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Mosacism in Cutaneous Disorders

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Abstract

Genetic mosaicism arises when a zygote harbors two or more distinct genotypes, typically due to de novo, somatic mutation during embryogenesis. The clinical manifestations largely depend on the differentiation status of the mutated cell; earlier mutations target pluripotent cells and generate more widespread disease affecting multiple organ systems. If gonadal tissue is spared—as in somatic genomic mosaicism—the mutation and its effects are limited to the proband, whereas mosaicism also affecting the gametes, such as germline or gonosomal mosaicism, is transmissible. Mosaicism is easily appreciated in cutaneous disorders, as phenotypically distinct mutant cells often give rise to lesions in patterns determined by the affected cell type. Genetic investigation of cutaneous mosaic disorders has identified pathways central to disease pathogenesis, revealing novel therapeutic targets. In this review, we discuss examples of cutaneous mosaicism, approaches to gene discovery in these disorders, and insights into molecular pathobiology that have potential for clinical translation.

INTRODUCTION

Genetic mosaicism describes an organism harboring two or more genetically distinct cells (90, 118). There are many potential causes of somatic mutation, which include UV radiation, viral integration, environmental genotoxic agents, errors occurring during DNA replication, and X chromosome inactivation. The great majority of somatic mutations occurs in noncoding DNA with little or no effect on cell viability or function (98), but if rare mutations with potentially larger effect occur during embryonic development or after birth and confer a growth or selective advantage, a mutant clone will expand and reach clinical significance (24, 127). More than 30% of genes are estimated to be indispensable to development in mammals, and many mutations in critical housekeeping genes or oncogenes cause embryonic lethality when arising de novo in a zygote and causing constitutional disease. Such mutations can be tolerated, however, in a limited, mosaic state (59, 114). Mutations arising after the establishment of immune tolerance can be limited by a T cell–mediated immune response against resulting neoantigens (24, 127). Thus, only those somatic mutations that permit viability and evade immune response lead to sustained mosaicism that can be visually appreciated.

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Postnatal mutations can give rise to acquired benign seborrheic keratosis (56), nevi (51, 70, 74, 80, 81) and sporadic lobular capillary hemangiomas (53, 82, 84), but somatic genomic mosaicism is also a precursor to malignant transformation seen in basal cell carcinoma (18), squamous cell carcinoma (1), and melanoma (41, 59).Mutations occurring in embryonic development can affect cells of broad differentiation potential, giving rise to localized or generalized involvement of the organism, and are readily apparent in nature including the patterned coat color in calico or tortoiseshell cats (23, 89), the dual-colored eyes of heterochromia iridis (2), and the color variation in maize pericarp (108). In 1925, Calvin Bridges first observed genetic mosaicism in Drosophila melanogaster, after crossing wild-type males with Minute-n females harboring the X-linked dominant Minute gene mutation (which causes shorter thoracic bristles and a smaller, paler body) (20). Some of the daughters, which Bridges termed piebalds, exhibited spots on the thorax with normal bristles as well as mixed colors of the eyes, corresponding to random inactivation of the maternal X-linked dominant allele (20).

Postzygotic de novo mutations initiate all forms of genomic mosaicism, which is further classified on the basis of the presence or absence ofmutation in gonadal tissue, and hence, its heritability (16).Germline—or gonadal—mosaicism describes genetic heterogeneity within the gametes, permitting mutations to be inherited and expressed constitutionally by subsequent generations (9), whereas somatic mosaicism precludes mutation in gonadal tissues, restricting mutation to somatic cells and, consequently, the proband (57). Gonosomal mosaicism is the co-occurrence of both somatic and germlinemosaicism, where mutation is found in both somatic and gonadal tissue, and results from an early mutagenesis event (9, 116). When somatic mosaicism is present, the phenotypic consequence ofmosaicism is largely determined by cell lineage, gene function, and mutation timing (Figure 1) (16). Mutations earlier in embryogenesis likely affect pluripotent or multipotent cells, leading to multilineage effects observed in syndromic disorders such as epidermal nevus syndrome (58).

Cutaneous mosaic disorders offer a unique opportunity to investigate genetic mosaicism, as lesional skin is easily identified and mutant cells can be isolated via skin biopsy. Further, predictable embryonic dorsoventral migration patterns of ectodermal progenitors, which differentiate into the neural crest and cutaneous ectoderm, result in linear bands of involved tissue known as the lines of Blaschko in the setting of embryonic somatic mutation (17, 63). Somatic mosaicism can also give rise to proliferative/hamartomatous lesions such as congenital hemangiomas and nevi. Recently, a new system of classification of mosaic skin disorders based on genomic versus epigenetic etiology, and segmental versus nonsegmental distribution, was proposed (59). In this review, we discuss exemplary mosaic skin disorders, focusing on understanding pathogenesis and identification of potential targets for therapy. However, we must first review the types of genomicmosaicism found in genodermatoses and the current technologies employed to identify disease-causing mutations.

MENDELIAN OR MOSAIC?

