



## Review

## Cutaneous mosaicism: Special considerations for women

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## ABSTRACT

Genetic mosaicism results from postzygotic mutations during embryogenesis. Cells harboring pathogenic mutations distribute throughout the developing embryo and can cause clinical disease in the tissues they populate. Cutaneous mosaicism is readily visualized since affected tissue often follows predetermined patterns, such as lines of Blaschko. Due to its clinical accessibility, cutaneous mosaicism is well suited for genetic analysis. An individual's unaffected tissue can be used as an inpatient genetic control, a technique that has yielded insight into the genetic etiologies of many disorders, several of which bear mutations in genes that would otherwise be embryonic-lethal. Particular mosaic diseases can also disproportionately impact women. Two such diseases, incontinentia pigmenti (IP) and congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, arise from mutations on the X chromosome. Both diseases result in fetal demise in males in most cases, thus making the two diseases largely specific to women. Women with McCune–Albright Syndrome, caused by somatic mutations in *GNAS*, often experience precocious puberty and infertility as a result of uncontrolled cAMP regulation in affected tissue. Women with cutaneous mosaicism carry a risk of transmission to offspring when gonosomal mosaicism is present, yet cutaneous disease burden does not correlate with germline transmission risk. Cutaneous mosaic disease represents a biologically unique set of disorders that can warrant special clinical attention in women.

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### What is known about this subject in regard to women and their families?

- Certain cutaneous mosaic diseases disproportionately affect women. McCune–Albright syndrome is a mosaic disease with endocrine effects that can impact fertility in women.
- X-linked disorders, such as incontinentia pigmenti and congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome, are lethal in utero for XY genotypes, unless somatic mutations arise in men. Women with these diseases may experience higher rates of spontaneous abortion during pregnancy.

### What is new from this article as messages for women and their families?

- Although cutaneous mosaicism is a visible sign of overall mosaicism in an individual, it does not correlate with the risk of germline mosaicism; thus, genetic counseling is warranted in all cases where somatic mosaicism is suspected, regardless of the disease burden.

## Introduction

Genomic variation is integral to variation between and within species. Although present in all regions of the genome, genetic variants (i.e., mutations) vary in their significance as a result of where within the genome they fall. Most mutations occurring in intronic or intergenic positions may persist without consequence, whereas mutations in the coding sequence of genes can drastically alter cell function and cause clinical disease. Although most inherited disorders result from familial transmission of damaging mutations, mutations arising during gametogenesis can lead to de novo disease in offspring. Postnatally, genetic variants accumulate over time, often resulting in neoplasm. These pathophysiologies of inherited disorders and cancer have anchored our understanding of genetic drivers of disease, but genetic mosaicism accounts for another class of disorders caused by mutations arising during crucial stages of embryogenesis.

Genetic mosaicism occurs when postzygotic mutations produce genetically distinct cell populations within an organism. These populations arise when mosaic mutations confer selective growth advantage or novel phenotypes to the cell. As such, clones of positively selected cells harboring mosaic oncogenic mutations have been described in the phenotypically normal tissue of healthy adults (Martincorena 2015; 2019; Yizhak et al., 2019). Conversely, mutations that are detrimental to cell growth lead to clonal elimination, and others trigger clearance by the immune system (Cheever, 1995); neither results in clinical findings. Clearance of mutant cells can also occur after producing clinical manifestations. In IP, skin lesions evolve, with mutant clones driving the initial clinical presentation and their clearance resulting in a changing phenotype. Evolution of skin lesions is seen in other mosaic diseases, though, as seen in CHILD syndrome, a disease with persistent skin involvement, and Conradi–Hunerman–Happle syndrome, where lesions fade over time (Canueto et al., 2014; Happle, 1979), genetic perturbations within the same biochemical pathway do not necessarily result in the same cutaneous consequences.

Genetic mosaicism intermixes cells harboring pathogenic mutations within a milieu of genotypically normal cells. This unique circumstance permits visualization of tissue-specific consequences of mutations in genes that, when inherited, would lead to in utero

demise. Examples of such a paradigm include Proteus syndrome, caused by mosaic *AKT1* mutations, which manifests overgrowth phenotypes (Lindhurst, 2011). Vertical transmission of mutations has not been documented, suggesting embryos with constitutional disease involvement are not viable.

