Review Article

Disorders Caused by Genetic Mosaicism

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Summary

Background: Genetic mosaics arise through new mutations occurring after fertilization (i.e., postzygotic mutations). Mosaics have been described in recent years as the cause of many different disorders; many of these are neurocutaneous diseases and syndromal developmental disorders, each with a characteristic phenotype. In some of these disorders, there is a genetic predisposition to the development of tumors. This article is intended as an overview of selected mosaic diseases.

Methods: This review is based on publications retrieved by a selective search in PubMed, with particular attention to recent articles in high-ranking journals dealing with asymmetric growth disturbances, focal brain malformations, mosaic diseases due to dysregulation of the RAS/RAF signaling pathway (mosaic RASopathies), and vascular malformations.

Results: The identification of postzygotic mutations has led to the reclassification of traditional disease entities and to a better understanding of their pathogenesis. Diagnosis is aided by modern next-generation sequencing (NGS) techniques that allow the detection even of low-grade mosaics. Many mosaic mutations are not detectable in blood, but only in the affected tissue, e.g., the skin. Genetic mosaic diseases often manifest themselves in the skin and brain, and by facial dysmorphism, asymmetrical growth disturbances, and vascular malformations.

Conclusion: The possibility of a mosaic disease should be kept in mind in the diagnostic evaluation of patients with asymmetrical growth disturbances, focal neuronal migration disturbances, vascular malformations, and linear skin abnormalities. The demonstration of a postzygotic mutation often affords relief to the parents of an affected child, since this means that there is no increased risk for recurrence of the same disorder in future children. Correct classification is important, as molecular treatment approaches are already available for certain mosaic diseases, e.g., *PIK3CA*-related overgrowth spectrum (PROS) disorder.

Cite this as:

Moog U, Felbor U, Has C, Zirn B: Disorders caused by genetic mosaicism. *Dtsch Arztebl Int* 2020; 117: 119–25. DOI: 10.3238/arztebl.2020.0119

In genetic disorders, the genetic mutation responsible for the disorder is usually present in all body cells. In contrast, when not all body cells have the same genetic make-up and a pathogenic mutation is found in some of the cells, one speaks of mosaic status. Disorders caused by genetic mosaicism, such as postzygotic chromosomal maldistribution, have long been known. Mosaic trisomy 21 was described as early on as 1961 (1). In principle, any monogenic disorder can also occur in mosaic form, in which case it is associated with a milder or atypical course compared to mutations that affect all body cells.

New methods of genome analysis, in particular the high-throughput next generation sequencing (NGS) method introduced in 2005, have greatly advanced the detection of mosaicism and thus our understanding of mosaic disorders (2). Pioneering work has been done on disorders that appear to occur only in mosaic form. These are caused by mutations in central signaling pathways that would be fatal if present on a constitutional level (in all cells) (3, 4). These disorders often manifest clinically as partial overgrowth, focal brain malformations, cutaneous symptoms, and vascular malformations. Each clinical picture is in itself rare, but together these disorders form a growing group of identifiable clinical pictures displaying characteristic abnormalities (5–8). A predisposition to cancer is not uncommon.

While it may be therapeutically relevant to detect a mosaic disorder, this requires concrete suspicion and the selection of the appropriate method for genetic diagnosis, since detection in blood is rarely successful. Without claiming to be exhaustive, this article provides an overview of disorders caused by genetic mosaicism and illustrates when a mosaic disorder should be considered. A selection of clinical pictures are presented and the diagnostic procedure discussed.

Methods

The presentation of the disease groups, as well as the selection of the entities described, is based on our expert opinion. We conducted a selective literature search in PubMed for the following terms combined with the term “genetic” in each case: “focal cortical dysplasia” (90 hits), “hemimegalencephaly” (29 hits), “mosaic RASopathy” (4 hits), “*PIK3CA* related overgrowth spectrum” (10 hits), AND “review” with each of these four keywords; “port-wine stain” AND “Sturge Weber syndrome” (7 hits), “capillary malformation-arteriovenous malformation (CM-AVM)” AND “vascular” (43 hits), AND “mutation” with both of these search strings. Following correction for redundancies, a total of 184 references were taken into consideration.

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FIGURE 1

Schematic representation of types of mosaicism. Each square represents an individual. The ellipses represent individual cells. White denotes normal alleles. Light blue denotes heterozygosity for a mutated allele; dark blue represents the occurrence of a second mutation event in an individual with a heterozygous mutation and an autosomal-dominant disorder (modified from [7]).

Genetic mosaicism

Mosaics are formed by spontaneous new mutations mostly during early embryonic or fetal development (9). Therefore, these are not inherited mutations that were already present in the egg or sperm, but are instead postzygotic events, i.e., occurring after fertilization. The information that a genetic mutation is postzygotic is important for the parents of an affected child, since this means that there is no increased risk for recurrence of the same disorder in future children. For its part, the child can only pass on the mutation to the next generation if its germ cells (egg or sperm cells) are affected by the mosaic. However, if the mutation is passed on, the offspring are not affected by mosaicism, but rather a constitutional mutation.

The severity and clinical symptoms of postzygotic mosaicism depend on the time of the mutation event, the type of cell in which the mutation takes place, the expansion of cells with mutations, the mutated gene, and the mutation (3). The later mosaics occur during embryonic development, the milder the symptoms. For example, certain types of nevi are caused by local mosaicism in skin cells (10, 11).

Mosaicism can be classified as follows:

- Mosaicism for lethal mutations causes clinical pictures that exist only in mosaic form, such as Proteus, Sturge–Weber, or McCune–Albright syndromes (12). Thus, these disorders cannot be passed on by affected individuals to their children, since, in the case of inheritance, the mutation would be constitutionally present and lethal.
- Mosaicism for mutations known in autosomal-dominant disorders. Depending on the time of the mutation event, these mosaics occur either in a disseminated manner (*Figure 1*), in which case they cause atypical or attenuated forms of a clinical picture, or localized in the form of segmental mosaicism type 1 (*Figure 1*) with generally milder effects (4). Examples include segmental neurofibromatosis type 1 (NF1) or mosaic forms of tuberous sclerosis (13, 14).

- Rare mosaicism that causes aggravation of the phenotype in a segmental area due to a second mutation event on the other allele (usually loss of heterozygosity) in autosomal-dominant inherited disorders (segmental mosaic type 2) (*Figure 1*) (4, 12).

Indications of mosaic disorders can include visible, persistent skin lesions distributed in an isolated, disseminated, segmental, or linear pattern. The lines of Blaschko, a system of lines in the skin corresponding to cell migration during embryogenesis, represent the most frequent distribution pattern of postzygotic mosaicism (e1, e2). For example, pigmentary mosaicism in chromosome disorders, as well as isolated or syndromic epidermal nevi (*Figure 2*), may follow the lines of Blaschko.

The skin is a frequent manifestation site for mosaics. Cutaneous lesions are readily accessible and, as such, can be used for diagnostic purposes. A number of the mosaic disorders discussed below are also associated with skin lesions.

Asymmetric growth disorders

Asymmetric growth disorders can be caused by activating (gain-of-function) mosaic mutations in genes that lead to increased cell division, and thus increased tissue growth, and affect the P13K/AKT signaling pathway (*Figure 3*; 7, 15). The *PIK3CA* gene in particular (at the top of the signaling cascade) is often affected by mosaic mutations and causes a highly variable phenotypic manifestation depending on which cells and tissue are affected.

In 2012, *PIK3CA* mutations were described as causal in a number of previously clinically defined phenotypes (16). *PIK3CA*-related overgrowth spectrum (PROS) has become established as an umbrella term (6, 17). This entity includes megalencephaly-capillary malformation-polymicrogyria (MCAP) syndrome (*Figure 4*), in which the asymmetric growth disorder is generally present from birth and continues to progress over the course of childhood. Affected

children often exhibit macrocephaly and capillary vascular malformation (port-wine stain or nevus flammeus), as well as marbled skin. Hemimegalencephaly, asymmetric hydrocephalus, and variable gyration disorders, in particular polymicrogyria, may also be present. This also explains the risk for generally difficult-to-treat epilepsy and impaired development or reduced intelligence.

It is usually not possible to detect mosaic *PIK3CA* mutations in blood, but only in DNA from affected tissue. Skin biopsies are particularly suited to this end. Constitutional *PIK3CA* mutations that affect all cells (non-mosaicism) are present in only around 10% of cases. In such cases, the growth disorder is not asymmetric (e3). It is likely that most constitutional *PIK3CA* mutations are severe and lethal.

Proteus syndrome is an example of an asymmetric growth disorder that manifests only over the course of childhood. At the age of 2–4 years, individual areas of the body, for example, toes or an entire extremity, begin to grow excessively. Particularly on the soles of the feet, a cerebriform nevus with tissue overgrowth may appear, the surface of which resembles the furrows of the brain. Severe impairments due to the mosaicism-related overgrowth often appear on the entire body in the further course. Intelligence is typically normal. Proteus syndrome is caused by a specific mosaic mutation in the *AKT1* gene (18).

The PI3K/AKT signaling pathway also includes genes in which loss-of-function (LOF) mutations (loss of function and “brake” failure) cause cell overgrowth (for example, *PTEN*, *TSC1/2*, Figure 3). LOF mutations in these genes are more often constitutionally present on an allele as a heritable germline mutation. Disease-specific lesions only develop when the second allele loses its function due to a somatic, locally confined mutation (Knudson’s two-hit hypothesis).

Focal brain malformations

Postzygotic mutations in the PI3K/AKT signaling pathway genes are associated not only with brain malformations in MCAP syndrome, but can also cause asymmetric “overgrowth” of brain tissue, either in isolation or as part of other clinical pictures, in particular hemimegalencephaly (HME) and abnormal focal neuronal migration, focal cortical dysplasia (FCD) (19). These two disorders are on a spectrum of cerebral malformation, the manifestations of which depend on the time at which the postzygotic mutation occurs and on the neuronal precursor cells it affects (8, 20). They are also frequently associated with treatment-refractory focal epilepsy in childhood. Postzygotic mutations are suspected in up to 30% of patients with neuronal migration disorders (8, e4).

FCD and HME are important indications for epilepsy surgery in children (21). Genetic studies on affected brain tissue have demonstrated activating mutations in *MTOR* and its activators (Figure 3, for example *PIK3CA*) in FCD type 2/HME, as well as

Figure 2: Mosaic RASopathy due to a mosaic *KRAS* mutation in a 21-year-old woman with linear hyperpigmentation and sebaceous nevi primarily on the left side of the body. The patient also exhibited a smaller left leg, scoliosis, a hairless fatty tissue nevus involving the scalp (nevus psiloliparus), and fibrous dysplasia of the left femur (not shown). The mutation was detectable in DNA from affected scalp tissue, but not in blood DNA.

LOF mutations—which can also be present as germline mutations—in a number of negative regulators of the signaling pathway (8, 19, 21). In FCD type 1, on the other hand, postzygotic variants are present in a glycosylation gene in around 30% of cases (*SLC35A2*) (21). The mosaic mutations can generally only be detected in affected tissue—in FCD often to a low degree, while in HME in up to 30% (8, 21).

Mosaic RASopathies

RASopathies refer to a group of diseases including the Noonan syndrome that are based on dysregulation of the RAS/RAF signaling pathway due to mostly activating, constitutional mutations in the genes involved. Clinical features they share in common include:

- Cardiovascular anomalies
- Short stature
- Dysmorphism
- Skin abnormalities
- Developmental disorders of varying severity.

A cancer predisposition is present in some cases (22). Like the PI3K/AKT signaling pathway, to which it is linked, the RAS/RAF signaling pathway stimulates cell growth and is mediated by the RAS protein after the binding of growth factors to receptors on the cell surface (Figure 3). The classical RAS proteins are encoded for by the *HRAS*, *KRAS*, and *NRAS* genes. Somatic mutations in these genes, which occur spontaneously in isolated cells and lead to clonal expansion due to a growth advantage, play a widespread role in oncogenesis (23).

Mosaic RASopathies have a different phenotype to the constitutional RASopathies, being based on postzygotic gain-of-function mutations in *RAS/RAF* genes, which would presumably be lethal if they were constitutional (5, 22). *HRAS* mutations represent an exception. Mutations are generally only detected in affected tissue. Neurocutaneous melanosis affects a

FIGURE 3

PI3K/AKT and RAS/RAF signaling pathways with main genes involved.

Following binding of a growth factor to the corresponding receptor, for example, receptor tyrosine kinase (RTK), insulin growth factor 1 receptor (IGF-1R), both signal pathways are activated. There is also interaction (crosstalk) between several subsequently activated genes. The PI3K/AKT signaling pathway (left) results in increased cell division and angiogenesis. The *PIK3CA* gene encodes for a catalytic subunit (p110 α) of phosphatidylinositol-3-kinase (PI3K). *PIK3CA* mutations (usually present in mosaic form) cause *PIK3CA*-related overgrowth spectrum (PROS). This includes megalencephaly capillary malformation (MCAP), hemimegalencephaly, fibroadipose overgrowth (FAO), and congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies (CLOVES). The protein kinase AKT activates mammalian target of rapamycin (mTOR), leading to increased cell division and tissue growth. Mosaic mutations in the *AKT1* gene are the cause of Proteus syndrome, while *MTOR* mutations are responsible for Smith–Kingsmore syndrome, as well as hemimegalencephaly and focal cortical dysplasia. Mutations in the above-mentioned genes are gain-of-function mutations. Antagonists of growth activation via the PI3K/AKT signaling cascade include *PTEN* (Cowden syndrome, macrocephaly/autism syndrome, Bannayan–Riley–Ruvalcaba syndrome), and tuberous sclerosis (*TSC1/2*); the loss of which also results in overgrowth due to loss-of-function mutations. These mutations are usually not present in mosaic form, but are instead constitutional mutations.

The RAS/RAF signaling pathway (right) regulates the cell cycle, cell differentiation, and apoptosis. Mutations in the involved genes result in what are referred to as RASopathies (Noonan syndrome: *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS*, *SHOC2*, *CBL* genes; Costello syndrome: *HRAS* gene; cardiofaciocutaneous (CFC) syndrome: *BRAF*, *MAP2K1/2*). Gain-of-function mutations are found in the above-mentioned genes. Neurofibromatosis type 1 (NF1) is a negative regulator of the RAS/RAF signaling pathway. As in syndromes associated with the PI3K/AKT signaling pathway, the phenotypic overlap is great (7, 15).

small proportion of patients with the common congenital melanocytic nevi (CMN) and is characterized by large (giant) CMN in combination with a frequently symptomatic leptomeningeal melanocytosis (24). It is caused by an early embryonic *NRAS* mutation in the neuroectoderm. The risk for melanoma depends on the extent of CMN and is around 1% in CMN in general compared to 12% in giant CMN (25). Neurocutaneous melanosis is also associated with an

increased risk for CNS melanoma. Locally confined postzygotic mutations in various genes lead to further nevi, for example, keratinocytic epidermal nevus and nevus sebaceous.

If the mutations occur early on in development and affect several tissues, one sees syndromic disorders with a particular, characteristic nevus (3). Worthy of note here is Schimmelpenning syndrome, which has been known clinically for decades and which can affect in particular the CNS, eyes, and bones (osteomalacia, hypophosphatemic rickets) (26), with mosaic mutations detected in *HRAS*, *KRAS*, and *NRAS* (10). Its identification as a mosaic disorder was able to explain the remarkable variability in clinical symptoms. Syndromes with congenital ocular and skin anomalies have also been identified as mosaic RASopathies: oculocutaneous syndrome (OES, *KRAS* mutations), the main features of which include epibulbar dermoids and congenital scalp defects (27, 28), and encephalocraniocutaneous lipomatosis (ECCL, *FGFR1* and *KRAS* mutations), in which the eponymous lipomas are also present in the CNS (29, 30). Both syndromes may exhibit further skin abnormalities, including nevus sebaceous. They also include a predisposition to odontogenic tumors, non-ossifying fibromas, and, in the case of ECCL, also low-grade gliomas (31). Since it is not always possible to conclusively apply previously used clinical diagnoses, the term (*KRAS*-associated) mosaic RASopathy is often more appropriate (Figure 2).

Vascular malformations

The diagnostic differentiation between isolated port-wine stain and sporadic Sturge–Weber syndrome (SWS) with facial nevus flammeus, as well as intracranial and intraocular vascular malformations, is of prognostic relevance. Leptomeningeal angiomas in SWS can cause epileptic seizures as early on as in the first year of life, affecting psychomotor and mental development. Other severe manifestations include stroke-like episodes and glaucoma.

From an etiological perspective, the common port-wine stain and the rare SWS are two extreme clinical manifestations of the same molecular mechanism. A specific postzygotic point mutation in the *GNAQ* gene that activates the RAS/RAF signaling pathway is identified in the malformed capillaries in the majority of cases in both disorders (32). It is likely that non-syndromic port-wine stains develop as a result of a late, and in the case of SWS an early, postzygotic mutation. Mutations in *RAS* and other genes involved in the RAS/RAF signaling pathway have also been identified in sporadic vascular malformations (33).

Pink capillary malformations affecting the skin combined with arteriovenous malformations in at least one other family member, occasionally accompanied by hemihyperplasia, form a clinically variable disorder (CM-AVM) that was only first described following identification of LOF variants in the *RASA1* gene (34). *RASA1* is a negative regulator of RAS;

Figure 4: MCAP syndrome due to mosaic *PIK3CA* mutation in a 5-month-old boy. Facial phenotype with marked asymmetry and overgrowth of the left cheek as well as cMRI showing pronounced left hemimegalencephaly. MCAP, megalencephaly-capillary malformation-polymicrogyria; MRI, magnetic resonance imaging

therefore, a loss of function also activates the RAS/RAF signal pathway.

Whereas SWS based on an activating point mutation in the *GNAQ* gene is seen only in mosaic form, *RASAI*-associated phenotypes can be inherited in an autosomal-dominant manner. In addition to the dominantly inherited mutation in a gene copy, a second, new mutation in the second gene copy can result in loss of function in the *RASAI* gene.

Molecular genetic diagnosis

High-level genetic mosaicism can be seen in classic Sanger sequencing as a second base that appears as an additional small peak on the chromatogram. However, NGS is able to diagnose and quantify mosaicism significantly more reliably. At high sequencing depths, even low-level mosaicism can be identified using this technique (35). In principle, NGS analysis can be performed on DNA from various sources (for example, blood, fibroblasts, urine sediment, brain tissue). DNA from fibroblasts is particularly suitable. A skin biopsy can be taken, for example, during other planned procedures. With regard to other special techniques, we refer the reader to an overview article published in 2018 (8).

Treatment

The PI3K/AKT signaling pathway is already the target of a number of treatment strategies and numerous drugs are under development. The primary aim here is the inhibition of mTOR, which mediates PIK3CA- and AKT-related overgrowth (for example, everolimus/sirolimus) (20, 36). Promising results for growth inhibition in

patients with PROS were recently obtained in a study on the oral PIK3CA-inhibitor BYL719, which achieved a significant reduction in the volume of lesional tissue (by 27.2 ± 14.6 and $37.8 \pm 16.3\%$ at 3 and 6 months, respectively, on radiological follow-up) and a marked improvement in quality of life (37). Treatment approaches in FCD/HME also include mTOR and PIK3CA inhibitors, as well as dietary measures in *SLC35A2*-related cases (21). Treatment with an AKT inhibitor has been reported in a female patient with Proteus syndrome and ovarian cancer (38).

