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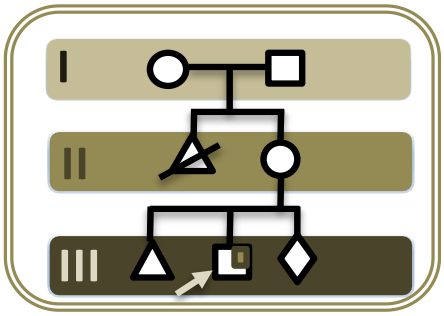

From the desk of Editor

The genetic division of the Pediatric Department is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

Neurometabolic/Intellectual Disability/ X-Linked/ PORCN-Related Developmental Disorders/ Focal dermal hypoplasia; FDH / GOLTZ-GORLIN SYNDROME- (Part -I)

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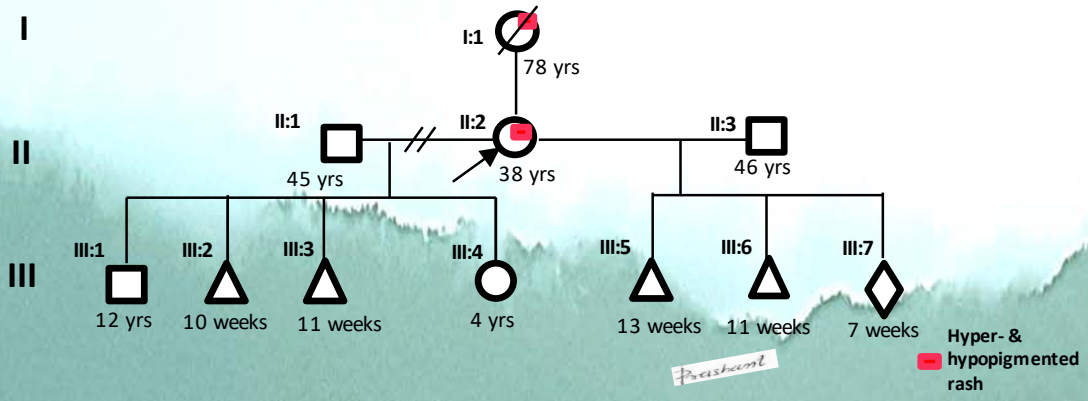

Hyper- and hypopigmentation rash follow the line of Blaschko

- **The lines of Blaschko:** lines that follow the cells migration on body; develop in embryonic life

- **Hyper- and hypopigmented rash:** reticulated macular lesion with different shades from black to white colour due to variable melanin level in affected cell lines

- **Clinical relevance:** Mosaic pattern might be transmitted to next generation even in asymptomatic mutant carrier person

Insight:

1. What are the clinical features in a patient with a classical PORCN-Related Developmental Disorders?
2. What is the "line of Blaschko" & what is their relationship with Hyper- and hypopigmentation rash?
3. What are the syndromes with Hyper- and hypopigmented rash that follow the 'line of Blaschko"?
4. Is there any clinical relevance to clinically screen for hyper- and hypopigmented rash preconceptionally in each female?

Syndromes with hypo- and hyperpigmentation, following the line "Blaschko"

OMIM	Syndrome	Gene / MOI	Function
#300337	Hypomelanosis of Ito; HMI	Not known/SM	NK
#302960	Chondrodysplasia Punctata 2, X-Linked Dominant; CDPX2	EBP/ XLD	Key enzyme in the final steps of the sterol biosynthesis pathway
#614323	Nevoid Hypermelanosis, Linear and Whorled; LWNH	Not known/ AD	NK
#301220	Pigmentary Disorder, Reticulate, with Systemic Manifestations, X-Linked; PDR	POLA1/XLR	DNA replication
#305600	Focal Dermal Hypoplasia; FDH	PORCN/XLD	Regulator of Wnt signalling pathway
#163200	Schimmelpenning-Feuerstein-Mims Syndrome; SFM	N/H/K RAS/ SM	RAS proteins regulate GDP/GTP levels
#300652	Angioma Serpiginosum, X-Linked, Asymptomatic Punctate and Linear Erythematous Rash	Not known/XLD	NK
#106050	Angioma Serpiginosum, Autosomal Dominant	Not known/AD	NK
#300968	Intellectual Development Disorder, X-Linked 99, Syndromic, Female-Restricted; MRXS99F	USP9X/XLD	Processing of ubiquitin precursors
#301066	Intellectual Developmental Disorder, X-Linked, Syndromic, with Pigmentary Mosaicism and Coarse Facies; MRXSPF	TFE3/XL	Transcription factor, master regulator of lysosomal biogenesis and immune response
#308300	Incontinentia Pigmenti; IP	IKBKG/XLD	Activates NF-kB and genes involved in inflammation, immunity
#613000	Palmoplantar Keratoderma, Nonepidermolytic, Focal 1; FNEPPK1	KRT16/AD	Epidermis specific type 1 keratin for innate immunity
#613001	Encephalocraniocutaneous Lipomatosis; ECCL	FGFR1/SM	Cell surface receptor for fibroblast growth factor
#309801	Linear Skin Defects with Multiple Congenital Anomalies 1; LSDMCA1	HCCS/XLD	Holocytochrome C-type synthetase, involved in electron transport pathway
#113800	Epidermolytic Hyperkeratosis 1; EHK1	KRT1/AD & AR	Terminal differentiation in mammalian epidermis
#124200	Darier-White Disease; DAR	ATP2A2/AD	Hydrolysis of ATP, autophagy
#144200	Palmoplantar Keratoderma, Epidermolytic, 1; EPPK1	KRT9/AD	Keratin filament assembly
#305000	Dyskeratosis Congenita, X-Linked; DKCX	DKC1/XLR	Pseudouridylation of rRNA-Ribosome biogenesis and telomere maintenance
#162900	Nevus, Epidermal	NRAS, /PIK3CA, FGFR3, HRAS/ SM	Cell cycle regulation
#176920	Proteus Syndrome	AKT1/SM	Serine/Threonine-protein kinases regulate several processes-metabolism, proliferation, survival, etc
#600501	ABCD Syndrome; ABCDS	EDNRB/AR	Receptor for endothelin 1,2, 3
#618727	Ectodermal Dysplasia with Facial Dysmorphism and Acral, Ocular, and Brain Anomalies; EDFAOB	RHOA/SM	Cytoskeleton organisation

Somatic Mosaicism – **SM,** # - Not known (**NK**)

Syndromes with hypo- and hyperpigmentation +/- following the line "Blaschko"

OMIM	Syndrome	Gene / MOI	Function
#308205	IFAP Syndrome 1, with or without Bresheck Syndrome; IFAP1	MBTPS2/XLR	Intramembrane proteolysis
#603165	Dermatitis, Atopic	ATOD1/AD	NK
#148210	Keratitis-Ichthyosis-Deafness Syndrome, Autosomal Dominant; KIDAD	GJB2/AD	Structural component of gap junctions
#604292	Ectrodactyly, Ectodermal Dysplasia, and Cleft Lip/Palate Syndrome 3; EEC3	TP63/AD	Sequence specific DNA binding, transcriptional activator or repressor
#613776	Chromosome 17p13.1 deletion Syndrome	Not Known/AD	NK
#158350	Cowden Syndrome 1; CWS1	PTEN/AD	Tumor suppressor gene
#166700	Buschke-Ollendorff Syndrome; BOS	LEMD3/AD	Repressor of TGF-beta, activin, and BMP signalling
#600268	Oculoectodermal Syndrome; OES	KRAS/SM	Cell proliferation regulator
#616459	Al-Raqad Syndrome; ARS	DCPS/AR	Inhibits activation-induced cell death
#617025	Nevus Comedonicus; NC	NEK9/SM	Regulator of mitotic progression

Plausible tenets:

Clinical phenotypes: XL linked MOI, Developmental birth defects in derivative of ectodermal and mesodermal germs layer, predominantly the skin, face, eye, and limbs

Findings in Ectodermal derivatives:

Dermal: congenital cutis aplasia (atrophic or hypoplasia of skin), **visible underlaying subcutaneous tissues** like fat (yellowish-pink nodular areas) & capillaries (telangiectasias) hypo- or hyperpigmentation along the lines of Blaschko, premature ageing changes on skin, Verrucous papillomas (**mucosal also**)

Nails: dys-hypoplastic, ridged,

Hair: alopecia, sparse

Teeth: enamel dysplasia/hypoplasia, microdontia (peg teeth), Notched incisors

Eye: anophthalmia, microphthalmia, eye cleft (Iris / chorioretinal coloboma), strabismus, cataract

Findings in Mesodermal derivatives:

Appendicular: variable reduction defects (longitudinal & transverse) like split hand(ectrodactyly)/foot/ oligo; and syndactyly

Facial features: (facial & skull asymmetry)

Head: Mild Microcephaly **Nose**-cleft nostril (notched nostril), broad nasal tip

Chin – tapered with acute angle

Ear – microtia, dysplastic

Mouth - Papillomas (lip, gingiva)

Other head to toe findings:

Supernumerary nipples

Midclavicular dysplasia

Genital hypoplasia

Skeletal changes:

Osteopathia striata, Joint laxity, Scoliosis

Thought Riveting:

- ***What is the molecular factor that decide to escape the X linked dominant lethality in the male besides a hypomorphic mutation in the gene or mosaicism?***
- ***What are the factors that increase more pigmentation along Blaschko lines, while others do reverse to it?***
- ***What are the non-DNA repair Gene pathways that help in reversion of the mutation in cell lines?***
- ***Is epimutation responsible for genetic mutation through malfunctioning of the DNA repair mechanism; is it in the root of the evolution of species?***
- ***Are there age dependent changes in epigenetic signature in the gametes?***

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