Mosaicism is not independent fromMendelian inheritance, and the two are notmutually exclusive. The same genetic mutations underlying heritable disorders can occur in mosaic

patterns, as in segmental neurofibromatosis type 1 (SNF1) due to somatic mutation in neurofibromin 1 (NF1) (91, 125). Unlike the generalized form of neurofibromatosis type 1 (NF1) caused by inherited autosomal dominant NF1 mutation, demonstrating disseminated neurofibromas, Lisch nodules of the iris, intellectual disability, and numerous café-au-lait spots, SNF1 presents with lesions occurring in a single, unilateral segment of the body, and these do not cross the midline (91, 105). A lack of systemic involvement or family history of disease is common in segmental disorders (47). Notably, the identical p.R1947X nonsense mutation in *NF1* can lead to both SNF1 (32) and NF1 (142). Parents with SNF1 can also produce offspring with generalized NF1 in cases where gonosomal mosaicism underlies the segmental phenotype (32). Mutations that are only found in mosaic disease are likely lethal when constitutionally expressed even with widespread systemic involvement and suspected gonosomal mosaicism. This is likely the case for the activating p.E17K *AKT1* mutation leading to the Proteus syndrome, which features segmental overgrowth of various tissues and organs, skin lesions including lipomas, nevi, and café-au-lait macules, and an increased susceptibility to developing tumors (88). To date, neither constitutional mutation nor intergenerational transmission has been reported, and the mutation is presumed to be embryonic lethal (21). Another example of obligate mosaic mutation is the activating *GNAS1* mutations that lead to McCune-Albright syndrome (MAS) (139). Precocious puberty, which is part of the characteristic triad of MAS alongside café-au-lait spots and polyostotic fibrous dysplasia, results from large ovarian cysts secreting high levels of estrogen, and despite this confirmed presence of *GNAS1* mutation in ovarian cells, the mutation is presumed to be lethal when constitutional (78,104). Other examples of presumed obligatory somatic mutations include activating mutations in *IDH1* leading to Maffucci syndrome (3); *PIK3CA* mutations in congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies (CLOVES) syndrome (76); *KRAS* mutations in Schimmelpenning syndrome (51); and activating *GNAQ* mutations underlying Sturge-Weber syndrome (115). Mendelian inheritance of other mutations may potentiate disease or alter its severity following postzygotic acquisition of a second mutation, according to Knudson's two-hit model of disease pathogenesis (124). These second-hit scenarios can generate highly variable phenotypes of a dominantly inherited disorder, as seen in tuberous sclerosis complex (TSC), in which various non-nervous-system tumors can arise from second somatic mutations in *TSC1*, *TSC2*, and *KRAS*(102). These second hits may be loss of heterozygosity (LOH) of the wild-type allele leading to type 2 segmental mosaicism, whereby the areas with LOH display a more severe phenotype in the setting of milder, diffuse disease, as seen in Hailey-Hailey and Darier diseases (60, 99). This is in contrast to type 1 segmental mosaicism, whereby the mutation is confined to the affected tissue in an otherwise wild-type individual (Figure 2) (99).

IDENTIFYING GENETIC MOSAICISM IN SKIN DISORDERS

Genetic mosaicism is detected by comparing affected tissue to unaffected tissue from the same individual. The study of mosaicism was historically restricted to those disorders with visible clinical features that permitted collection of lesional tissue with sufficient purity (16, 45). Even among cutaneous mosaic disorders distinguished by clear phenotypic distinctions of texture, color, thickness, or other features, a low mutant allele fraction due to admixture

with wild-type cells can prevent the detection of mutation (45, 131). Selection of the appropriate unaffected control tissue is also critical, and in cutaneous mosaic disorders, buccal swabs, saliva, or blood is commonly employed. Adjacent, phenotypically normal-looking skin may be a suitable control in cases where the mutation is limited to the affected tissue (type 1 segmental mosaicism). In cases where type 2 segmental mosaicism is suspected, comparison of SNP genotyping data between the segmental lesion and adjacent tissue or blood can help identify LOH (22) (see the section titled Microarray SNP Genotyping). Syndromic cutaneous disorders with widespread skin involvement may also have a subset of mutant cells in other tissues including saliva and blood, complicating identification of an appropriate normal control.

Laser Capture Microdissection

Isolation of pure mutant cell populations can be limited in routine skin biopsy by the presence of unaffected cells of the same or different lineages. For example, in a keratinocytic disorder, a punch biopsy is contaminated by dermal and subdermal fibroblasts, adipocytes, and endothelial cells. Furthermore, disorders accompanied by inflammation exhibit variable degrees of immune infiltration, which can further dilute the proportion of mutant cells (110). When histologic features or fluorescent markers can precisely delineate affected tissue, laser capture microdissection (LCM) can be employed to increase the fraction of affected cells sampled forDNAisolation (15, 96). LCM is a microscope-controlled technique using a focused laser beam to selectively isolate single cells or areas of tissue without compromising genetic content, and it was first successfully used for PCR-based mutation analysis in 1996 (40). Briefly, frozen or paraffin-embedded tissues are sectioned onto polyethylene naphthalate membrane-coated slides, which can be cut by the laser during capture (75). Dissected pieces of tissue fall directly into a lysis reservoir for immediate DNA extraction. Guiding the laser to areas of disease limits admixture from nearby cells, aiding the detection of low fraction mutations lying within complex tissues (34). Comparison of sequences from laser-captured lesions to control DNA can successfully identify mosaic mutations.

Mutation Detection

Early studies of mosaicism investigated chromosome integrity via cytogenetic analyses such as karyotyping and fluorescence in situ hybridization, which were employed to identify distinct karyotypes and aneuploidy within patient cells. These methods were successfully employed to identify genetic mechanisms in some of the earlier disorders to be solved, including the mixture of XY and XO sex-chromosome bone marrow cells in hermaphrodites (62) and trisomy 8 mosaicism syndrome (73). Advances in genotyping and sequencing technology, and the availability of large data repositories, have enabled the rapid detection and functional annotation of mutations underlying mosaic skin disorders.

