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# Mosaic abnormalities of the skin – review and guidelines from the European Reference Network for rare skin diseases (ERN-Skin)

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## Keywords

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## Abstract

Cutaneous mosaicism is an area of Dermatology in which there has been an explosion of knowledge within the current decade. This has led to fundamental changes in the understanding of the conditions in this field, and to an ongoing paradigm shift in the approach to management of mosaic skin disorders. In this consensus expert review as part of the European Reference Network project (ERN-Skin), we lay out the general principles of mosaicism as they are currently understood, summarise the known cutaneous mosaic abnormalities of the skin with associated phenotypic and genotypic information, review the latest trials on targeted therapies and propose guidelines for the general approach to a suspected mosaic patient.


## What is already known about this topic?

- Cutaneous mosaicism is a complex field of Dermatology which encompasses most birthmarks, and many rare syndromes
- Some cutaneous patterns are known to be seen in mosaicism
- Very few treatment options are available for most mosaic abnormalities of the skin
- Recent high sensitivity genetic techniques have led to an explosion of knowledge about genotype and phenotype in the literature

## What does this study add?

- Expert consensus from the European Reference Network ERN-Skin project
- Review of knowledge of the confirmed mosaic disorders, including cutaneous phenotype, extra-cutaneous associated features and genotype

- Proposed new classification of mosaic abnormalities of the skin by inheritance potential
- Practical tips on correct sample collection and genetic investigation for different mosaic abnormalities of the skin
- Review of trials of targeted therapies in mosaic disorders
- Guidelines for a practical clinical approach to the suspected mosaic patient

## Introduction

The field of cutaneous mosaicism effectively began with the systematic phenotypic observations of Blaschko in 1901[1], and the subsequent proposal that the observed patterns were due to the genetic mechanism of mosaicism by Jackson in 1976[2]. Certain fundamental concepts of cutaneous mosaicism were then elaborated and championed by Happle, in a series of key publications since the late 1970s[3-5]. In particular, the concept of lethal mutations surviving by mosaicism[3] has become axiomatic, and provides an explanation for why most mosaic disorders recognised in Dermatology appear to be sporadic. Over the same period of time, cohorts of patients with certain mosaic disorders have been studied, and disease-specific classifications for the cutaneous findings have been proposed. These have allowed some conclusions to be drawn about clinical management, by associating cutaneous features with outcome measures, and with extra-cutaneous features. In general, however, there is a lack of robust disease-specific guidelines for cutaneous mosaic disorders, compounded by the publishing bias towards more severe cases that frequently dogs the literature on rare diseases.

Molecular proof of mosaicism has been much slower to emerge, due to the technical limitations of detecting low level mutations. Two relatively early discoveries, the causes of McCune-Albright syndrome[6] and mosaic epidermolytic hyperkeratosis[7], came about by astute observation of the phenotypic similarity to germline conditions, and subsequent candidate gene sequencing. Otherwise, molecular causes remained elusive until the present decade, when the advent of more

sensitive methods of DNA sequencing has allowed more reliable candidate gene sequencing, and unbiased genome-wide screening.

The European Reference Network (https://ec.europa.eu/health/ern_en) is a European Union initiative to optimise management of patients with rare diseases. As part of the ERN-Skin project the field of mosaic cutaneous disorders has been highlighted as an area where guidelines for patient management are scarce, and new publications on genetic aetiology are appearing at a remarkable rate, making it difficult for practitioners to keep up to date with the latest knowledge. This document therefore serves as a review and consensus guideline for the general approach to the suspected mosaic patient, as is currently understood by an expert panel.

## Definition of mosaic abnormalities of the skin, and of mosaic disorders

Mosaicism has traditionally been defined as the coexistence of at least two genotypes in an individual derived from a single zygote, and this was considered to be an abnormal state. It has, however, become eminently clear that we are all mosaic by this definition, due to a strikingly-high but normal post-zygotic mutation rate *in utero*[8], and variable somatic mutation throughout life[9]. This definition therefore no longer delineates an abnormality. In addition, there is general consensus that small, single birthmarks are so common as to be part of the normal range rather than a disease phenotype. Therefore, we propose to define a mosaic abnormality of the skin as the coexistence of cells with at least two genotypes, at least one of which is pathological, by the time of birth, in an individual derived from a single zygote, and which leads to a disease phenotype[10]. The definition of a mosaic disorder proposed here, however, would only include truly mosaic phenotypes, rather than inherited disorders with a mosaic abnormality of the skin as part of the phenotype. In other words, it would not include the superimposed mosaic manifestations of autosomal dominant diseases, or revertant mosaicism (see below). A mosaic disorder could therefore be defined as the coexistence of cells with at least two genotypes, at least one of which is

pathogenic, by the time of birth, in an individual derived from a single zygote, where the post-zygotic mutation has led to the whole disease phenotype.

## Factors governing the phenotype of mosaic disorders

With genotypic diagnosis, many clinical diagnostic labels are now being found to be part of a disease spectrum[11,12]. This spectrum is, in general, far greater in mosaic disorders than in germline disorders, as there are many more variables which can affect the final phenotype. A summary of the main variables which alter the phenotype in mosaic disorders is shown in **Figure 1**. The first key variable is the timing of the mutation during embryogenesis. For example, it is now clear that the same mutation is responsible for single capillary malformations of the port wine stain type, as well as for Sturge-Weber syndrome[13], or for a single circular sebaceous naevus and Schimmelpenning syndrome[14]. The second key variable is the embryonic destiny of the cell which is hit by that mutation, elegantly demonstrated in Nature by entirely separate clinical entities produced by an identical genetic defect. For example, a mosaic *BRAF* p.V600E mutation can lead to linear synringocystadenoma papilliferum[15], or to an arteriovenous malformation[16], or to multiple congenital melanocytic naevi[17]. The timing and embryonic destiny are of course linked to some degree, and in general earlier mutations will produce a more severe phenotype and will be more likely to be associated with non-cutaneous features. Other factors which alter phenotype include the exact mutation, with clear phenotype-genotype associations demonstrated in some conditions[14,18,19], the background germline genotype[20], and of course the normal function of the gene. Lastly the pattern of gene expression is important in determining which organ systems develop clinically-important disease, and whether that expression is pre- or post-natal determines congenital and post-natal disease behaviour. For example, in Proteus syndrome the epidermal naevus and vascular malformations are frequently present at birth but are usually stable thereafter[21,22], in contrast to bony and soft tissue overgrowth which are usually not present at birth but progress dramatically in

the postnatal period[23,24]. This suggests that *AKT1* in keratinocytes, for example, is expressed both pre- and post-natally in a similar manner, whereas expression in bone is predominantly after birth.

## Classification of mosaic abnormalities of the skin by inheritance potential

Mosaicism has typically been divided in clinical genetics textbooks into three categories based on inheritance potential, namely somatic only, gonadal only, and both somatic and gonadal. Gonadal (germline) mosaicism is a key concept in genetic counselling to explain recurrence of autosomal dominant diseases in sibs from asymptomatic parents. Practically-speaking, however, it is only really possible to test whether a mutation has affected the gonads in an adult male patient[25,26], by sequencing sperm with high sensitivity techniques, and even then it is rarely done. Furthermore, it is only really of value if it is known that the mutation in question is non-lethal, as lethal mutations affecting the gonads could be passed on to the zygote but would lead to a miscarriage. More useful therefore is to divide mosaic abnormalities of the skin as defined above (and eventually individual causative mutations) into germline lethal, or germline heritable, on the basis of the literature. This broad but useful classification is included in the summary of mosaic disorders in **Table 1**.

