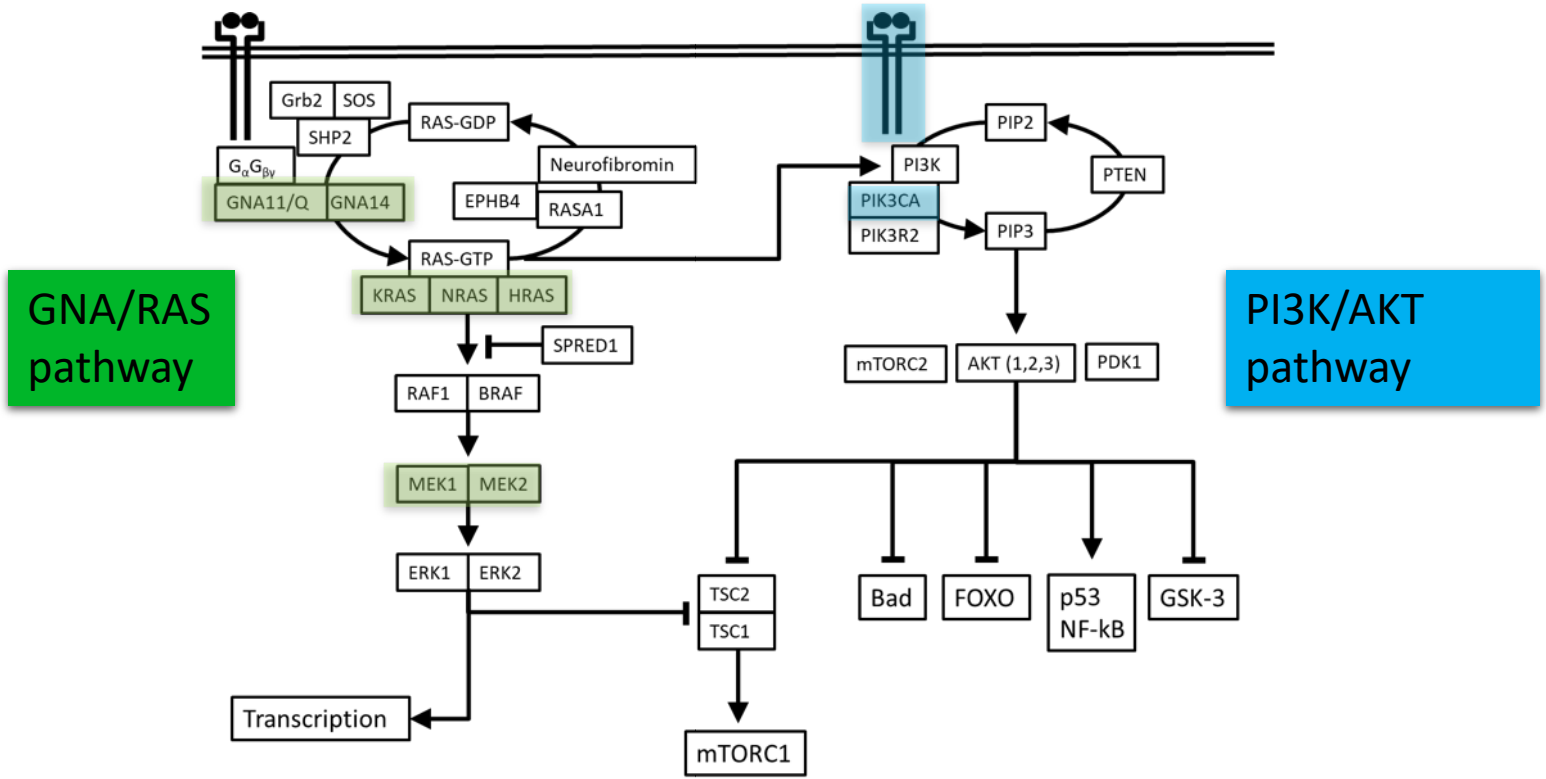
Adult life



Cancer

Bladder cancer

How do Mosaic mutations act?



How much Mosaic tissue?

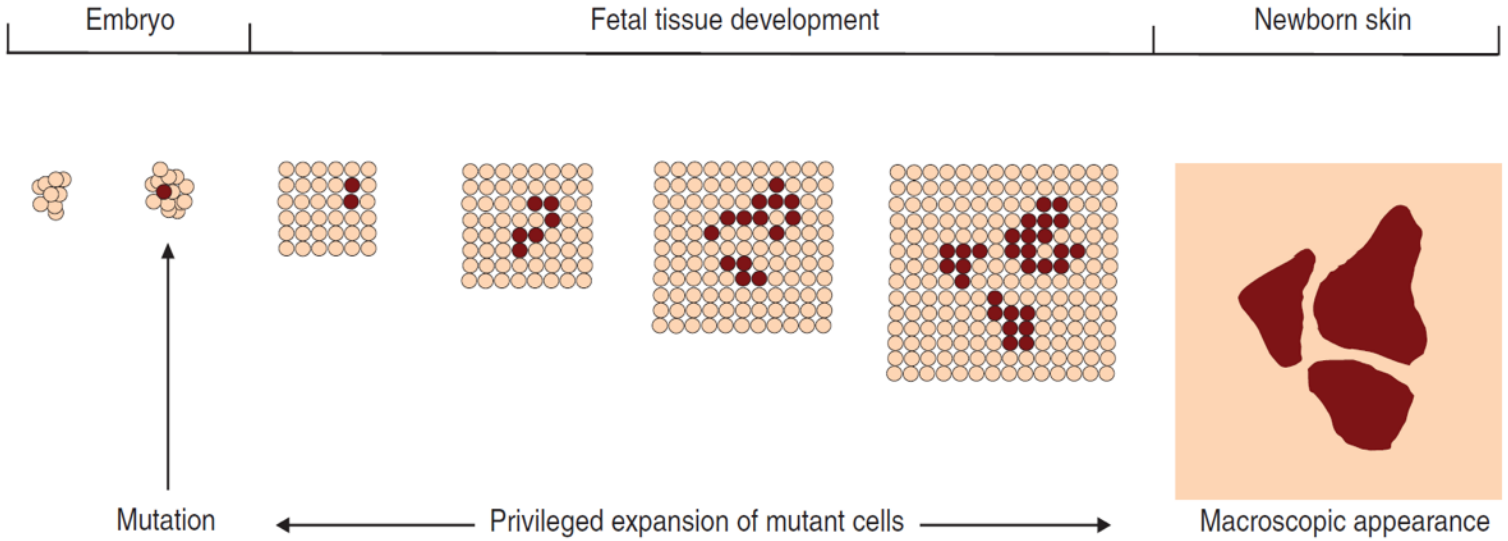


Fig. 3.1 After mutation occurs during embryonic development, normal and mutated cells develop together in an admixture. Mutant cells often show an advantage in growth and may outnumber normal cells in the eventually resulting nevus tissue

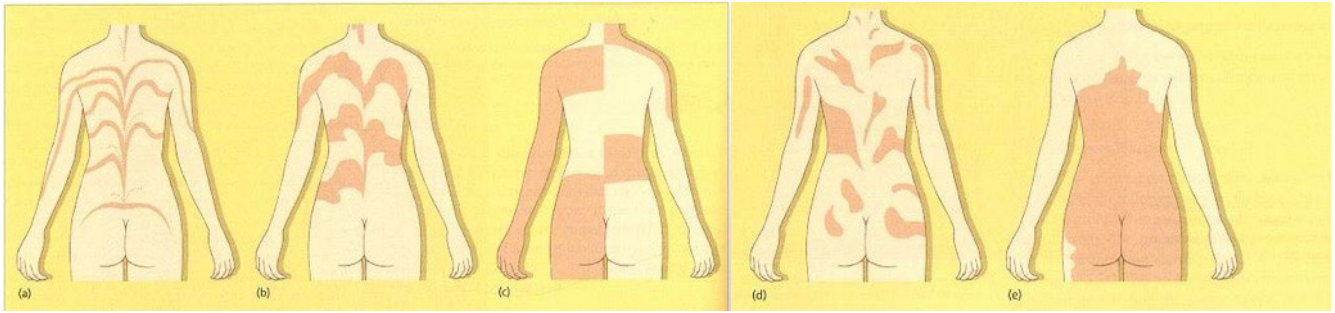
Allelic frequency usually low (< 15 %)

Part 1. The fundamentals of cutaneous mosaicism

Part 2. Diagnostic approach to cutaneous mosaicism

My approach to mosaic disorders

1. Identify a mosaic disorder: PATTERNS



2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY

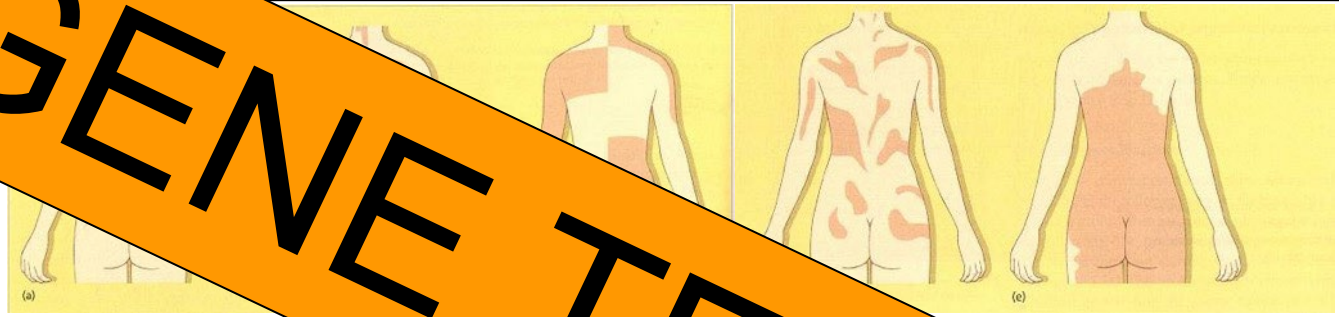
3. Associated conditions: IMAGING & LAB

4. Molecular confirmation: GENE TESTING

5. Therapy: IF EXISTING

Future approach to mosaic disorders

1. Identify a mosaic disorder: PATTERNS



2. Diagnose disorder: [illegible]ATHOLOGY

3. Associated conditions: [illegible]

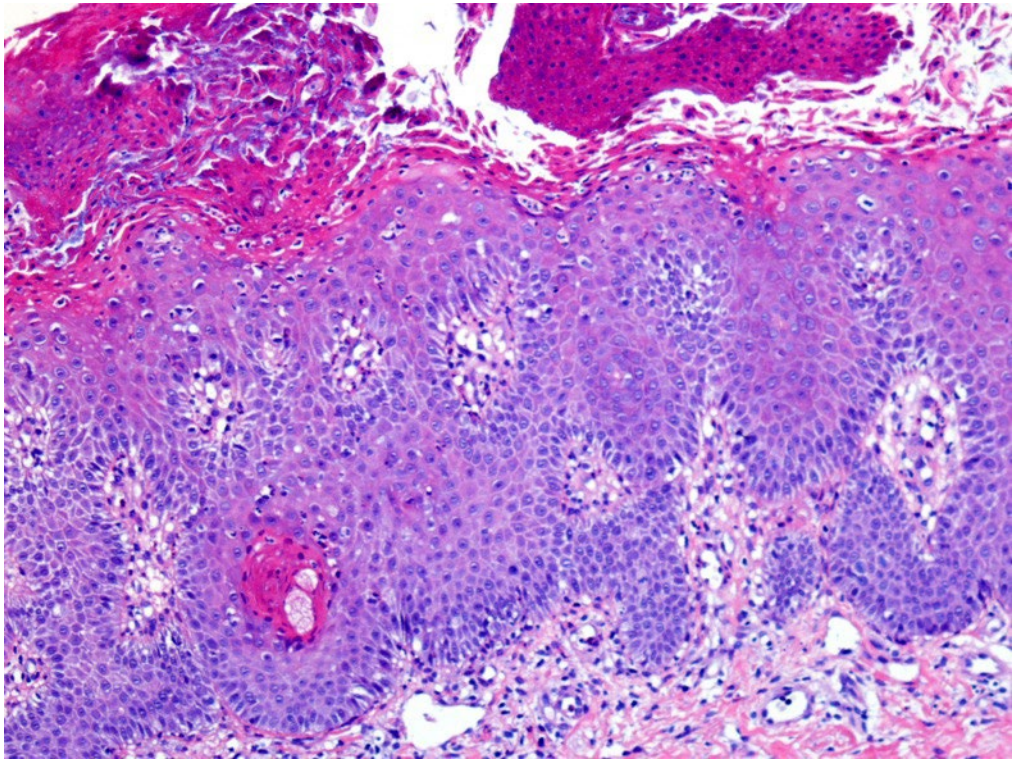
4. Molecular confirmation: GENE TEST[illegible]

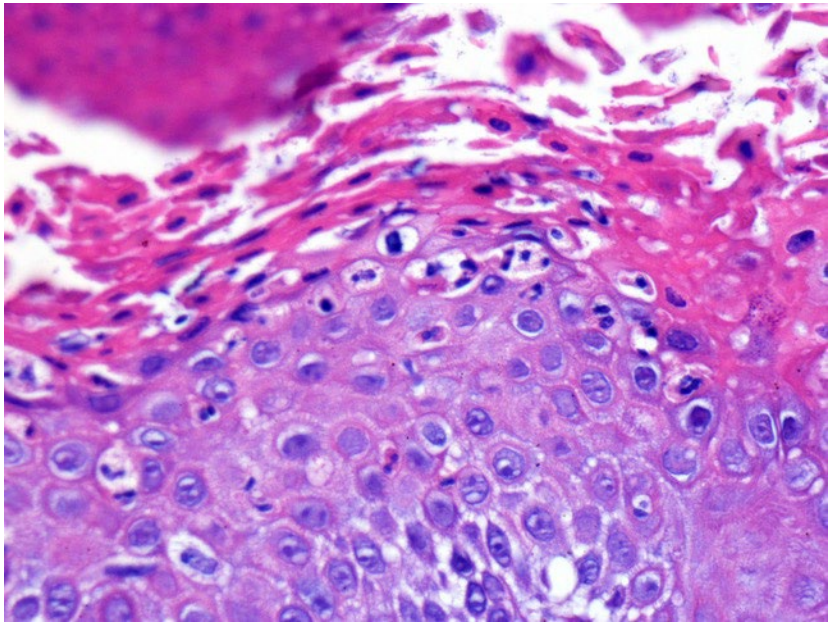
5. Therapy: IF EXISTING

GENE TESTING

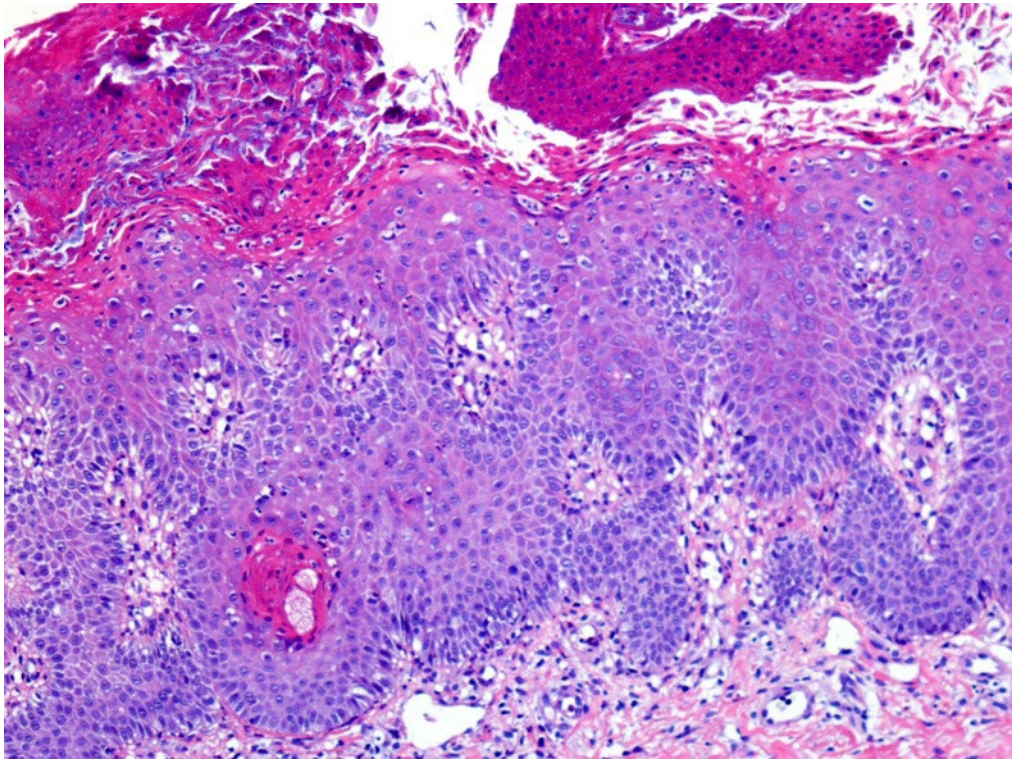
1. Identify a mosaic disorder: PATTERNS

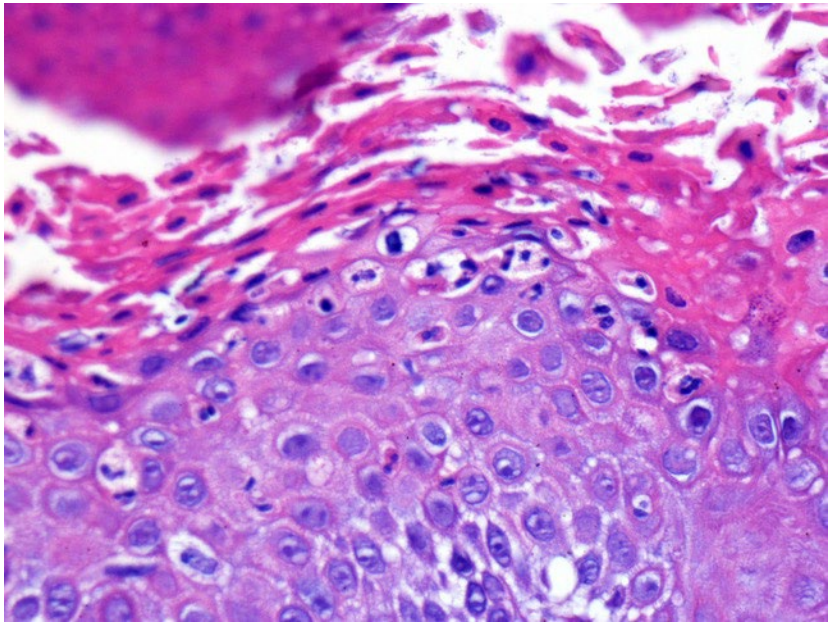
2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY





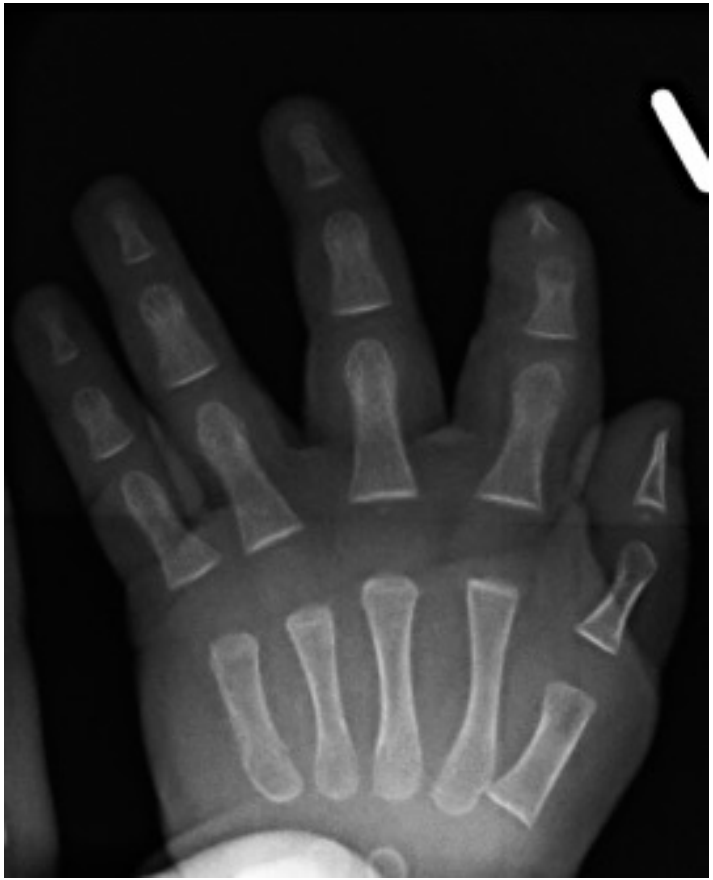
2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY

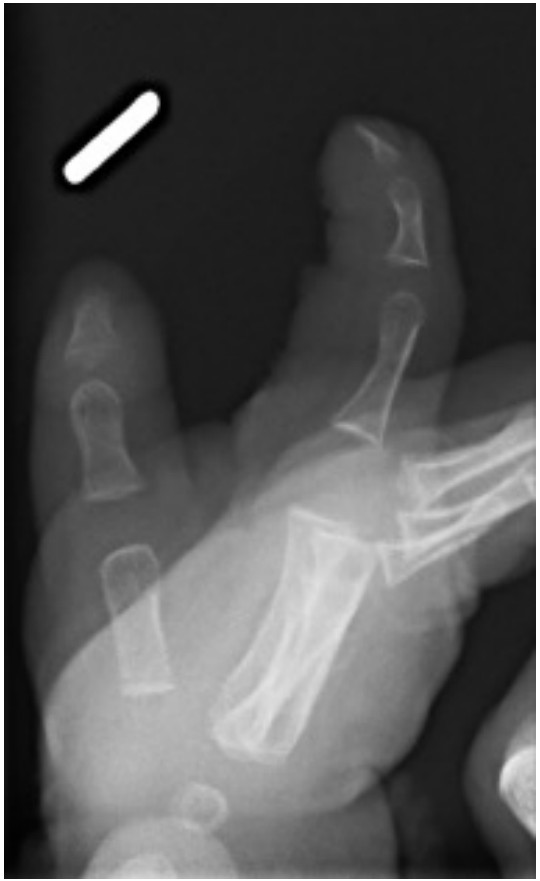




Parakeratosis of Cerroni

3. Associated conditions: IMAGING & LAB





Congenital

Hemidysplasia

Ichthyosiform erythroderma

Limb

Defects

AJMG AMERICAN JOURNAL OF medical genetics

Mutations in the NSDHL gene, encoding a 3β-hydroxysteroid dehydrogenase, cause CHILD syndrome

Arne König[1], Rudolf Happle[1,*], Dorothea Bornholdt[2], Hartmut Engel[2] and Karl-Heinz Grzeschik[2]

American Journal of Medical Genetics

Volume 90, Issue 4, pages 339–346, 14 February 2000

CHILD syndrome caused by deficiency of 3β-hydroxysteroid-Δ^8, Δ^7-isomerase

Dorothy K. Grange[1,*], Lisa E. Kratz[2,3], Nancy E. Braverman[3] and Richard I. Kelley[2,3]

American Journal of Medical Genetics

Volume 90, Issue 4, pages 328–335, 14 February 2000

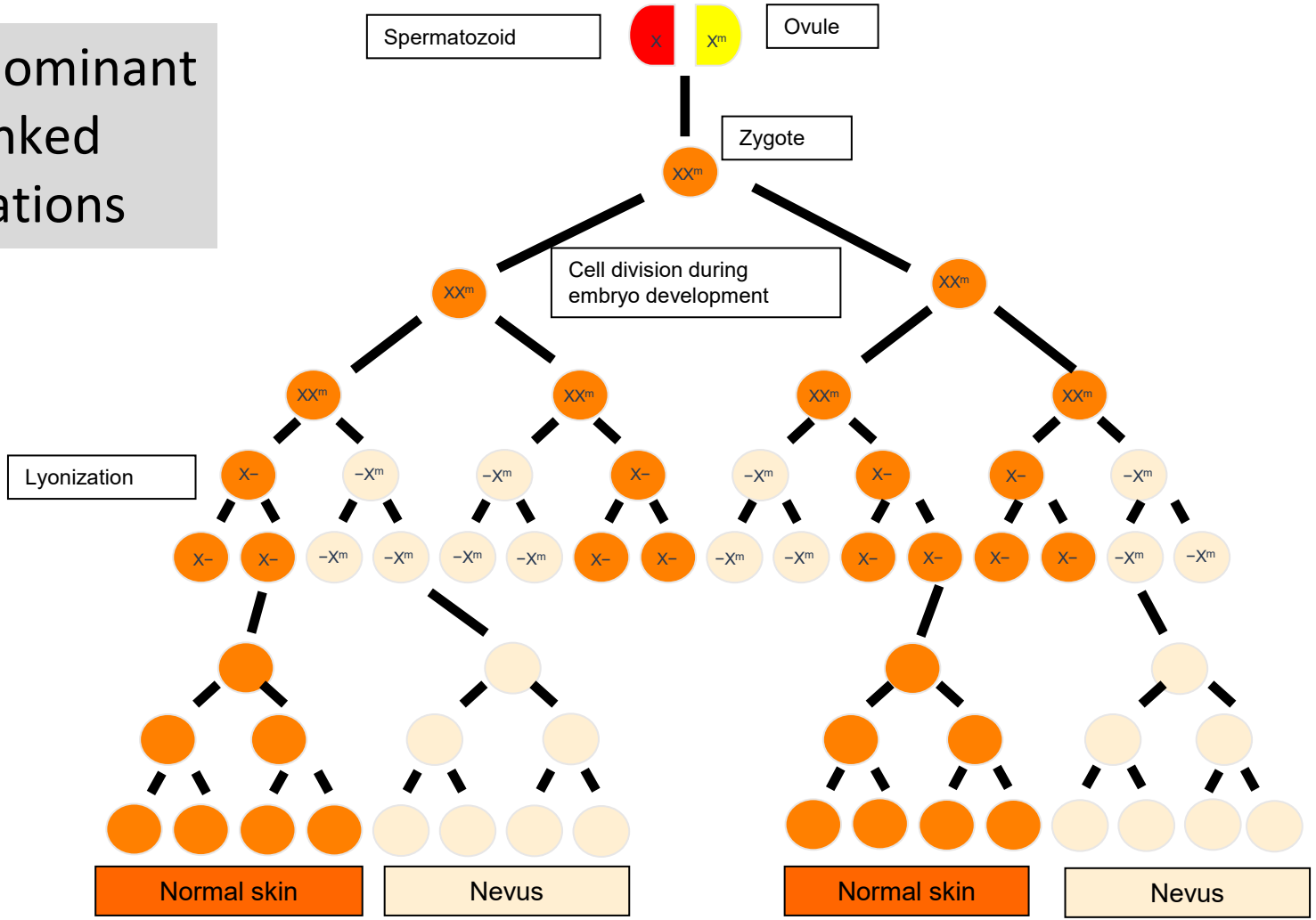
4. Molecular confirmation: GENE TESTING

Gene	Result	Summary
NSHD L	c.[262C>T] p.[Arg88Ter]	Detection of the heterozygous change c.262C>T in the *NSDHL* gene in DNA. The result was confirmed in a second, independent PCR reaction

The mutation c.262C>T (p.Arg88Ter; R88X) in exon 3 of the NSHDL gene has been already reported in a patient with CHILD syndrome (König et al, 2000). Therefore, the mutation was classified as pathogenic.

5. Therapy IF EXISTING

Lethal dominant X-linked mutations



Epigenetic mosaicism of X-linked genes

Dominant

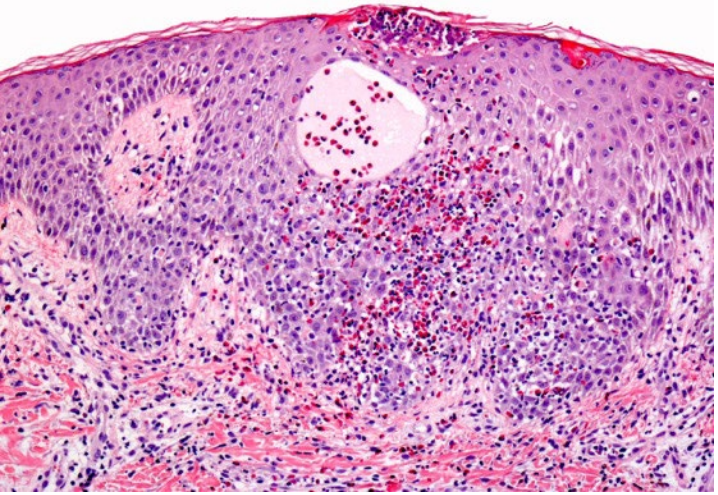
Females affected (lethal* in males)

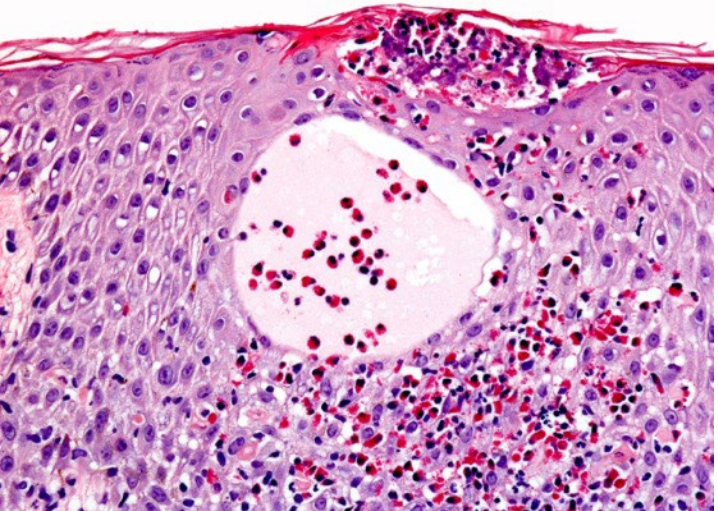
- Incontinentia pigmenti (NEMO)
- Focal dermal hypoplasia (PORCN)
- Conradi-Hünermann-Happle syndrome(EBP)
- CHILD nevus (NSDHL)
- MIDAS / MLS syndrome (COX7B)
- Oro-facial-digital type 1 (CXORF5)
- Aicardi syndrome (? Xp22)

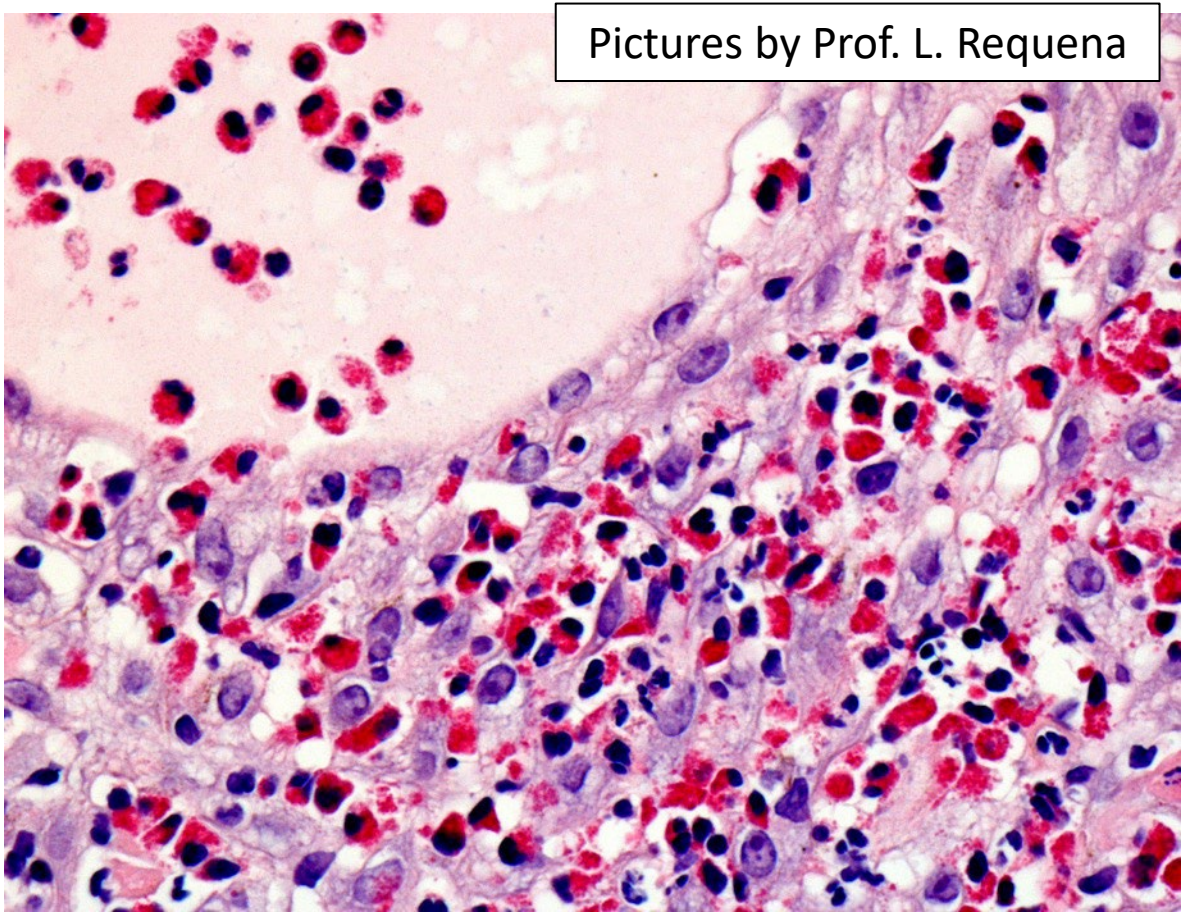
Recessive

Males affected, carrier females (healthy or mosaics)

- Hypohidrotic ectodermal dysplasia, X-linked (EDA)
- Diskeratosis congenita, X-linked (DKC1)
- Menkes syndrome (ATP7A9)
- IFAP syndrome: ichthyosis follicular, atrichia, photophobia (MBTPS2)
- Reticulated pigmentary anomaly of Partington (POLA1)
- Borjesson-Forssman-Lehman syndrome (PHF6)
- Albinism-deafness syndrome, X-linked (? Xq24-26)
- Hypertrichosis, dominant X-linked (? Xq27.1)