Microarray SNP Genotyping

Mosaic chromosome-level abnormalities including small copy number variations require alternate identification strategies with higher resolution, and microarray-based techniques such as array comparative genomic hybridization and SNP genotyping have demonstrated marked sensitivity, detecting mosaicism at levels of <5% aneuploidy (31). Genome-wide analysis of SNPs across all chromosomes provides visualization of regions of LOH by

plotting the B allele frequency and surveying for deviations from baseline that demonstrate loss of one haplotype. To differentiate between LOH resulting from deletion and copy-neutral LOH that can occur through recombination, the LogR ratio, which is the ratio of measured SNP signal intensity to the expected intensity of two alleles, is also measured. Targeted arrays permit assessment of genotypes in focused genomic regions. SNP genotyping was used to identify the copy-neutral LOH at the qter of chromosome 17 underlying the revertant mosaicism (RM) found in ichthyosis with confetti (25).

Whole Exome Sequencing

First employed to identify a disease-causing gene in an inherited disease in 2005, high-throughput sequencing platforms have permitted large-scale, low-cost DNA sequencing, accelerating the discovery of genetic mutations underlying human disorders and giving rise to the field of functional genomics (11). Although they comprise merely 1% of the human genome, the coding regions, also known as the exome, are estimated to host approximately 85% of disease-causing mutations. As such, limiting sequence analysis to the exome is a time-saving and cost-effective approach for identifying pathogenic mutations (27, 103). Whole exome sequencing (WES) platforms share a central workflow of hybridizing fragmented genomic DNA to exon-specific probes that isolates the exons and flanking sequences from nontargeted DNA. The resulting fragments are amplified for high-throughput sequencing (48, 94). Reads are aligned to the human genome and processed with custom or commercialized pipelines, such as the Genome Analysis Toolkit (GATK) Best Practices or VarScan, to then generate a variant call format (.vcf) file containing the proper headers and formatting for annotating mutations (37, 71).

Somatic variants underlying cutaneous mosaic disorders require paired WES, which includes adjacent sequencing and analysis of a controlDNA, most often blood (leukocytes) or a saliva/buccal swab (oral epithelial cells). Additional software such as MuTect/MuTect2 (Broad), Ingenuity Variant Analysis (QIAGEN), and Strelka can help automate the comparison of variants from lesional and control sequencing data and selectively identify the sites of difference by filtering for mutations unique to, or enriched in, the lesion (12, 28, 109). In cases where the causal mutation is intronic or lies within regions of transcriptional regulation, whole genome sequencing may be necessary (138). It is important to note that carefully selecting the source of control DNA is critical to ensure successful discovery of somatic mutations, as widespread mosaicism can affect end organs without an overt phenotype and lead to failed detection (35).

MOSAIC CUTANEOUS RASOPATHIES AND THE MAPK PATHWAY

Activating mutations in the Ras family of GTPases, including HRAS, KRAS, and NRAS, cause inherited and somatic mosaic disease as well as up to 30% of cancers (100, 101, 111). Like other G-proteins, Ras proteins exist in a binary “on” or “off ” state, characterized by their binding to guanosine triphosphate (GTP) or guanosine diphosphate (GDP), respectively (100). Following activation, Ras feeds two major signaling cascades: the Ras-Raf-MEK-ERK pathway and the PI3K-Akt pathway (111). Critical amino acid residues at codons 12 (glycine), 13 (glycine), and 61 (glutamine) mediate the hydrolysis of GTP to GDP necessary

for proper inactivation of active Ras. Indeed, the missense mutations affecting these residues, which lead to a constitutively active GTP-bound Ras, account for the majority of identified mutations in cancer and RASopathies (55, 100). Most are considered embryonic lethal as they are not observed in a constitutional state, and widespread embryonic expression of *KRAS* p.G12D in amousemodel was demonstrated to be uniformly lethal (129). Missense mutations at other loci of *KRAS*, such as p.V14I and p.T58I, lead to only a mild reduction of GTPase activity and can constitute germline disorders like Noonan syndrome and cardiofaciocutaneous syndrome (36, 112). Similarly, the recurrent p.G12S *HRAS* mutation underlying the germline Costello syndrome was determined to be less potent than valine or aspartic acid substitutions at this position (4, 43). The attenuated molecular consequences of these alternate mutations evade the embryonic lethality characteristic of more strongly activating mutations.