It is worth mentioning that a truly mosaic disorder cannot be passed on as a mosaic disorder – they can only be passed on by a mutation being present in a gamete, and that a single-cell haploid gamete can only be either mutated or not mutated. If mutated it will give rise to a heterozygous zygote, and if not mutated it will give rise to a normal zygote. Thus, a mosaic disorder can only be passed on as a germline heterozygous condition, if at all. Where clinically it appears that a mosaic pattern condition is seen in successive generations (for example Blaschko-linear patterning), this is usually because the condition is in fact X-linked dominant with a germline mutation, and the mosaic pattern is due to the phenomenon of X inactivation. Well-known examples of this are incontinentia pigmenti and Goltz syndrome.

## Classification of mosaic abnormalities of the skin by genetic pathogenesis

The cause of mosaic abnormalities of the skin by the definition above is a genetic mutation arising *in utero*, whether or not the resultant abnormality is visible at the time of birth. The term mutation should be considered *sensu lato*, including various chromosomal anomalies, although their pathogenicity remains to be explained. An alternative method of classifying (and understanding) mosaic skin disorders is by the type of mutation which occurs *in utero*, in combination with knowledge of the inherited (germline) genotype of the individual (**Table 2**).

A schematic for visualising this proposed pathogenetic classification easily is laid out in **Figure 2**. Of note, these could be divided into types 1 to 3, but we have avoided a numeric classification so as not to be confused with previously proposed classifications of mosaicism. Firstly, in most cases of what we currently think of as mosaic disorders the germline genotype will be "normal" (with the caveat that not only is no germline normal, but there are almost certainly more important predisposing skin disease genes to be found), and the autosomal dominant post-zygotic mutation will lead to a mosaic disorder phenotype. This includes mutations which are either germline-lethal and therefore not passed on, and germline-heritable mutations with potential for passing on as a heterozygote. Secondly, the germline genotype can be of an autosomal dominant mutation, which leads to a recognisable syndrome or a clear phenotype that is not only restricted to the mosaic abnormality. In this case a second post-zygotic mutation leading to loss of the normal allele leads to a "superimposed" more severe mosaic phenotype. This phenomenon has been proven at molecular level for certain diseases including Hailey-Hailey[5], Darier[27], Cowden syndrome[28], and Gorlin syndrome[29]. Thirdly, there are conditions in which the germline genotype is of a single recessive mutation, which does not confer a clinical phenotype or a recognisable syndrome itself, but where a post-zygotic second recessive mutation will lead to a mosaic disorder phenotype. A recent first example of this at genetic level is ectodermal dysplasia skin fragility syndrome[30].

Theoretically a mosaic abnormality of the skin could also be generated by epigenetic alterations (other than the aforementioned X-inactivation due to methylation) however as this does not alter DNA genotype it would not fall within our here-proposed definition of a mosaic abnormality or disorder.

Lastly to be addressed there is the phenomenon of revertant mosaicism[31]. This is not by this definition a mosaic disorder, as it is in fact a phenomenon of phenotypic rescue within a pre-existing genetic skin disease. It can, however, also be understood in the same mechanistic way (**Figure 3**). It has so far been described on the background of an autosomal dominant germline, or an autosomal recessive germline. It can also occur theoretically occur on the background of a "normal germline", in the context of a mosaic disorder.

## Clinical assessment of the patient with a suspected mosaic disorder

### Is the clinical presentation suggestive of a mosaic disorder?

**Table 1** summarises the cutaneous mosaic disorders where molecular mosaicism has been confirmed in at least a proportion of cases. However, in many cases in clinical practice the clinical presentation does not fit with any known diagnostic group, or it may be atypical. Key features in the history and examination which are highly suggestive of a mosaic disorder in an undiagnosed patient are as follows:

1) Sporadic occurrence – no family history, even of a mild phenotype;
2) Congenital or early childhood onset;
3) Mosaic patterning on the skin - see below;
4) Variability/patchiness of the overall body phenotype – some areas affected, some not, which may involve asymmetry of body parts or of growth.

## Patterns of cutaneous mosaicism

Patterns of cutaneous mosaicism were originally inferred to be mosaic, before molecular confirmation was available. Blaschko's description of linear and whorled patterning is the most familiar image of cutaneous mosaicism[1], later extended to the head by Happle[32], however Blaschko also described some segmental patterns at that same time. Happle expanded and classified the mosaic cutaneous patterns into between 5 and 7 types[33], 6/7 of which have now been proven to be the result of at least one mosaic disorder (with the sash pattern being the only one outstanding at this time). These patterns are likely to continue to be useful for phenotyping and documentation in a clinical setting. Recent and ongoing interpretation of patterns from an embryonic staging viewpoint, however, is beginning to group these differently[34-37], which may allow better prediction of the chance of extra-cutaneous anomalies. In addition, other patterns can be seen in mosaic disorders, in particular multiple small round/ovoid pigmented lesions.

## Full clinical phenotyping and high resolution photography

It is important to document the clinical phenotype as precisely as possible, as it has become clear that this is pivotal in differentiating between diagnoses, and for directing appropriate genetic testing. It is important to extend this depth of clinical phenotyping to all body systems, as the presence of other features is usually unpredictable from the cutaneous phenotype. Phenotyping, at least at first visit, should therefore include a full history, and full examination. History for a child should include detailed family history, history of previous miscarriages from the parents, history of this pregnancy, weight and condition at birth, neurodevelopmental milestones and any concerns, and a general systems enquiry. Examination should include the whole skin, as very often more minor skin findings have not been noticed or not reported, as well as the neurological, respiratory, cardiovascular, and abdominal systems. As regards growth, height, weight and head circumference should be recorded, and any limb length or girth discrepancy measured.

For a few diseases, there have been classifications proposed on the basis of the cutaneous phenotype. The most recent versions of these are referenced here, which can be used for more accurate phenotyping for the following diseases: Proteus syndrome[23], congenital melanocytic naevi[38,39], *PIK3CA*-related overgrowth spectrum[40,41], facial port wine stains/Sturge-Weber syndrome[35,42] and phakomatosis pigmentovascularis[43].

While written descriptions are important, a full set of clinical photographs should also be taken, where possible in a professional hospital setting. These serve to document the overall patterning of the disease, and to get detailed close ups of subtle cutaneous features. Moreover, as new phenotypic features are increasingly being described, detailed photographs are invaluable in the revisiting or classification of difficult cases.

## Associated abnormalities in other organ systems

A summary of the commonest associated non-cutaneous abnormalities is included in **Table 1**. For a few confirmed mosaic disorders where reasonably large cohorts of patients have been studied, there is robust information on the nature and prevalence of the associated non-cutaneous features. In this category, we can include Proteus syndrome[23], Sturge-Weber syndrome[35,44-47], *PIK3CA*-related overgrowth spectrum disorders[40,41,48], phakomatosis pigmentovascularis (I, II, V, cesioflammea and cesiomarmorata types) and congenital melanocytic naevus syndrome[49-53], with the references given here as key recent publications in the relevant fields. Further work within these diagnoses is still required and ongoing, particularly with sub-stratification by genotype, as not all patients have the same causal genes. In all other proven mosaic disorders, cohort studies are lacking, and reporting of associated features is therefore subject to publication bias of the most severe cases. Nonetheless, these publications serve to delineate the spectrum of disease, and to some extent to identify the organs most commonly involved.