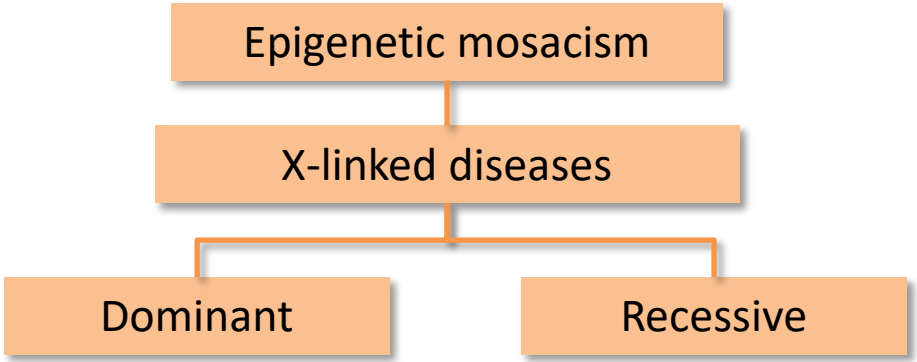


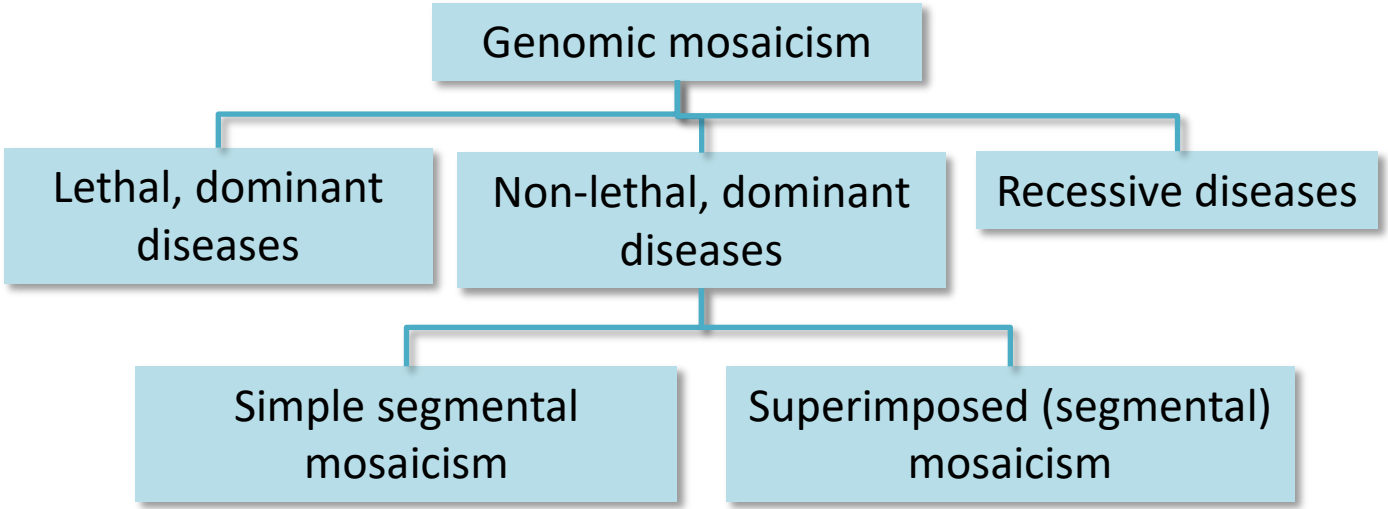




Pictures by Prof. L. Requena

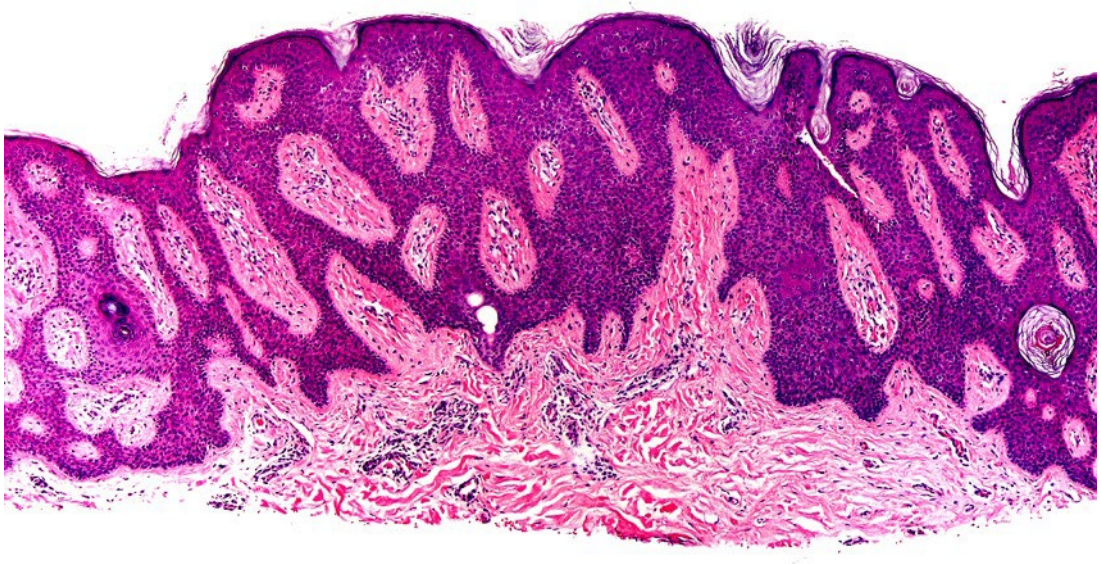
Incontinentia pigmenti: NEMO

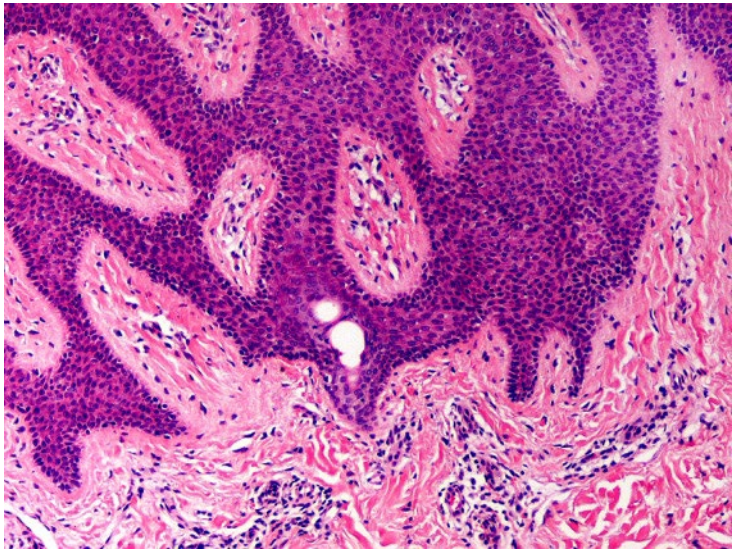

Epigenetic mosacism
X-linked diseases
Dominant
Recessive


Genomic mosaicism
Lethal, dominant diseases
Non-lethal, dominant diseases
Recessive diseases
Simple segmental mosaicism
Superimposed (segmental) mosaicism

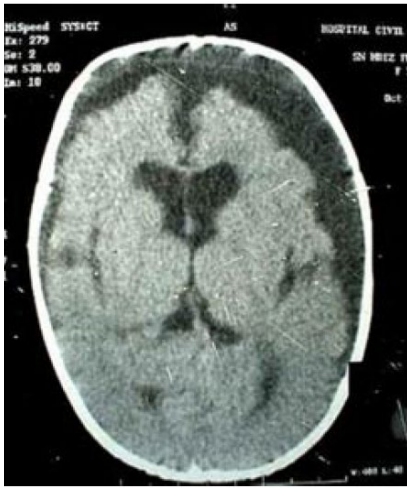
1. Identify a mosaic disorder: PATTERNS

2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY





3. Associated conditions: IMAGING & LAB



4. Molecular confirmation: GENE TESTING

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.

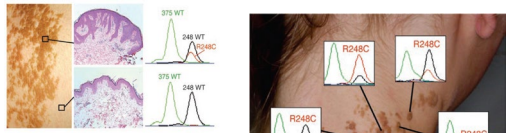
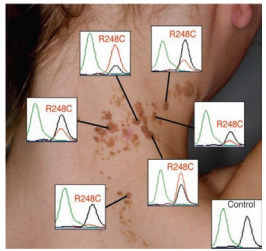


Figure 3
Patient 32 had a common soft-type epidermal nevus on his back. Two biopsies were taken from the epidermal nevus and the adjacent normal skin. The epidermal nevus histologically showed the typical acanthosis and papillomatosis (H&E staining; original magnification, ×40) and an R248C mutation 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.

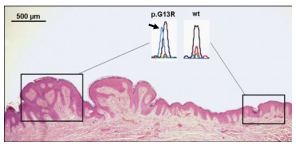


Somatic mosaicism

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]



ELSEVIER

Journal of Investigative Dermatology

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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[3], 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 Autònoma 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

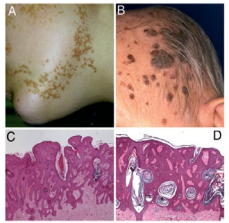


Fig. 1. Morphological similarities of linear lesions of congenital EN from a child following Blaschko's lines (*A*) and SK from an elderly patient (*B*). At the microscopic level, both lesions are characterized by acanthosis, papillomatosis, and variable degrees of hyperkeratosis and hyperpigmentation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

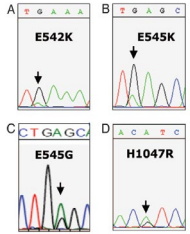
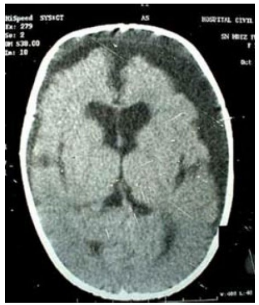


Fig. 2. Mutational analysis of EN and SK. In all cases, the mutant sequence was accompanied by the presence of the WT allele, indicating heterozygosity.

An Epidermal Nevus Syndrome with Cerebral Involvement Caused by a Mosaic *FGFR3* Mutation

Alejandro García-Vargas,[1] Christian Hafner,[2] Adriana G. Pérez-Rodríguez,[1] L. Ximena Rodríguez-Rojas,[1] Pedro González-Esqueda,[1] Robert Stoehr,[3] Mercedes Hernández-Torres,[1] and Rudolf Happle[1]*



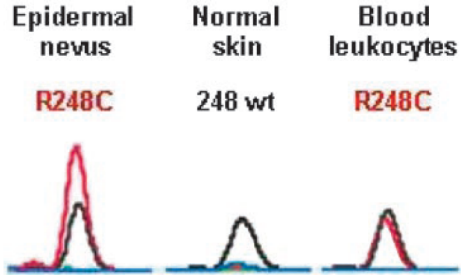
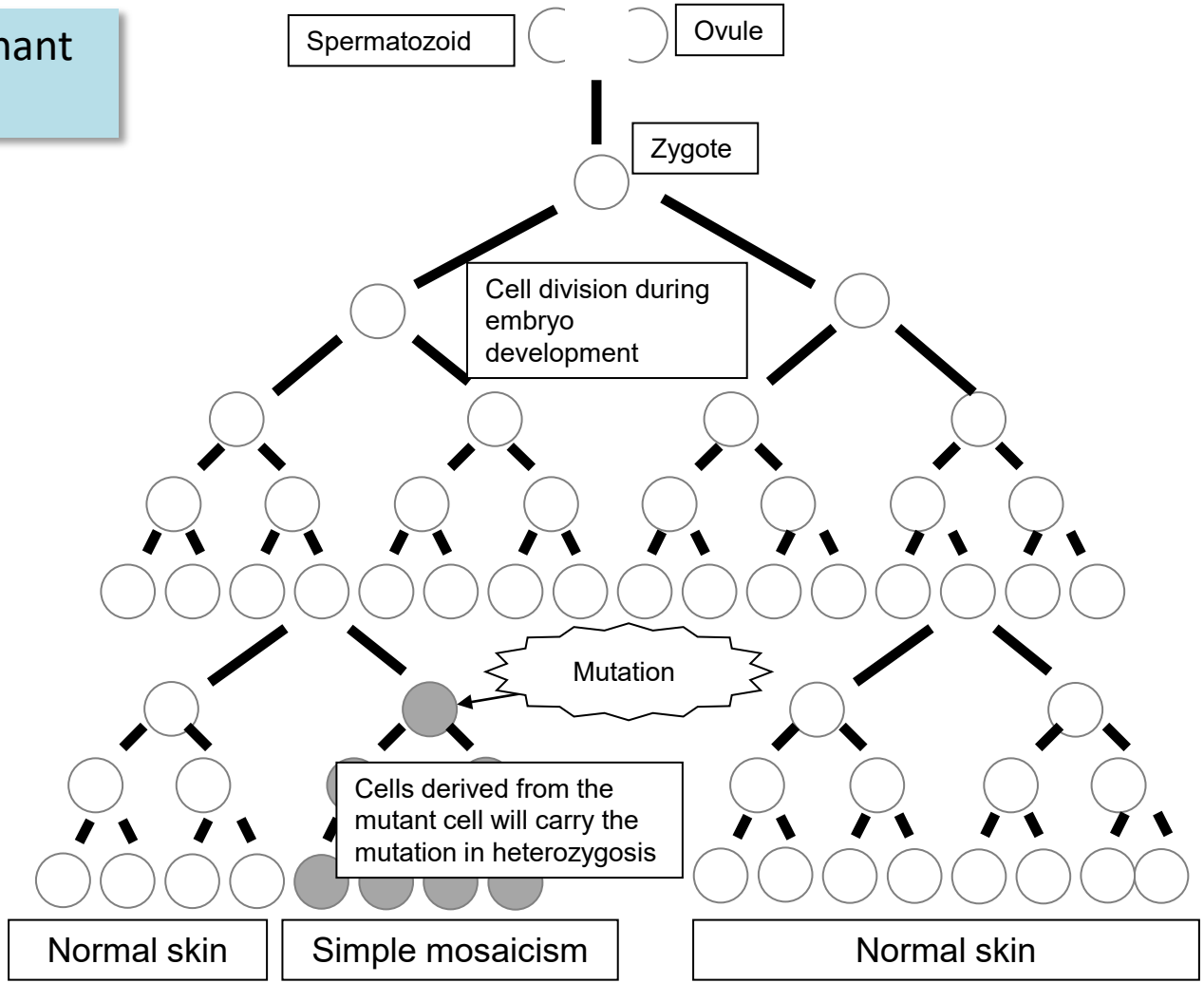


FIG. 4. SNaPshot multiplex assay shows a heterozygous R248C mutation within the *FGFR3* gene in the epidermal nevus and also in blood leukocytes, whereas unaffected skin next to the epidermal nevus was wild-type, indicating mosaicism of the *FGFR3* mutation.

Lethal, dominant diseases



Genomic mosaicism of lethal mutations

Genetically confirmed

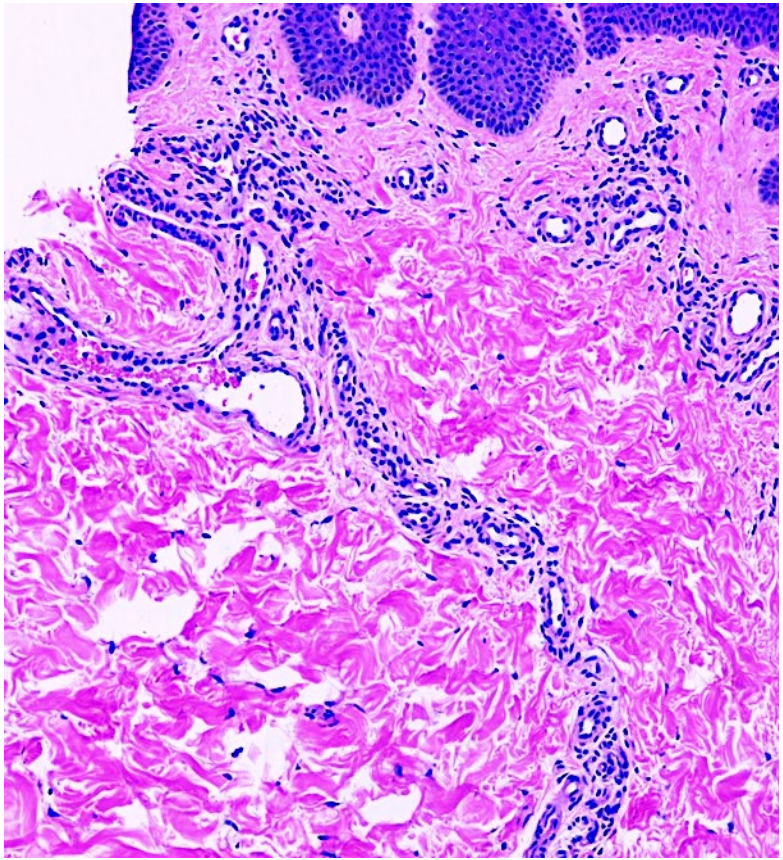
- PROS overgrowth spectrum (PIK3CA)
- Proteus syndrome (AKT1)
- Port wine stains and Sturge-Weber syndrome (GNAQ/GNA11)
- Epidermal nevus and epidermal nevus syndrome (FGFR3, FGFR2, HRAS, PIK3CA)
- Sebaceous nevus and sebaceous nevus syndrome (KRAS, HRAS, FGFR2)
- Nevus spilus and related (HRAS, PTPN11)
- McCune-Albright syndrome (GNAS)
- Maffucci syndrome (IDH1, IDH2)
- Melanocytic nevus and melanocyti nevus syndrome (NRAS)
- Becker nevus and Becker nevus syndrome (ACTB) – and CSMH
- Nevus comedonicus and nevus comedonicus syndrome (NEK9)
- Encephalocraniocutaneous lipomatosis (FGFR1)
- Vabres syndrome (RhoA)

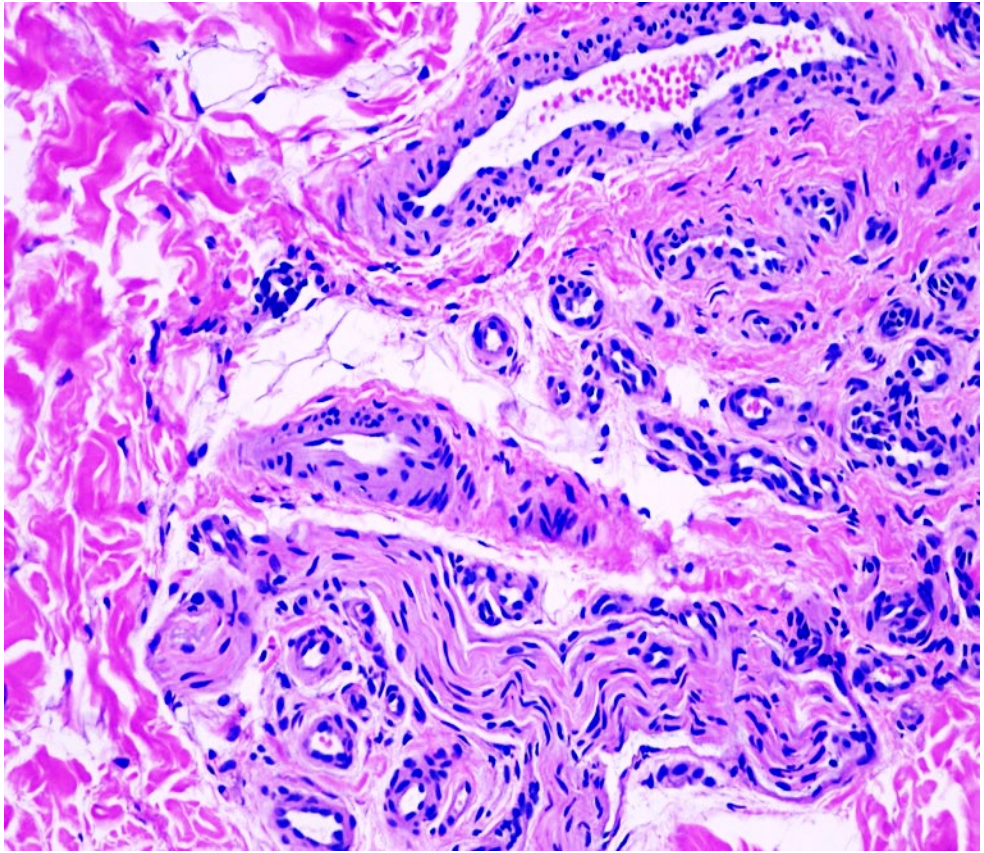
Awaiting genetic confirmation

- Angora hair nevus syndrome
- Castori syndrome
- NEVADA syndrome
- Cutis marmorata telangiectática congénita (?)
- Nevus trichilemmocysticus and nevus trichilemmocysticus syndrome