The temporal and spatial distribution of mosaic mutations can be used to define different types of mosaicism based on the tissues affected. First, germline mosaicism refers to mutations present within a portion of sperm or oocytes, and carries the ability to pass mutations onto progeny. Somatic mosaicism includes cases in which somatic tissues, but not germ cells, harbor mutations. This type of mosaicism thus does not confer the risk of transmission to progeny. Lastly, gonosomal mosaicism describes cases in which both somatic and germline mosaicism is present.

When considering somatic or gonosomal mosaicism, the ability to detect genetically distinct populations is typically hindered by the inaccessibility of most tissues. In contrast, cutaneous mosaic diseases have visible clinical manifestations. Cutaneous mosaicism arises from mutations in early embryologic precursors. During embryogenesis, clonal expansion of these progenitor cells follows specific migratory paths. Mutations in cells that track along this developmental axis often result in lesions that adhere to particular body patterns. A commonly seen distribution is the lines of Blaschko, linear streaks along the trunk and extremities that represent the migratory path of epidermal progenitors. Because the epidermis is readily visualized and skin lesions along the lines of Blaschko offer a distinct clinical hallmark, cutaneous mosaicism represents an excellent model to investigate the biology of mosaic diseases.

In cutaneous mosaic disorders, biopsies taken from affected tissue can be analyzed via exome, genome, and transcriptome sequencing and paired with sequencing of unaffected tissue, saliva, or blood from the same individual to discover genetic mutations unique to the affected tissue. In such analyses, a patient serves as their own genetic control, an advantage that greatly increases the power and speed of candidate gene discovery. This technique has been performed with great success to define the genetic etiologies of mosaic disorders. For example, the mosaic mutations that drive the previously described Proteus syndrome were first identified through exome analysis of affected tissue paired with tissue from visually normal skin (Lindhurst, 2011). Because of the highly visible distribution of mosaic skin lesions, individuals with somatic mosaicism often first present clinically with dermatologic concerns. Although skin involvement alone in mosaic disease can require clinical management, it is also often a clue to initiate a broader systemic evaluation. Mutations arising early in development can affect multiple tissue types, as is commonly seen in neurocutaneous disease, due to shared embryologic ancestors (Arefi et al., 2019). Through its visibility and accessibility, cutaneous mosaicism can be an early clue to clinicians regarding the full spectrum of disease involvement and the required steps to take for diagnosis and management.

## Mosaic disease can disproportionately affect women

The biologic sex of an individual can be crucial to prompt and accurate diagnosis, because many mosaic diseases have differing symptomatology between the sexes. Specifically, mutations found on the X chromosome can lead to different clinical presentations between male and female individuals. For the purposes of this report, the terms “women” and “female” refer to individuals born with an XX karyotype. In addition to disorders affecting XX individuals exclusively, women with particular mosaic disorders caused by mutations on autosomal chromosomes may experience different clinical complications than their male counterparts if mutated genes are involved in estrogen signaling (Lala, 2007). These

two classes of cutaneous mosaicism with added implications for women will be discussed in this review.

### X-linked obligate female mosaicism

#### *Incontinentia pigmenti*

IP is a X-linked dominant disorder caused by mutations in *NEMO* (also referred to as *IKBKKG*). In women, a loss-of-function deletion spanning exons 4–10 accounts for 65% of cases (Scheuerle, 2019). *NEMO* encodes a nuclear factor kappa B regulatory protein; thus, cells lacking proper *NEMO* protein function are susceptible to increased levels of tumor necrosis factor alpha (TNF $\alpha$ ) and aberrant cytokine signaling (Liao et al., 2013). Although *NEMO* mutations are inherited rather than arising postzygotically, X-inactivation occurs in all cells with two X chromosomes, resulting in functional mosaicism in X-linked dominant disorders. Interestingly, disturbance of the random X-inactivation in normal populations is a genetic hallmark of IP and can be assessed during the diagnostic genetic workup (Martinez-Pomar et al., 2005). Cells expressing the mutation-carrying X chromosome are identifiable during early stages of disease, but mutant allele representation diminishes over time in fibroblasts and leukocytes of patients, suggesting that cells expressing the mutant *NEMO* protein are expunged over time (Migeon, 1989; Parrish, 1996).

This shifting of cell populations parallels the dermatologic changes seen in IP. Cutaneous involvement starts in infancy with blistering, vesicular lesions in a distribution along the lines of Blaschko during stage 1 of the disease (Hadj-Rabia, 2003). These lesions may resemble other dermatologic conditions, such as bullous impetigo, complicating the initial diagnosis. After approximately 4 months, linear verrucous lesions emerge on the limbs and persist until roughly 2 years of age (stage 2). Stage 3 develops during early childhood and involves hyperpigmentation in a whorled distribution. The hyperpigmentation that defines stage 3 can present as early as infancy in rare cases, but remains into late teens and early adulthood in almost all individuals (Hadj-Rabia, 2003). The accompanying histology of this stage is said to contain basal keratinocytes incontinent of melanin, hence the name for the disease (Spallone, 1987). Lastly, stage 4 develops during adulthood with permanent, hypopigmented, atrophic regions devoid of hair follicles. The progression of these skin lesions results from mutant epidermal cells' inappropriate interleukin-1 secretion, triggering TNF $\alpha$  from wild-type neighbors. Mutant cells consequently apoptose upon TNF $\alpha$  exposure, leading to mutant cell clearance during the first stage, with resolution occurring over the next stages (Courtois, 2006).

Extracutaneous manifestations of IP include ocular, central nervous system, dental, hair, and nail changes. Natural history studies of IP have concluded that 30% of children with IP have central nervous system involvement, most commonly with seizures. Microdontia, anodontia, hypodontia, and alopecia are also commonly seen in these female patients (Hadj-Rabia 2003, Scheuerle 2019). Interestingly, male fetuses are viable when inheriting separate, less damaging mutations in *NEMO*, termed hypomorphic alleles. These male fetuses develop hypohidrotic ectodermal dysplasia and immunodeficiency rather than the clinical symptoms of IP (Fusco et al., 2008). Rare cases of exon 4–10 deletions have been observed in men, either through somatic mosaicism of the X chromosome or Klinefelter syndrome (XXY karyotype) with one X carrying the *NEMO* exon 4–10 deletion (Kenwick et al., 2001). Because of the lethality of the exon 4–10 deletion in an XY karyotype, miscarriages are commonly experienced by women with IP, typically during the second trimester (Kenwick et al., 2001).

#### *CHILD syndrome*

CHILD syndrome is an X-linked dominant disease that, like IP, is lethal in males with a few rare exceptions. CHILD syndrome is caused by mutations in *NSDHL*, a gene critical for cholesterol biosynthesis. Sequelae of the disease are thought to arise from the buildup of toxic cholesterol precursors within cells. CHILD syndrome presents with Blaschko-linear areas of waxy, scaly erythroderma (CHILD nevi). Histologic analysis of affected skin shows hyperkeratosis and parakeratosis with foam cells in the papillary dermis (Ramphul, 2021). Inflammatory linear verrucous epidermal nevi syndrome and linear psoriasis are in the differential diagnosis for CHILD syndrome, but clinical and histologic features distinguish these disorders. Unlike inflammatory linear verrucous epidermal nevi syndrome, CHILD nevi are not typically pruritic and show more widespread involvement. Limb and axial defects in CHILD syndrome include hypoplasia of the limbs, syndactyly of the digits, absence of ribs, scoliosis, and hypoplasia of the vertebrae. Absence of the kidneys, pectoral muscles, and facial muscles has also been observed on the ipsilateral side of skin involvement (Seeger and Paller, 2014). In total, there have been <70 cases of CHILD syndrome documented. Two of these cases were in males exhibiting somatic mosaicism. Additionally, most cases show evidence of sporadic rather than inherited mutations (Bittar, 2006; Ramphul, 2021). Several cases of vertical transmission of CHILD syndrome have been reported, with varying degrees of penetrance in each affected individual (Bittar, 2006; Happle, 1990). The fluctuating degree of phenotypic involvement between affected women within families transmitting *NSDHL* mutations adds biologic and clinical complexity to a severe X-linked disorder with multisystem effects.