## Investigations

### Blood sampling for associated non-cutaneous complications

In general, in mosaic disorders there are very few blood tests which are useful. In patients with Schimmelpenning syndrome or the intimately-related condition phakomatosis pigmentokeratotica (or other unclassifiable or overlapping epidermal naevus syndromes due to *KRAS* or *HRAS* mosaicism) metabolic bone disease can be a serious feature. In these cases, blood (and urine) for serum calcium, phosphate, Vitamin D, and FGF23 should be checked at least once, and both monitored and treated if found to be abnormal. Individuals with extensive naevoid epidermolytic hyperkeratosis can also be lacking in Vitamin D[54] , as in other types of extensive ichthyoses, and this should be optimised, particularly if they are taking retinoids. In overgrowth syndromes such as CLOVES, Klippel-Trénaunay or Proteus syndrome, as well as venous, lymphatic, arterial, or complex vascular malformations[55-58], monitoring of clotting parameters including platelets, fibrinogen and D-dimers is recommended[59], particularly before any surgical or interventional radiology procedure, particularly in adolescents or young adults , or with an acute painful presentation.

### Histology

Skin histology may be useful in the diagnosis or subclassification of mosaic skin disorders. It can sometimes help in characterisation or differential diagnosis of certain epidermal naevi, for instance to look for epidermolysis (histological feature of naevoid epidermolytic hyperkeratosis), for alternating orthokeratosis and parakeratosis in ILVEN (inflammatory linear verrucous epidermal naevus) or to differentiate EN from linear porokeratosis (cornoid lamella), although these are not totally robust measures. It can be helpful in diagnosing naevus psiloliparus in encephalocraniocutaneous lipomatosis, and sometimes basaloid follicular hamartomas in Happle-Tinschaert/Curry-Jones syndrome. It can also be helpful for subclassification of complex vascular malformations, although the combination of radiology and genetic testing with histology is more

powerful than either one of these alone. It is usually diagnostic in the diagnosis of childhood vascular tumours, differentiating between congenital haemangioma, tufted haemangioma, and kaposiform haemangioendothelioma[60]. Routine histology is not usually needed for pigmented lesions – in melanocytic naevi the diagnosis is usually easily made clinically, and in fine and whorled Blaschko-linear hypo- or hyperpigmentation the histological findings are usually non-specific.

## Radiology/Imaging

Radiological or imaging investigations are strongly recommended in some mosaic disorders, where cohort data are available, and whenever monitoring can be seen to alter management. In Proteus syndrome, radiological monitoring of bone growth and organomegaly is part of recommended management[23,24], individuals with cranial hyperostosis may need investigation for meningioma development[61], and the high incidence of thrombotic complications requires a low threshold for imaging should this be suspected clinically[59]. Routine monitoring for tumour formation are not however recommended[23]. In the *PIK3CA*-related overgrowth spectrum (PROS), brain magnetic resonance imaging (MRI) is required to diagnose cortical malformation in macrocephaly-capillary malformation-polymicrogyria syndrome (MCAP), and radiological characterisation and monitoring may be required for overgrowth and vascular malformations (independent of the genetic diagnosis), in general dictated by the clinical symptomatology and the resultant need for intervention. Routine ultrasound monitoring for Wilms tumour has been recommended by some authors in proven cases of PROS[40,62], as in Beckwith-Wiedemann syndrome, However, the total number of cases reported is very low in PROS[62], and there is currently no concensus amongst experts as yet regarding repeated abdominal ultrasound screening.

Magnetic resonance imaging (MRI) of the CNS is recommended in infants with multiple congenital melanocytic naevi (CMN) and in those with new neurological symptoms at any stage, as the best prognostic indicator for adverse neurological outcomes and risk of melanoma[49,51]. Ophthalmological

assessment and MRI/angiography are recommended for infants with facial port wine stains affecting the forehead area or those who demonstrate neurological symptoms, to look for features of Sturge-Weber syndrome[35,47]. This also applies for those with a diagnosis of phakomatosis pigmentovascularis[63]. Doppler USS and/or MRI/MRA and/or angiography are frequently essential in the diagnosis, management and monitoring of vascular malformations and congenital childhood vascular tumours.

## Genetic testing

### Which genetic test to order – getting the sample to the right laboratory

Genetic investigation has been radically altered by the techniques of massively parallel sequencing also known as next generation sequencing (NGS), and whole genome copy number analysis. These are well-established techniques for germline mutations, which can be looked for from a standard blood sample. However, they have only recently come into clinical practice for mosaic mutations, and require a sample of affected tissue, for which a skin biopsy is usually the easiest. These new techniques have allowed the detection of mosaic mutations with much higher sensitivity, which is the first crucial factor in obtaining a genetic diagnosis. Results are expressed in percentage of mutant alleles (lower than 50% for heterozygous mutations), which merely reflects the proportion of affected cells in the tissue sample studied, not the extent of mosaicism in a patient's whole body. Current methods allow detection of mutant alleles as low as 1%, however traditionally all mosaic mutations have required validation by a second independent method before they can be confirmed diagnostically. This standard however is beginning to change, as NGS is so far superior to most other second methods. A summary of which type of genetic test to request for which type of mosaic abnormality of the skin is given in **Table 2**. Clinical utility of genetic testing in mosaic disorders remains to be carefully assessed, but it already has many implications. For a start, genetic diagnosis is usually beneficial for patients and families in coping with the disease. It is also increasingly important for genetic counselling, confirming that occurrence is sporadic, that the risk of recurrence

in siblings is low, and identifying whether there is a risk of transmission to the next generation in heterozygous form. Also, it may provide a rationale to consider innovative drugs specifically targeted at the molecular anomaly, which should ideally be evaluated in the context of a clinical trial.

If chromosomal level (as opposed to single gene) mosaicism is suspected, either a karyotype or fluorescent *in situ* hybridisation (FISH) may be required, which requires cultured cells from a fresh biopsy. This has historically been fibroblasts by default, however in certain specialist laboratories, culture of keratinocytes or melanocytes may be available. More recently, direct DNA extraction and comparative genomic hybridization (CGH) or SNP arrays have often been used for chromosomal mosaicism instead, however the data can be difficult to interpret. Very recently mosaic chromosomal mosaicism has been demonstrated robustly from NGS data (personal communication, Vabres P.), and it is highly likely that this will be the method of choice from now on where available.

### Sampling and testing the right tissue

The second crucial factor is to sample the right tissue, accessing the cells which actually carry the mutation. For example, culture and sequencing of fibroblasts from an area of affected skin will not reveal a mutation if the mutation was never in the fibroblasts but confined to the keratinocytes. In general, therefore, if it is not known with certainty which cell type is affected, a skin biopsy from affected skin should be taken in its entirety, and DNA extracted directly from the tissue. Only if it is already well-documented which cell type carries the mutation, such as melanocytes in the café-au-lait macules of mosaic NF1[64], or the same in McCune-Albright syndrome[65], should culture of a cell type be attempted before DNA extraction (specialist laboratories only). A 4mm punch biopsy is adequate to generate enough DNA for whole exome sequencing. The third crucial factor is that any skin biopsy for genetic testing must not be fixed in formalin. This renders genetic testing extremely difficult, or impossible, depending on the test. If DNA is to be extracted directly from the whole

biopsy, the fresh biopsy should be taken immediately to the genetics laboratory on saline-soaked gauze, or put into a small vial of solution which protects nucleic acids from degradation, such as RNAlater (Merck), or snap frozen in liquid nitrogen (with appropriate training).