NS and keratinocytic epidermal nevi (KEN) are examples of segmental mosaic RASopathies and appear linearly along Blaschko's lines. Both can result from somatic activating mutations in one of the three Ras family members (51) and are benign; congenital lesions occur in 1–3 per 1,000 births (51). KEN are nonorganoid, appearing as lines and swirls of pigmentation frequently on the trunk or extremities, whereas NS are organoid nevi that appear as waxy plaques most commonly on the scalp, face, and neck (13). Secondary neoplasms like syringocystadenoma papilliferum (SCAP) can arise within these nevi and harbor the same *RAS* mutation as their associated nevi (51, 79, 97). Although the mutation is restricted to the epidermis in NS and KEN, somatic *RAS* mutations occurring earlier in embryogenesis can affect other cell lineages and end organs. Mutation in a multipotent progenitor cell giving rise to keratinocytic and melanocyte lineages causes phacomatosis pigmentokeratotica, a combination of NS and speckled lentiginous nevi occurring in the Blaschkoid pattern (52).Cutaneous skeletal hypophosphatemia syndrome (CSHS) is the clinical manifestation of RAS mutation affecting a progenitor cell prior to gastrulation, such that the phenotype affects not only the skin but also the mesoderm-derived skeleton and other organs. In CSHS, Ras activation in the bone leads to abnormally elevated levels of serum FGF23, causing skeletal dysplasia and rickets due to renal phosphate wasting (85).Earlier mutation targeting a cell with even greater potency leads to Schimmelpenning-Feuerstein-Mims (SFM) syndrome, which describes a more widespread constellation of symptoms involving the brain (seizures, mental retardation, structural defects), eyes (ocular colobomas), bone (osteomalacia, hypophosphatemic rickets), and skin (KEN and NS) (135, 137). In cases of SFM and CSHS, the identical RAS mutation can be isolated from the affected skin, skeleton, and other tissues, implicating a single mutant progenitor (42).

Spitz nevi and GCMN are melanocytic lesions caused by activating RAS mutations, predominantly in *HRAS* at glycine 13 and *NRAS* at glutamine 61, respectively (70, 107). Unlike NS and KEN, these lesions are nonsegmental: Spitz nevi are single point mosaic lesions occurring as a solitary benign tumor, whereas GCMN represent patchy mosaicism, often appearing in a coat-like pattern crossing the midline (59). Syndromic cases involving these melanocytic lesions are similar to the epidermal nevus syndromes, though GCMN syndrome can be associated with characteristic facies, including a wide forehead, orbital hypertelorism, a broad nasal tip, a prominent/long philtrum, and an everted lower lip (69). One of the first five cases of CSHS was a four-year-old girl with GCMN (85).

Recently, a subset of childhood hemangiomas was also identified as arising from somatic RAS mutation, adding to the spectrum of cutaneous RASopathies and nonsegmental mosaic tumors (53, 84). The most common tumors of infancy, hemangiomas affect 5–10% of all newborns, though most are benignGLUT-1-positive infantile hemangiomas that will spontaneously regress by three years of age (143). Activating RAS mutations are estimated to be responsible for up to 10% of childhood lobular capillary hemangiomas [also known as pyogenic granulomas (PGs)], as well as a small population of GLUT-1-negative, non-involuting congenital hemangiomas (NICHs).

Mutation in non-Ras members of the MAPK pathway, like *BRAF*, are frequently found in disorders classified as cutaneous RASopathies, including SCAP(79) and melanocytic nevi (74). The *BRAF* p.V600E mutation, which is the most common variant identified in mosaic disorders and cancer, dramatically increases the BRAF kinase activity, and, like activating RAS mutations, leads to increased phosphorylation of ERK1/2 to promote oncogenic MAPK activity. Alternatively, the discovery of novel mutations in disorders classified as RASopathies has helped to identify new proteins regulating the Ras-MAPK pathway. For example, activatingmutations of the Gaq family, including *GNAQ*, *GNA11*, and *GNA14*, were recently found to cause NICHs and PGs, the same group of vascular tumors arising from *RAS* and *BRAF* mutations (8, 82), and somatic mutation in *GNAQ* and *GNA11* was also found to cause phacomatosis pigmentovascularis, a combination of melanocytic nevi and vascular birthmarks (123). Previously, mutations in *GNAQ* and *GNA11*, specifically at arginine 183 and glutamine 209, were associated with uveal melanoma and blue nevi (133, 134), whereas somatic *GNAQ* mutation at arginine 183 was associated with Sturge-Weber syndrome (115), a neurocutaneous disorder characterized by a congenital, extensive port-wine stain of the face involving the trigeminal nerve, leptomeningeal angioma, and variable neurological symptoms including seizures, hemiparesis, and glaucoma (120). The somatic mutations of Gaq family members occur at key residues (*GNAQ* and *GNA11*: arginine 183 and glutamine 209; *GNA14*: glutamine 205) located in their respective catalytic domains. The residues facilitate GTP hydrolysis, and their mutation leads to a constitutively active conformation of the Gaq proteins (8, 82).Gaq mutations were also recently found to specifically upregulate the MAPK pathway, but not the Akt-mTOR pathway (8, 53, 82, 84), and their expression in primary human melanocytes and umbilical vein endothelial cells was found to render the cells growth factor independent, suggestive of oncogenic transformation. Vascular anomalies caused by Gaq mutation can also be associated with disseminated nonsegmentalmosaicism, like the recently reported case of congenital hemangiomatosis with dozens of lesions all harboring the same *GNA11* p.Q209P mutation (46).

Activation of Ras initiates a complex cascade of downstream signals involving diverse pathways including ERK-MAPK, and it is notable that mutations in *GNAQ*, *GNA11*, *GNA14*, *BRAF*, and *RAS* members give rise to similar vascular anomalies and, in the case of PGs, the same tumor. Therefore, it is intriguing to consider whether targeted inhibition of the MAPK pathway (e.g., MEK inhibitors) may prove effective against vascular lesions that are refractory to treatment. Furthermore, it is interesting to consider whether other G-protein disorders, likeMAS, that arise from a multilineage activating GNAS mutation leading to café-au-lait spots, polyostotic fibrous dysplasia, and precocious puberty may also respond to MAPK inhibition.