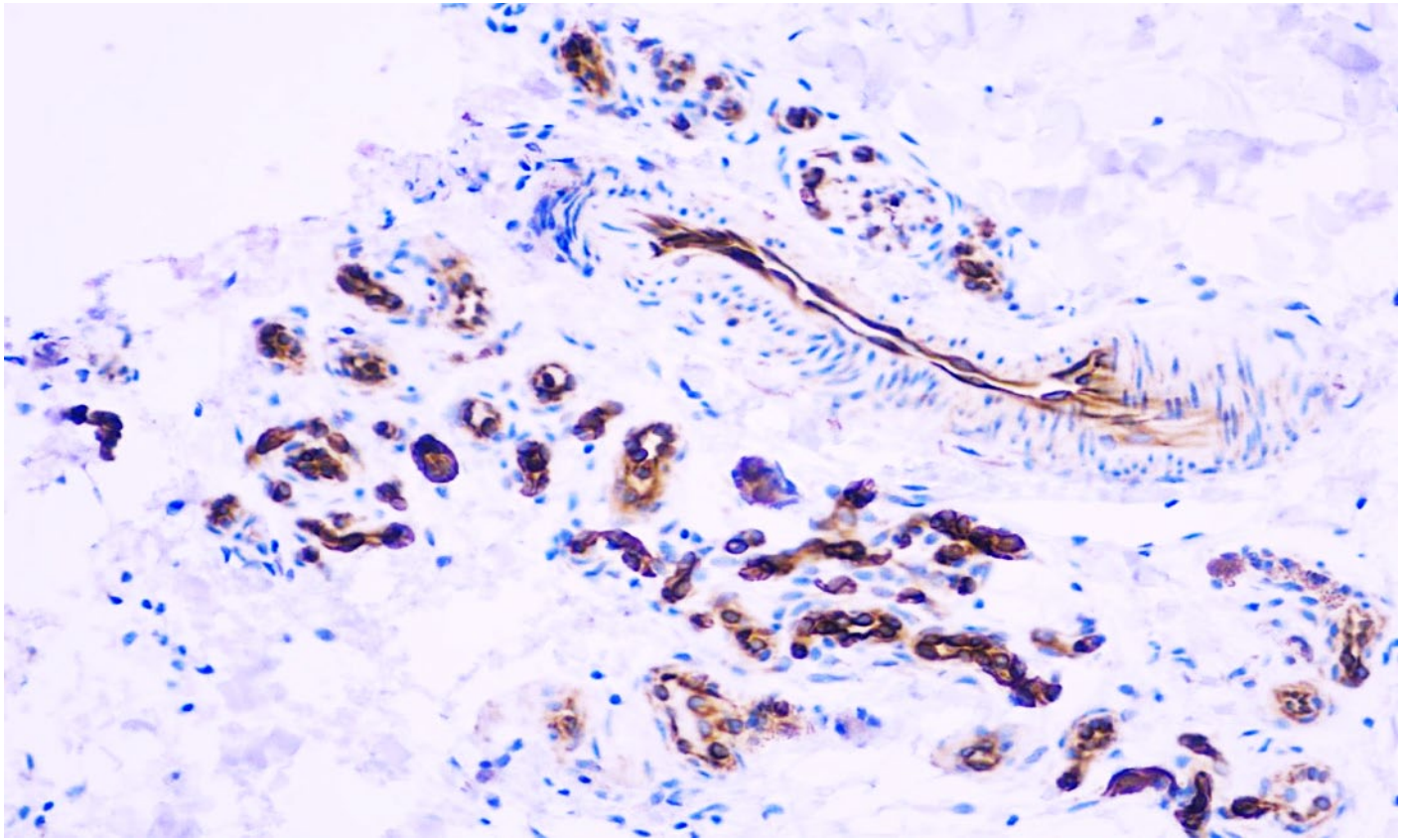
1. Identify a mosaic disorder: PATTERNS

2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY



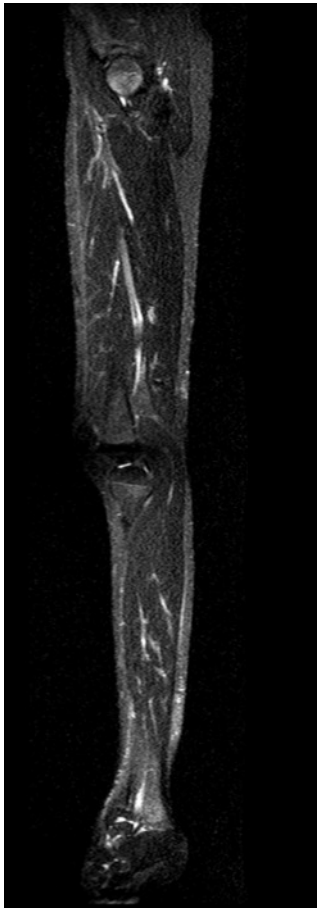


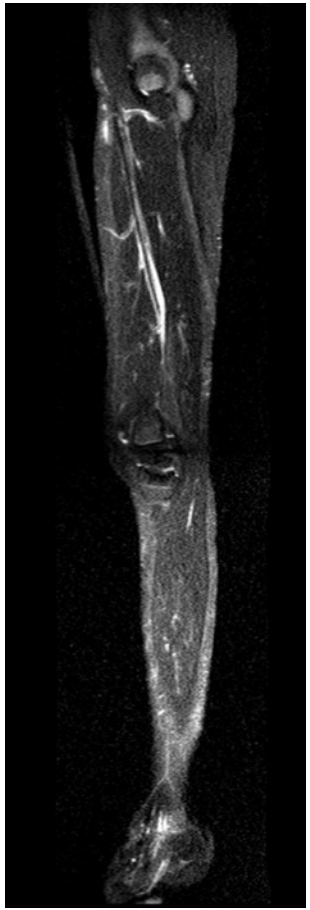
2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY



WT1

3. Associated conditions: IMAGING & LAB





4. Molecular confirmation: GENE TESTING

RESUMEN DE RESULTADOS

*La paciente cuenta con un informe previo de 2020 con resultado negativo en el que no se detectaron variantes patogénicas.

El re-análisis de las muestras utilizando la nueva versión del panel MALVA (v5), que incluye nuevos genes asociados a malformaciones vasculares, nos ha permitido detectar la variante ***MAP2K1*** (NM_002755): **c.17[G>C (p.Lys57Asn)** en ADN obtenido a partir de tejido en un mosaico del 2-3%. Según la clasificación de variantes del ACMG (American College of Medical Genetics) se considera esta variante como **patogénica**.

Dado que este gen está relacionado con malformaciones arteriovenosas, **la pres paciente.**

MAP2K1

INTERPRETACIÓN DE LOS RESULTADOS

En la paciente se detecta una variante en forma de mosaico en la secuencia de ADN del gen ***MAP2K1***. Este gen está relacionado con malformaciones arteriovenosas (Couto JA, 2017; PMID: 28190454).

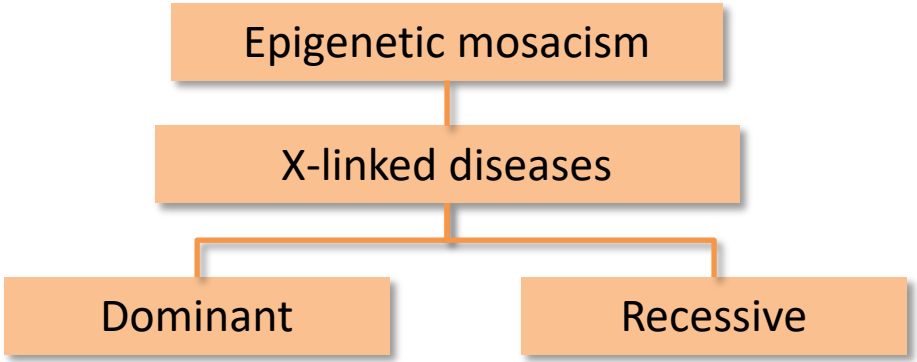
La variante ha sido clasificada por 10 predictores de patogenicidad *in silico* como patogénica (DANN, DEOGEN2, FATHMM-MKL, LIST-S2, M-CAP, MVP, MutationAssessor, MutationTaster, PrimateAI, y SIFT) y por 2 como benigna (BayesDel_addAF, y EIGEN). Además, la variante no está presente ni en los exomas (cobertura = 99.2), ni en los genomas de GnomAD (cobertura = 30.0).

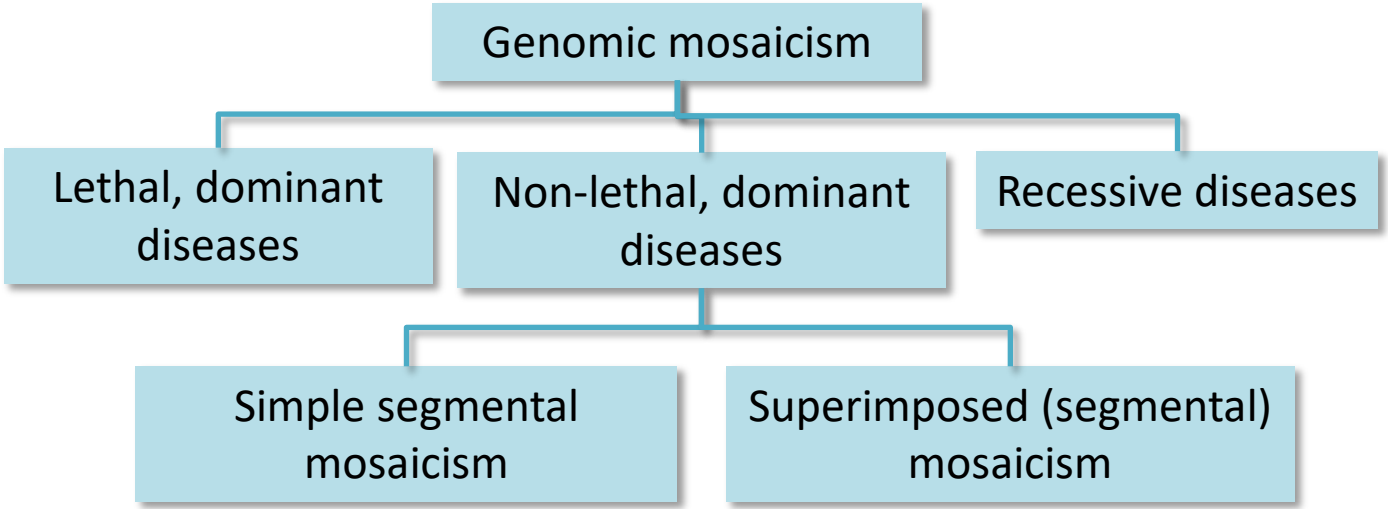
Por otro lado, la variante está descrita en la base de datos de variantes dbSNP (rs39751679) clasificada como patogénica y en la base de datos de enfermedades ClinVar asociada a diferentes patologías.

5. Therapy IF EXISTING

Surgery ?

Trametinib – MAPK inhibitors ?


Epigenetic mosacism
X-linked diseases
Dominant
Recessive


Genomic mosaicism
Lethal, dominant diseases
Non-lethal, dominant diseases
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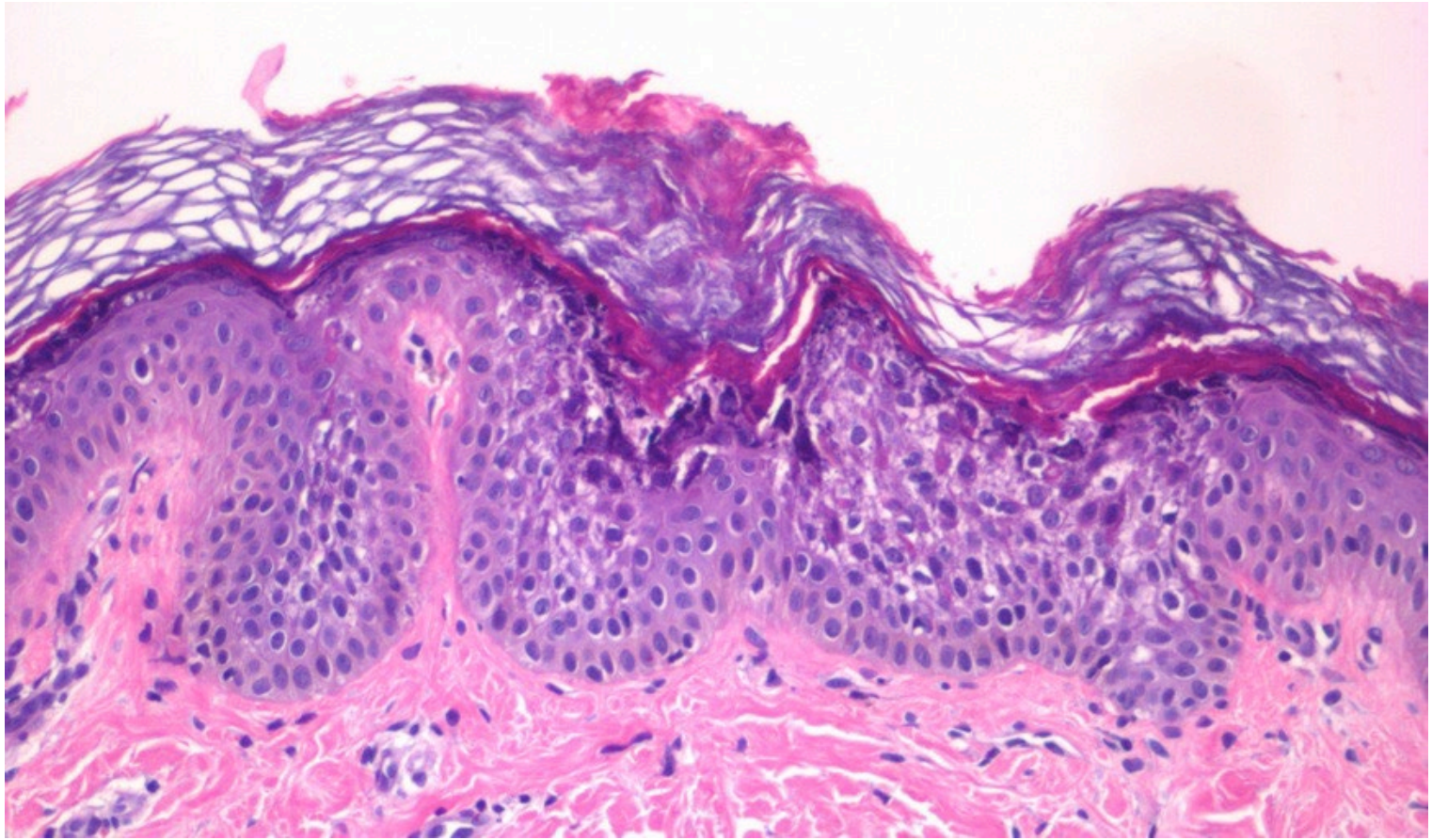
Simple segmental mosaicism
Superimposed (segmental) mosaicism

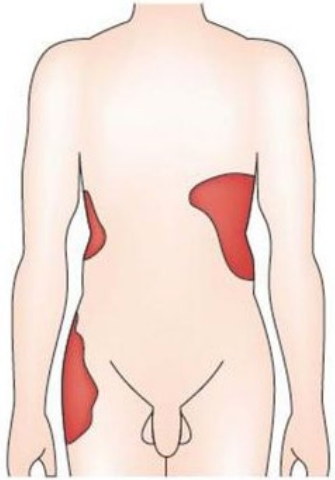
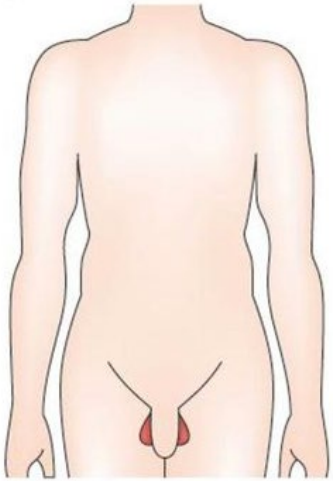
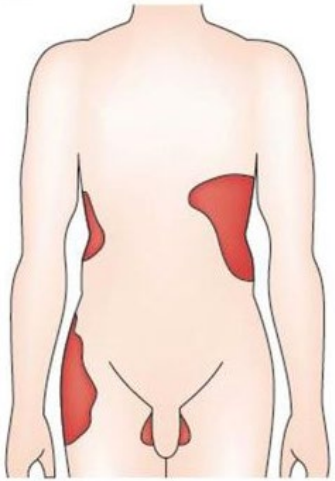
1. Identify a mosaic disorder: PATTERNS