DNA can be extracted if necessary from formalin-fixed paraffin-embedded (FFPE) tissue, however the fixation process is known to fragment the DNA and to lead to sequencing artefacts[66]. If, however, all that is required is sequencing for a known point mutation (for example the typical *NRAS* mutation in congenital melanocytic naevi), or for use on a targeted sequencing panel designed for FFPE, these tests can be done from archival FFPE tissue if necessary to avoid a further biopsy[16,48,67]. Whole exome sequencing for mosaic mutations in general is not recommended from FFPE DNA, although it is becoming more reliable.

Blood sampling for DNA extraction from leukocytes is recommended if taking a skin biopsy for genetic testing, as this can be either used as control DNA in conditions where the mutation is not detectable in the blood, or it can be tested for the mosaic mutation once it is identified in the skin. Blood sampling procedures should be as locally prescribed, however if in doubt, in general DNA can be extracted from any bottle used for a full blood count, containing EDTA, and will be stable either at room temperature or the fridge for several days if necessary.

## Management

### Multi-disciplinary team

Our recommendation is that patients with rare mosaic skin disorders should initially be seen in a specialist centre with access to a multi-disciplinary team. Initial presentation is often to a

Dermatologist or Paediatric Dermatologist, and if not, Dermatological advice should be sought for accurate clinical diagnosis. Once preliminary assessments and investigations have been carried out, follow up in local services may be appropriate, depending on the individual case. Re-assessment in the specialist centre, however, should be considered at regular intervals, as this field is changing rapidly, and new management options may come to light. Ideally the patient should be registered either locally or internationally in a rare diseases registry for the same reason, allowing contact with the patient to be re-established if, for example, relevant clinical trials of new therapies are begun.

## Malignancy risk in mosaic abnormalities of the skin

Overall the risk of malignancy in mosaic abnormalities of the skin is low. Management guidelines for malignancy exist for a few conditions.

For sebaceous naevi it is now well-documented that, in contrast with benign tumours (such as syringocystadenoma papilliferum) that frequently arise, malignant tumours are rare, and arise principally in adulthood[68-70]. Routine resection of sebaceous naevi for prevention of malignancy is therefore not advocated. For other *HRAS* and *KRAS* mosaics, many of these are individual cases, and not all fit into a clear diagnostic category. They do, however, definitely seem to carry a malignancy risk, but similar to sebaceous naevi and melanocytic naevi this is likely to be low at least in childhood.

For congenital melanocytic naevi it is well-documented that the absolute risk of melanoma in childhood is low[49,71,72], but that there is an approximately 10% risk in children who have complex congenital neurological abnormalities on screening MRI after birth[49]. This is one of the key reasons for doing a screening MRI and this specific group should be monitored more closely, whilst all other groups can be reassured that the risk is approximately 1-2%. Melanoma can arise in the CNS or in the skin.

For PTEN hamartoma syndrome new guidelines were published recently[73], and pertain to the diagnosis and management of the high risk of tumours in *PTEN* conditions[74].

Where the condition is a mosaic manifestation of a germline condition known to carry a malignancy risk in the skin, such as dominant dystrophic epidermolysis bullosa, or porokeratotic eccrine and ostial duct naevus, it could be assumed there is a similar risk of malignancy in the affected skin of a mosaic individual, although this is not proven.

## Psychological support services and patient support groups

Individuals affected by rare mosaic skin disorders, and their families, frequently require a substantial amount of psychological support, due to the psychosocial impact of both visible difference, and of medical complications including malignancy risk. This is often delivered to some degree by the expert physicians involved, simply by delivering accurate information on diagnosis and prognosis, however the value of formal psychological support cannot be underestimated and should be offered in the multidisciplinary team setting where possible. This can be appropriate both soon after birth for parents of an affected child, and for the child at a later date, often useful at the transition into teenage years. Patient support groups form a vital part of the psychological and practical support network for patients and families, and access to an up to date list of relevant support groups in Europe is available here[75]. In addition, PSGs often produce high quality online and in print written information on the condition in question, which can be accessed via their websites[75].

## Genetic counselling

All cases of autosomal dominant mosaic disorders occur sporadically, as they are caused by mutations originating in the embryo, not transmitted by parental gametes. Hence in general the risk of recurrence in siblings is extremely low. It is possible that some families are predisposed to either postzygotic mutations, or to the development of a mosaic disorder after a mutation, as suggested by

a confirmed increased family history of birthmarks in some conditions[20], however the risk in these families for sibling recurrence would still be very low.

Mosaic forms of Mendelian disorders are however being recognised increasingly, and it is always worth checking the literature for descriptions of potential transmission to offspring, and in particular for the exact mutation. Mosaic neurofibromatosis type 1 (NF1) is the best studied, passed on as heterozygous full-blown NF1[76-78], but another well-known occurrence is of epidermolytic epidermal naevi being passed on as generalised heterozygous epidermolytic ichthyosis due to mutations in *KRT1* or *KRT10*[7,79]. More recent descriptions are mosaic dominant dystrophic epidermolysis bullosa (EB) due to a mutation in *COL7A1* which was passed on as EB[80], and some which from their genotype could be predicted to be passed on in the germline. These include porokeratotic eccrine and ostial dermal duct naevus due to a mosaic *GJB2* mutation which could be passed on as KID syndrome[81], keratinocytic epidermal naevus due to *FGFR3* mutation which could be passed on as thanatophoric dwarfism[82], and keratinocytic epidermal naevus due to *HRAS* mutation which could be passed on as Costello syndrome[83].

Genetic counselling for autosomal dominant disorders with a superimposed mosaic phenotype is the same as for any type of Mendelian autosomal dominant disorder. Counselling for autosomal recessive mosaic disorders would be that offspring could inherit a heterozygous carrier status, but would be highly unlikely to have the second somatic hit in required to produce a phenotype.

Genetic counselling is therefore relatively complex, and is not recommended to be attempted by Dermatologists alone, unless this is the agreed mechanism in certain countries. In general, patients and families should be referred to Clinical Genetics services for counselling by trained counsellors,

provided they have an up-to-date knowledge of mosaicism, and in particular the inheritance potential of specific mutations in mosaic disorders.

## Targeted therapies for mosaic skin disorders

With the discovery of the genetic basis of many of these conditions, the potential for targeted therapies has arrived (**Figure 4**). The attraction of such therapies lies in the ability to personalise these, not just to the diagnosis, but to the genetic variant responsible for the disorder in that particular individual. Indeed, both the phenotypic diagnosis and the genotype are highly likely to be important in directing therapy in the future, as has become increasingly the case in cancer therapeutics. Currently, targeted therapies for mosaic disorders are being used in one of two ways, either as part of clinical trials, or on a named-patient compassionate-use basis. Clinical trial participation is optimal, however depending on numbers of patients and the urgency of the clinical situation, this may not always be possible.

The main area of treatment of mosaic cutaneous disorders with targeted therapy so far has been in the area of vascular malformations, with the mTOR inhibitor Rapamycin. Publications thus far, however, have been largely without genotypic information. The first clinical approach was with high doses of Rapamycin (mean serum trough levels 10-15ng/ml), over a year in a large cohort of 57 patients with different types of vascular anomaly where over 80% of patients demonstrated partial or response or stabilisation after six months[84]. This study reported a relatively high level of changes in blood indices (27%), however there were no deaths related to the drug, and only two patients stopped the treatment due to adverse effects[84]. A prospective non-controlled open label phase II trial of low dose Rapamycin in *PIK3CA*-mutation positive patients with overgrowth has shown a slight decrease in tissue volume after 6 months, but a substantial proportion of patients experienced adverse events[85]. A recent compassionate usage study with a more targeted inhibitor, which inhibits

p110α activity directly (the protein encoded by *PIK3CA*) rather than blocking the downstream effects, has also been promising[86], although assessment of efficacy and safety will require additional well-designed clinical trials.

AKT inhibitors have been considered as possible therapy for Proteus syndrome. Cellular studies confirmed that patient cells treated with an AKT inhibitor reduced the upregulation of the AKT-PI3K-mTOR pathway[87]. Clinical trials and compassionate usage trials of the same inhibitor ARQ092 (Miransertib) are currently underway.

MEK inhibition has been used on a compassionate basis for patients with congenital melanocytic naevus syndrome with primary CNS melanoma. In the first case the drug was only begun two days before death[88], and the trial would not therefore be considered valid. Use of Trametinib in four patients in a subsequent study was associated with rapid and objective symptomatic improvement, which appeared to prolong symptom-free survival at least, however it was not sufficient to halt the usual progression to a fatal outcome[89]. Trametinib has also been trialled in one case of *FGFR1*-mosaic encephalocraniocutaneous syndrome which presented with an astrocytoma, with no further growth at six months into treatment[90].

## Conclusions

This review uses the phenotypic observational knowledge and hypotheses developed over the last century, combined with the molecular genetic knowledge from the last decade, to take an overview of mosaic abnormalities of the skin, and hypothesise future advances in therapy. We propose a systematic pathogenetic classification, which not only clarifies what has been a complex subject in the literature, but has clinical relevance for the method of investigation and for counselling of

patients and their families. On this basis, guidelines are proposed for the general management of the suspected mosaic patient (**Figure 5**), which serve as a starting point for diagnosis and investigation, with published guidelines on individual conditions referenced for further reading.

# Tables

## Table 1

Summary of established mosaic disorders affecting the skin where at least one causative mosaic genotype has been confirmed at molecular level. For an explanation of the classification by inheritance potential and by molecular mechanism see the text and table 2.

| **Clinical diagnosis** | **Cutaneous features** | **Commonest associated non-cutaneous features** | **Tumour risk** | **Causal genes (or chromosomal abnormality)** | **Classification by inheritance potential** | **Classification by molecular mechanism** (based on current knowledge of the causative genes listed here) |
|---|---|---|---|---|---|---|
| Arteriovenous malformations | Arteriovenous malformations | Involvement of any other organ | Not described | *MAP2K1*[91]; *KRAS*[16], *BRAF*[16] | Germline lethal for *KRAS* and *BRAF*, not known but likely for *MAP2K1* | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |
| Becker's naevus and Becker's naevus syndrome | Becker's naevus | Pectoralis muscle and breast absence or underdevelopment | Not reported | *ACTB*[92] | Germline lethal as far as is known | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |

| | | | | | | |
|---|---|---|---|---|---|---|
| Blue rubber bleb syndrome | Multiple venous malformations | Internal venous malformations, typically gut | Not reported | *TEK*[93] | Germline lethal likely in that form, however other *TEK* mutations can be passed on | Post-zygotic dominant mutation *in utero*<br><br>Likely germline lethal |
| Congenital haemangioma | Congenital non-involuting or rapidly involuting haemangiomas (NICH and RICH respectively) | | Not reported | *GNA11, GNAQ*[94] | Germline lethal | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |
| CLAPO syndrome | Capillary malformation, lymphatic malformation | Overgrowth | Not reported | *PIK3CA*[95] | Usually Germline lethal. Potentially Mendelian dependent on the mutation | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| CLOVE(S) syndrome | Keratinocytic epidermal naevus, vascular malformations, lipomas | Overgrowth | Wilms tumour[62] | *PIK3CA*[96] | Usually Germline lethal. Potentially Mendelian dependent on the mutation | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | depends on exact mutation |
| Happle-Tinschert or Curry-Jones syndrome – NB these two syndromes are likely the same entity, separately described in different specialties. | Segmental basaloid follicular hamartomas, linear hypopigmentation, | Polysyndactyly, cerebral malformations, craniosynostosis, iris colobomas, microphthalmia, intestinal malrotation, dental anomalies, nail dysplasia | Cutaneous hamartomas, gastrointestinal myofibromas, medulloblastoma (single case), trichoblastoma (single case)[97] | *SMOH*[97] | Not known | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| Encephalocraniocutaneous lipomatosis/oculoectodermal (Toriello) syndrome. | Naevus psiloliparus | Ocular abnormalities, neurodevelopmental delay, seizures, CNS lipomas | Low-grade gliomas[98], dysembryoplastic neuroepithelial tumor (single case)[99], Wilms tumour (single case)[100] | *KRAS*[101]; *FGFR1*[102] | Not known, likely germline lethal | Post-zygotic dominant mutation *in utero*<br><br>Likely germline lethal |
| Extensive or atypical dermal melanocytosis | Extensive or atypical dermal melanocytosis | Scleral melanocytosis, glaucoma | Melanoma, eye or skin[103-106] | *GNAQ*[12] | Germline lethal | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |
| Fine and whorled Blaschko-linear hyperpigmentation (or linear and whorled naevoid hypermelanosis) | Fine and whorled Blaschko-linear hyperpigmentation | Wide phenotypic spectrum dependent on cause. | Not reported but is a theoretical possibility given the wide range of possible causes. | *KITLG*[107]; multiple chromosomal mosaicisms described | Potentially Mendelian – for *KITLG* .<br><br>Chromosomal | Post-zygotic dominant mutation *in utero* |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | abnormalities could theoretically be passed on | Germline inheritance potential depends on exact mutation |
| Fine and whorled Blaschko-linear hypopigmentation (previously within hypomelanosis of Ito) | Fine and whorled Blaschko-linear hypopigmentation | Wide phenotypic spectrum dependent on cause. For *MTOR* cases – hemimegalencephaly. | Rare, but various described[108-110] (none so far with *MTOR*. Again is likely to depend on individual genetic cause) | *MTOR*[111]; multiple chromosomal mosaicisms described | Potentially Mendelian – for *MTOR* (Smith-Kingsmore syndrome).<br><br>Chromosomal abnormalities could theoretically be passed on | Post-zygotic dominant mutation *in utero*<br><br>N.B. this phenotype can also be caused by chimaerism<br><br>Germline inheritance potential depends on exact mutation |
| Kaposiform haemangioendothelioma | Kaposiform haemangioendothelioma | Kasabach-Merritt phenomenon | Not reported although locally aggressive | *GNA14*[112] | Not known | Not known |
| Keratinocytic *FGFR3* epidermal naevus syndrome | Blaschko-linear keratinocytic epidermal naevus | Craniofacial dysmorphism, neurological abnormalities | Not reported | *FGFR3*[113] | Potentially Mendelian – theoretically could be passed on as thanatophoric dwarfism dependent on mutation | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | exact mutation |
| Keratinocytic *KRAS* epidermal naevus syndrome | Blaschko-linear keratinocytic epidermal naevus | Polycystic renal disease | Rhabdomyosarcoma | *KRAS*[114] | Germline lethal | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |
| Linear naevus comedonicus | Linear naevus comedonicus, acne | Not reported | Not reported | *FGFR2*[115] | Potentially Mendelian, dependent on mutation could be passed on as Apert's syndrome | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| Linear syringocystadenoma papilliferum | Linear syringocystadenoma papilliferum | Ocular abnormalities | Astrocytoma in single case[116] | *BRAF*[15] | Germline lethal | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |
| Lymphatic malformations /generalised lymphatic anomaly | Lymphatic malformations /generalised lymphatic anomaly | Involvement of any other organ | Not reported | *PIK3CA*[117]; *NRAS*[118] | *PIK3CA* – Potentially Mendelian dependent on mutation<br>*NRAS* – germline lethal as far as is known | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | potential depends on exact mutation |
| Macrocephaly-capillary malformation syndrome | Reticulate capillary malformation | Macrocephaly, neurological abnormalities, overgrowth | Wilms tumour | *PIK3CA*[67] | Potentially Mendelian dependent on the mutation | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| McCune-Albright syndrome | Segmental or broad Blaschko-linear café-au-lait macular hyperpigmentation, pigmentation of oral mucosa | Polyostotic fibrous dysplasia, autonomous endocrine overactivity | Overall incidence of all types <1%[119] | *GNAS*[6] | Germline lethal | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |
| Mosaic dominant dystrophic epidermolysis bullosa | Linear blistering | Not reported | Not reported | *COL7A1*[80] | Potentially Mendelian – can be passed on as epidermolysis bullosa | Post-zygotic dominant mutation *in utero*<br><br>Germline heritable |
| Mosaic Legius syndrome | Café-au-lait macules, freckling. Likely could be localised or generalised. | Not reported | Not reported | *SPRED1*[120] | Potentially Mendelian – could be passed on as germline Legius syndrome | Post-zygotic dominant mutation *in utero* |

