A six-attribute classification of genetic mosaicism

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Mosaicism denotes an individual who has at least two populations of cells with distinct genotypes that are derived from a single fertilized egg. Genetic variation among the cell lines can involve whole chromosomes, structural or copy-number variants, small or single-nucleotide variants, or epigenetic variants. The mutational events that underlie mosaic variants occur during mitotic cell divisions after fertilization and zygote formation. The initiating mutational event can occur in any types of cell at any time in development, leading to enormous variation in the distribution and phenotypic effect of mosaicism. A number of classification proposals have been put forward to classify genetic mosaicism into categories based on the location, pattern, and mechanisms of the disease. We here propose a new classification of genetic mosaicism that considers the affected tissue, the pattern and distribution of the mosaicism, the pathogenicity of the variant, the direction of the change (benign to pathogenic vs. pathogenic to benign), and the postzygotic mutational mechanism. The accurate and comprehensive categorization and subtyping of mosaicisms is important and has potential clinical utility to define the natural history of these disorders, tailor follow-up frequency and interventions, estimate recurrence risks, and guide therapeutic decisions.

INTRODUCTION

Mosaicism has been established as a cause of miscarriage, congenital anomalies, developmental delay, and cancer. Mosaicism denotes the presence of two or more clones of cells in an individual with distinct genotypes (genetic variants), all which are derived from a fertilized egg.[1]

The genetic variant can range from whole chromosomes to copy-number variants (CNVs), structural variants, indels, single-nucleotide variants (SNV), and epigenetic changes. Here we focus on pathogenic variants for two reasons. The first is that benign mosaic variation is essentially universal and unassociated with a phenotypic consequence, thus it is not of interest or concern to the clinician. The second reason is that the pathogenicity of the variant determines what we call the directionality of the mutational event (benign to pathogenic versus pathogenic to benign). These mosaic pathogenic variants are associated with highly variable clinical expressivity (and perhaps incomplete penetrance) depending on their tissue-specific involvement, body pattern distribution, and the proportion of cells with the variant, meaning the proportion of chromosomes or alleles and cells (heterozygous or homozygous) with the variant, which is described as the variant allele fraction (VAF). Mosaicism (for multiple genetic/genomic/epigenetic variants) is likely the rule and not the exception in any multicellular organism. This has been proven in multiple studies of single cells in adult individuals and in early embryos.[2] However, mosaicism as a term is usually applied only when the proportion of cells with the genetic/ epigenetic variant that was not present in the germline is sufficient in any tissue to be detectable by standard (cytogenetic, genetic, or genomic) testing and/or functionally relevant. Detectable mosaicism may result from a very early mutational event in development or, any time later,

through clonal selection and proliferation of the cells with the postzygotic variant.

Mosaicism caused by postzygotic mutational events is a well-known mechanism of skin disorders,[3] cancer,[4] neurodevelopment disorders with or without central nervous system (CNS) malformations,[5] and for numerous partial and generalized overgrowth disorders,[6–8] among others. Mosaicism has been widely underestimated and all individuals are complex mosaics with multiple genotypes acquired from embryonic development to adulthood, which can have overt phenotypic consequences or may predispose to specific diseases.[9–11] In addition, recent work has shown that the detection of somatic structural variants in blood cells increases with age and may be related to a reduction in blood cell clonality.[12–14] The most common somatic pathogenic change in humans, associated with smoking and aging, is mosaic loss of the Y chromosome in men, which is a biological factor that contributes to several age-related disorders and overall male mortality apparently through extreme deregulation of some key chromosome Y genes.[15–17] Mosaicism must be distinguished from chimerism, which designates an individual comprised of multiple genotypically distinct cell lineages derived from two or more fertilized zygotes,[18] which typically have divergent genotypes throughout the genome.

The first descriptions of human mosaics were published about 60 years ago in patients with sex chromosomal aneuploidies, including mosaic Turner and mosaic Klinefelter syndromes[19–22] (for historical notes see Supplementary. Material). Since then, multiple reviews have been published,[9,18,23–26] and many authors, including some of us, have proposed mosaicism classifications, focusing on the pattern of affected regions of the body and the type of underlying mechanism.[25] As well, there have been many attempts to classify genetic mosaicism of the skin.[25,27] Happle[3,28] emphasized the overlapping nature of proposed categories. Biesecker and Spinner[18] also contributed to the clarification of many aspects of mosaicism, reinforcing the notion of "gonosomal" mosaicism (now gonadosomatic, see below), and reviewing genetic and genomic etiologies and techniques to interrogate each of these mechanisms. Happle[25] recently reviewed cutaneous mosaicism and proposed a morphological classification scheme distinguishing among the types of genomic and epigenetic mosaicism and discriminating nonsegmental from segmental manifestations of skin mosaicism. While each of these efforts have merit, after reviewing these classifications and categories, we concluded that aspects associated with mosaicism have not been sufficiently addressed and a classification that integrates all the attributes involved in this phenomenon is lacking and necessary.

Here we propose a new systematic categorization of mosaicisms, applicable to all types of tissues, including consideration not only of the affected tissue, and the pattern and distribution of the mosaicism, but also the cause, direction of the change, and the mutational mechanism. We have designated these attributes "A to F" as a memory aid. We propose that an individual with mosaicism can be classified using these six attributes and that this will lead to clinically useful categorizations.

A SIX-ATTRIBUTE CLASSIFICATION: THE A TO F EVALUATION

This novel classification of mosaicism is based on six attributes, listed in Table 1, Fig. 1, and in Figs. S1–S6. The six attributes are designated with the letters A to F, as a memory aid, and the subclassifications thereof are numbered. When information on a specific attribute is missing or unknown, we assign the subclassification attribute a 0 (zero).

In this classification we start from the premise that based on current technologies and the logical limitations for obtaining multiple human samples, it is impossible to determine the true or full extent of the affected tissue(s) as this would require examination of many types of cells.[29] Further, in postzygotic mosaicism, varying VAFs can be found among an affected individual's various tissues.[30] This may be due to mosaicism being present in one or more cell types but also because not all cell types within a biopsy have the variant. In these cases, the VAF could be related to the percentage of a specific cell type within the sample studied.

A. Affected tissue

The A of this classification indicates the affected tissue, taking into account its location in relation to its ability to transmit variants to subsequent generations of individuals. In mosaicism, variants may affect somatic cells, gonadal (germinal) cells, or both (gonadosomatic). We here preferred the term "gonadosomatic" instead of "gonosomal" since the latter may be confused with the meaning of the term accepted in genetic terminology, i.e., "mosaicism related to sex chromosomes".[31] In addition, it may affect the placental tissue and not the fetus.[32]

In general, the developmental timing of the mutational event and the cell lineage affected, combined with the phenotypic consequences of the variant, ultimately determine the tissue and cell type distribution of mosaicism (that is, somatic, germline, or gonadosomatic) and also the patterns of disease recurrence within families.[18] This attribute is divided in four classes: somatic, germinal (gonadal), gonadosomatic, and confined placental mosaicism (Fig. S1).

A1. "Apparent" somatic mosaicism

This refers to mosaicism apparently affecting any tissue/cell type in the body except the germinal cells (eggs or spermatozoids). The term "apparently" is preferred because the involvement of the germline can only be inferred based on the absence of transmission in other cases and typically not objectively demonstrated.

Somatic mosaicism is probably the commonest form of mosaicism and it is seen in many skin, vascular, and overgrowth disorders, sometimes as isolated manifestations such as different types of nevi, skin tumors, or regional overgrowth. Somatic mosaicism is also the main mechanism

Table 1 Proposed list of attributes for evaluation of individuals with mosaicism: the "A to F" evaluation of mosaicism.

| Letter	Item to be evaluated	Explanation	Subdivision of the attribute
A	**A**ffected tissue	The part of the body harboring the variant cells, which are either somatic cells, germinal cells, a combination of somatic and germinal cells or not affecting the embryo/neonate but only the placental tissue.	A1. Somatic mosaicism A2. Gonadal (germinal) mosaicism A3. Gonadosomatic mosaicism A4. Confined placental mosaicism A0. If unknown
B	**B**ody pattern	The B of the classification refers to the body pattern. This is an anatomic category in which the extent and distribution patterns of mosaic clinical manifestations are classified. We propose two major classes: nonsegmental and segmental mosaicisms.	Nonsegmental patterns B1. Single point B2. Disseminated B3. Patchy without midline separation B0. No pattern (e.g., hematologic) Segmental patterns B4. Blaschko lines, narrow bands B5. Blaschko lines, broad bands B6. Checkerboard B7. Phylloid B8. Lateralization/ half body B9. Other
C	**C**hange of the direction	From benign to pathogenic, pathogenic to benign (revertant) or normal to more than one pathogenic variant.	C1. Benign to pathogenic mosaicism C2. Pathogenic to benign mosaicism C3. Didymosis C0. If unknown
D	**D**evelopmental mechanism	This means the status of the variant cells: heterozygous changes, loss of heterozygosity, or epigenetic variants. This attribute includes type 1 and type 2 postzygotic segmental mosaicism, the functional mosaicism of epigenetic mutations, and the	D1. Type 1 segmental mosaicism D2. Segmental mosaicism with an early second hit including type 2 segmental mosaicism of autosomal dominant traits D3. Type 3 Functional X-chromosome

Table 1 continued

Letter	Item to be evaluated	Explanation	Subdivision of the attribute
		lethal autosomal mutations surviving as mosaics.	mosaicism with or without male lethality D4. Type 4. Disorders that manifest only as mosaics 4a (Autosomal)/4b (X-linked) D0. If unknown
E	Etiology	This refers to the size of the genetic/ genomic variation or when the change does not affect the size but the functionality of the genome due to epigenetic or positional effects.	E1. Genomic changes (large variations) E2. Genetic changes (small variations) E3. Epigenetic changes E4. Positional effect variants E0. If unknown
F	**F**raction of the affected tissue	The percentage of the affected tissue in comparison with normal tissue. See text for definitions of these ranges.	F1. Mild involvement F2. Moderate involvement F3. Severe involvement F4. Very severe (extreme) involvement F0. If unknown

See also Fig. **1** and Fig. S1–S6.

of cancer, where the tumor has neoplastic cells with pathogenic variant(s) sometimes accompanied by constitutive pathogenic variant(s), in combination with normal, wild-type cells.[33] There is also growing evidence that many cortical brain malformations, eye, kidney, and liver diseases are due to postzygotic mosaicism, as well as a significant proportion of neurodevelopmental disorders.[7,34–36] For example, mosaic *mTOR* gain-of-function (GOF) pathogenic variants in the brain cortex lead to cortical brain dysplasia and mosaic variants in several genes cause ocular disorders such as microphthalmia, anophthalmia, and coloboma.[7,35] Somatic pathogenic variants affecting neurodevelopmental genes are more frequently detected in the brain of individuals with dementia compared with controls, suggesting that accumulating mosaic somatic pathogenic variants promote brain pathology.[37]

A2. Gonadal or germinal mosaicism
This refers to a mosaic state that is confined to germinal cells, and does not affect other tissues. Note that formally,
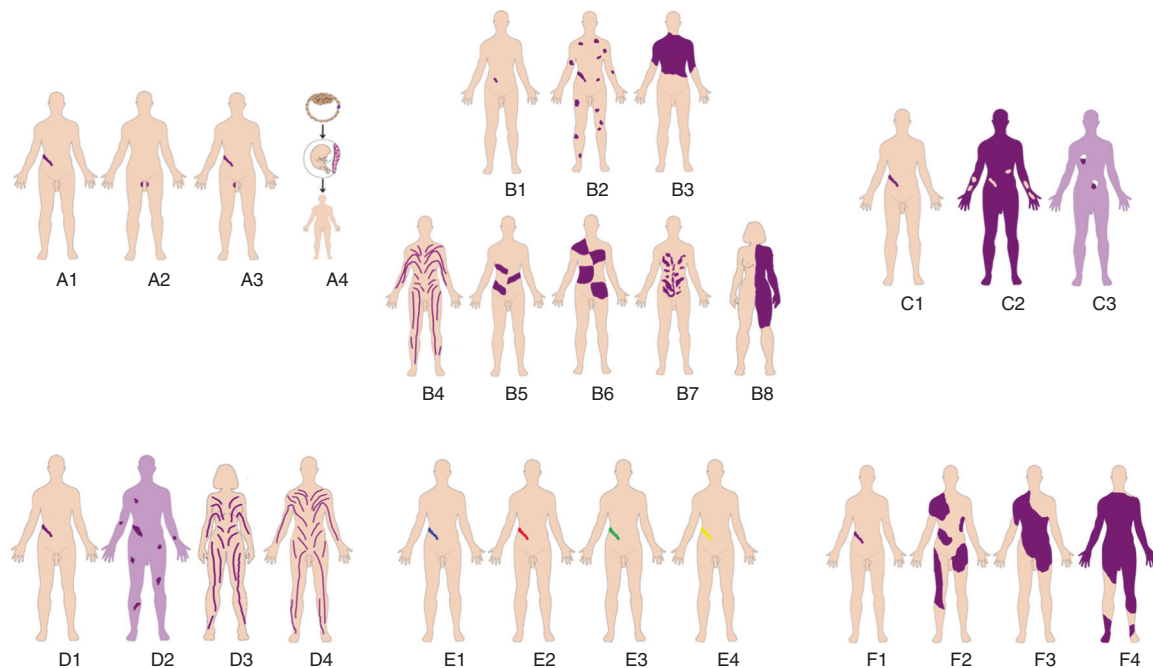
Fig. 1 Summary of the six-attribute classification of genetic mosaicism. (**a**) Affected tissues. A1: somatic mosaicism. A2: Germinal (gonadal) mosaicism. A3: Gonadosomatic mosaicism. A4: Confined placental mosaicism. (**b**) Body patterns. B1–B3 are nonsegmented mosaicism. B1: single point mosaicism. B2: disseminated mosaicism. B3: Patchy mosaicism without midline separation. B4–B8 are segmental mosaicism. B4: Blaschko lines in narrow bands. B5: Blaschko lines in broad bands. B6: Checkerboard. B7: Phylloid. B8: Lateralization/half body. (**c**) Change in direction. C1: From benign (wild type) to pathogenic. C2: From pathogenic to benign (wild type): revertant mosaicism. C3: Didymosis. (**d**) Developmental mechanism. D1: Type 1 segmental, heterozygous state. D2: Type 2 segmental reflecting loss of the corresponding wild-type allele. D3: functional X-chromosome mosaicism with or without lethality for males. D4: Disorders due to autosomal lethal mutations that manifest only as mosaics. (**e**) Etiology. E1: genomic changes. E2: genetic changes. E3: epigenetic changes. E4: positional effects. (**f**) Fraction of the affected tissue. F1: Mild involvement. F2: Moderate involvement. F3: Severe involvement. F4: Very severe (extreme) involvement (See also text and Supplementary. Fig. 1–6).

this category of mosaicism does not apply to the stromal, non–germ cell component of the gonads. This type of mosaicism is most often diagnosed at the birth of more than one affected offspring from an apparently unaffected but mosaic (in gonads) parent, and difficult to detect or suspect otherwise. Diagnosis requires analysis of sperm in males, which has proven utility for genetic counseling,[38,39] or ovarian biopsy in females, which is a more complex and invasive procedure. Further, the mutational event in this type of mosaicism may have occurred in the fetal period, but it is thought to arise more commonly in male germinal cells in adulthood[40] as it has been proven in some forms of craniosynostosis.[41,42] Germline mosaicism may be seen in several conditions that are typically inherited in an autosomal dominant or X-linked pattern but that occasionally manifest in a pattern that mimics and may be confused with autosomal recessive inheritance. The prototype of these disorders is osteogenesis imperfecta type II, a disease inherited in an autosomal dominant pattern, which was observed to have sibling recurrences with parents that were apparently unaffected. This was shown to be due to a mutational event occurring during gametogenesis in one of the parents: the subset of parental gametes affected will rarely have a phenotypic consequence in that parent but can be passed on constitutionally to multiple offspring[38,43,44] (Fig. S1). Other examples of gonadal mosaicism have been described in diseases inherited in an X-linked pattern (i.e., *GPC3*; Simpson–Golabi–Behmel syndrome) and in diseases inherited in an autosomal dominant pattern (i.e., *mTOR*; Smith–Kingsmore syndrome)[7,45] (Fig. 1).

A3. Gonadosomatic mosaicism (formerly gonosomal)

This implies mosaicism in both the germinal cells of the gonads and other extragerminal tissues. In some individuals with dermatologic disorders, gonadosomatic mosaicism can manifest this subtype of mosaicism with affected skin in the genital area or pelvis, but this is an exception, not a rule. Gonadosomatic mosaicism has been described in many genetic diseases with either autosomal dominant or X-linked recessive inheritance after the observation of two or more affected siblings with apparently unaffected parents.[38,46–48] In these situations, an analysis of father's sperm together with deep sequencing of DNA from blood may help to differentiate among true germinal and gonadosomatic mosaicism in that parent.[18,25] On the other hand, studies to look for gonadosomatic mosaicism have demonstrated that this type of mosaicism is more frequent than previously suspected. Deep sequencing in parents of patients with "apparently de novo" pathogenic variants in

diseases with autosomal dominant inheritance demonstrated that one of the parents was actually a low-level mosaic for the variant. Thus, about 0.5–8.3%, of these parents (tested in blood or saliva) had a low to moderate degree (VAF 2–29%) of gonadosomatic mosaicism for the pathogenic variant of his/her son/daughter usually (but not always) without any clinical feature of the given disease[49–54] (Fig. 1 and Fig. S1).

A4. Confined placental mosaicism (CPM)

This is designated when the mosaicism is restricted to placental tissues and does not affect the fetus/neonate. While most commonly used currently for chromosomal disorders, we have generalized these concepts to all variant types.

When mosaicism occurs in placental chorionic cells, it does not propagate to the embryo.[55] Mutational events that occur after placental determination are typically confined to the placenta.[56] This has implications for prenatal testing, especially in the case of chorionic villus sampling, in which the placenta is sampled. At 10–11 weeks of gestation and at the time when placental chorionic villi testing is usually done, about 1–2% of tests will demonstrate placental mosaicism. Nonetheless, confined placental mosaicism usually causes abnormalities in the fetus by two different mechanisms: (1) placental dysfunction caused by the genomic abnormality and (2) trisomy of the zygote, with chromosomal nondisjunction leading to trisomy rescue. If the resulting euploid cells go on to form the fetus, but a portion of the aneuploid cells form the placenta, then confined placental mosaicism will result. Owing to the trisomy rescue, the euploid fetus might have constitutional uniparental disomy (UPD), which may have disease implications if the affected chromosome(s) contain imprinted genes or recessive variants.[18] However, placental mosaicism can also occur for other aneuploidies, such as monosomy X, as well as in theory for any other genetic/genomic variant that could be rescued: by nondysjunction, somatic recombination, or other mechanisms. Type 2 confined placental mosaicism (mosaicism restricted to the mesenchymal core of the placenta) has no apparent effect on pregnancy outcome, although type 3 (CPM found in cytotrophoblast and mesenchymal core) is associated with low levels of first trimester serum pregnancy-associated plasma protein A, preterm birth, small for gestational age newborns, and adverse pregnancy outcomes.[32] Note that in the case of CPM (A4) there is no overlap with categories B, C, and D, which refer to patterns of mosaicism in the body but could potentially be categorized for E and F, which addresses the etiology and fraction of the tissue that is affected (see below).

Finally, there is the potential for placental and somatic (fetal) mosaicism: when mosaicism is present in placental tissues and also in the fetus/neonate, thus it is not confined to the placenta. Mutational events that precede placental determination may affect both the placenta and the fetus. In such cases, the fetus/neonate should be included in either category A1 or A3, depending on the presence of the

mosaicism in either the extragonadal tissues only, or in both the somatic and gonadal tissue, respectively.

B. Body pattern

The B of the classification refers to the body pattern. This is an attribute for which the extent and distribution patterns of mosaic clinical manifestations are classified, which is easier (or possible) to define when the skin is one of the organs affected by the consequences of the mosaic variant. We propose two major classes: nonsegmental and segmental mosaicism[25] (Fig. 1 and Fig. S2).

Nonsegmental patterns

The nonsegmental distributions are more common than the segmental.[25] The nonsegmental patterns include mosaicism confined to only one location of the body (single point), disseminated mosaicism, and patchy mosaicism without midline separation. This latter type of distribution has the peculiarity that it does not respect the midline and may be distributed in any part of the body irrespective of the body segments (Fig. 1, Fig. S2). The embryologic mechanism for this is unknown.

B1. Single point mosaicism

This type of mosaicism is recognized in the presence of lesions or abnormalities in a single location. Single hamartomatous lesions and some isolated malformations could be due to single point mosaicism. Most solitary benign tumors and malignant cancers in specific tissues or cells due to genetic/genomic anomalies also belong to this class,[25] which is the most common type of mosaicism. On the skin, benign and malignant tumors such as the solitary seborrheic keratoses, common melanocytic nevi, Spitz nevi, cylindromas, syringomas, trichoepitheliomas, pilomatricomas, basal cell carcinomas, squamous cell carcinomas, and melanomas may be observed as a single, mosaic lesion.[57–63] There is no consensus as to whether an affected individual who has two lesions of the same disease/tumor may still be classified as having single point mosaicism. When there are only two lesions, the differentiation between single point and disseminated mosaicism is difficult.[25] We here propose that when one lesion is observed the term single point mosaicism is used and with two or more the mosaicism should be designated as disseminated (Fig. 1, Fig. S2), though we recognize that this is arbitrary.

B2. Disseminated mosaicism

This refers to the presence of two or more lesions in the body, seen most commonly with the skin involvement of many genodermatoses (Fig. S2). All disorders that are inherited in an autosomal dominant pattern that are characterized by multiple tumors belong to this category. Examples include the hamartomas of tuberous sclerosis, cylindromatosis, leiomyomatosis, the café-au-lait macules of neurofibromatosis 1, and Legius syndrome.[64–70] Also belonging in this category would be early embryonic mosaicism for chromosomal or genetic

variants that could be detected in blood and other tissues. These mosaic chromosomal or DNA variants could lead to diffuse developmental or other disease manifestations due to multicellular or multiorganic dysfunction, such as dysmorphism, intellectual disability, autism, epilepsy, or other organ anomalies.[36,71,72]

B3. Patchy without midline separation
This is a pattern without midline separation (Fig. S2). Classical examples are large congenital melanocytic nevi, including giant melanocytic nevus. Most of these nevi are caused by postzygotic heterozygous *NRAS* variants.[73,74]

Segmental patterns
More rarely, cutaneous mosaicism can have a segmental distribution. The word "segmental" is an umbrella term to denote that a skin lesion involves one or more separate body areas, usually in an asymmetric configuration and respecting the midline. These segments likely reflect clonal expansion and body movements in the developing embryo, mechanisms that are, as of now, not fully understood.[25] So far, the formation of some skin segmental patterns, such as checkerboard and phylloid, remain poorly explained by standard embryologic mechanisms.

B4. Blaschko lines in narrow bands
This pattern follows the lines of Blaschko in narrow bands. This pattern is observed in several skin disorders inherited in an autosomal dominant pattern, such as Darier disease, Hailey–Hailey disease, or epidermolytic ichthyosis of Brocq.[28,75,76] This pattern is also observed in female carriers of heterozygous X-chromosome variants associated with skin manifestations, due to the mechanism of random X-chromosome inactivation described below (Fig. S2).

B5. Blaschko lines in broad bands
This pattern follows the lines of Blaschko in broad bands. We define "broad" as bands that are wider than 2 cm. Broad bands are less common than narrow bands.[25] The café-au-lait macules of McCune–Albright syndrome are a typical example.[28,77] Other less common examples are those observed in mosaic aneuploidies of autosomes.

B6. Checkerboard, block, or flag-like
In this segmental form of mosaicism, the skin lesions take the form of large squares, with a clear midline demarcation. When multiple, bilateral lesions in different areas appear, they resemble a checkerboard, blocks, or flag-like arrangement. It is seen in many disorders such as papular nevus spilus and macular nevus spilus and many vascular anomalies. This is also the pattern seen in individuals with phacomatosis melanorosea[78] (Fig. S2).

B7. Phylloid
This type is characterized by a leaf-like pattern of the skin lesions. For instance, phylloid hypomelanosis is characterized by congenital hypopigmented round, oval, or oblong macules resembling leaves or floral ornaments. These lesions have been linked to mosaic trisomy or tetrasomy 13q[52,79–81] (Fig. S2).

B8. Lateralization/half body
This highly unusual pattern is noted in female patients with CHILD syndrome (congenital hemidysplasia with ichthyosiform nevus and limb defects). Usually, the CHILD nevus shows a unilateral arrangement with a strict midline separation. Sometimes, the other side of the body may be involved by some Blaschko-linear lesions of the CHILD nevus.[28] The disorder is inherited in an X-linked dominant pattern and is a male-lethal trait. Sometimes it spares the face and head, but not always. This pattern (Fig. 1, Fig. S2) probably reflects the temporal interference of the mechanism of X inactivation with the outgrowth of organizer cells controlling the bilateral development of the skin and extracutaneous organs including the brain, bones, lung, and kidneys.[82] The asymmetric regional body overgrowth observed in many patients with Beckwith–Wiedemann syndrome and mosaicism at the genomic/genetic level may also be an example of this class.[83]

C. Change direction of the mutational event
C1. Healthy (normal) to pathogenic
In this case a wild-type cell changes to a mutant cell, meaning that the direction of change is from normal (no pathogenic variant) or benign to pathogenic variant. The great majority of affected individuals with postzygotic mosaicism in most tissues will have this direction of the mutational event (Fig. 1, Fig. S3).

C2. Pathogenic to normal (revertant mosaicism)
In this form of mosaicism, the direction of the change is from pathogenic to benign. In some way, this can be considered a "natural gene therapy",[25] a phenomenon relatively common in a small number of genetic skin diseases.[84] In other words, in affected individuals with generalized forms of a given disease, particularly in some dermatologic disorders typically inherited in an autosomal dominant or autosomal recessive pattern, the affected individuals may show one or more areas of healthy skin because some cells may genetically normalize, reverting the affected tissue to unaffected. Thus, cells with pathogenic variants coexist with cells in which the inherited variant was genetically corrected (reverted) by a spontaneous, mosaic mutational event.[30] They may result from diverse revertant molecular events such as reversion point mutational event, mitotic recombination, slipped-strand mispairing, mitotic gene conversion, or second-site mutations like base-pair addition, base-pair deletion, or a suppressor variant[85,86] (Fig. 1, Fig. S3).

Though it has been reported in liver and hematopoietic cells,[87,88] revertant mosaicism is most commonly recognized in skin, but it may happen in any tissue. Revertant mosaicism is also recognized in hematological disorders and used as a

prognostic factor.[88,89] Revertant mosaicism (Fig. 1, Fig. S3), with patches of normal skin, can be observed in a few diseases of skin such as ichthyosis with confetti (ichthyosis variegata), epidermolysis bullosa (dystrophic or junctional types, Kindler syndrome, and non-Herlitz junctional epidermolysis bullosa) In these, however, the rate of revertant mosaicism is strikingly high.[85,90–94] The revertant areas may have point mutational mosaicism as demonstrated in epidermolysis bullosa, or disseminated mosaicism as demonstrated in ichthyosis with confetti, or segmental mosaicism as reported in epidermolytic ichthyosis of Brocq.[84,86,95–101] In ichthyosis with confetti, reversion via loss of heterozygosity (LOH) is a recognized mechanism and, notably, the mitotic recombination events may be multiple and occur independently, each with different inferred start sites for LOH.[102] These LOH events take place less frequently when caused by a *KRT1* variant compared with those caused by *KRT10* variants.[25,90] Revertant mosaicism in nonskin diseases has been also reported in tyrosinemia type I, Fanconi anemia, and Wiskott–Aldrich syndrome, among others[87,103] (Fig. 1, Fig. S3).

C3. Didymosis (twin spotting)

Didymosis comprises paired patches of mutant tissues that differ genetically from each other and from the background tissue (Fig. 1, Fig. S3). It has been observed in an affected individual with cutis tricolor characterized by paired hypo- and hyperpigmented macules with double mutant aneuploidy mosaicisms (45,X/47,XX + 7).[104] Other possible examples are the paired linear areas of either excessive or absent involvement as noted in Darier disease and epidermolytic ichthyosis of Brocq[25,105] and the mixed vascular nevus syndrome reported in two patients.[106] Although it has not yet been demonstrated in humans, didymosis could be caused by mitotic recombination.[3]

D. Developmental mechanism

Classification of mosaic types based on their developmental mechanism is a well-known and widely used stratification method. For example, type 1 and type 2 segmental mosaicism can be caused by lethal autosomal mutations that can only survive as mosaics. This is also true for functional X-chromosome mosaicism with or without lethality in males. From a clinical point of view, it is very important to distinguish among these types[25] (Fig. 1, Fig. S4).

D1. Type 1 segmental mosaicism

This type originates from a postzygotic mutational event (usually a dominant nonlethal event) occurring in a single cell that was wild type for that specific locus, prior to the mutational event (Fig. 1, Fig. S4). This in turn means that the mutational change results in a heterozygous state of the variant that may also involve the gonads, which is why patients have an increased risk to have offspring with a nonsegmental form of the disorder. Examples of type 1 segmental mosaicism in pleiotropic disorders include segmental tuberous sclerosis, epidermolytic ichthyosis of

Brocq, neurofibromatosis type 1, and Darier disease.[75,76,107,108] In several dermatologic disorders such as epidermolytic ichthyosis of Brocq, Hailey–Hailey, and Darier disease, the postzygotic mutational event affects the keratinocytes while in other diseases such as tuberous sclerosis or neurofibromatosis type 1, the phenomenon may also affect extracutaneous organs (brain, eye, etc.).[28,109,110]

D2. Segmental mosaicism with an early second hit including type 2 segmental mosaicism of autosomal dominant traits

In contrast to type 1, type 2 segmental mosaicism manifests in traits where biallelic variants cause the mosaic phenotype. In this scenario, the individual is a constitutional heterozygote and undergoes a postzygotic mutational event occurring in the wild-type allele in *trans* to the inherited variant.[25,111] The phenotype and the degree of segmental involvement depend on the biology of the mutated gene. Therefore, there are two possible mechanisms. The first is mosaicism in autosomal recessively inherited conditions. In this case, heterozygotes have no clinically detectable phenotype and hence only the parts of the body with the second hit mosaic variant would be affected and the parts of the body without the second hit mosaic variant would not be affected. A recent example of this mechanism has been identified in a patient with ectodermal dysplasia–skin fragility syndrome[112] and in another with autosomal recessive congenital ichthyosis related to *ABCA12*.[113] Second, type 2 segmental mosaicism in autosomal dominantly inherited conditions. In this case heterozygotes have a clinically detectable phenotype and the parts of the body with the second hit mosaic variant would be more severely affected and the parts of the body without the second hit mosaic variant have the typical germline heterozygote phenotype. Clinical examples of this category of mosaicism have been described in more than 30 different skin disorders and in many of them the concept has already been proven at the molecular level.[25,28] This type of mosaicism is seen in Darier disease and Hailey–Hailey disease with superimposed segmental manifestations of the disorder.[114,115] Similarly, further examples are neurofibromatosis type 1, Legius syndrome, PTEN (phosphatase tensin homolog) hamartoma syndrome, and Gorlin syndrome[66,111,114–119] (Fig. 1, Fig. S4).

D3. Functional X-chromosome mosaicism with or without male lethality

Random postzygotic inactivation of one of the X chromosomes occurs in every female embryo, giving rise to functional X-chromosome mosaicism (lyonization). In the case of diseases with X-linked inheritance, mosaic lesions may be observed in females with X-linked, male-lethal traits such as focal dermal hypoplasia or X-linked, nonlethal traits such as reticulate pigmentary disorder of Partington. Differential expression of *XIST* (X-inactive-specific transcript)[120] occurring at an early developmental stage results, in a female embryo, in mosaic patterns of either abnormal or healthy skin,

being mostly arranged along Blaschko's lines as noted in X-linked male-lethal traits such as incontinentia pigmenti, focal dermal hypoplasia (Goltz–Gorlin syndrome), Conradi–Hünermann–Happle syndrome and oculofaciocardiodental syndrome.[25] Similarly, mosaic skin manifestations can be seen in female carriers of nonlethal diseases (Börjeson–Forssman–Lehman syndrome, and IFAP (ichthyosis follicularis, atrichia, and photophobia) syndrome, Christ–Siemens–Touraine syndrome, X-linked dyskeratosis congenita, X-linked generalized hypertrichosis, and of the male-sublethal Menkes syndrome (Fig. 1, Fig. S4).

D4. Type 4a. Disorders that manifest only as mosaics (D4a: autosomal)

Some multisystem congenital anomalies that have a monogenic basis are never vertically transmitted because the underlying variant, when present in all cells of the embryo, is lethal, resulting in early intrauterine death.[25] Thus, the most deleterious variants that are not compatible with embryonic development are only recognized clinically as postzygotic mosaics and not as heritable traits.[121] The existence of this mechanism is based on the observations that there are no familial occurrences, and all affected individuals present cutaneous symptoms only in a segmental pattern.[122] Furthermore these disorders have also been seen in discordant monozygotic twin pairs, attributed to a mutational event in somatic cells of one twin but not in the parental germline or in the shared embryo pretwinning (alternatively, the variant could have a sufficiently lower VAF or be present in noncritical cells in the apparently unaffected twin). In these traits, the mutant cell clone can only survive in a mosaic state, that is, in an admixture with normal cells. The prototype of this class of disorders is the McCune–Albright syndrome,[77,123] due to mosaic GOF variants in *GNAS1*. Other examples include Proteus syndrome, Schimmelpenning–Feuerstein–Mims syndrome, and many others associated with GOF variants. This picture is complicated by the allelic heterogeneity of some of these genes. An example of this is PROS (the *PIK3CA*-related overgrowth spectrum),[124] a continuous spectrum caused by GOF variants in *PIK3CA* that may manifest as isolated alterations such as isolated macrodactyly or as syndromic disorder as in MCAP (megalencephaly–capillary malformation–polymicrogyria syndrome). Pathogenic variants in PROS associated with a higher function gain appear to be lethal in the nonmosaic (constitutional) state, and only in the case of MCAP the pathogenic variants have been detected, in addition to the clinically affected tissues, in blood samples in the form of low mosaics. As expected, MCAP is located at the most severe end of the PROS spectrum. In some cancers, there are germline pathogenic variants that are observed almost exclusively in the mosaic state. Mosaic germline *PPM1D* protein truncating variants leading to GOF of this gene are associated with predisposition to breast and ovarian cancer.[125,126] Similarly, pathogenic mosaic variants of *TET2*, *ASXL1*, and *DNMT3A* are associated with hematologic cancers.[127,128] Finally, there are also several chromosomal syndromes that are only seen in a mosaic form, including Pallister–Killian syndrome and trisomies for several distinct chromosomes, such as 8, 9, and 14 ref. [18] (Fig. 1, Fig. S4).

Type 4b. Disorders that manifest only as mosaics (D4b: X-linked)

The model in this category is early onset epileptic encephalopathy type 9 with intellectual impairment. Pathogenic germline variants in the *PCDH19* gene only affect females while hemizygous males are unaffected and transmit the disease to all their daughters.[129] However, males with somatic variants are affected.[130] Therefore, the condition is underpinned by cellular mosaicism due to X-chromosome inactivation in heterozygous females or postzygotic pathogenic variant in hemizygous males (Fig. 1, Fig. S4).

E. Etiology

Mosaicism arises as a result of genetic alterations of distinct types and sizes, ranging from epigenetic alterations of single nucleotides, to single-nucleotide variants (SNVs), to copy-number variants (CNVs), to simple or complex chromosomal rearrangements (Fig. 1, Fig. S5). Moreover, in the past few years, large-scale analyses have shown many mutational patterns across the spectrum of human cancer types. Different mutational processes generate unique combinations of mutation types, termed "mutational signatures." The molecular mechanisms underlying these etiologies together with the size of the variants are shown in Fig. 2.

E1. Genomic variants

Mosaicisms included in this group are due to genomic aberrations, namely (1) large losses or gains (>100 Mb) of chromosomes, including ploidy, that are usually visible under the light microscope (e.g., Down syndrome); (2) medium-size (4–100 Mb) losses or gains of part of chromosomes, normally deletions and duplications visible under the light microscope (e.g., Wolf–Hirschhorn syndrome); (3) losses or gains of small parts of a chromosome (0.1–4 Mb), detected by high sensitivity cytomolecular techniques such as fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), or chromosome microarrays (e.g., Phelan–McDermid syndrome); (4) long interspersed nuclear elements (LINE or L1) retrotranspositions (1–100 Kb); (5) short interspersed nuclear elements (SINE or Alu element) retrotranspositions (100 bp–1 Kb) that can only be interrogated with molecular techniques; and (6) copy-neutral genomic variants, including whole chromosome, genomic inversions, and segmental uniparental disomies of nonimprinting regions without epigenetic consequences. Currently, structural multimegabase mosaic rearrangements are mainly detected by array technologies.[18,131] Both comparative genomic hybridization (CGH) and single-nucleotide polymorphism (SNP) microarrays are
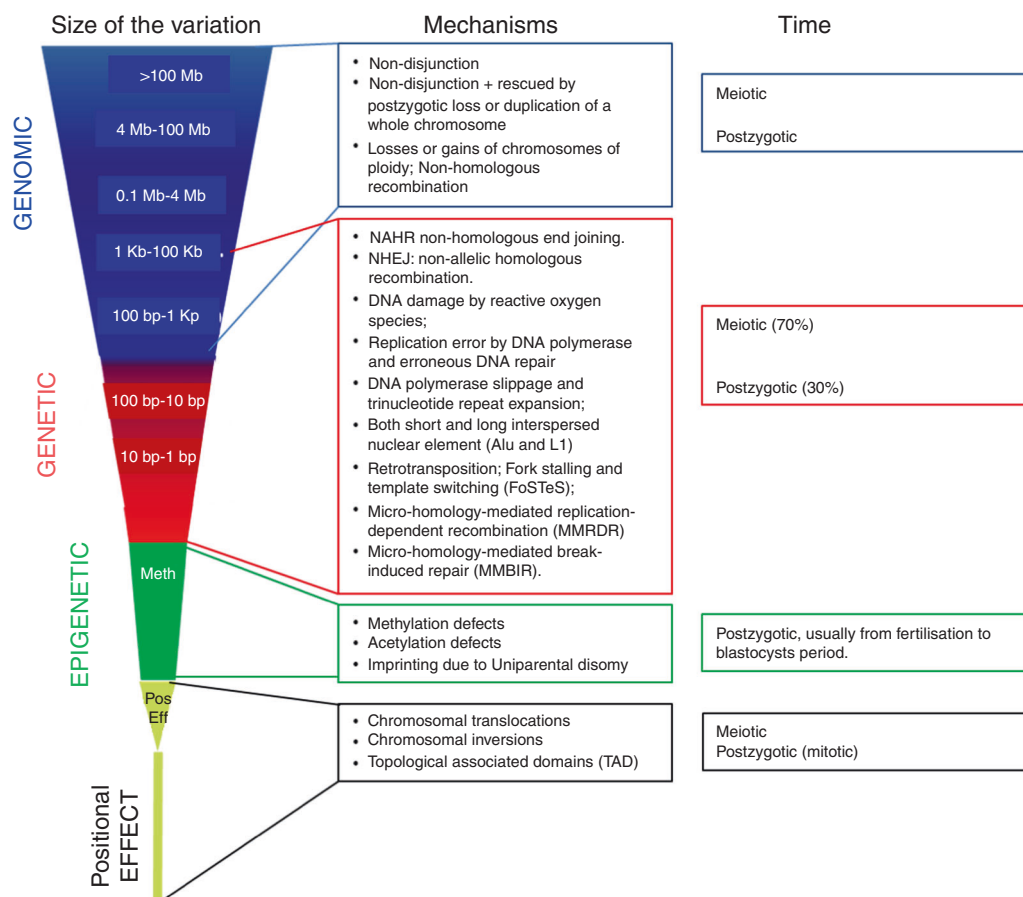
Fig. 2 Scaled classes of variants (depending on the size of the variant, mechanism, and timing of the event). There are numerous endogenous molecular mechanisms that generate postzygotic somatic variants causing mosaicism during the lifetime of an individual, whereas others (such as Alu and L1 retrotransposition) are likely to have specific temporal patterns.[1,37] The main genomic and epigenetic mechanisms are: 1) DNA damage by reactive oxygen species; 2) replication error by DNA polymerase and erroneous DNA repair; 3) DNA polymerase slippage and trinucleotide repeat expansion; 4) both short and long interspersed nuclear element (Alu and L1) retrotransposition; 5) fork stalling and template switching (FoSTeS); 6) nonhomologous end joining (NHEJ); 7) nonallelic homologous recombination (NAHR); 8) microhomology-mediated replication-dependent recombination (MMRDR); 9) microhomology-mediated break-induced repair (MMBIR); and 10) losses or gains of chromosomes of ploidy, as reviewed in detail in[1] (See also Table S1). Exogenous factors such as tobacco and alcohol usage, and ultraviolet (UV) exposure may also be involved in postzygotic somatic mutational events.[37] We have divided these into four categories but recognize that the spectrum of variation is continuous, from a single-nucleotide change to a diploid genome.

capable of identifying large aberrations. Additionally, SNP arrays are also able to detect copy-neutral losses, gains, and mosaics.[13,132,133] Both CGH and SNP microarrays are capable of identifying mosaic aberrations present in 4–8% (SNPs) to 10% (CGH) of the cells.[134–136]

Mosaic structural variations are seen in about 1:200 to 1:400 children investigated for clinical diagnostic testing (Fig. 1, Fig. S5).[137]

E2. Small nucleotide variants (SNV)
These mosaicisms represent relatively small changes and variations, mostly at the single-nucleotide level. The most common variants observed in this group are DNA polymerase slippage and trinucleotide repeat expansions affecting a short segment of DNA (10–100 bp) and SNV and indels, single-nucleotide deletions, and insertions due to DNA damage, replication errors, and erroneous DNA repair mechanisms (Fig. 2, Table S1). Pathogenic mosaic variants at low VAF have

been reported in many genes such as *MFN2*, *PAFAH1B1*, *CATA1*, *GATA6*, *SCN1A*, *SLC1A2*, and *CACNA1A*, among others,[138] not only in affected individuals but also in apparently unaffected parents of affected individuals in what has incorrectly been assumed to be de novo mutational events.

E3. Epigenetic changes
Epigenetic mosaics reflect the action of "epimutations" that, by methylation or demethylation of nearby regulatory regions, give rise to alternate monoallelic expression.[139] The mosaic paternal UPD, comprising total or partial UPD of the short arm of chromosome 11 observed in Beckwith–Wiedemann syndrome is due to an imbalance among imprinted genes that complementarily promote or restrict growth.[83,140] Similarly, epigenetic mechanisms involved in functional mosaicism by X-chromosome inactivation (lyonization) are included in this class (Fig. 2, Table S1).

E4. Positional effect variant

This etiology is due to mechanisms that do not result in losses or gains but to disruptions of gene(s) or regulatory elements secondary to translocation, inversions, or alterations of topological domains (Fig. 2, Table S1). An example in oncology is the mosaic Philadelphia chromosome in leukemia cells due to the reciprocal translocation t(9;22)(q34;q11) that creates the fusion gene *BCR-ABL1*. This gene encodes for a hybrid protein (a tyrosine kinase signaling protein) that leads the cell to divide uncontrollably by interrupting the stability of the genome and impairing various signaling pathways governing the cell cycle.[141] Positional effects are an uncommon etiology of skin mosaicisms, though some linear hypo or hyperpigmented lesions in skin are due to this mechanism.[142–144]

F. Fraction of the tissue affected

This attribute evaluates the percentage of tissue(s) (skin, bone, CNS, neoplastic, etc.) involved (Fig. 1, Fig. S6). Using the skin as an example, we arbitrarily subdivided this item into four subcategories: F1: mild involvement, <10% of affected tissue (<5% VAF); F2: moderate involvement: 10–30% of the body (5–15% VAF); F3: severe involvement, 30–50% (VAF 15–25%) of involvement; and F4: very severe, >50% (>25% VAF) of involvement. The classification of the fraction of tissue affected has been designed for skin disorders, but could be theoretically applicable for other diseases such as vascular or bone diseases. The VAF can be used for quantification but it should be noted that molecular testing normally assesses variants, not cells. As noted above, since most genes are diploid, molecular assays report out the VAF, which is typically half the fraction of mutant cells. For dermatologic disorders, the fraction of affected tissue can only be determined by quantification of the affected body surface area, because depth and volume quantification is virtually impossible. For other mosaic disorders in which there is a quantifiable anatomic or morphologic attribute, this anatomic feature with or without VAF may be used for quantitation. In the event of discordance between the percentage of affected tissue evaluated by clinical examination and the VAF, the priority should be given to the value of VAF over the percentage of affected tissue; this is arbitrarily valid only in order to be classified and included within this categorization.

DISCUSSION

There have been a number of classifications of mosaicism, many of which have evaluated several attributes of genetic (mainly pigmentary) mosaicism and have considered such attributes in a less systematic manner. We have compiled all these attributes and present them in a comprehensive and systematic classification (Fig. 1, Figs. S1–S6). In the fields of oncology and pathology, classification of tumors using letters and numbers is usual; e.g., the Tumor, Nodes and Metastasis (TNM) classification, which measures tumor size and extent, lymph node involvement, and metastasis.[145,146] This form of standardization helps scientists to communicate more clearly and objectively when describing a tumor. The TNM scheme is also useful in understanding the natural history, prognosis, follow-up, and potential therapies of tumors.

Genetic variants can arise at any cell division at any stage of development. Variants can be inherited, occur newly during meiosis as the germ cells are being formed, or during mitosis, after fertilization, either during development of the embryo/fetus or extrauterine life. Thus, the timing during development when a mutational event occurs as well as the cell type and specific location where the mutational events occur strongly influences the distribution and phenotypic consequences of the cells with the variation[56] (Fig. S7). If it occurs early in development, e.g., during the very first mitoses, theoretically a significant proportion of the body will harbor the variant, but this fact is not always biologically true. An example of the importance of mutation timing can be seen when one monozygotic twin has a genetic disorder and is mosaic for a pathogenic variant and the other twin is unaffected and has no detectable variant.[147–149]

It can be challenging to understand the basis of the variable expressivity of germline, constitutional disorders. The dimension of mosaicism adds even more complexity given that a human is comprised of on the order of 3.7^{13} cells and mosaicism has a wide range of involvement from just one cell to the vast majority of them, and everything in between. Furthermore, the variant cells are rarely (if ever) uniformly distributed within the individual. The distribution of cells bearing the pathogenic variant is probably not entirely random, as these pathogenic mosaic variants may have effects on the cell division, differentiation, migration, and longevity of the cell in which they reside. As a further confounding factor, some variants yield a phenotypic consequence that is not limited to the cell harboring the variant, but to many others, i.e., there may be non–cell autonomous effects.[150] Thus, the enormous and potentially continuous variation of random mutational events, in combination with the pathophysiologic effect of the variant, could be considered an impassable barrier to classification. Yet, clinicians must have a classification system to sort affected individuals into practical categories. These complexities and needs have led to several important efforts at classification starting with one of the simplest organs, the skin. While skin is functionally complex, the ready visibility of the phenotypes provides an enormous advantage for the recognition and study of the phenomenon of mosaicism. We have included some examples of patients as a sample of the use of this classification (Fig. 3 and Supplementary. Material).

The appropriate classification of mosaic disorders including determination of potential involvement of the germline is essential for the definition of transmission risks and accurate genetic counseling. Mosaicism quantification in paternal sperm DNA has been proposed as a tool to stratify recurrence risk in neurodevelopmental disorders caused by apparently de novo pathogenic changes. While most cases will have a negligible recurrence risk, some cases will have a higher and quantifiable risk. This suggests, therefore, that genetic risk
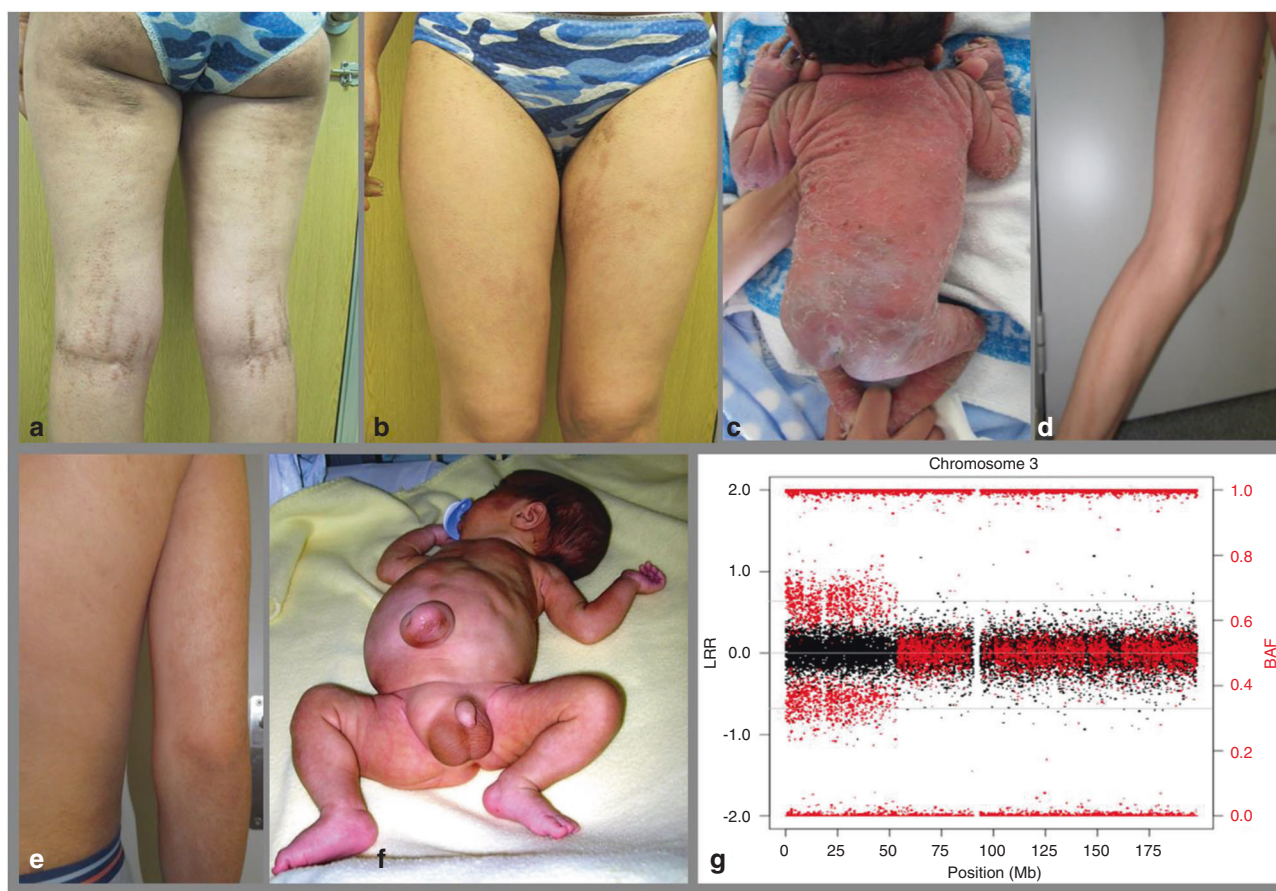
Fig. 3 Example of the use of the proposed classification. (**a**, **b**) Epidermolytic epidermal nevus following Blaschko's lines in a young woman and nonsegmental epidermolytic ichthyosis of Brocq in her son (**c**). The mosaicism in the mother can be designated as A3B4C1D1E2bF2: presumed to be gonadosomatic (A3), with a Blaschko pattern in narrow bands (B4), with a benign to pathogenic mutational direction of the variant (C1), type 1 postzygotic mechanism (heterozygous state) (D1), due to a genetic etiology (SNV in the gene KRT1) (E2b) and between 10% and 30% of the tissue (skin) involved (F2) (see Supplementary material). (**d**, **e**) Cutaneous mosaicism following the Blaschko lines in a young man. The pigmented lesions showed a trisomy 20 mosaicism (46,XY[24]/47,XY + 20[14]). The mosaicism in this young man can be designated as A1B4C1D1E1F1: a somatic mosaicism (A1), with a narrow lines of Blaschko pattern (B4), with a benign to pathogenic mutational direction of the variant (C1), type 1 postzygotic mechanism (heterozygous state) (D1), due to a genomic etiology (mosaic of chromosomes) (E1) and with mild involvement (<10%) of the tissue (skin) involved (F1) (see Supplementary material). (**f**) A patient with Beckwith–Wiedemann syndrome and mosaic paternal uniparental disomy of the short arm of chromosome 11. Lateralized asymmetric overgrowth of the right side of the body, mainly in the leg. The mosaicism in this child can be designated as A1B8C1D1E1fF3: a somatic mosaicism (A1), with a lateralization pattern (B8), with a healthy to pathogenic mutational direction of the variant (C1), a postzygotic mechanism (heterozygous state) (D1), due to an genomic etiology (mosaic of UPD of about 45 Mb) (E1f) and with moderate involvement (about 13%) of the tissue (the entire left leg) involved (F3) (see Supplementary material). (**g**) SNP array plot detecting mosaic UPD 3p in peripheral blood DNA of a patient with Fanconi anemia. The chromosome 3 plot shows normal dosage along the entire chromosome (black dots represent total intensity values –LRR: Log R Ratio–) and abnormal allelic dosage for the informative SNPs located in the distal 53 Mb of the p arm (red dots represent relative allelic values –BAF: B Allelic Frequency–). Mosaicism in this child with an autosomal recessive disorder and a rescue mosaic UPD can be designated as A1B0C2D1E1fF3: somatic mosaicism (A1), no pattern (B0), pathogenic to healthier (less pathogenic) mutational direction of the variant (C2), a postzygotic reversal mechanism (compound heterozygous to homozygous state) (D2), genomic etiology (UPD of 53 Mb) (E1f), involvement of about 33% (blood and buccal cells) (F3). (see Supplementary material).

assessment would benefit from the addition of sperm mosaicism assessment.[39]

The classification proposed herein has some limitations related to the lack of information with respect to other potentially important aspects of mosaicism. These include the chance to test only a small sample and not all cells of a specific tissue (i.e., in cancer or other tissues), the limitations of the diagnostic approach for every tissue, and the potential mosaicisms that may concur at other biological levels such as the transcriptomic, proteomic, or metabolomic, among others.

The clinical utility of this classification system and its potential utility to improve the management of affected individuals, refine our prognostic abilities, and improve clinical outcomes must be demonstrated in prospective studies. It is our hope that such a system will provide new insights into the molecular pathophysiology of mosaicism, which may be used for improved medical management, to refine genetic recurrence risk estimates, tailor therapies, and prevent the morbidity and mortality of disorders with mosaic states.

SUPPLEMENTARY INFORMATION

The online version of this article (https://doi.org/10.1038/s41436-020-0877-3) contains supplementary material, which is available to authorized users.

ETHICS STATEMENT

We obtained consent for including patients' photographs even though none of them show recognizable individuals.

DISCLOSURE

L.G.B. receives in-kind research support from ArQule Inc. (now wholly owned by Merck, Inc.) and is an uncompensated member of the Illumina Corp medical ethics board. L.A.P.-J. is founding partner and scientific advisor of qGenomics Laboratory SL. The other authors declare no conflicts of interest.

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