Recurrent *FGFR1* p.N546K and p.K656E mutations were recently found to cause encephalocraniocutaneous lipomatosis, a neurocutaneous disorder featuring unilateral lipomatous cutaneous neoplasms devoid of hair, and both mutations were found to upregulate the MAPK pathway (14). Previously, other mosaic FGFR1 disorders, like dysembryoplastic neuroepithelial tumor (106) and pilocytic astrocytoma (65), were found to result from activating *RAS* or *BRAF* p.V600E mutations (64). Hence, like the G-protein disorders, cutaneous disorders resulting from activating mutations in FGFR1 may also respond to agents targeting the MAPK pathway.

EPIGENETIC MOSAIC SKIN DISORDERS

In the absence of postzygotic genetic mutation, alterations of gene expression can be induced by retrotransposon insertion, methylation/demethylation, and imprinting, which cause functional, rather than genomic, mosaicism. In such cases, a genomic mutation capable of causing an observable phenotype may be inherited, but its expression is mosaically modified. Random X-chromosome inactivation (XCI), which depends on the differential expression of the XIST RNA gene on the X-chromosome, occurs during female embryogenesis and can generate regions of healthy and diseased skin in the setting of X-linked inheritance, often occurring in the Blaschkoid pattern. X-linked epigenetic mosaic skin disorders can be largely divided into malelethal [X-linked dominant, e.g., incontinentia pigmenti (IP)], sublethal (e.g., Menkes disease), and nonlethal disorders (e.g., hypohidrotic ectodermal dysplasia) (59). IP, which is caused by genomic rearrangements within the X-linked *NEMO* gene encoding a regulatory component of the IκB kinase that activates the NF-κB pathway, features perinatal inflammatory vesicles that resolve into patterns of hyperpigmentation and dermal scarring alongside other highly variable abnormalities of the nails, teeth, eyes, and nervous system (117). Early cytolysis of cells selectively expressing the mutant X-chromosome leads to skewed XCI in female patients, and, in lesional tissue, activity of themutant allele interferes with NF-κB activation (117). Conradi-Hünermann-Happle syndrome is another example of an X-linked dominant, epigenetic cutaneous mosaic disorder, and it is due to differential expression of the X-linked *EBP* gene that encodes sterol isomerase, an enzyme critical for cholesterol biosynthesis (19). Affected skin expressing the *EBP* mutation is characterized by follicular atrophoderma and diffuse erythema with scaly keratotic lesions (44). Other associated systemic features can include alopecia, asymmetrical limb shortening, cataracts, and skeletal dysplasias (44). Rarely, survival of males with these traditionally X-linked lethal mosaic disorders has also been reported, bypassing in utero lethality via hypomorphic mutations, a 47,XXY karyotype (Klinefelter's syndrome), or somatic mosaicism (6, 68).

Menkes disease is an X-linked recessive disorder due to mutation of *ATP7A*, a copper transporting P-type ATPase leading to copper deficiency, characterized by neurodegeneration, kinky hair, and connective tissue disease (128). Skewed XCI of the normal X-chromosome leads to a mild phenotype in the mosaic females compared with affected males (38, 92) who will rarely survive to adolescence (128). In nonlethal disorders like X-linked recessive hypohidrotic ectodermal dysplasia (also known as Christ-Siemens-Touraine syndrome), which demonstrates the triad of sparse hair (hypotrichosis), dental problems (hypodontia/anodontia), and the inability to sweat (hypohidrosis/anhidrosis) due to

mutation in X-linked *EDA*/*EDAR*, females demonstrate abnormal skin temperature and sweating along the pattern of the lines of Blaschko (29). In fact, sweat testing has been suggested to identify female carriers (30).

Effective therapeutics for epigenetic mosaic skin disorders have not been identified. Although studies have revealed factors regulating the initiation of XCI like the X-inactivation center (Xic), dependable means of skewing XCI do not yet exist (7, 122). The utility of miRNAs, which are noncoding RNAs that act as posttranscriptional regulators of gene expression by targeting and cleaving mRNA, has been discussed in the treatment of human cancers, although both the delivery of miRNAs to vital layers of the skin and their potential cellular toxicity continue to be challenges (93). For mosaic epigenetic skin disorders, therapy is therefore limited to supportive care and symptom management.

REVERTANT MOSAICISM

Whereas mosaic pathogenic mutations lead to areas of lesional skin, RMappears on a background of completely affected skin, with genetic self-correction giving rise to patches of healthy skin. Several genetic mechanisms underlie RM. Back mutation site-specifically corrects the disease-causing mutation. Second-site mutations are compensatory secondary mutations that mitigate the effects of a disease-causing mutation, such as an insertion mutation via DNA polymerase slippage that restores a normal reading frame, or an enhancer or promoter mutation that silences a mutant gene. Finally, gene conversion or mitotic recombination can remove the mutant haplotype via nonreciprocal or reciprocal exchange of genetic information between sister chromatids, respectively, during repair of a double-strand break (39, 61, 66, 77). Although it is rare overall, RM is more common in some cutaneous disorders: Up to 36% of *COL17A1* mutation-mediated epidermolysis bullosa (EB) patients and 33% of *LAMB3* mutation-mediated EB patients demonstrate RM as patches of visibly normal skin with recovered expression of these genes (67, 95).Numerous revertant patches may occur within a patient over time via independent reversion events, and these areas may result from one or more distinct corrective mechanisms (25, 67).