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|---|---|---|---|---|---|---|
| | | | | | | Germline heritable |
| Mosaic neurofibromatosis type 1 (NF1) (localised or generalised) | Either localised/segmental café-au-lait macules, freckling, or cutaneous neurofibromas, or generalised low levels of same features | Neurodevelopmental abnormalities, epilepsy, bony abnormalities | Neurofibromas common, Hodgkin's lymphoma (single case), ganglioneuroblastoma (single case)[121] | *NF1*[76,122] | Potentially Mendelian – can be passed on as germline NF1 | Post-zygotic dominant mutation *in utero*<br><br>Germline heritable |
| Multiple congenital melanocytic naevi (CMN) or CMN syndrome | Congenital melanocytic naevi | Neurological abnormalities, characteristic facial features, subtle endocrinological disturbances | Melanoma, CNS or skin, incidence varies with phenotype 1-12%[49]; rarely rhabdomyosarcoma | *NRAS*[123]; *BRAF*[17] | Germline lethal | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |
| Naevoid epidermolytic hyperkeratosis | Keratinocytic epidermal naevus | Not reported | Not reported | *KRT10*[7]; *KRT1*[124] | Potentially Mendelian – can be passed on as germline epidermolytic ichthyosis | Post-zygotic dominant mutation *in utero*<br><br>Germline heritable |
| Naevus comedonicus | Naevus comedonicus | Not reported | Not reported | *NEK9*[125] | Not known | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | exact mutation |
| Papillomatous pedunculated sebaceous naevus | Papillomatous pedunculated sebaceous naevus | Not reported | Not reported | *FGFR2*[126] | Not known | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| Parkes-Weber syndrome | Arteriovenous malformation or other large vascular malformation, small ovoid capillary malformations usually with surrounding halo | Central nervous system | Not reported | *RASA1*[127] | Mendelian | Post-zygotic second hit or loss of normal allele *in utero*<br><br>Germline heritable |
| Phakomatosis pigmentokeratotica | Naevus spilus, keratinocytic epidermal naevus, rarely congenital melanocytic naevus, woolly hair naevus | Overgrowth (rare), congenital skeletal abnormalities, Vitamin D resistant hypophosphataemia | Rhabdomyosarcoma[128] (single cases) | *HRAS*[129], *KRAS*[128], *BRAF*[130] | Potentially Mendelian – theoretically could be passed on as Costello syndrome, or Cardio Facial Cutaneous syndrome dependent on mutation | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| Phakomatosis pigmentovascularis, (cesioflammea, | Capillary malformations (port wine stain/naevus flammeus, or reticulate, | Glaucoma, neurological vascular abnormalities, overgrowth or | Melanoma, eye or skin[131,132] | *GNA11*, *GNAQ*[12] | Germline lethal | Post-zygotic dominant mutation *in* |

| | | | | | | |
|---|---|---|---|---|---|---|
| cesiomarmorata and achromiomelanomarmorata types) | with or without naevus anaemicus) | undergrowth | | | | *utero*<br><br>Germline lethal |
| Phylloid hypermelanosis | Phylloid pattern hyperpigmentation | Craniofacial dysmorphism, neurological abnormalities, skeletal abnormalities, eye anomalies, sensorineural hearing loss, cicatricial alopecia, tooth abnormalities | Not reported | Copy number changes affecting chromosome 13q[133], or 5p[134] | Chromosomal abnormalities could be passed on in the germline – lethality would depend on the exact change | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| Phylloid hypomelanosis | Phylloid pattern hypopigmentation | Neurodevelopmental delay, conductive hearing loss, short stature, skeletal abnormalities asymmetric growth, craniofacial abnormalities, choroidal and retinal coloboma | Not reported | Copy number changes affecting chromosome 13q[135] | Chromosomal abnormalities could be passed on in the germline – lethality would depend on the exact change | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| Porokeratotic eccrine and ostial dermal duct naevus | Porokeratotic eccrine and ostial dermal duct naevus | Not reported | Squamous cell carcinoma[136,137] | *GJB2*[138] | Potentially Mendelian – theoretically could be passed on as KID syndrome dependent on the mutation | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | depends on exact mutation |
| Proteus syndrome | Keratinocytic epidermal naevus, vascular malformations, lipomas, cerebriform connective tissue naevus | Relentless progressive post-natal overgrowth | Meningioma (13% in those with typical skull involvement[61]), ovarian cystadenoma, parotid adenoma, breast cancer, male reproductive tumours all described. Overall tumour incidence increased but low[23] | *AKT1*[19] | Germline lethal | Post-zygotic dominant mutation *in utero*<br><br>Germline lethal |
| PTEN hamartoma or Cowden syndrome or SOLAMEN syndrome | Keratinocytic epidermal naevus, connective tissue naevi, lipomas, arteriovenous malformations, penile hyperpigmented macules, vascular anomalies | Macrocephaly, other overgrowth, dysmorphic facies | Multiple benign and malignant tumours [73,74] | *PTEN*[28,139] | Mendelian | Post-zygotic second hit or loss of normal allele *in utero*<br><br>Germline heritable |
| Sebaceous naevus syndrome/Schimmelpenning syndrome | Linear sebaceous naevi, rarely lymphatic malformations[140], | Skeletal, neurological, ophthalmological abnormalities, Vitamin D resistant hypophosphataemia | Trichoblastoma, syringocystadenoma papilliferum; malignancy rare, basal cell carcinoma | *HRAS, KRAS*[14] | Potentially Mendelian – theoretically could be passed on as Costello syndrome, dependent on mutation | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |
| Sturge-Weber syndrome | Capillary malformations | Glaucoma, neurological | Not reported | *GNAQ*[13] | Germline lethal | Post-zygotic |

| | | | | | | |
|---|---|---|---|---|---|---|
| | (port wine stain/naevus flammeus) | vascular abnormalities, overgrowth or undergrowth | | | | dominant mutation *in utero*<br><br>Germline lethal |
| Tufted angioma | Tufted angioma | Kasabach-Merritt phenomenon | Not reported | *GNA14*[112] | Not known | Not known |
| Woolly hair naevus | Woolly hair naevus, epidermal naevus, agminated melanocytic naevi | Focal cortical dysplasia, cerebral cavernous malformation (single case) | Not reported | *HRAS*[141]; *BRAF*[130] | Potentially Mendelian - theoretically *HRAS* could be passed on as Costello syndrome and *BRAF* could be passed on as cardiofaciocutaneous syndrome dependent on the mutation | Post-zygotic dominant mutation *in utero*<br><br>Germline inheritance potential depends on exact mutation |

Table 2

Proposed classification of mosaic abnormalities of the skin, by genetic pathogenesis and inheritance potential, and rule-of-thumb guidelines for the type of genetic testing to order. For sample preparation see text for details.

| **Classiciation of mosaic abnormality of the skin by inheritance potential** | **Suspected genetic mechanism of the mosaic abnormality of the skin in the affected individual** | **A classical example** | **Classified as a mosaic disorder of the skin?** | **Samples to take if genetic investigation required or desired** | **Sample preparation and testing type to request** |
|---|---|---|---|---|---|
| Autosomal dominant mosaic abnormality of the skin, germline lethal | "Normal" germline genotype.<br><br>Single heterozygous post-zygotic pathogenic mutation *in utero,* resulting in mosaic disorder of the skin, which would be lethal in the germline and therefore not passed on to future generations. | Proteus Syndrome[19] | Yes | Skin biopsy for diagnosis, blood sample for comparison (or in case of McCune-Albright or MCAP may pick up mutation in blood or saliva) | For single gene disorders – direct DNA extraction from skin biopsy and DNA sequencing by high sensitivity method (unless cell culture of correct cell type available)<br><br>For chromosomal abnormalities – either direct DNA extraction from skin biopsy, with microarray or preferably next generation sequencing for copy number changes, or cell culture of appropriate cell and karyotype with mosaicism screen |
| Autosomal dominant mosaic abnormality of the skin, germline heritable | "Normal" germline genotype.<br><br>Single heterozygous post-zygotic pathogenic mutation *in utero*, resulting in mosaic disorder of the skin, which could be tolerated in the | Segmental mosaic neurofibromatosis type 1[76] | Yes | Skin biopsy, blood sample, possibly cheek swab (can be useful in *PIK3CA* mutations with MCAP phenotype, and in generalised mosaic | For single gene disorders – direct DNA extraction from skin biopsy and blood (and cheek swab), with DNA sequencing by high sensitivity method (unless cell culture of correct cell type available) |

| | | | | | |
|---|---|---|---|---|---|
| | germline and therefore with potential for transmission as a heterozygous autosomal dominant condition. | | | NF1) | For chromosomal abnormalities – either direct DNA extraction from skin biopsy and blood, with microarray or preferably next generation sequencing for copy number changes, or cell culture of appropriate cell and karyotype with mosaicism screen |
| Autosomal dominant condition, germline heritable, with mosaic component superimposed | Single dominant mutation in the germline, either inherited or *de novo,* which leads to a recognisable disease phenotype/syndrome in the patient independent of the mosaic skin phenotype.<br><br>Post-zygotic second-hit pathogenic mutation *in utero,* loss of heterozygosity, and resultant superimposed mosaic pattern, in the context of a wider phenotype of a recognised inherited syndrome. | Hailey-Hailey disease[5] | No – superimposed mosaic manifestation of autosomal dominant condition | Blood sample for diagnosis.<br><br>Skin biopsy only if wish to investigate mechanism for superimposed mosaic pattern | DNA extraction from blood sample, with standard DNA sequencing |
| Autosomal recessive mosaic abnormality of the skin, germline carrier status heritable | Single recessive mutation in the germline which leads to no recognisable phenotypic manifestations *per se*.<br><br>Post-zygotic second-hit pathogenic mutation *in utero,* resulting in mosaic disorder of the skin, and which is the only manifestation of the disease – i.e. it is not part of a recognised phenotype/syndrome. Could not be passed on. | Ectodermal dysplasia skin fragility syndrome[30] | Yes | Skin biopsy and blood sample if wish to investigate mechanism | DNA extraction from blood sample, with standard DNA sequencing. Direct DNA extraction from skin biopsy, with DNA sequencing by high sensitivity method |

# Figures

**Figure 1**

Principal variables which contribute to the unique phenotype of a mosaic disorder of the skin in any one individual.

**Figure 2**

Schematic representing the molecular mechanisms which underlie mosaic abnormalities of the skin, including mosaic disorders (lethal and non-lethal in the germline) superimposed mosaic manifestations of dominant Mendelian disorders and mosaic presentations of recessive Mendelian disorders.

**Figure 3**

Schematic representing the molecular mechanisms which underlie revertant mosaicism, not classified as a mosaic disorder as it is a phenomenon of phenotypic rescue.

**Figure 4**

Schematic of the main intracellular signalling pathways involved in mosaic disorders, with potential drug targets indicated.

**Figure 5**

Patient pathway - practical management flow chart for the suspected mosaic patient

## References


1 Blaschko A. Die Nervenverteilung in der Haut in ihrer Beziehung zu den Erkrankungen der Haut. In: *Bericht erstattet dem VII. Congress der Deutschen Dermatologischen Gesellschaft*. Breslau. 1901.

2 Jackson R. The lines of Blaschko: a review and reconsideration: Observations of the cause of certain unusual linear conditions of the skin. *The British journal of dermatology* 1976; **95**: 349-60.

3 Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. *Journal of the American Academy of Dermatology* 1987; **16**: 899-906.

4 Happle R. Mosaicism in human skin. Understanding the patterns and mechanisms. *Archives of dermatology* 1993; **129**: 1460-70.

5 Poblete-Gutierrez P, Wiederholt T, Konig A *et al.* Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. *J Clin Invest* 2004; **114**: 1467-74.

6 Weinstein LS, Shenker A, Gejman PV *et al.* Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *The New England journal of medicine* 1991; **325**: 1688-95.

7 Paller AS, Syder AJ, Chan YM *et al.* Genetic and clinical mosaicism in a type of epidermal nevus. *The New England journal of medicine* 1994; **331**: 1408-15.

8 Ju YS, Martincorena I, Gerstung M *et al.* Somatic mutations reveal asymmetric cellular dynamics in the early human embryo. *Nature* 2017; **543**: 714-8.

9 Rahbari R, Wuster A, Lindsay SJ *et al.* Timing, rates and spectra of human germline mutation. *Nature genetics* 2016; **48**: 126-33.

10 Kinsler VA. *"An introduction to mosaicism", in Harper Textbook of Pediatric Dermatology*, 4 edn.: Wiley. in press.

11 Keppler-Noreuil KM, Sapp JC, Lindhurst MJ *et al.* Clinical delineation and natural history of the PIK3CA-related overgrowth spectrum. *American journal of medical genetics. Part A* 2014; **164A**: 1713-33.

12 Thomas AC, Zeng Z, Riviere JB *et al.* Mosaic Activating Mutations in GNA11 and GNAQ Are Associated with Phakomatosis Pigmentovascularis and Extensive Dermal Melanocytosis. *The Journal of investigative dermatology* 2016; **136(4)**: 770-8.

13 Shirley MD, Tang H, Gallione CJ *et al.* Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. *The New England journal of medicine* 2013; **368**: 1971-9.

14 Groesser L, Herschberger E, Ruetten A *et al.* Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. *Nature genetics* 2012; **44**: 783-7.

15 Levinsohn JL, Sugarman JL, Bilguvar K *et al.* Somatic V600E BRAF Mutation in Linear and Sporadic Syringocystadenoma Papilliferum. *The Journal of investigative dermatology* 2015.

16 Al-Olabi L, Polubothu S, Dowsett K *et al.* Mosaic RAS/MAPK variants cause sporadic vascular malformations which respond to targeted therapy. *J Clin Invest* 2018.

17 Etchevers HC, Rose C, Kahle B *et al.* Giant congenital melanocytic nevus with vascular malformation and epidermal cysts associated with a somatic activating mutation in BRAF. *Pigment cell & melanoma research* 2018.

18 Kinsler VA, Krengel S, Riviere JB *et al.* Next-generation sequencing of nevus spilus-type congenital melanocytic nevus: exquisite genotype-phenotype correlation in mosaic RASopathies. *The Journal of investigative dermatology* 2014; **134**: 2658-60.

19 Lindhurst MJ, Sapp JC, Teer JK *et al.* A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *The New England journal of medicine* 2011; **365**: 611-9.

20 Kinsler VA, Abu-Amero S, Budd P *et al.* Germline melanocortin-1-receptor genotype is associated with severity of cutaneous phenotype in congenital melanocytic nevi: a role for MC1R in human fetal development. *The Journal of investigative dermatology* 2012; **132**: 2026-32.

21 Beachkofsky TM, Sapp JC, Biesecker LG *et al.* Progressive overgrowth of the cerebriform connective tissue nevus in patients with Proteus syndrome. *Journal of the American Academy of Dermatology* 2010; **63**: 799-804.

22 Twede JV, Turner JT, Biesecker LG *et al.* Evolution of skin lesions in Proteus syndrome. *Journal of the American Academy of Dermatology* 2005; **52**: 834-8.

23 Biesecker LG, Sapp JC. Proteus Syndrome. In: *GeneReviews(R)* (Pagon RA, Adam MP, Ardinger HH et al., eds). Seattle (WA). 1993-2018.

24 Crenshaw MM, Goerlich CG, Ivey LE *et al.* Orthopaedic Management of Leg-length Discrepancy in Proteus Syndrome: A Case Series. *J Pediatr Orthop* 2018; **38**: e138-e44.

25 Fusco F, Conte MI, Diociauti A *et al.* Unusual Father-to-Daughter Transmission of Incontinentia Pigmenti Due to Mosaicism in IP Males. *Pediatrics* 2017; **140**.

26 Ejerskov C, Farholt S, Skovby F *et al.* Clinical presentations of 23 half-siblings from a mosaic neurofibromatosis type 1 sperm donor. *Clinical genetics* 2016; **89**: 346-50.

27 Folster-Holst R, Nellen RG, Jensen JM *et al.* Molecular genetic support for the rule of dichotomy in type 2 segmental Darier disease. *The British journal of dermatology* 2012; **166**: 464-6.

28 Loffeld A, McLellan NJ, Cole T *et al.* Epidermal naevus in Proteus syndrome showing loss of heterozygosity for an inherited PTEN mutation. *The British journal of dermatology* 2006; **154**: 1194-8.

29 Torrelo A, Hernandez-Martin A, Bueno E *et al.* Molecular evidence of type 2 mosaicism in

Gorlin syndrome. *The British journal of dermatology* 2013; **169**: 1342-5.

30 Vazquez-Osorio I, Chmel N, Rodriguez-Diaz E *et al.* A case of mosaicism in ectodermal dysplasia-skin fragility syndrome. *The British journal of dermatology* 2017; **177**: e101-e2.

31 Schuilenga-Hut PH, Scheffer H, Pas HH *et al.* Partial revertant mosaicism of keratin 14 in a patient with recessive epidermolysis bullosa simplex. *The Journal of investigative dermatology* 2002; **118**: 626-30.

32 Happle R, Assim A. The lines of Blaschko on the head and neck. *Journal of the American Academy of Dermatology* 2001; **44**: 612-5.

33 Happle R. *Mosaicism in human skin*. Berlin Heidelberg: Springer-Verlag. 2014.

34 Kinsler VA, Larue L. The patterns of birthmarks suggest a novel population of melanocyte precursors arising around the time of gastrulation. *Pigment cell & melanoma research* 2018; **31(1)**: 95-109.

35 Waelchli R, Aylett SE, Robinson K *et al.* New vascular classification of port-wine stains: improving prediction of Sturge-Weber risk. *The British journal of dermatology* 2014; **171**: 861-7.

36 Haggstrom AN, Lammer EJ, Schneider RA *et al.* Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics* 2006; **117**: 698-703.

37 Weitz NA, Bayer ML, Baselga E *et al.* The "biker-glove" pattern of segmental infantile hemangiomas on the hands and feet. *Journal of the American Academy of Dermatology* 2014; **71**: 542-7.

38 Krengel S, Scope A, Dusza SW *et al.* New recommendations for the categorization of cutaneous features of congenital melanocytic nevi. *Journal of the American Academy of Dermatology* 2013; **68**: 441-51.

39 Martins da Silva VP, Marghoob A, Pigem R *et al.* Patterns of distribution of giant congenital melanocytic nevi (GCMN): The 6B rule. *Journal of the American Academy of Dermatology* 2017; **76**: 689-94.

40 Keppler-Noreuil KM, Rios JJ, Parker VE *et al.* PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *American journal of medical genetics. Part A* 2015; **167A**: 287-95.

41 Mirzaa G, Timms AE, Conti V *et al.* PIK3CA-associated developmental disorders exhibit distinct classes of mutations with variable expression and tissue distribution. *JCI Insight* 2016; **1**.

42 Dutkiewicz AS, Ezzedine K, Mazereeuw-Hautier J *et al.* A prospective study of risk for Sturge-Weber syndrome in children with upper facial port-wine stain. *Journal of the American Academy of Dermatology* 2015; **72**: 473-80.

43 Happle R. Phacomatosis pigmentovascularis revisited and reclassified. *Archives of dermatology* 2005; **141**: 385-8.

44 Comi AM. Sturge-Weber syndrome and epilepsy: an argument for aggressive seizure management in these patients. *Expert Rev Neurother* 2007; **7**: 951-6.

45 Comi AM, Bellamkonda S, Ferenc LM *et al.* Central hypothyroidism and Sturge-Weber syndrome. *Pediatric neurology* 2008; **39**: 58-62.

46 Lance EI, Sreenivasan AK, Zabel TA *et al.* Aspirin use in Sturge-Weber syndrome: side effects and clinical outcomes. *J Child Neurol* 2013; **28**: 213-8.

47 Comi A. Current Therapeutic Options in Sturge-Weber Syndrome. *Semin Pediatr Neurol* 2015; **22**: 295-301.

48 Kuentz P, St-Onge J, Duffourd Y *et al.* Molecular diagnosis of PIK3CA-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing. *Genetics in medicine : official journal of the American College of Medical Genetics* 2017; **19**: 989-97.

49 Kinsler V, A, O'Hare P, Bulstrode N, Chong WK, