

## The Unchecked Colorant- Incontinentia Pigmenti

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### Preface

Incontinentia pigmenti is an exceptional, inherited, X-linked genodermatosis with a dominant pattern of disease transmission. Although disease penetrance of incontinentia pigmenti is absolute (100%), the genetic expression is markedly variable. It is additionally designated as Bloch- Sulzberger disease. Defective cellular components enunciating mutated X chromosomes are selectively eliminated in birth. Majority of implicated females demonstrate a non-random inactivation of X chromosome as cogitated in the peripheral blood leukocytes and fibroblasts. Although incontinentia pigmenti is typically lethal in pre-natal stage, especially with male foetuses, instances of mosaicism and minimal mutations of NEMO gene are compatible with survival in a few individuals [1,2].

### Disease characteristics

Incontinentia pigmenti is engendered by chromosomal mutations of NEMO gene situated upon the Xq28 locus. NEMO protein constitutes a singular subunit of complex multiprotein kinase, a molecule which is crucial for mobilizing transcription factor NF-kappa B, considered as an essential component of regulating the inflammatory, immune and apoptotic pathways. Chromosomal mutations within NEMO gene delineate a majority (80%) of freshly occurring mutations. Besides, a bulk (80%) of chromosomes display a deletion of exon 4 to exon10 within the NEMO gene. Point mutations, nonsense mutations and modified genomic directions are discerned in exon 2 to exon 10. Chromosomal insertions and deletions can also manifest with a consequently deranged activation of NF- kappa B within cells manifesting incontinentia pigmenti. A singular chromosomal mutation within NEMO gene can ensure altered cytokine production, particularly within the neonatal period, thereby inducing inflammatory cutaneous manifestations [1,2].

### Organ specific manifestations

Ocular manifestations are delineated in incontinentia pigmenti with the proportion of 35% to 77%, persist throughout life time and are commonly unilateral. Bilateral incrimination is associated with unequally affected eyeballs. Neurological involvement is concomitant to appearance of ocular symptoms. Unilateral or bilateral blindness occurs in an estimated 7% to 23% subjects. Retinal ischaemia induces relevant modifications with subsequent proliferation of newly formed blood vessels, retinal exudation, pre-retinal gliosis and retinal detachment due to traction. Aforesaid phenomenon are self limiting with the persistence of retinal sequelae such as avascular foci, tortuous vessels, retinal exudation, vitreous haemorrhage, pre- retinal fibrosis, altered retinal pigment epithelium, appearance of a retro-lental mass and retinal detachment. Fundus examination demonstrates specific alterations such as foveolar hyperplasia, atypical transverse blood vessels of the macula, colobomas and optic nerve atrophy.

Non-retinal features associated with incontinentia pigmenti comprise of cataract, strabismus, ptosis, conjunctival pigmentation, micro-ophthalmia, corneal alterations, uveitis, nystagmus and myopia. Neurological manifestations are composed of pseudo-encephalitis, acute neurological symptoms, cerebral necrosis, multiple focal infarctions and seizures. Ischemia or cerebro-vascular accidents engender cogent neurological symptoms. Seizures appear in an estimated 13% to 25% individuals [2,3].

Dental manifestations are constituted by missing teeth, conoid teeth, delayed tooth eruption, anomalous primary and permanent dentition, lack of teeth, disrupted formation of dental enamel, appearance of dental cavities and dento-facial deformities. Congenital dental malocclusion can be encountered with incontinentia pigmenti.

Breast anomalies occur in nearly 1% individuals and are denominated by supernumerary nipples, hypoplastic nipples, hypoplasia of breast tissue and anomalous pigmentation of the nipple. Skeletal abnormalities arise in around 20% subjects and are designated as scoliosis, hemivertebra, spina bifida, syndactyly, ear defects, increased rib quantification, chondrodystrophy, club foot, short stature and dwarfism [2,3].

Oral lesions are defined by soft palate hypoplasia, cleft palate, cleft lip, ogival palate, high arched palate and disorders of swallowing and voice enunciation.

Cardiac aberrations essentially manifest as ventricular endo-myocardial fibrosis, tricuspid insufficiency and pulmonary hypertension.

Eosinophilia ( $\approx 65\%$ ) can be elucidated in approximately 88% individuals implicated with incontinentia pigmenti [1,3].

### Clinical elucidation

Cutaneous manifestations indicative of disease progression appear in distinct chronological stages with proportionate overlapping or failure of emergence of distinctive stages.

Stage one is designated as the inflammatory or vesicular stage and exhibits a characteristic occurrence of papules, vesicles and pustules superimposed upon an erythematous substratum. Lesions are exemplified in a linear fashion along lines of Blaschko and vary in magnitude from one millimetre to one centimetre or beyond. Lesions appearing in stage one require a demarcation from herpes simplex or impetigo. Although preponderant in the extremities, lesions can arise in the torso or head and neck. Vesicular stage is detected in a majority (90% to 95%) of subjects which usually demonstrate lesions at birth or within first few weeks of neonatal life. Lesions usually disappear at four months. Relapsing, self limited lesions can be associated with an acute febrile illness in older children or adolescents [4,5].

Stage two is cogitated as the verrucous stage and typically displays a linear distribution of plaques or warty papules within lines of Blaschko which are superimposed upon an erythematous substructure. The torso, extremities, head and neck are incriminated. Lesions arise within 2 weeks to 6 weeks of neonatal life and usually disappear within six months.

Warty lesions are frequently encountered (70%), depict a penchant for palms or soles, appear as linearly configured, verrucous striae during the course of disease and can extend into adulthood.

Stage three is denominated as the hyper-pigmented stage and exhibits linear or whorled, brownish, pigmented lesions accompanied with tissue atrophy. Stage of hyperpigmentation occurs in a majority (90% to 98%) instances of incontinentia pigmenti. Lesions are commonly configured upon the torso, extremities or cutaneous folds of the head and neck. Nipples, axilla and groin can be implicated with hyperpigmentation. The lesions may not always be situated within the preceding area of cutaneous involvement or sites of preliminary lesions. Thus, hyperpigmentation can ensue as an independent phenomenon, apart from the activation of inflammatory process. Lesions are generally discerned within the first month of life and disappear during adolescence. Nevertheless, hyperpigmentation of axilla and groin can subsist up to forty years of age [4,5].

Stage four is nomenclated as the atrophic stage or stage of hypo-pigmentation and is characterized by foci of hypopigmentation, atrophy and absence of hair. Frequently, lower extremities are implicated. Lesions arise during adolescence and can be discerned in adulthood. Patches of hypopigmentation can be permanent. Stage of hypopigmentation is delineated in an estimated 30% to 75% subjects with incontinentia pigmenti or subtle, atrophic lesions can occur in a majority of individuals [4,5].

Histopathological elucidation is contingent to the specific stage of cutaneous lesions. Stage one or the vesicular stage demonstrates an intra-epidermal spongiosis accompanied with an eosinophilic, neutrophilic or infrequently basophilic inflammatory infiltrate. Enlarged, dyskeratotic epithelial cells are observed.

Stage two or verrucous stage can exhibit acanthosis, hyperkeratosis and papillomatosis of the superimposed epithelium. Eosinophilic infiltration eventually ensues.

Stage three or stage of hyperpigmentation depicts severe incontinence of melanin pigment. Stage four or the atrophic phase characteristically delineates an absence of melanin pigment within the epidermis accompanied by a lack of eccrine glands [6,7].

Hair modifications with incontinentia pigmenti are encountered in an estimated 28% to 38% individuals. Scarring alopecia of the vertex is a frequent manifestation along with absence or hypoplasia of eyebrows and eyelashes. Infants can display sparse hair which subsequently appear dull and brittle.

Ungual alterations are implicated in around 40% instances with modifications of nails of hand and feet or incrimination of a singular nail. Fingernails are commonly implicated with koilonychia, yellowish pigmentation of nails and nail dystrophy. Nails are fragile, brittle and demonstrate longitudinal or transverse slits with extensions up to foci of hyperkeratosis and onycholysis. Infrequently, incontinentia pigmenti can depict manifestations within a singular nail. Periungual and subungual keratotic tumours can be cogitated in adolescents or adults and are usually associated with pain, bone deformities and lytic lesions of underlying phalanges [6,7].

### Diagnostic criterion

Approach to diagnosis of incontinentia pigmenti necessitates elucidation of specific criterion.

Major Criterion Cogent features can be discerned with disease evolution from infancy to adulthood:

- Erythema with subsequent emergence of linearly arranged blisters or vesicles abound at various body sites excluding the face and commonly arise in stage one.
- Verrucous lesions predominantly appear upon extremities within lines of Blaschko and are cogitated in stage two.
- Hyper-pigmented streaks and whorls arise chiefly on the trunk along lines of Blaschko during stage three and mitigate during adolescence.
- Pale-tinged, hairless, atrophic, linear streaks or patches commonly arise in stage four and persist through adulthood. Aforementioned lesions can concur within diverse stages and site of lesions may vary [1,2].

Minor Criterion Specific regions can be implicated such as

- Tooth can delineate hypodontia, anodontia, microdontia and abnormally structured teeth.
- Hair alterations can enunciate alopecia, woolly, lusterless, wiry and coarse hair.
- Nails can depict minimal ridging or pitting or onychogryphosis with hypertrophied and curved nails.
- Retina can demonstrate peripheral neovascularization.
- Family history can exemplify an X-linked inheritance and multiple miscarriages [1,2].

### Differential diagnosis

Stage one or blistering stage requires a demarcation from conditions such as congenital herpes simplex, varicella zoster, streptococcal bullous impetigo and severe or dystrophic epidermolysis bullosa. Stage two or verrucous stage necessitates a segregation from simple warts and molluscum contagiosum. A histological examination can be beneficial in ambiguous instances.

Stage three or hyper-pigmented stage requires a distinction from disorders such as linear and whorled pigmentation associated with chromosomal mosaicism, intellectual disability or congenital malformations such as brain anomalies and pigmentation disorders. Hypomelanosis of Ito demonstrates a phenotype akin to chromosomal mosaicism. Incontinentia pigmenti depicts atypical foci of hyper-pigmentation whereas in hypomelanosis of Ito hypo-pigmented zones configure the disease process. Degree of normal pigmentation can be difficult to assess [1,2].

Stage four or atretic phase requires a differentiation from foci recapitulating scarring, vitiligo, localized alopecia or hypopigmentation. Progressive stages of vitiligo can emerge and areas of hypopigmentation are usually circumscribed by hyper-pigmented foci. However, vitiligo is not accompanied by adjunctive, specific stages of incontinentia pigmenti or non cutaneous manifestations. Piebaldism is a non-progressive autosomal dominant condition confined to cutaneous surfaces.

Naegeli syndrome is an exceptional, autosomal dominant condition implicating cutaneous surfaces and derivatives. Additionally, hyperhidrosis or punctate hyperkeratosis of palms and soles can be observed. The syndrome lacks various clinical stages. Genomic variants of KRT14 can be detected [1,2].

Retinal neovascularization can be observed in retinopathy associated with prematurity and familial exudative vitreo-retinopathy. The condition depicts an X- linked recessive inheritance and constitutes within a spectrum of Norrie disease. It can also demonstrate an autosomal dominant manner of disease penetration [1,2].

### Investigative assay

Molecular methodologies of investigation can be employed such as Single gene testing which employs targeted analysis for discerning the commonly observed IKBKG chromosomal deletion. The assay can be performed singularly or along with sequence analysis of IKBKG gene with a subsequent gene- targeted deletion/duplication chromosomal analysis.

Multigene genomic testing of a chromosomal panel comprised of IKBKG and associated genes can be performed singularly or along with genetic sequence analysis or a deletion/duplication analysis and as an accompaniment of non sequence based genomic tests.

Cutaneous tissue samples can be obtained for cogent histopathological examination, particularly in subjects demonstrating IKBKG genomic variants undetected or non-classifiable with molecular testing [7,8]. Implicated females can delineate eosinophilic infiltration and/or accumulation of extracellular melanin granules on histological examination of the incriminated cutaneous tissue associated with characteristic clinical features.

Implicated males can be clearly diagnosed, particularly in instances of genetic mosaicism. Histological examination and molecular genetic testing can be performed on similar tissue specimen.

Magnetic resonance imaging (MRI) of the brain can be adopted to exclude functional neurologic anomalies. Additionally, magnetic resonance angiography, assessment of physical and mental development and a cogent ophthalmologic examination is mandated [7,8].

### Therapeutic options

Vesiculo-pustular lesions of incontinentia pigmenti usually appear in the neonatal phase and require a demarcation from adjunctive dermatoses displaying enhanced morbidity such as impetigo, neonatal congenital bullous dermatoses and autoimmune blistering.

Cutaneous manifestations of incontinentia pigmenti commonly undergo spontaneous resolution. Topical steroids can be administered for inflammatory lesions.

Ocular manifestations can be appropriately managed with laser photocoagulation or cryotherapy of ischemic retinal foci in order to curtail the vasculopathy. Surgical intervention is usually unsuccessful when employed in concurrence with retinal detachment. Retinal detachment can be managed with cryotherapy or laser photo-coagulation [8,9].

Neurological symptoms of incontinentia pigmenti do not mandate any specific therapy. Seizures is usually managed symptomatically.

Relevant treatment of blisters and topical treatments can be adopted to relive discomfort and symptoms of superficial cutaneous involvement. Infections or cellulitis can be managed with suitable agents.

Tooth eruption can be appropriately evaluated by a pedodontist. Consultation with a speech pathologist and paediatric nutritionist can be beneficial.

Developmental stimulation or special education can be beneficial for treating developmental delay.

Pulmonary hypertension can be approached with standard measures [8,9].

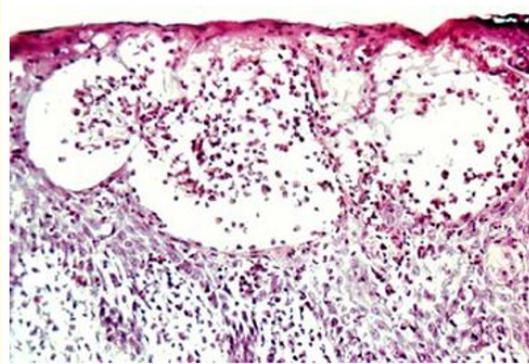
Major Criterion
Typical neonatal vesicular rash (erythema, vesicles, eosinophilia)
Typical hyperpigmentation (along lines of Blaschko on the trunk)
Linear atrophic alopecic lesions
Minor Criterion
Dental abnormalities
Alopecia
Woolly hair, nail abnormalities
Retinal disorders

**Table 1:** Incontinentia pigmenti in the absence of family history [1].

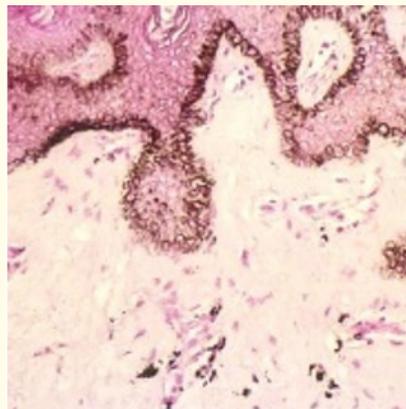
A singular major criterion is mandatory for diagnosis. Minor criterion supports the diagnosis of incontinentia pigmenti and a complete absence of minor criterion indicates an uncertain diagnosis.

Diagnostic criterion
Evidence of typical rash or indicative history
Cutaneous manifestations- hyperpigmentation, scarring, atrophic lesions, linear atrophic lesions with absence of hair, vertex alopecia
Dental abnormalities
Woolly hair
Retinal disorders
Multiple abortions of male fetuses

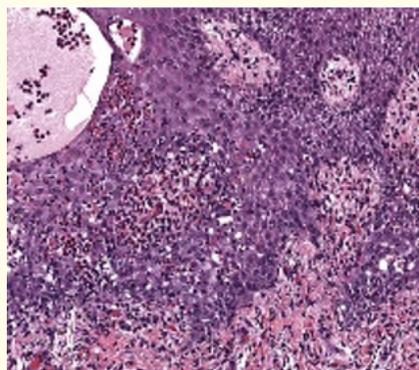
**Table 2:** Incontinentia pigmenti in the presence of family history [1].



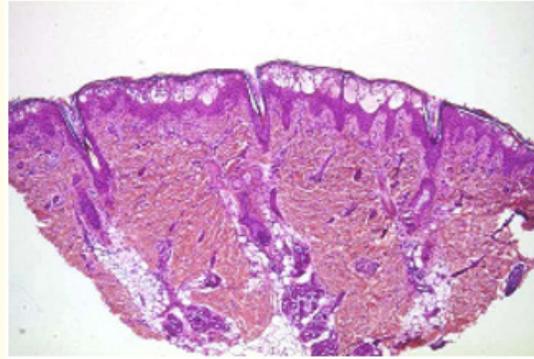
**Figure 1:** *Incontinentia pigmenti* with epithelial spongiosis, eosinophilic and neutrophilic exudate and enlarged dyskeratotic squamous epithelial cells [10].



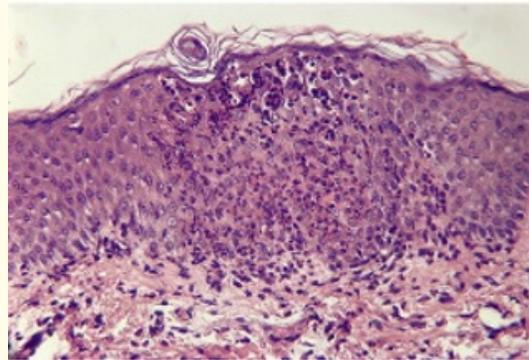
**Figure 2:** *Incontinentia pigmenti* with acanthosis, hyperkeratosis and papillomatosis [11].



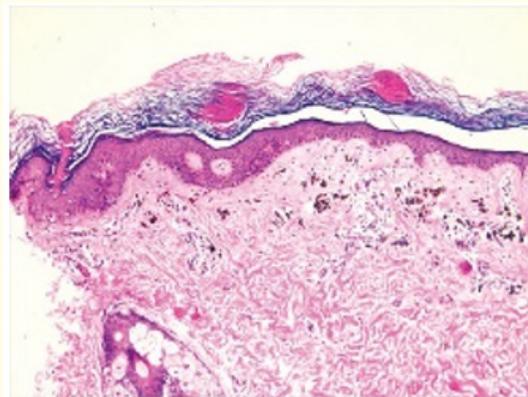
**Figure 3:** *Incontinentia pigmenti* with acanthosis, hyperkeratosis, papillomatosis and epithelial spongiosis [12].



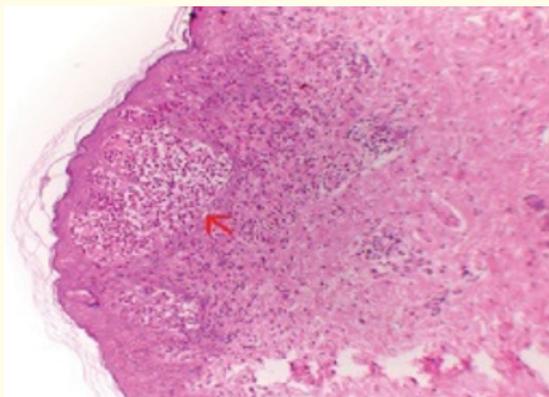
**Figure 4:** *Incontinentia pigmenti* with superficial spongiosis, acanthosis and melanin incontinence [13].



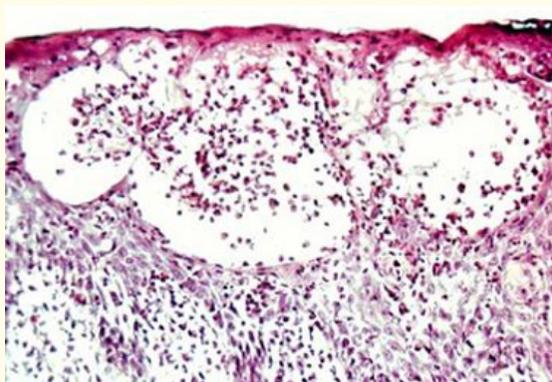
**Figure 5:** *Incontinentia pigmenti* with enlarged, hyperkeratotic epithelial cells, acanthosis, hyperkeratosis and melanin incontinence [14].



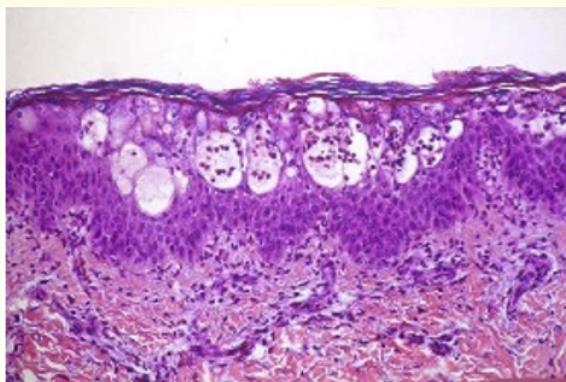
**Figure 6:** *Incontinentia pigmenti* with acanthosis, hyperkeratosis and severe epidermal atrophy [15].



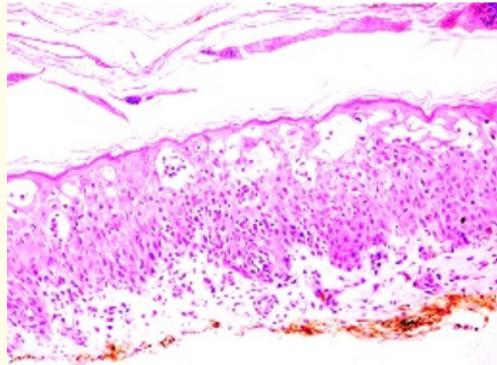
**Figure 7:** *Incontinentia pigmenti with acanthosis, papillomatosis, enlarged hyperkeratotic cells and melanin incontinence [16].*



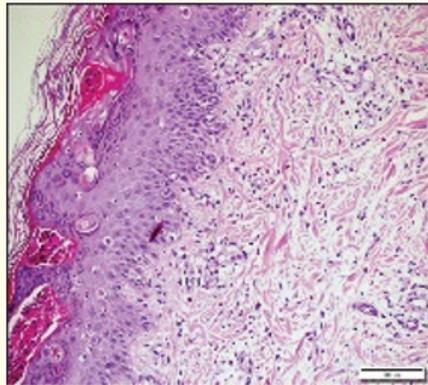
**Figure 8:** *Incontinentia pigmenti with superficial epidermal spongiosis, eosinophilic and neutrophilic infiltration and incontinence of melanin pigment [17].*



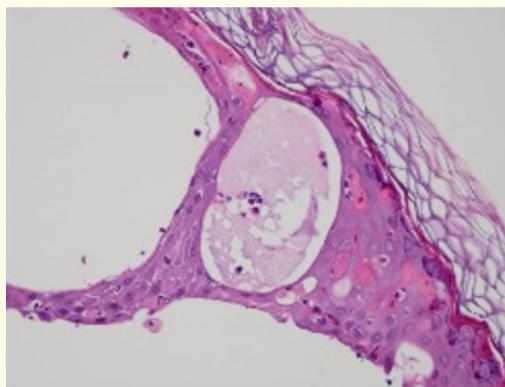
**Figure 9:** *Incontinentia pigmenti with marked acanthosis, hyperkeratosis, papillomatosis, spongiosis and enlarged hyperkeratotic cells [18].*



**Figure 10:** *Incontinentia pigmenti* with epidermal spongiosis, eosinophilic infiltration and acanthosis [19]. totic cells [18].



**Figure 11:** *Incontinentia pigmenti* with hyperkeratosis and marked dermal atrophy with lack of epidermal melanin and eccrine glands [20].



**Figure 12:** *Incontinentia pigmenti* with acanthosis, hyperkeratosis and spongiosis with eosinophilic infiltration [21].

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10. Image 1 Courtesy: Infinity path.
11. Image 2 Courtesy: Dermaamin.com.
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