2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY

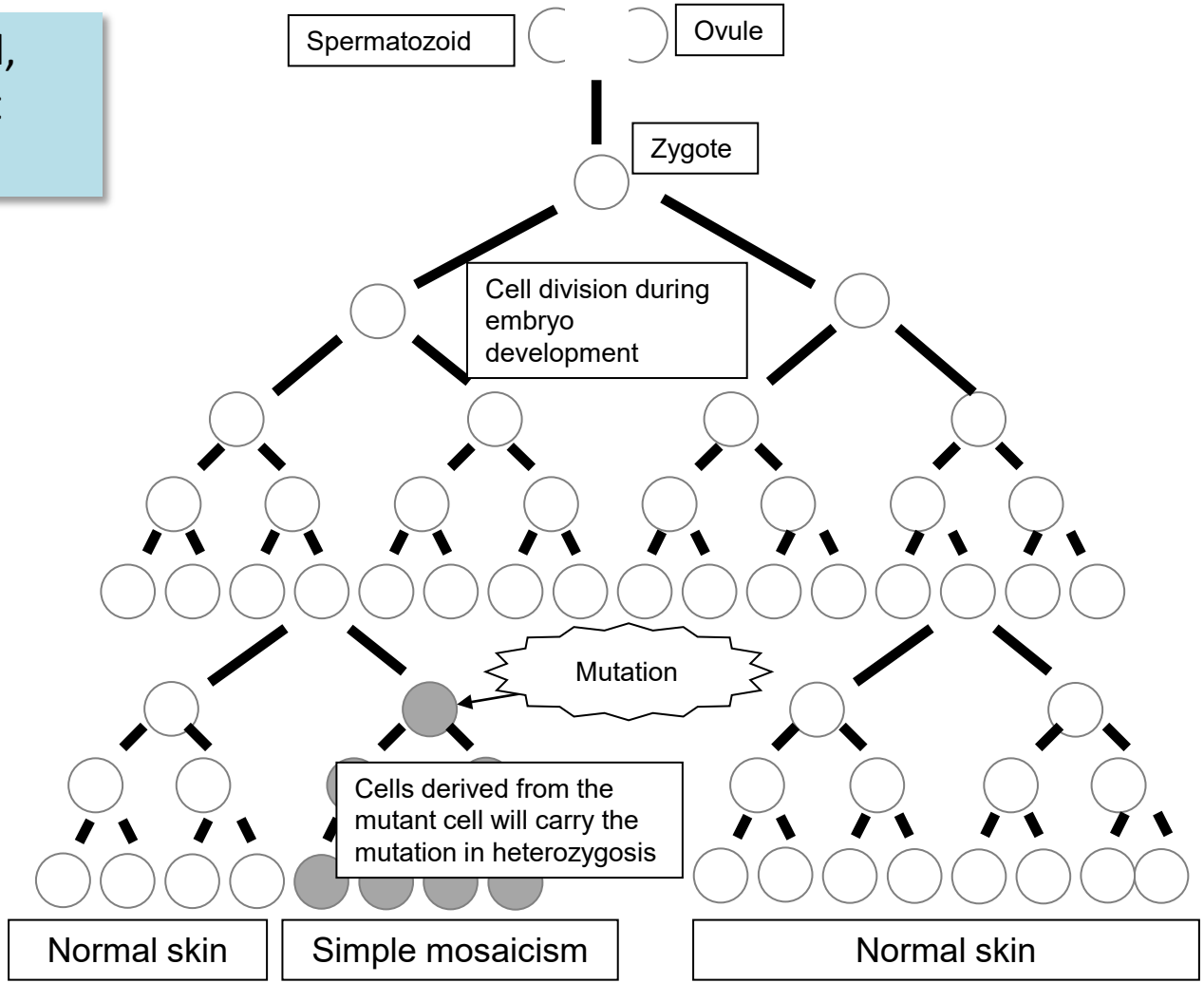


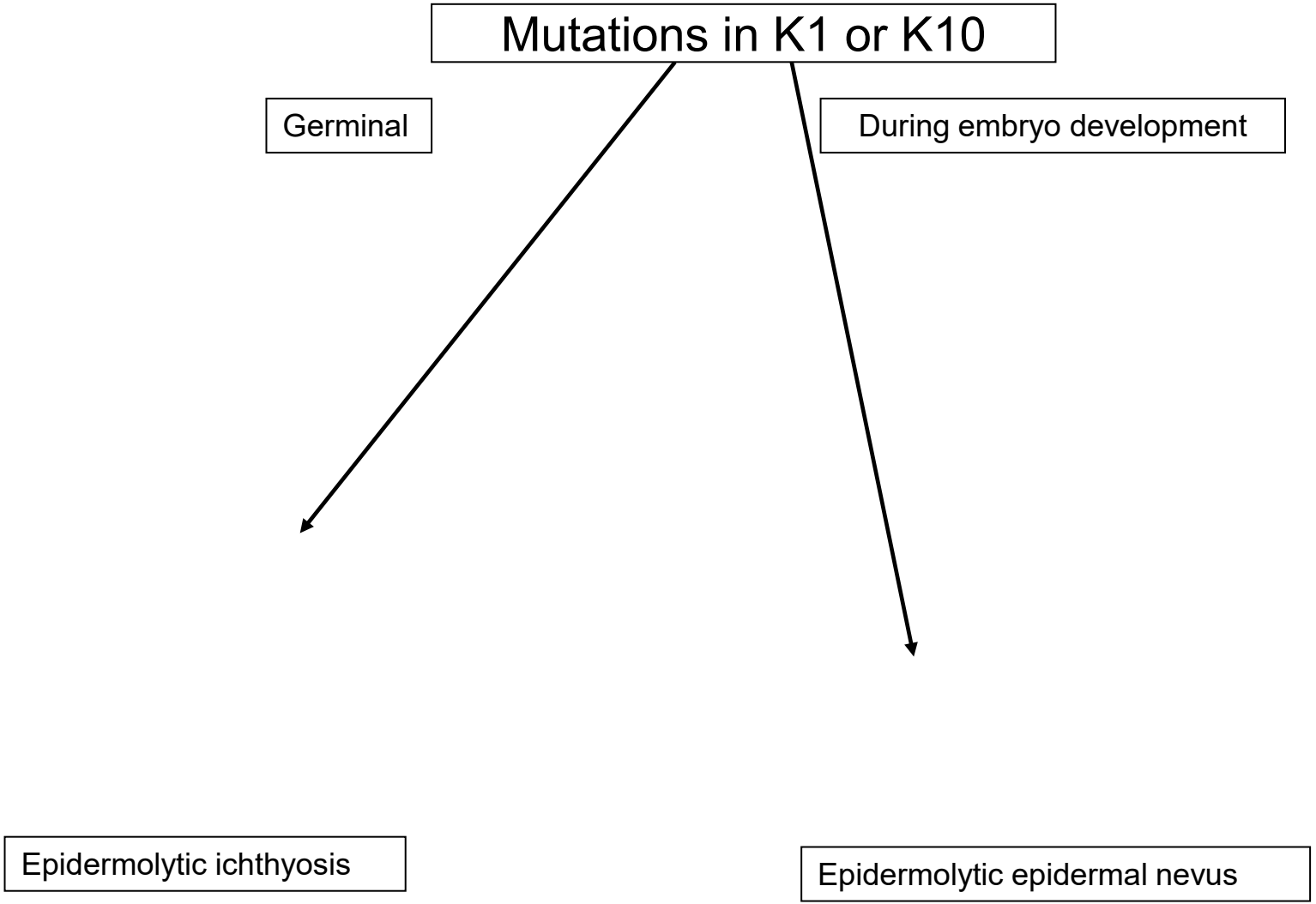
3. Associated conditions: IMAGING & LAB

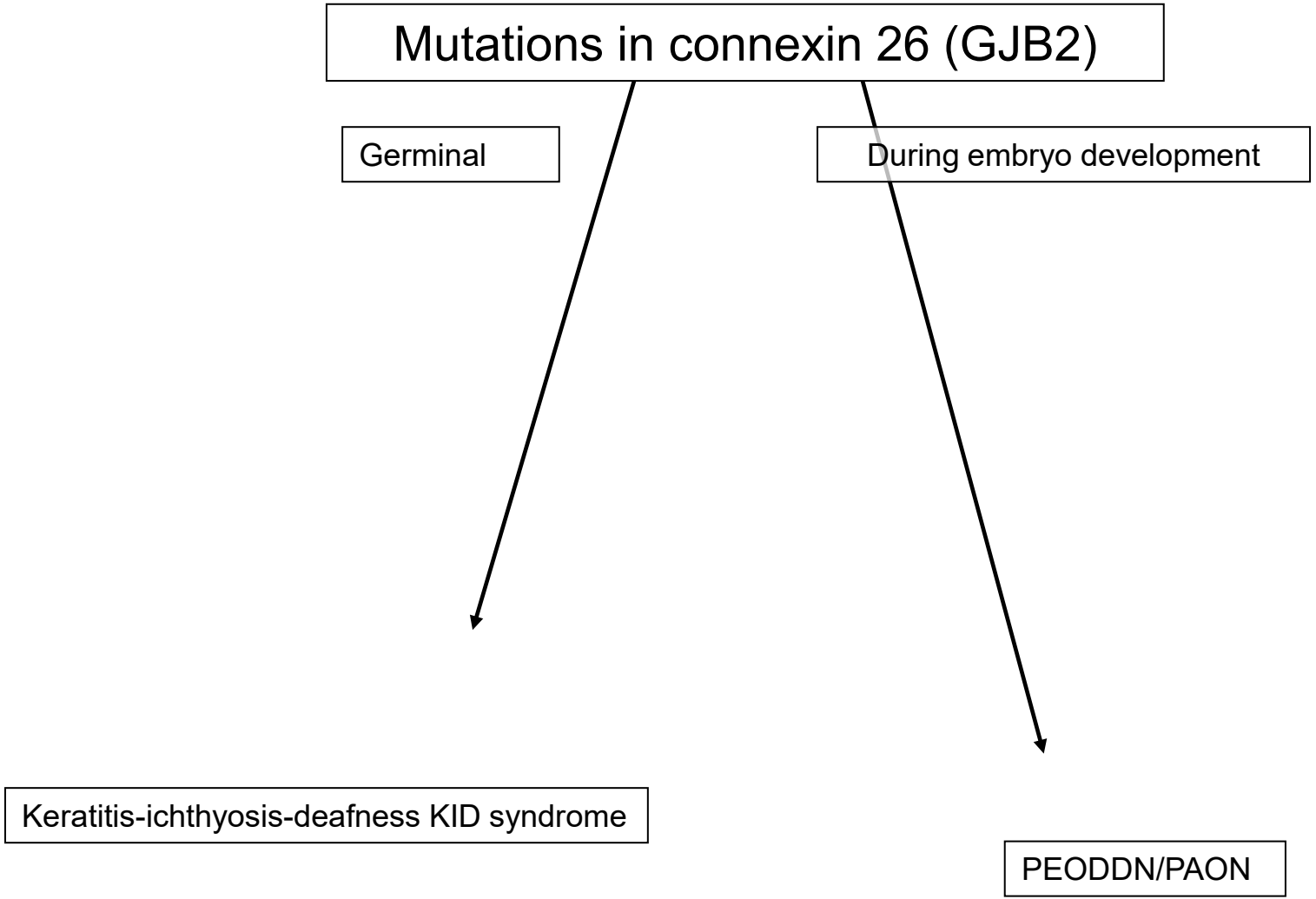
4. Molecular confirmation: GENE TESTING

Only somatic cells	Only gonadal cells (germinal)	Somatic and gonadal cells
		
Somatic mosaicism	Gonadal mosaicism	Gonado-somatic mosaicism
Not transmissible	Transmissible	Transmissible

Non-lethal, dominant diseases




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


Mutations in connexin 26 (GJB2)
Germinal
During embryo development
Keratitis-ichthyosis-deafness KID syndrome
PEODDN/PAON

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

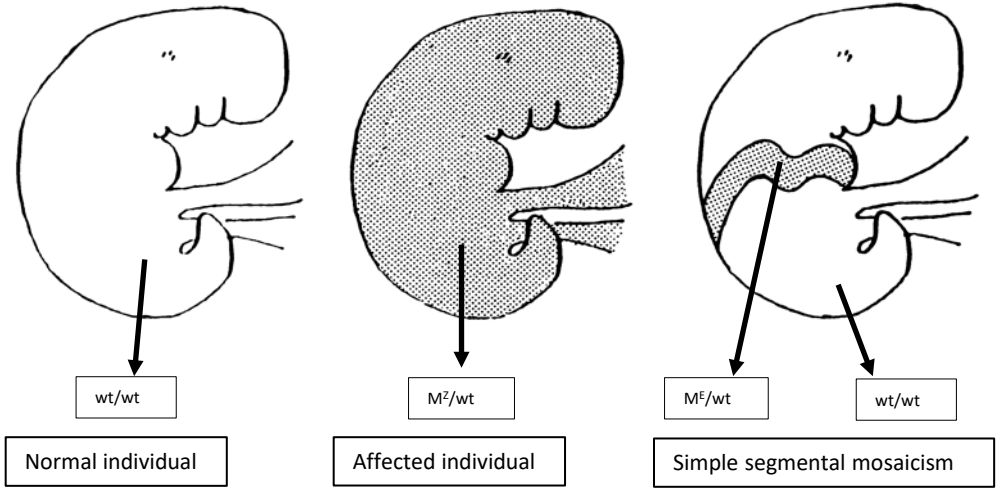
Of genuinely monoallelic diseases

- Epidermolytic ichthyosis Brocq (KRT1, KRT10)
- Superficial epidermolytic ichthyosis Siemens (KRT2)
- Darier disease (ATP2A2)
- Hailey-Hailey disease (ATP2C1)
- Pachyonychia congenita (KRT16)
- Dowling-Degos disease, Galli-Galli variant (KRT5)
- Keratitis-ichthyosis-deafness KID syndrome (GJB2)

Of biallelic diseases

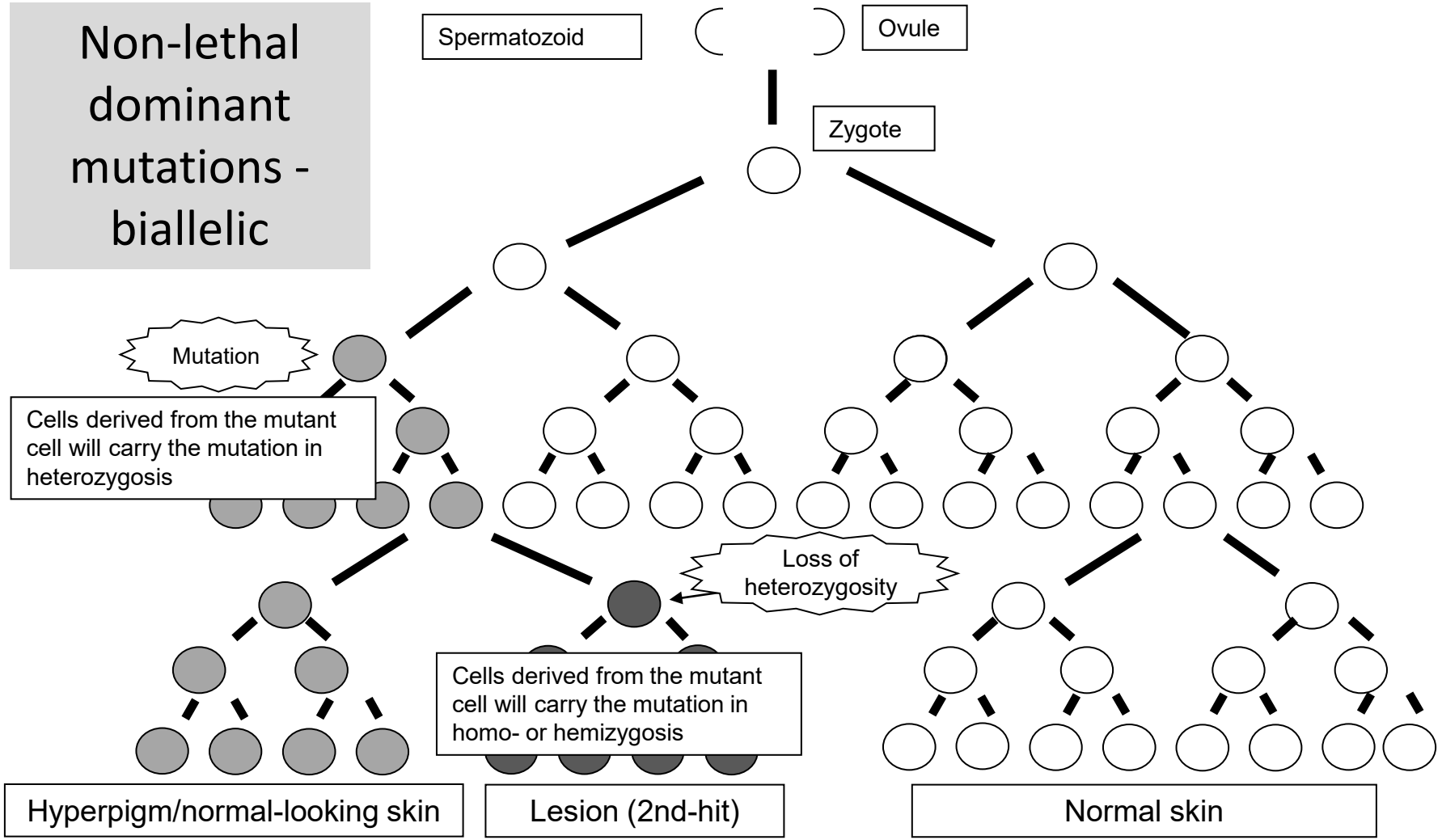
- Neurofibromatosis 1 (NF1)
- Gorlin syndrome (PTCH1, PTCH2, SUFU)
- Glomangiomatosis - GVM (GLML)
- Familial leiomyomatosis with renal cancer (FH)
- Tuberous sclerosis complex (TSC1, TSC2)
- Cylindromatosis (CYL)