### Obligate mosaic mutations presenting with gynecologic complications

#### *McCune–Albright syndrome*

McCune–Albright Syndrome (MAS) is a mosaic disease characterized by the triad of café-au-lait macules, fibrous dysplasia (FD) of the bone, and precocious puberty, although patients may also feature other findings, including hyperthyroidism, growth hormone excess, phosphate renal wasting, and neonatal hypercortisolism (Spencer et al., 2019). MAS is caused by postzygotic mutations in *GNAS*, a gene that encodes the alpha subunit ( $G\alpha_s$ ) of the G protein complex. Ninety-five percent of disease-causing mutations are found at the 201<sup>st</sup> amino acid, most commonly as R201C and R201H substitutions. No cases of vertical transmission have been documented; thus, this mutation is presumed to be lethal when inherited (Spencer et al., 2019). Mutations at this residue are considered gain of function, leading to an overactivation of the  $G\alpha_s$  and consequential cAMP upregulation in affected tissues (Landis, 1989). Given the crucial role of  $G\alpha_s$  for hormone receptor activation and downstream signaling in several endocrine tissues, patients with MAS can manifest a spectrum of hyperfunctioning endocrinopathies (Spencer et al., 2019).

In bone, increased cAMP stimulates osteoprogenitor proliferation and prevents their differentiation into normal-functioning osteoblasts. This results in an abnormal, poorly mineralized fibroosseous matrix in the bone marrow that is known as FD (Riminucci, 1999). In MAS, FD lesions are distributed in a mosaic pattern, commonly at the proximal femur and skull base, but any skeletal site can be affected (Collins et al., 2012). Given that FD tissue is weaker than healthy bone and lesions are often expansive, patients are prone to fractures and skeletal deformities, complications which typically present in early childhood and are often part of the initial presentation (Boyce and Collins, 2020).

**Table 1**

List of mosaic disorders mentioned in review

Mosaic disorder	Gene harboring mutation	Pathway implicated	Skin phenotype	Extracutaneous manifestations	Considerations for affected women	Inheritance pattern
<b>Incontinentia pigmenti</b>	<i>NEMO</i>	Nuclear factor kappa B inflammation signaling	Evolving erythrodermic rash through childhood that results in permanently hypopigmented, hairless regions in adulthood	Seizures, microdontia, anodontia, hypodontia, alopecia, nail changes, and neovascularization and detachment of the retina	High burden of miscarriages	X-linked, male embryonic lethal; survivable in males by somatic mosaicism of the X chromosome, aneuploidy of the X chromosome (Klinefelter syndrome)
<b>Congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome</b>	<i>NSDHL</i>	Cholesterol biosynthesis	Waxy, scaling erythrodermic rash with hyperkeratosis and foam cells in the papillary dermis	Limb hypoplasia, syndactyly, scoliosis, absence of ribs, vertebral hypoplasia, absence of pectoral and facial muscles, and single kidney. All involvement ipsilateral to cutaneous findings.	High burden of miscarriages	X-linked, male embryonic lethal; survivable in males by somatic mosaicism of the X chromosome, aneuploidy of the X chromosome (Klinefelter syndrome), and less damaging mutations (hypomorphic)
<b>McCune–Albright syndrome</b>	<i>GNAS</i>	cAMP regulation	Café-au-lait spots, coast-of-Maine borders	Precocious puberty, fibrous dysplasia, hyperthyroidism, renal phosphate wasting, increased risk of certain cancers, neonatal hypercortisolism, increased growth hormone levels	Precocious puberty, ovarian cysts, increased risk of polycystic ovarian syndrome, infertility, premature ovarian insufficiency, and breast cancer	Somatic mosaicism only
<b>Keratitis ichthyosis deafness syndrome</b>	<i>GJB2</i>	Gap junction protein function	Palmoplantar keratoderma, ichthyosiform erythroderma	Keratitis of the cornea, visual impairment, deafness, alopecia, nail deformities	Risk of germline mosaicism	Somatic mosaicism, germline inheritance is possible through gonosomal mosaic parents
<b>Proteus syndrome</b>	<i>AKT1</i>	Phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin	Cerebriform connective tissue nevi, linear verrucous epidermal nevi	Progressive, segmental, overgrowth, overgrowth and atrophy of adipose tissue hemimegacephaly, vascular malformations, tumors, dysmorphic facial features	High burden of miscarriage	Somatic mosaicism only

