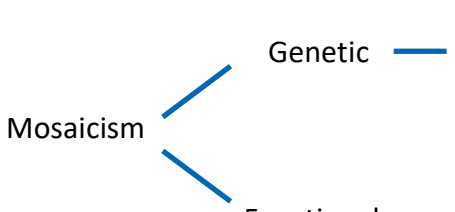
NATIONAL DERMATOLOGY RESIDENT LECTURE SERIES SUMMARY

Lecture: Cutaneous Mosaicism by Dr. Fatemeh Jafarian
Date: April 21, 2020 via Zoom
Compiled by: Abdulhadi Jfri, PGY4, McGill University



Genetic: Chromosomal alteration in #/structure within a given cell population happens post-zygotic → clonal expansion (diff. cells with diff chromosomal makeup. Ex. Pigmentary mosaicism

Functional: Due to X inactivation.
Lyonization: one X inactivation in early embryonic → fixed in activation in all descendant cells. Examples: IP, FDH

Mosaicism Phenotypes

Note: the earlier the mutation → the more generalized the presentation

Patterns (5)	Presentation	Example
Lines of Blaschko (Most common pattern)	Blaschko lines: map route of embryonic ectodermal cell migration and proliferation Present as: V (back), S (trunk), linear (extremities), and spiral (scalp)	Incontinentia pigmenti (narrow bands), McCune-Albright (broad bands)
Checkerboard	Alternating squares **with** sharp midline separation	Becker nevus
Phylloids	Multiple leaf-like patches	Mosaic trisomy 13
Large patches	Large patches **without** midlines separation	Congenital melanocytic nevus
Lateralization*	One side of body	CHILD

*added from Bolognia

Functional Mosaicism in X-linked Dominant

Incontinentia Pigmenti (IP)		
Mutation	**Presentation**	**Boys**
X-linked dominant (lethal in boys) *IKBKG* (*NEMO*) on Xq28 → TNF alpha induced apoptosis Mosaicism due to lyonization	Four stages (all Blaschko pattern) 1. Vesicular 2. Verrucous 3. Hyperpigmentation: irregular, whorl-like, slate-grey 4. Hypopigmented atrophic hairless streak 5. Other organs affected: Teeth, hair, nails, CNS, eyes, bones	IP is possible in boys in 2 scenarios: 1. Klinefelter syndrome (XXY) 2. Post-zygotic mutation

Focal Dermal Hypoplasia (FDH) = Goltz Syndrome	
Mutation	**Presentation**
X-linked dominant (lethal in boys) *Porcupine O-acetyltransferase* (*PORCN*) → Wnt pathway	Cutaneous, ocular, dental, craniofacial, and skeletal abnormalities

Functional Mosaicism in X-linked Recessive Disease

- Generalized in males and variable mosaic patterns in females
- Example: X-linked hypohidrotic ectodermal dysplasia due to *ectodysplasin-A mutation* (*EDA*)

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Autosomal Dominant Segmental Mosaicism

Type 1 Segmental Mosaicism		
Time of Mutation	**Features**	**Examples**
• Post-zygotic	• Germline may/may not be involved (=next generation may/may not be involved). • Skin outside affected area is normal clinically and genetically.	• Darier's disease • Tuberous sclerosis • Basal cell nevus syndrome (BCNS)

Type 2 Segmental Mosaicism		
Type of Mutation	**Features**	**Examples**
• Germline mutation + additional new postzygotic mutation → inactivate other allele (loss of heterozygosity)	• More severe manifestation of the disease in a mosaic pattern on a background of milder generalized disease.	• Darier's disease • Hailey-Hailey (AD germline in *ATP2C1* on chromosome 3q21-q24)

Other Mosaic Phenomenon

Pigmentary Mosaicism	Revertant Mosaicism
• Clone of cells with increased/decreased pigment production • Due to chromosomal/postzygotic • Replaces hypopigmentation of ito/linear and whorled nevoid hypermelanosis • Systemic involvement 4-30% • Dx: gene analysis of affected skin • Implication on next generation: unknown	• Both maternal and paternal alleles are mutated • Mosaic patches of normal skin (post-zygotic correcting one of the alleles) and on background of affected skin = "natural gene therapy" • Example: Generalized atrophic benign epidermolysis bullosa (AR; COLA17A1)

Gene Testing and Lethal Mutations Surviving as Segmental Mosaicism

Gene Testing in Cutaneous Mosaicism	Lethal Mutations Surviving as Segmental Mosaicism

• Always from affected area
• Chromosomal mosaicism → karyotype/fluorescent in situ hybridization on cultured cells from fresh biopsy
• Other modalities:
  ○ Direct DNA extraction
  ○ Comparative genomic hybridization
  ○ SNPs arrays
  ○ NGS
	• CLOVES (PIK2CA)
	• Megaloencephaly-capillary malformation syndrome (PIK3CA)
	• Oculoectodermal syndrome (KRAS)
	• Papular nevus spilus syndrome (HRAS)
	• Proteus syndrome (AKT1)
	• Schimmeplenning syndrome (HRAS/KRAS)
	• Struge-Weber syndrome (GNAQ in chromosome 9)

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Cases of Mosaic Disorders Presented in Lecture

- Segmental Neurofibromatosis (Mosaicism with Autosomal Dominant Inheritance)
  - Post-zygotic mutation in NF1 gene. The phenotype depends on timing and tissue affected by the mutation. The earlier → the more spread.
  - The more spread skin lesions/genital skin involvement → likely gonadal involvement (gonosomal mosaicism). This can be tested by sperm, NOT ova analysis. Tissue sample is difficult.
  - Full physical exam including eyes
  - Dx: genetic test of tissue, NOT blood with single nucleotide polymorphism (SNP) or next generation sequencing (NGS)
  - Low risk of disease-related complication compared to NF1 (AD)
  - Prenatal testing via: amniocentesis, chorionic villus sampling, preimplantation genetic analysis.
- McCune Albright Syndrome
  - Triade of polyostotic fibrous dysplasia, café au lait with coast of Maine macule, and endocrine dysfunction
  - Postzygotic mutation in the gene GNAS1 on chromosome 20
  - Mutation in zygote → early embryonic death
  - Normal surrounding cells/limitation to non-critical mass of cells → survival
- Proteus Syndrome (AKT1)
  - Epidermal nevus and vascular malformation present at birth and stable while bony and tissue over growth starts postnatally (due to AKT1 expression in bone predominate after birth)
  - Miransertib: protein kinase B (AKT) inhibitor in clinical trials for proteus
- Epidermal Nevus
  - Warty lesions along lines of Blaschko at or shortly after birth
  - Post-zygotic mutation in: FGFR3, PIK3CA, KRAS, HRAS
  - Epidermal nevus syndrome: extension of mosaicism to other orangs (CNS, MSK, ocular)
  - Widespread lesions → higher risk of systematic involvement
  - Risk of malignancy: urothelial carcinoma
  - Rx: localized = nothing vs. widespread (look for associations & evaluated for metabolic bone disease)
  - Grandchildren risk: if germline involved, don't survive
- Nevus Sebaceous
  - HRAS 95%, KRAS 5%
  - Nevus sebaceous syndrome: extensive nevus sebaceous + CNS, MSK, ocular abnormalities + hypophosphatemic vitamin D-resistant ricket with increased factor 23 (FGF23) level.
  - Epidermal nevus & sebaceous nevus caused by same HRAS why different phenotype? Location of mutation on body affects phenotype
- Congenital melanocytic nevus + neurocuatneous melanosis by NRAS. The CNS involvement was predicted in one study by facial dysmorphic features.
- Bullous icthyosiform erythroderma (BCIE) in a child, his mother has liner verrucous papules (keratin 1 gene mutation)
- Phacomatosis pigmentokeratotica: large sebaceous nevus + speckled lentiginous nevus, oral papillomatosis + cardiac/MSK, ocular abnormalities. Rhabdomyosarcomas. These mutations predispose to development of secondary tumors