Simple mosaicism in autosomal dominant disorders:
Mosaicism in genuinely monoallelic autosomal dominant disorders

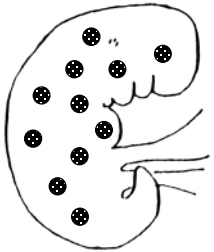


wt: wild type; M: mutated allele; Z: zygote; E: early; L: late

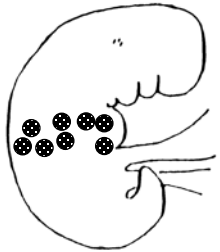
Non-lethal dominant mutations - biallelic



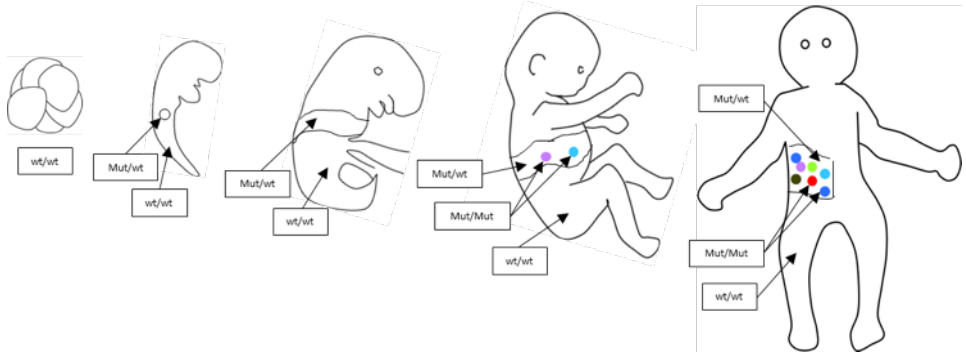
Normal individual

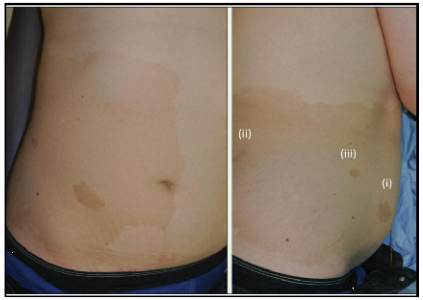


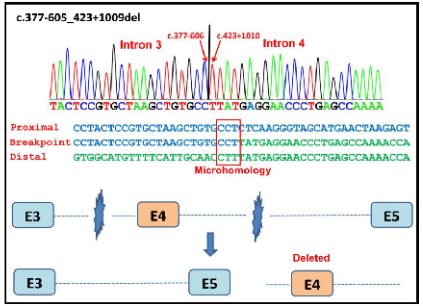
Non-segmental disseminated mosaicism

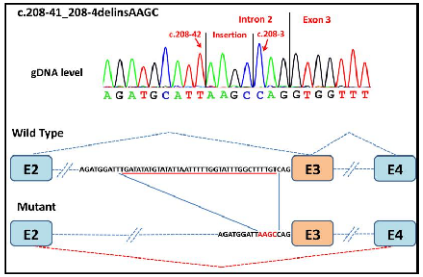


Simple segmental mosaicism



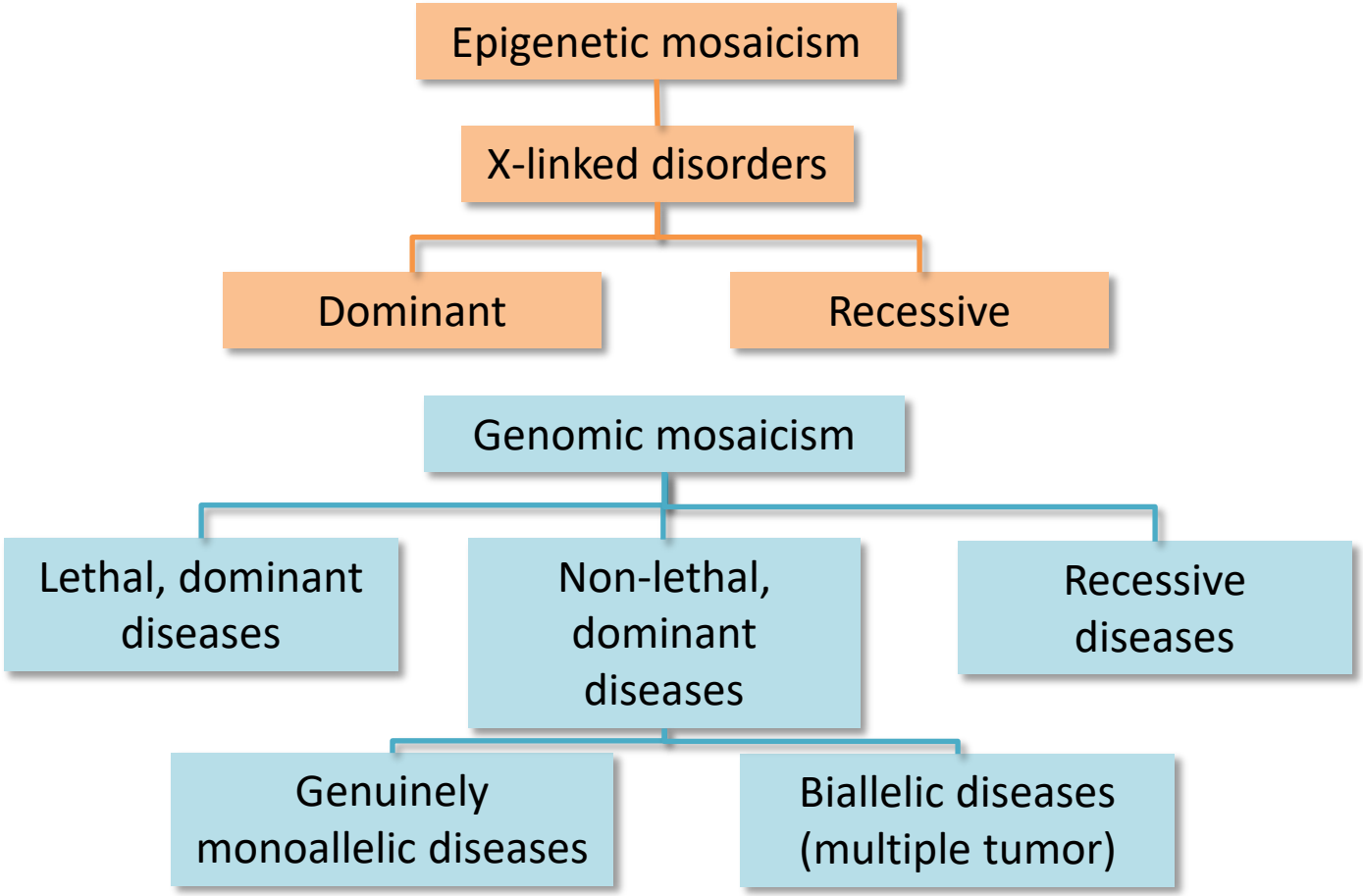






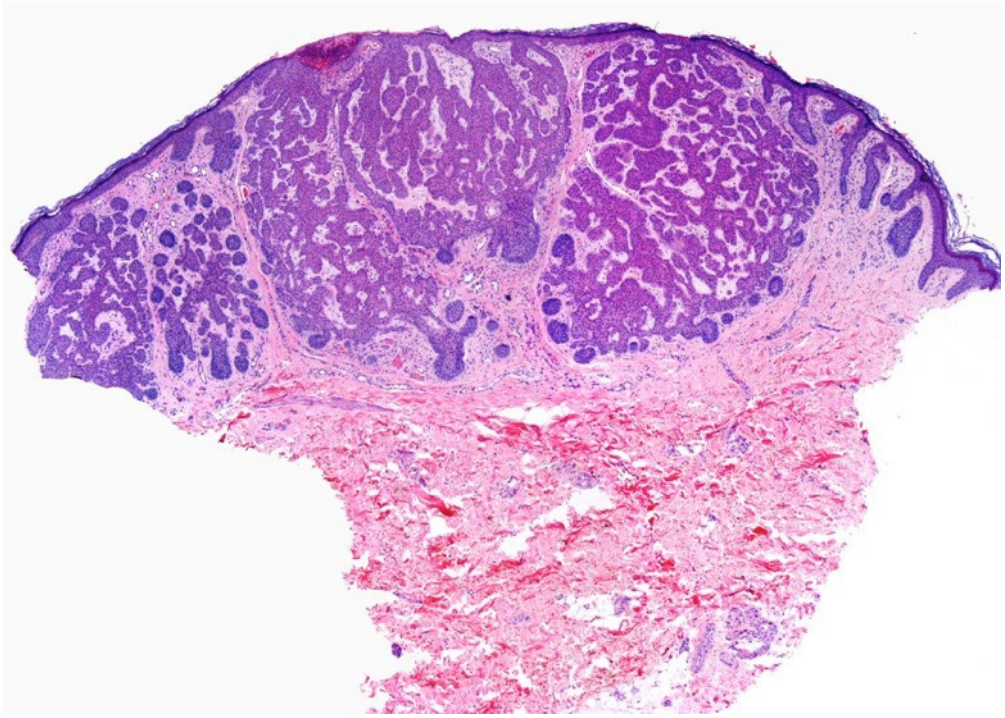
To our knowledge, this is the first reported patient with a documented post-zygotic *SPRED1* deletion causing mosaic Legius syndrome. We identified a common heterozygous *SPRED1* deletion in all three CALMs and propose this heterozygous change is responsible for the larger segmental area of hyperpigmentation, similar to segmental NF1, where a heterozygous somatic *NF1* gene deletion was detected in melanocytes cultured from a hyperpigmented skin area in a patient with no systemic features of NF1 and a second hit *NF1* mutation was detected only in the melanocytes from a CALM within the area[7]. Our study also reaffirms that the CALMs seen in Legius syndrome are the result of biallelic inactivating mutations in *SPRED1*[1].

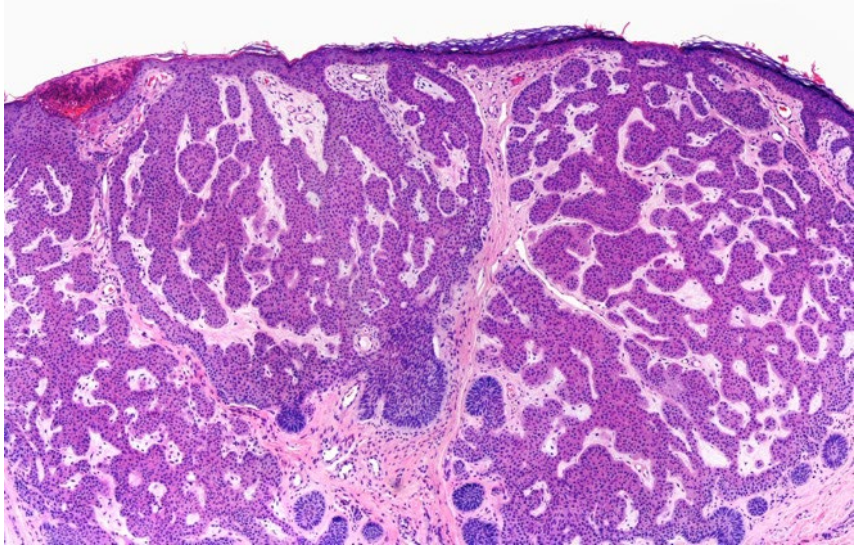
Cutaneous mosaicism



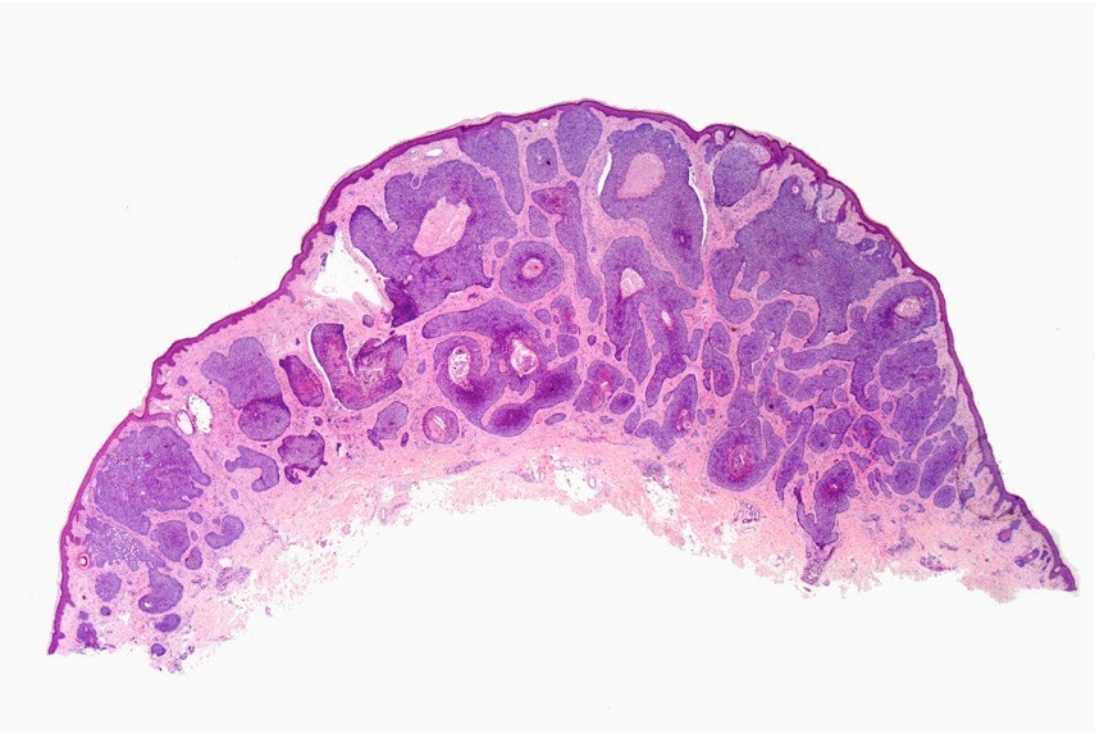
1. Identify a mosaic disorder: PATTERNS

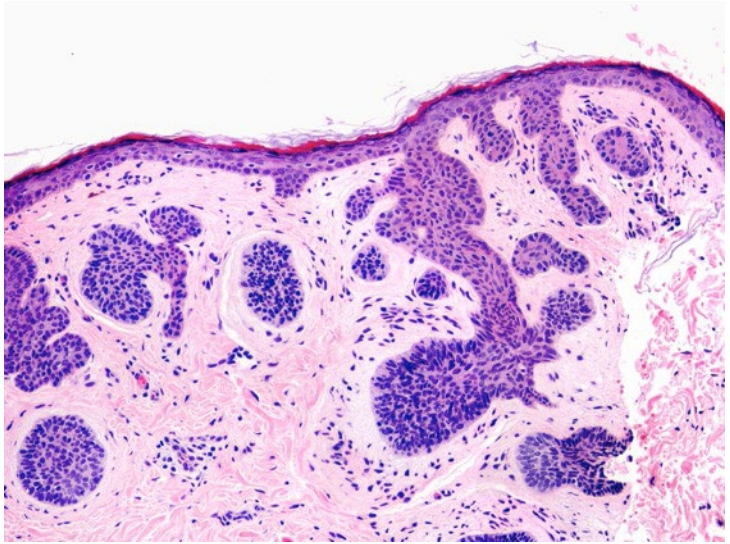
2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY





2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY



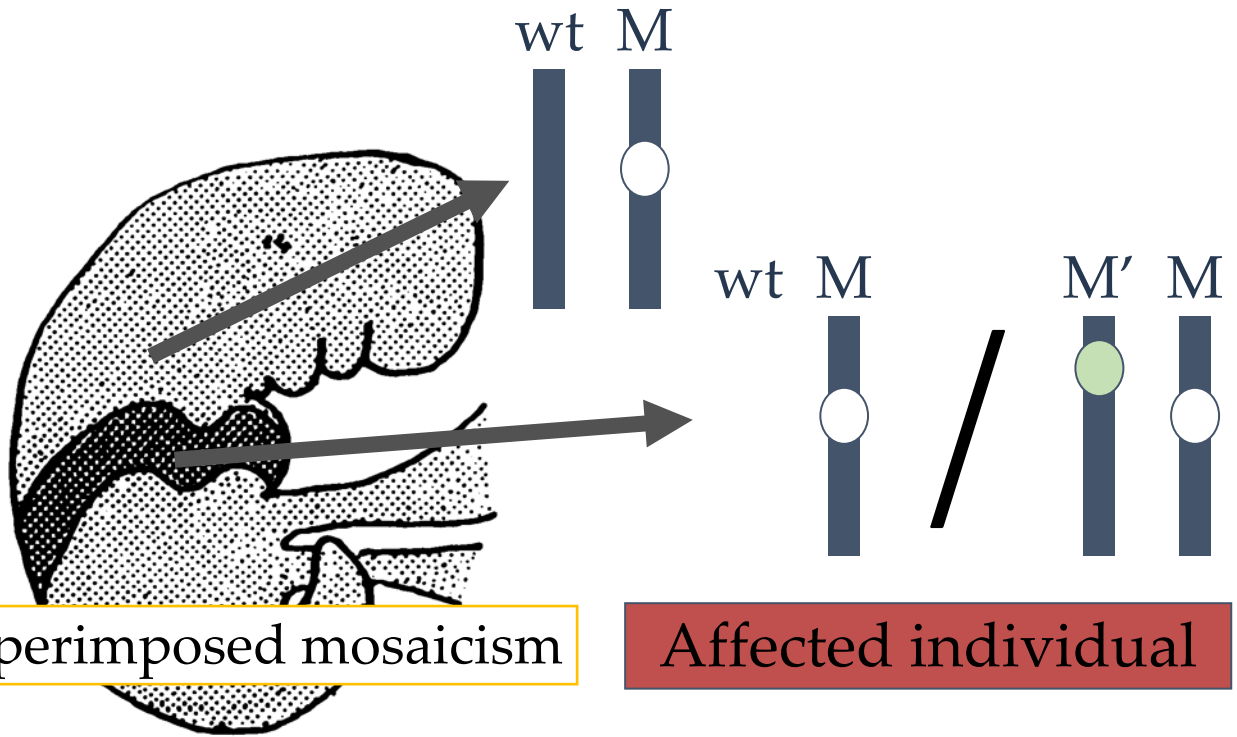


3. Associated conditions: IMAGING & LAB

- Neurologic exam, MRI – normal
- Chest X-ray – normal
- Orthopantomography – Odontogenic cyst