Gonadal abnormalities are also very common in MAS but differentially affect male and female patients. Approximately 85% of boys and men experience benign Leydig or Sertoli cell hyperplasia, seen as unilateral or bilateral macroorchidism (Boyce et al., 2012), yet only 10% to 15% develop autonomous testosterone production that leads to peripheral precocious puberty (Spencer et al., 2019). In contrast, precocious puberty affects up to 85% of female patients with MAS. Constitutive ovarian  $G\alpha_s$  activation causes intermittent estrogen-producing cysts that typically lead to vaginal bleeding, breast development, and growth acceleration as early as infancy (Boyce et al., 1993; Spencer et al., 2019; Van Doan et al., 2021). If left untreated, both in boys and girls, peripheral precocious puberty can progress into established central precocious puberty, affecting adult height in addition to negative impacts on psyche and behavior (Boyce et al., 1993).

Gynecologic complications are also common during adulthood. Rates of polycystic ovarian syndrome are statistically significantly higher in patients with MAS than in the general population (Ghidei et al., 2021). In a study of long-term gynecologic and reproductive outcomes of adult women with MAS, 77% reported dysfunctional uterine bleeding. Cases within this cohort also required blood transfusion and/or hysterectomy at early ages (<35 years).

Forty-three percent of women reported infertility, including cases secondary to primary ovarian insufficiency (Boyce et al., 2019). Another gynecologic complication of MAS is breast cancer presenting at early ages (36–46 years; Majoor et al., 2018). *GNAS* mutations have been identified in malignant tissue, suggesting that constitutive  $G\alpha_s$  activation might play a role in tumorigenesis (Majoor et al., 2018). In addition, most women with MAS and early appearing breast cancer had a history of precocious puberty, pointing to a causative role of excessive estrogen exposure on neoplastic development (Majoor et al., 2018).

Although precocious puberty and fibrous dysplasia develop during early years of life, cutaneous involvement in MAS can be seen from birth or shortly thereafter (Collins et al., 2012). Café-au-lait spots (i.e., hyperpigmented macules with uneven borders) develop with segmental distribution that respects the midline (Collins et al., 2012). Because these lesions arise in the neonatal period, they are the first clinical indication of disease (Spencer et al., 2019). Café-au-lait spots are not unique to MAS, however, and are also commonly seen in mosaic diseases, such as neurofibromatosis type 1, a disease caused by both mosaic and inherited mutations in *NF1* (Ruggieri and Pratico, 2015). Traditionally, subtle differences between the borders of the café-au-lait spots in each disease can



be used to inform differential diagnoses. Café-au-lait spots in neurofibromatosis type 1 are said to have a smoother border, referred to as coast-of-California edges, while the rougher, jagged edges of MAS café-au-lait spots are more akin to the coast of Maine phenotype (Shah, 2010). In practice, the distinction between the cutaneous manifestations of these diseases is challenging, and molecular diagnosis in conjunction with other medical history is always necessary to reach an accurate diagnosis.

### Implications for women

Cutaneous mosaicism is a visible manifestation of pathology often associated with systemic disease and can be an early indicator that further evaluation may be warranted. When cutaneous mosaicism is combined with sex, symptomatology can be pathognomonic for specific diseases. McCune–Albright syndrome is often first suspected in young girls with precocious puberty and/or abnormal uterine bleeding, yet café-au-lait spots precede these endocrine symptoms (Boyce et al., 2019; Van Doan et al., 2021). Although not diagnostic alone, the early emergence of skin findings might provide better preparedness for early detection and management of MAS-associated disorders (Boyce et al., 1993; Spencer et al., 2019).