Ichthyosis with confetti (IWC) is unique among the cutaneous disorders with RM given its striking phenotype and remarkable frequency of reversion: Individuals initially born with generalized erythema and scaling due to an autosomal dominant *KRT10* or *KRT1* mutation develop thousands of white, histologically and clinically normal skin areas, each representing an independent revertant clone arising via mitotic recombination leading to copy-neutral LOH that removes the mutant haplotype (25, 26, 86, 121). Other variable clinical features include ear malformations, mammillae hypoplasia, palmoplantar keratoderma, and hypertrichosis (54, 119). Unlike other keratinopathies, such as epidermolytic ichthyosis (EI), the mutations causing IWC have thus far been frameshift mutations targeting the tail domain of *KRT10* or *KRT1*, often replacing their endogenous glycine-serine-rich tails with polyarginine or polyalanine tails leading to mislocalization of the keratin from the cytosol to the nucleus and/or nucleolus (25, 26, 86, 121). Notably, no cases of EI have been reported to demonstrate RM, and no reversion has been found in animal models of EI that faithfully recapitulate the disease phenotypes of generalized erythema, cutaneous blistering, hyperkeratosis, and palmoplantar keratoderma (5) (Figure

3). This further highlights the distinction of IWC mutations and implicates a potential role of keratin tail domains in genetic reversion (83).

In IWC, the size and number of revertant spots increase with age, suggesting that revertant keratinocytes have improved fitness over mutant cells. However, studies that have attempted to culture revertant basal stem cells isolated from biopsies of patients with revertant EB found mutant keratinocytes to be dominant, with revertant cells declining down to <1% of the population in subsequent passages (50). Autologous grafting of revertant skin to other areas of the body has had mixed results; functional repair of the graft has previously failed in *COL17A1* mutant junctional EB (49), whereas punch grafting of split-thickness revertant biopsy specimens has been successful in an EB patient with *LAMB3* mutation (49, 50). Alternatively, induced pluripotent stem cells (iPSCs) generated from revertant keratinocytes (132), or virus-associated editing of mutant iPSCs to wild type (113), have successfully been employed for transplantation in animal models, suggesting the potentials of stem cell therapy and genome editing in cutaneous disorders with RM. Finally, recessive dystrophic EB patients undergoing allogeneic bone marrow transplantation were reported to generate revertant patches with prolonged survival and *COL7A1* expression in the basement membrane, and—with a large population of CD45 donor cells—in the skin. This finding suggests that hematopoietic stem cells can populate the skin and that such cells may be one potential source of revertant clones (126, 136). Indeed, bone marrow cells have previously been associated with the skin: Following cutaneous wounding in mice, bone marrow–derived cells were observed repopulating the skin (10), and some of these could potentially differentiate into keratinocytes (141).

Although clinical observations of RM in patients suggest expansion of revertant clones over time, this stands in contrast to the apparent reduced fitness observed to date in in vitro experiments. This paradox may result from the use of ex vivo culture, but specific mechanisms leading to the appearance of RM clones and their expansion over time remain unknown. Further, most genodermatoses do not exhibit clinically apparent reversion, and determining why only a subset of disorders undergo RM will be critical to understanding this phenomenon.

CONCLUSION

The discovery of novel mutations underlying cutaneous mosaic disorders continues at an unprecedented pace, supported by technological advances in genetic analysis. For example, just within the last two years, besides the identification of *GNA14*, *GNA11*, and *GNAQ* mutations causing childhood vascular tumors, somatic recurrent p. L412F mutation in *SMO* was found to cause Curry-Jones syndrome (130), *NEK9* mutations were found to cause nevus comedonicus (80), and somatic *PIK3CA* and *MAP3K3* mutations were found to cause venous malformations (33, 87). Functional investigation of these genetic mutations will enhance our understanding of epithelial biology and will identify novel therapeutic targets in the treatment of these disorders. Furthermore, the coexistence of wild-type and mutant cells, which defines mosaicism, has been shown to generate a unique cellular milieu involving cytokines and paracrine signaling pathways like the JAK-STAT system that modulates cell–cell competition, proliferation, and apoptosis (72, 140). Understanding the biology at this

interface of mosaic-affected and adjacent normal tissue will provide new insights into cancer, signaling pathways, and other systemic disorders.