4. Molecular confirmation: GENE TESTING

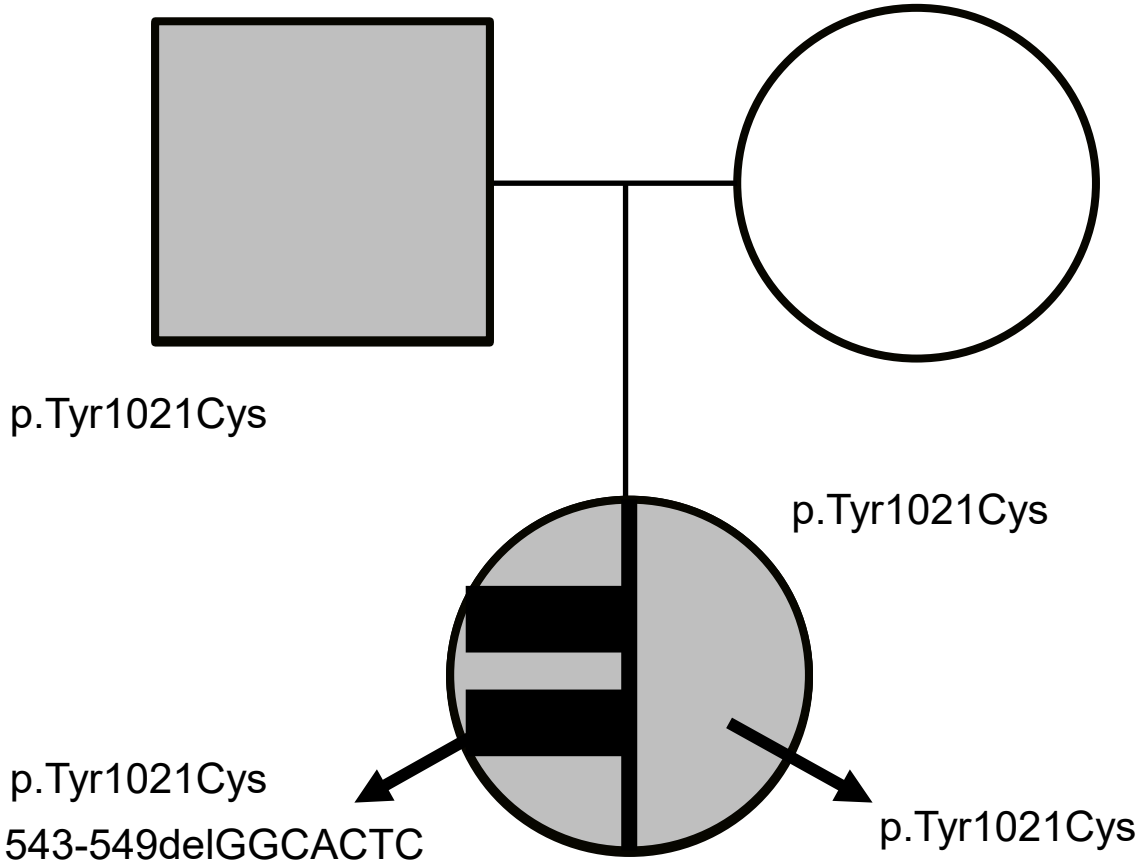
PTCH1



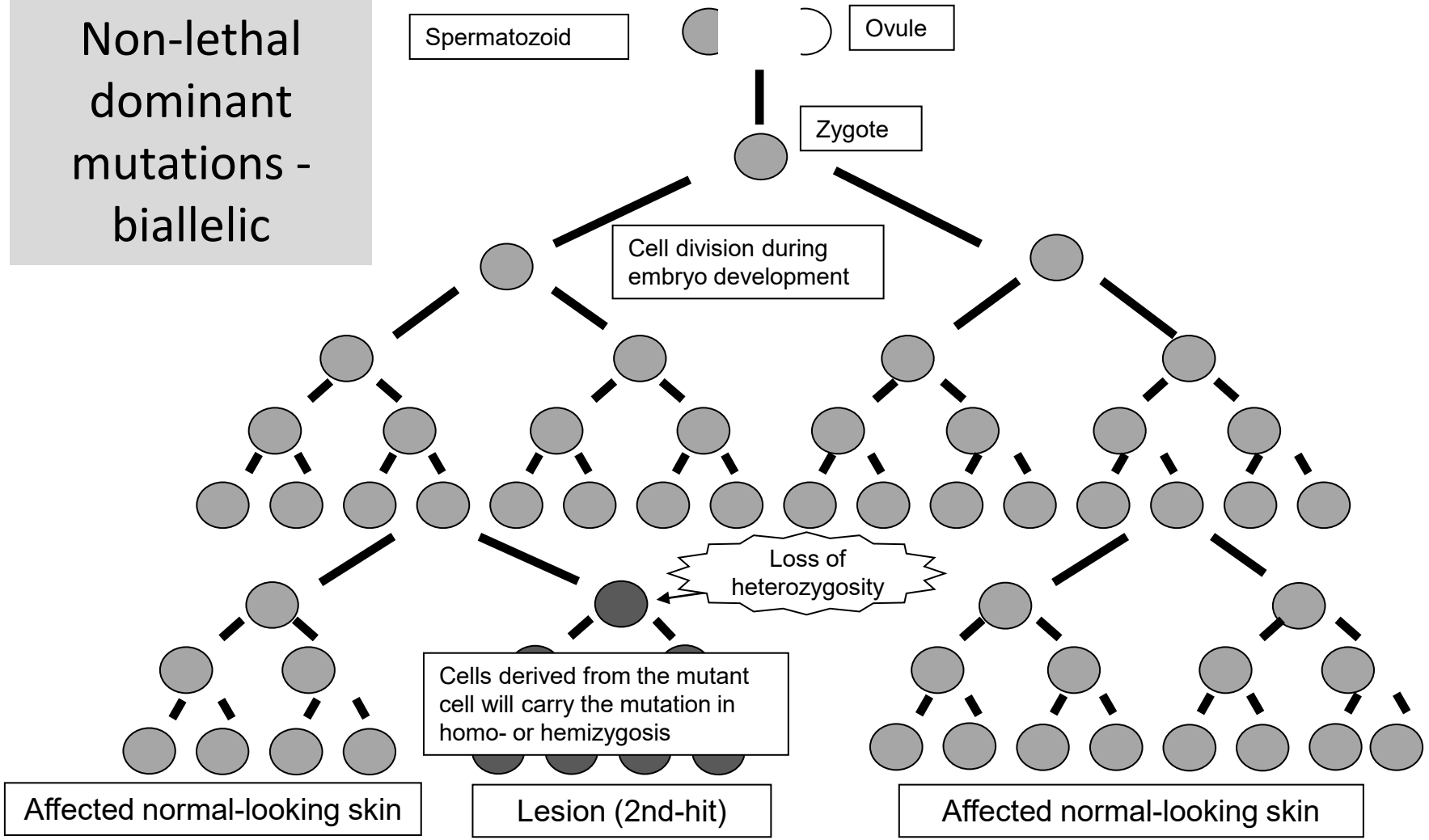
Gorlin syndrome + Segmental Gorlin

4. Molecular confirmation: GENE TESTING

PTCH1



Non-lethal dominant mutations - biallelic



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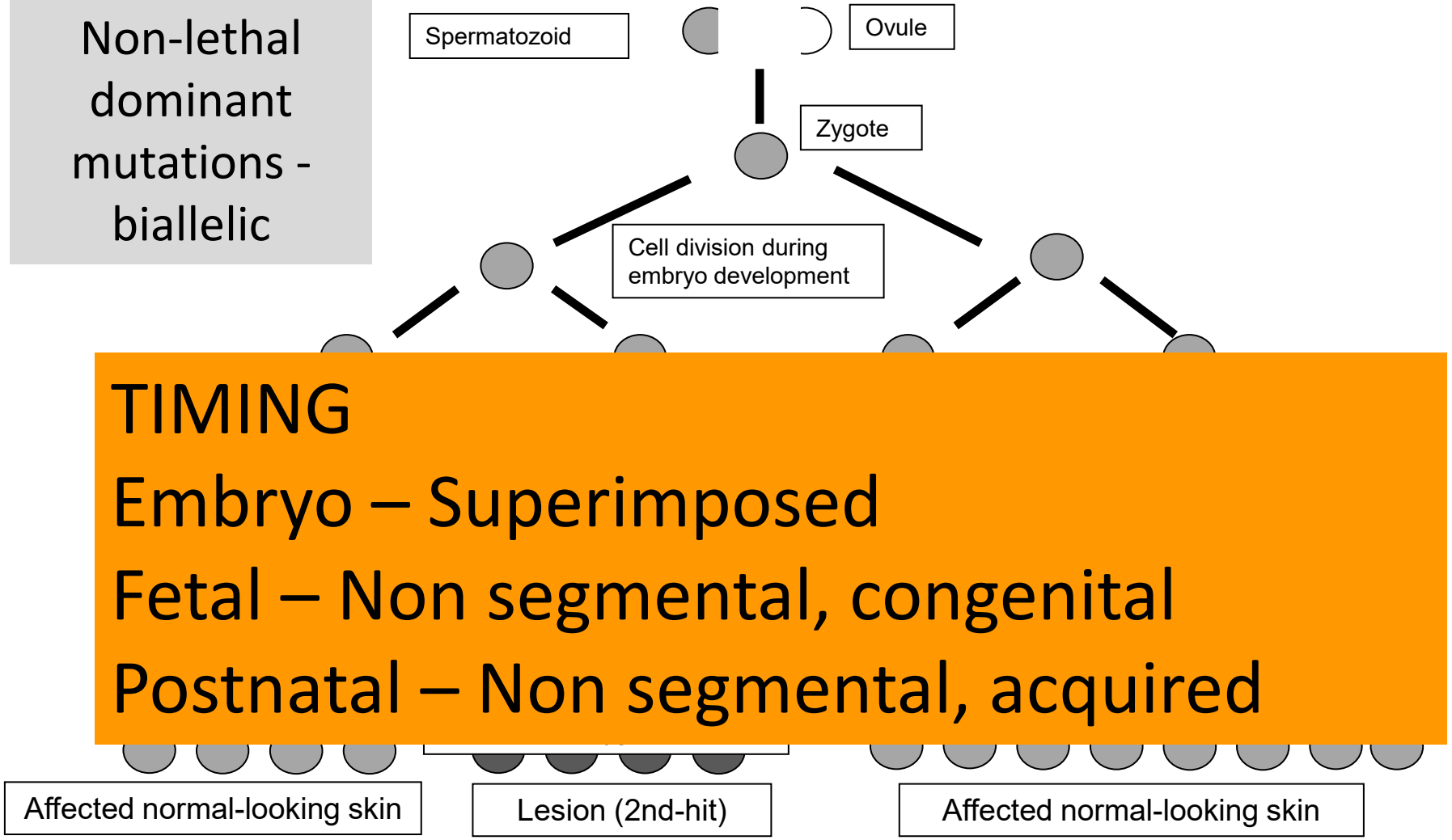


TIMING

Embryo – Superimposed

Fetal – Non segmental, congenital

Postnatal – Non segmental, acquired

Superimposed mosaicism in AD, non-lethal mutations

Genetically confirmed

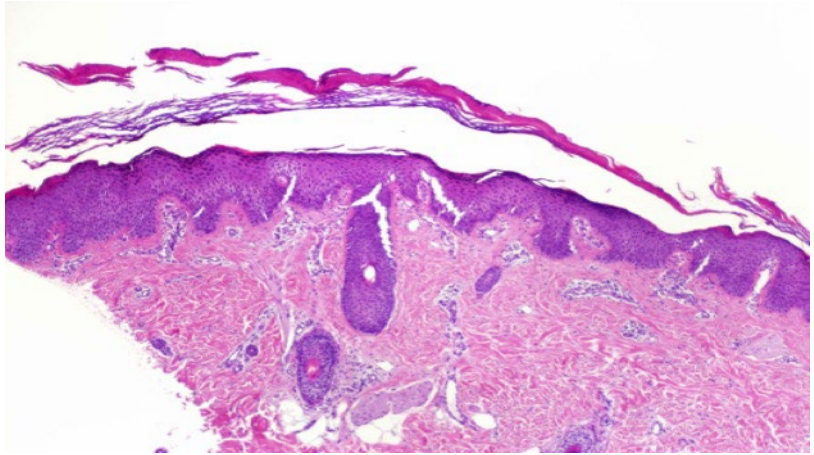
- Darier disease
- Gorlin syndrome
- Hailey-Hailey disease
- Osteomatosis cutis hereditaria
- Legius syndrome
- Neurofibromatosis 1
- Disseminated superficial actinic porokeratosis
- PTEN hamartoma syndrome
- CM-AVM syndrome

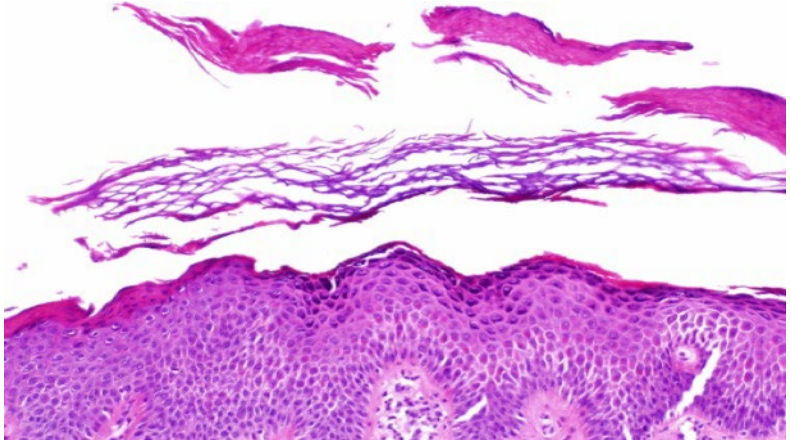
Pending genetic confirmation

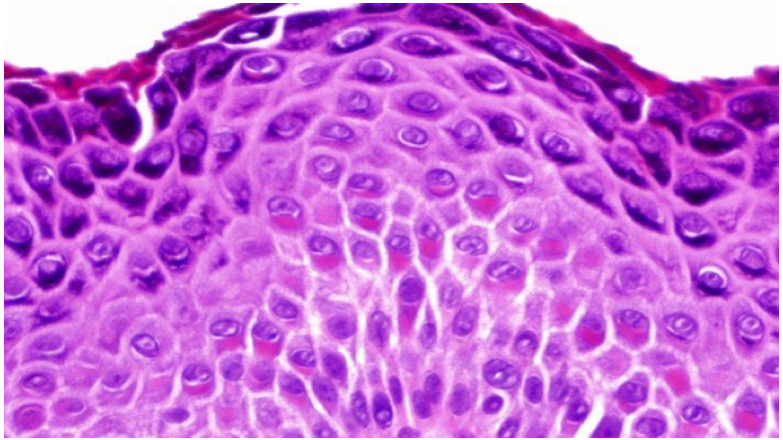
- Albright's hereditary osteodystrophy
- Acanthosis nigricans, autosomal dominant
- Buschke-Ollendorff syndrome
- Syringomatosis
- Trichoepitheliomatosis
- Tuberous sclerosis complex
- Familial leiomyomatosis with renal cancer
- Eccrine spiradenomatosis
- Epidermolytic ichthyosis Brocq
- Glomangiomatosis - GVM
- Hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber)
- Hereditary basaloid follicular hamartoma
- Marfan syndrome

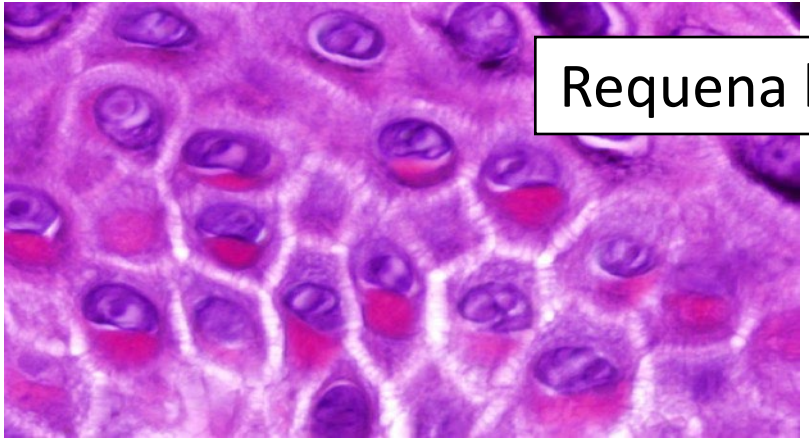
1. Identify a mosaic disorder: PATTERNS

2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY









Requena bodies

3. Associated conditions: IMAGING & LAB

Superficial erosions

Generalized pru

Diffuse erythe

Fissures on fo

Ectode

Nail dystrophy

plantar keratoderma

iffuse alopecia

ndrome

Skin fragility

Ectodermal dysplasia

Letter

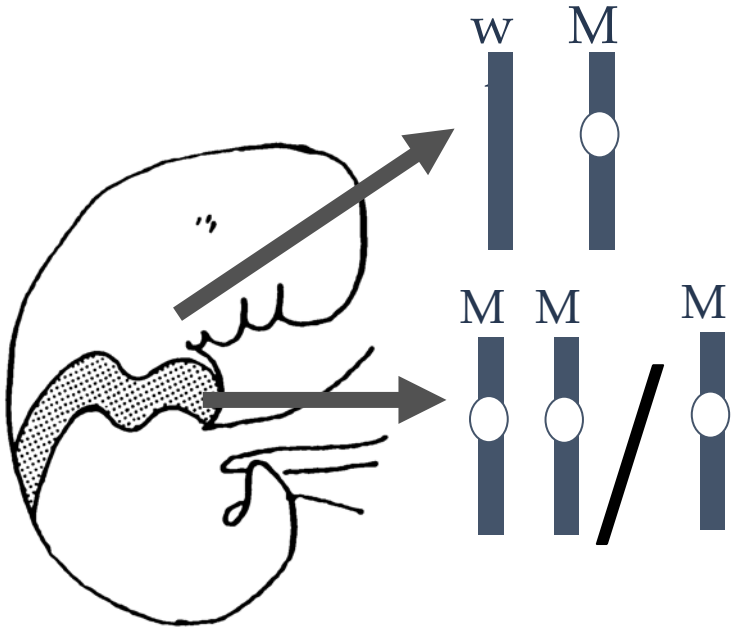
Nature Genetics **17**, 240 - 244 (1997)
doi:10.1038/ng1097-240