In IP, evolving skin lesions also precede other disease manifestations. By definition, hair and dental findings can only be detected once an individual is at the age where hair and teeth are developed. Other abnormalities often associated with IP are not as common; thus, skin findings prove the earliest, most consistent indicator of IP on which clinicians can rely (Hadj-Rabia, 2003). In mosaic disease, skin lesions can act as a canary in the coal mine for more systemic disease progression, highlighting the necessity of dermatologic examination and documentation in young women with mosaic skin disease.

Many cutaneous mosaic diseases fall under the umbrella of gonosomal mosaicism and carry the possibility of transmission to progeny. It has been theorized that the degree of cutaneous involvement in mosaic disease can predict the likelihood of accompanying germline mosaicism. Recent studies have shown that cells harboring somatic mutations are dispersed during embryogenesis with unequal contributions to specific tissue (Park et al., 2021). Because the burden of mutation in some tissues therefore may vary dramatically from others, the extent of cutaneous mosaicism cannot be directly correlated with the risk of germline mosaicism. Evidence of the independence of germline and somatic mutation burden has been documented in CHILD syndrome, keratitis ichthyosis deafness syndrome, and other genetic disorders (Arefi et al., 2019; Campbell et al., 2014). As previously discussed, CHILD syndrome has been documented to be a heritable condition in rare instances. In some of these inherited cases, the mothers and grandmothers of severely affected individuals showed much more limited phenotypes (Bittar, 2006). Cases of lethal keratitis ichthyosis deafness syndrome in a pair of twins resulted from transmission of a mutation in *GJB2* from a mother with palmoplantar keratoderma as her only disease manifestation (Jonard, 2008). Subtle presentations of parental somatic mosaicism may go missed in isolation, but are essential to proper genetic counseling regarding the risk of transmission to future generations.

Women with mosaic cutaneous disorders may also experience complications related to conception and pregnancy. Although the biologic correlation between increased activity of fibrous dysplasia lesions and pregnancy in individuals is disputed, 30% of pregnant individuals with MAS reported an increase in bone pain during their pregnancy (Boyce et al., 2019; Osada et al., 2005). Infertility with McCune–Albright syndrome also directly affects female childbearing potential (Boyce et al., 2019; Ghidei et al., 2021). Patients with IP and CHILD syndrome are also at an increased risk of

complications during pregnancy. XY fetuses carrying the *NEMO* and *NSDHL* mutations causative of IP and CHILD syndrome typically result in fetal demise, thus predisposing women with germline involvement to risk of spontaneous abortion in 50% of pregnancies (Bittar, 2006). Conversely, gonosomal mosaic mutations in genes that also cause inherited disease, such as *NF1*, confer an increased risk of systemic involvement in offspring because these mutations are survivable in utero. Together, the discussed mosaic disorders may confer a particular risk to women (Table 1).

### Conclusion

Mosaicism represents a unique form of genetic variation in which mutations arise postzygotically. Mosaicism can affect any tissue, but is easily visualized in the skin. The access to affected tissue afforded by studying cutaneous mosaicism greatly benefits our ability to uncover the genetic etiologies of these diseases. Certain mosaic conditions manifest themselves uniquely in women. Genetic diseases caused by mutations on the X chromosome can be lethal when male embryos inherit the mutation on their single X chromosome. Women with these disorders are at risk of high rates of spontaneous abortion or fetal demise as a consequence. Mosaic diseases affecting endocrine tissue can predispose young females to precocious puberty during childhood and infertility later in life. On a molecular level, genetic mosaicism poses a unique opportunity to study genes essential to life, because mutations in these genes are embryonic-lethal when inherited. As we continue to delve deeper into the biology of this class of genetic disorders, mosaicism will continue to provide crucial insights into human disease.

### Conflicts of interest

None.

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### Study approval

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