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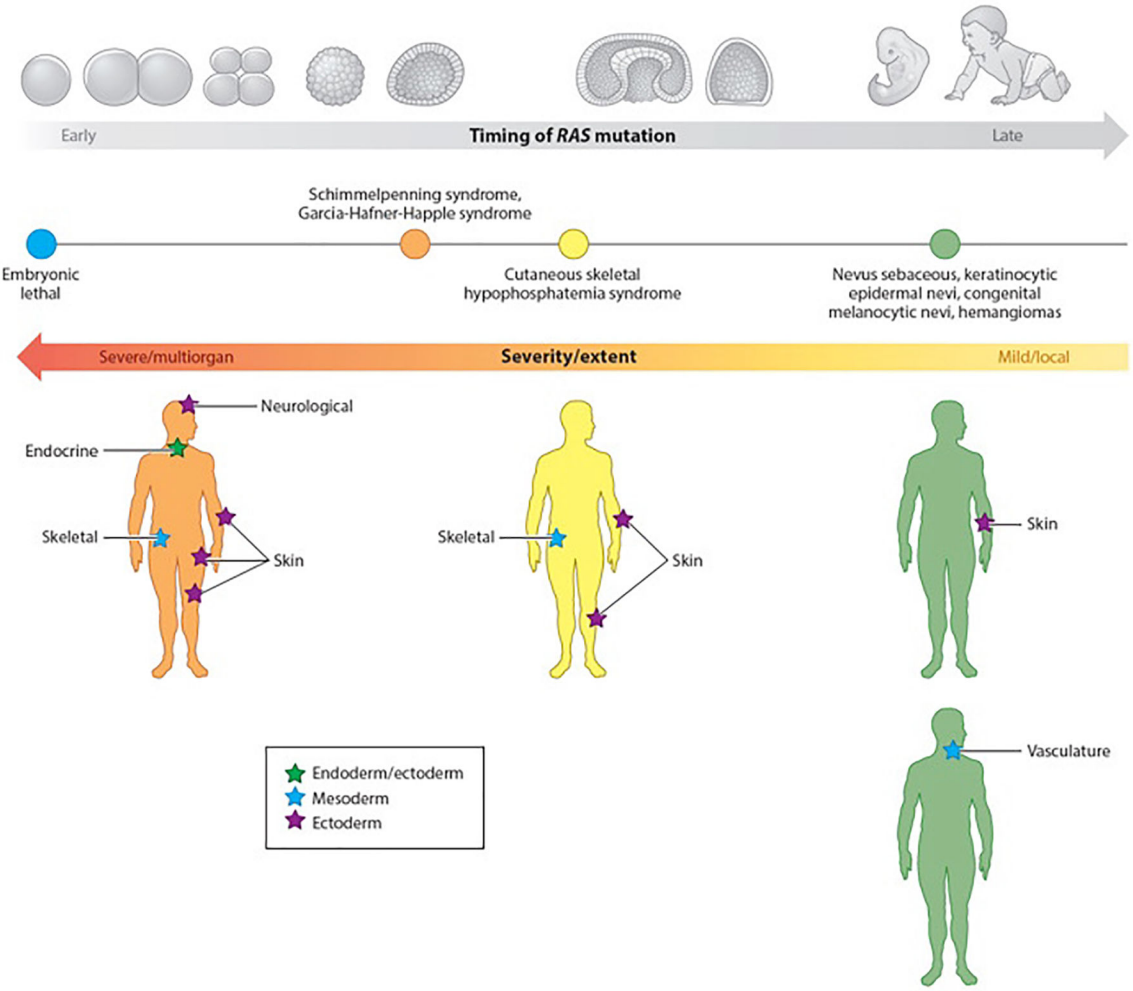

Figure 1. Mutation timing and end organ involvement.

Clinical manifestation of cutaneous, genomic mosaic disorders largely depends on the timing of mutation. Activating *RAS* mutations demonstrate a pleiotropic phenotype, with the severity and extent of disease dependent on the timing of mutation and the corresponding potency of the affected cell. The spectrum of disease includes effects on the endoderm (green star), mesoderm (blue stars), and ectoderm (purple stars). Stochastic, postzygotic mutation of a cell early in development leads to multilineage disease affecting end organs of all germ layers, as found in Schimmelpenning syndrome and Garcia-Hafner-Happle syndrome, both of which demonstrate neurological, endocrine, skeletal and skin phenotypes. Disorders such as cutaneous skeletal hypophosphatemia syndrome and phacomatosis pigmentokeratotica, which have phenotypes in the skin and bone or keratinocyte and melanocyte, respectively, result from mutation later in development of a cell with less potency. Mutation occurring in cells that have fully committed to one lineage (e.g., keratinocyte, melanocyte, blood vessels) is reflected by a milder clinical phenotype, in which the RASopathy is nonsyndromic and may be isolated tumors or single lesions.