MEK inhibitors in particular have been tested in individual cases of mosaic disorders of the RAS/RAF signaling pathway (25), while a combination of MEK and AKT inhibitors has been investigated in large CMN in the preclinical phase (39). The need for etiological classification would appear to be particularly urgent in mosaic RASopathies, since these are often characterized by a cancer predisposition. BRAF inhibitors are being investigated in animal models for the sporadic vascular malformations that can cause strokes, bleeding, and other complications (33).

Outlook

Postzygotic mutations have also been detected, particularly when re-analyzing exome data, in 3–9% of patients with developmental disorders without structural cerebral abnormalities, for example, autism or genetic epilepsy (8, 40). Due to methodological constraints, for example, insufficient sequencing depth, many mosaic disorders may currently still be evading detection. The inaccessibility of affected tissue can also limit the scope of molecular analysis of mosaicism. In the case

Key messages

- Asymmetric growth disorders combined with localized persistent skin lesions (for example, pigment spots, nevi), particularly along the Blaschko lines, and vascular malformations are clinically indicative of genetic mosaicism.
- The nosological differentiation of mosaic disorders is challenging. They are characterized by a broad phenotypic spectrum and a high degree of clinical variability.
- Mosaic disorders occur due to a new, postzygotic mutation in the affected individuals themselves and are not inherited. They can only be passed on by affected individuals to their children in the form of a constitutional mutation if the mutation is non-lethal and also affects the germline.
- Mosaicism is often not detectable in blood, but only in affected tissue.
- Treatment approaches are available in particular for genes involved in the PI3K/AKT and RAS/RAF signaling pathways.

of focal brain malformations, detection of a mosaic disorder is only possible if affected tissue can be obtained during surgery.

Numerous clinical pictures are currently undergoing molecular reclassification. This is important not only for our understanding, but also in terms of their possible inclusion in studies as well as for treatment. Moreover, the diagnostic differentiation between mosaicism and non-mosaicism makes it possible to estimate the recurrence risk within a family.

Conflict of interest statement

The authors state that they have no conflicts of interest.

Manuscript submitted on 23 April 2019, revised version accepted on 28 November 2019.

Translated from the original German by Christine Rye.

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Cite this as:

Moog U, Felber U, Has C, Zirn B: Disorders caused by genetic mosaicism. *Dtsch Arztebl Int* 2020; 117: 119–25. DOI: 10.3238/arztebl.2020.0119

► Supplementary material

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CLINICAL SNAPSHOT

Thrombophlebitis Migrans

A 90-year-old man presented with multiple acute, painful, palpable, planar, partly restiform areas of thrombophlebitis over his upper and lower arms. Within the previous 14 days no blood samples had been taken and no peripheral venous indwelling catheters had been inserted. A few weeks earlier, the patient had been diagnosed with hairy-cell leukemia (a low-malignant-potential B-cell non-Hodgkin lymphoma) and started on a course of cytostatic treatment with cladribine. On the basis of the patient's medical history and the characteristic clinical signs, we diagnosed thrombophlebitis migrans. This disease, also known as Trousseau syndrome, is a facultative paraneoplastic syndrome and thus may represent a sign of tumor disease. Etiologically, thrombophlebitis migrans probably arises from an intravascular coagulation caused by procoagulatory factors of the tumor disease. When confronted with an unusual presentation of thrombophlebitis without a readily identifiable cause, one should therefore always consider occult tumor disease as a possible cause. Besides anti-inflammatory drugs and compression treatment, coagulation inhibitors such as low-molecular heparins can be administered. In the case described here, treatment with the selective factor Xa inhibitor fondaparinux led to rapid healing of all the patient's lesions.

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Conflict of interest statement: The authors declare that no conflict of interest exists.

Translated from the original German by David Roseveare.

Cite this as: Koushk-Jalali B, Tigges C, Kreuter A: Thrombophlebitis migrans. *Dtsch Arztebl Int* 2020; 117: 125. DOI: 10.3238/arztebl.2020.0125

Supplementary material to:

Disorders Caused by Genetic Mosaicism

by Ute Moog, Ute Felbor, Cristina Has, and Birgit Zirn

Dtsch Arztebl Int 2020; 117: 119–25. DOI: 10.3238/arztebl.2020.0119

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