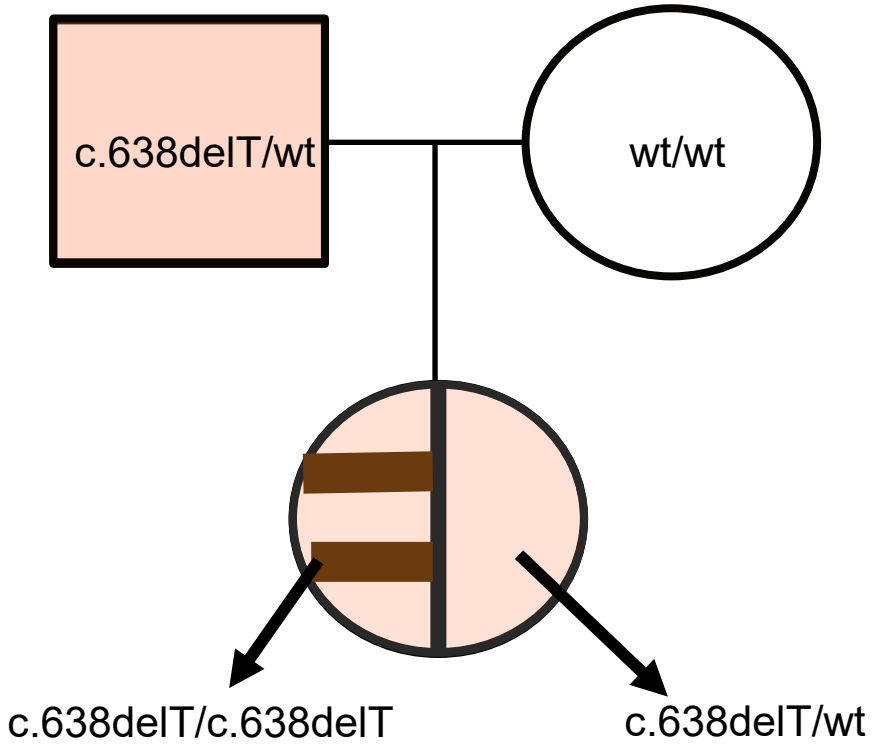
Mutations in the plakophilin 1 gene result in ectodermal dysplasia/skin fragility syndrome

John A. McGrath[1,5], James R. McMillan[1], Carrie S. Shemanko[2], Sarah K. Runswick[3], Irene M. Leigh[4], E. Birgitte Lane[2], David R. Garrod[3] & Robin A.J. Eady[1]

4. Molecular confirmation: GENE TESTING

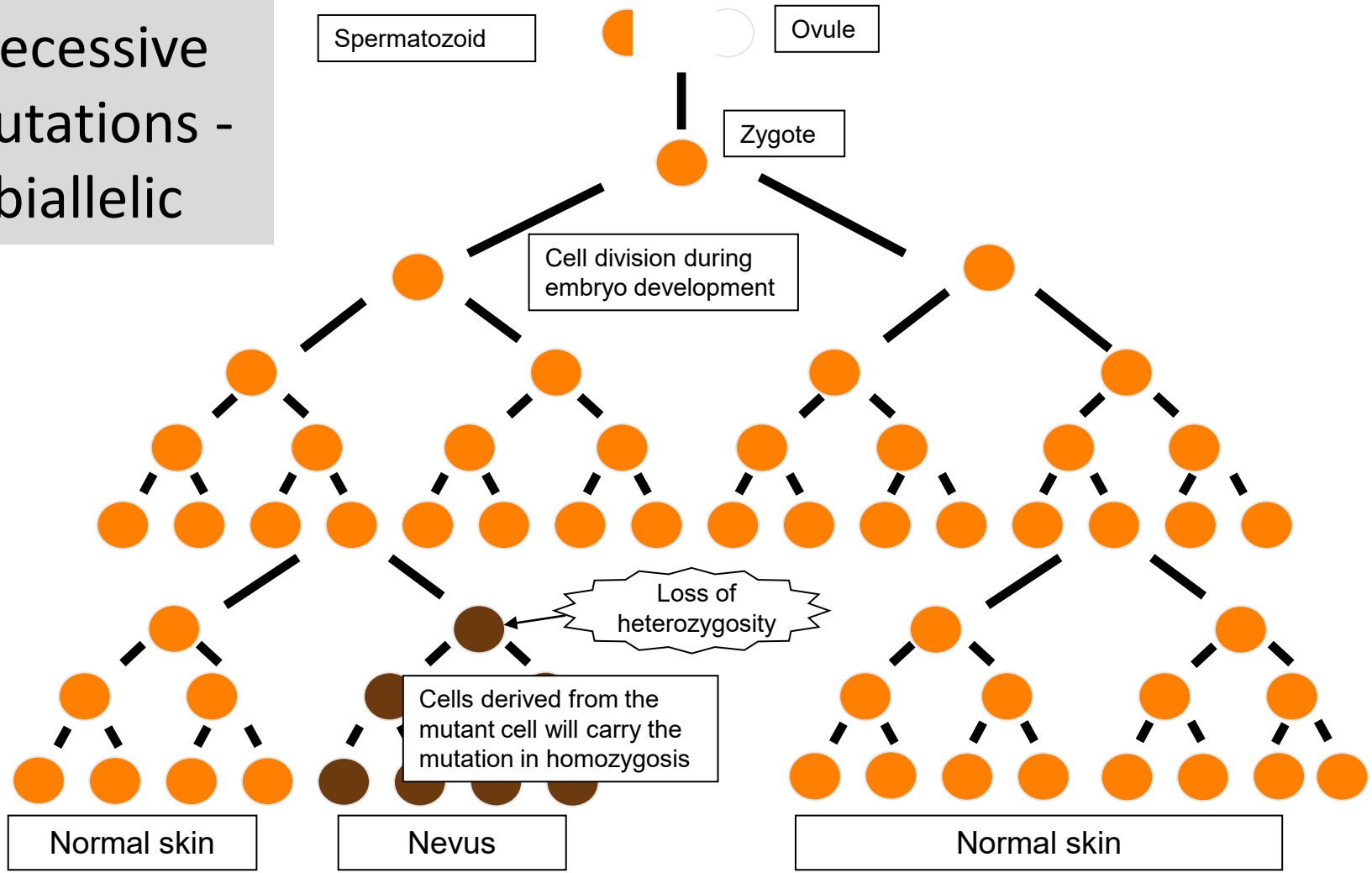
Plakophilin 1





Mosaic ED-SF

Recessive mutations - biallelic

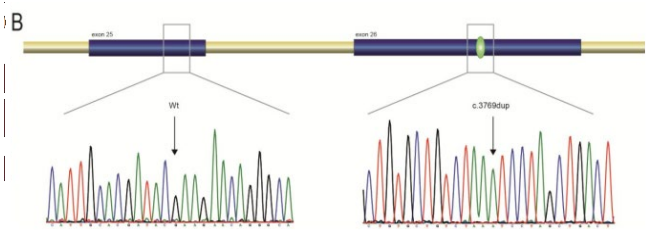


Br J Dermatol. 2019 Jun 17. doi: 10.1111/bjd.18216. [Epub ahead of print]

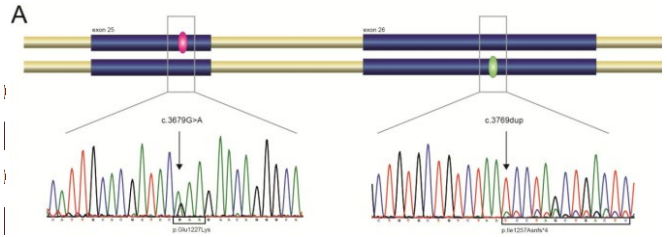
Recessive mosaicism in ABCA12 causes blaschkoid congenital ichthyosiform erythroderma.

van Leersum FS[1,2], Seyger MMB[3], Theunissen TEJ[1,2], Bongers EMHF[4], Steijlen PM[1,2], van Geel M[1,2,5].

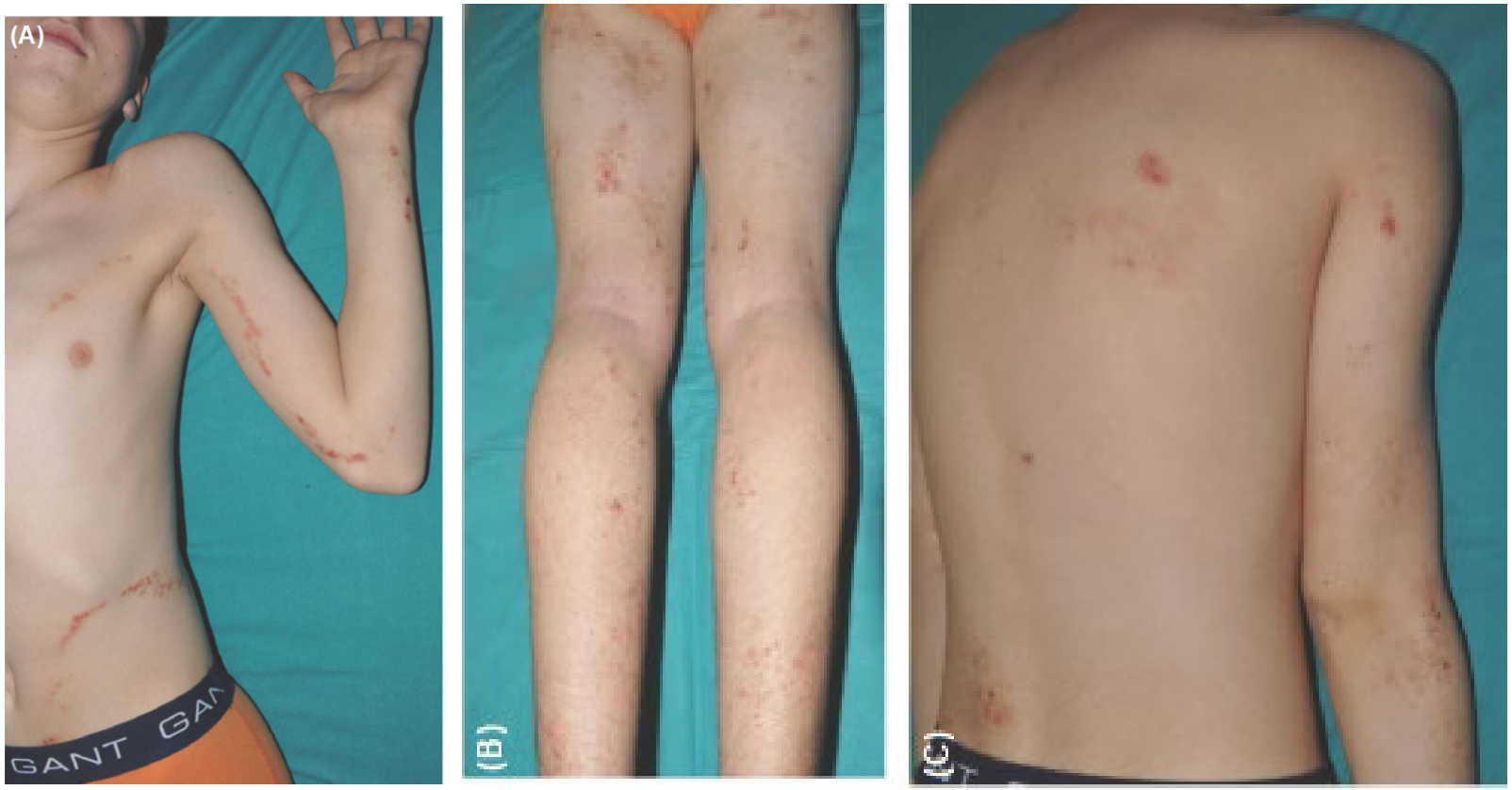
Blood



Skin



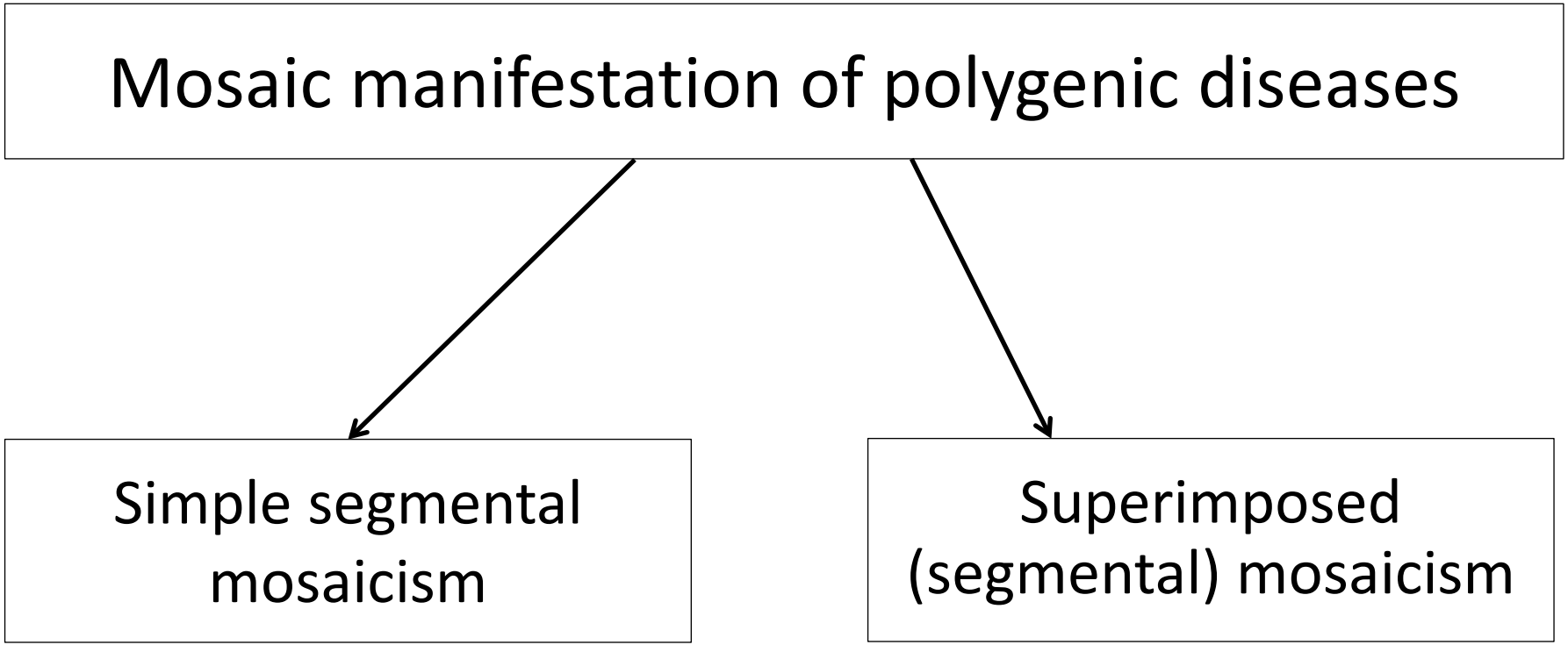
1. Identify a mosaic disorder: PATTERNS



2. Diagnose disorder: SKIN LESIONS & HISTOPATHOLOGY

Superimposed linear atopic dermatitis

Reference	Age, years	Sex	Location of segmental lesion	Arrangement	Concomitant relapsing AD	Age at onset of linear AD, years	Age at onset of generalized AD	Evolution	Atopic disease background
Taïeb et al[6]	8	Female	Left arm from axilla to wrist	Linear, unilateral	+	7	6 mo	Improved after 6 wk	Eczema, house dust mite, cat and dog dander, allergy
Hadlik et al[7]	36	Male	Left lower abdomen, leg, foot	Linear, unilateral	–	36	Childhood	Chronic, recurrent	Allergic rhinoconjunctivitis
Kawachi et al[8]	65	Male	Left leg	Linear, unilateral	+	62	45 y	Chronic, recurrent	Chronic prurigo
Case 1	4	Female	Right leg	Linear, unilateral	+	4	6 mo	Unknown	Eczema
Case 2	2	Female	Right leg	Linear, unilateral	+	2	2 y	Improved after 4 wk	Eczema
Case 3	15	Male	Trunk; left arm, leg	Linear, unilateral	+	15	2 mo	Chronic, recurrent (followed for 1 y)	Asthma


Mosaic manifestation of polygenic diseases
Simple segmental mosaicism
Superimposed (segmental) mosaicism

Superimposed linear atopic dermatitis

The n rule of genes

Germinal: n

Superimposed: n+1

Superimposed mosaicism on polygenic cutaneous diseases

- Acne vulgaris
- Atopic dermatitis
- Bullous pemphigoid
- Dermatomyositis
- Drug eruption
- Erythema multiforme
- Graft-versus-host disease
- Granuloma annulare
- Lichen planus
- Lichen nitidus
- Lichen striatus
- Discoid lupus erythematosus
- Subacute lupus erythematosus
- Systemic lupus erythematosus
- Morphea
- Pemphigus vulgaris
- Psoriasis
- Vitíligo