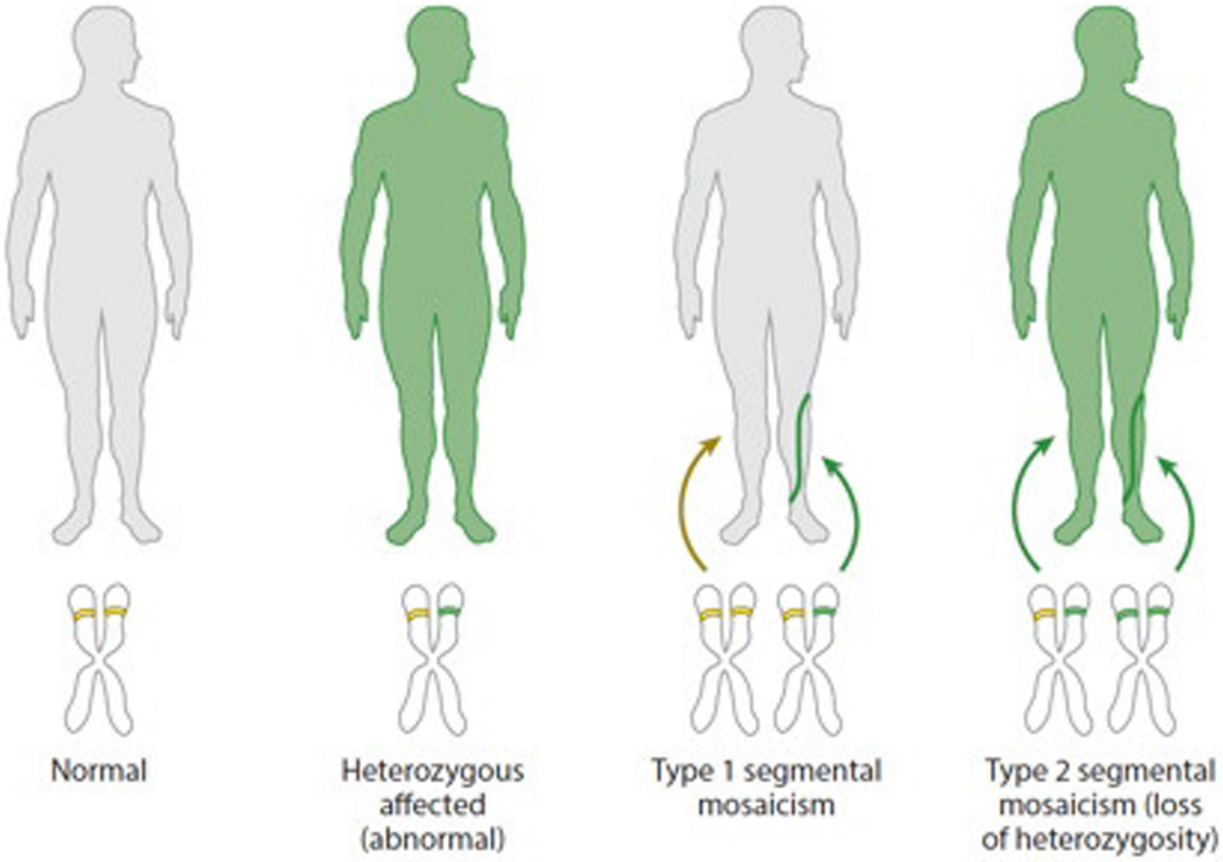

Figure 2. Types of segmental mosaicism.

Segmental mosaicism refers to the Blaschko-linear patterning of cutaneous lesions that respect the midline: Single postzygotic mutations leading to segmental lesions reflect type 1 segmental mosaicism, by which the mutation is limited to lesional tissue in an otherwise wild-type individual. Type 2 segmental mosaicism occurs when a second mutagenesis event, such as loss of heterozygosity, occurs in individuals already carrying heritable mutations, leading to segments with more severe phenotype.

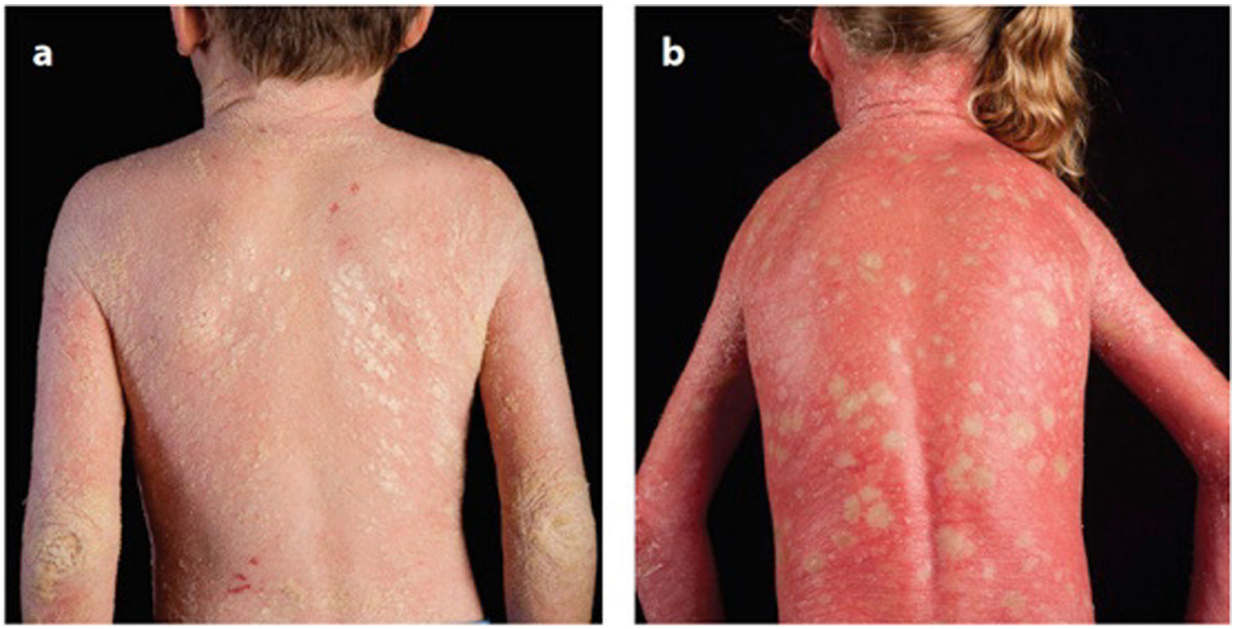

Figure 3. Epidermolytic ichthyosis (EI) versus ichthyosis with confetti (IWC).

Age-matched patients with (a) EI due to *KRT10* p.R156H mutation with extensive hyperkeratosis and plate-like scales and (b) IWC due to *KRT10* mutation with erythroderma and confetti macules. Revertant mosaicism in IWC is demonstrated by the white macules of normal skin that are also histologically normal. To date, IWC has been associated with frameshift mutations targeting only the tail domains of *KRT10* or *KRT1*, whereas mutations at other sites, such as the helical rod domains, lead to EI, which does not show clinical evidence of reversion.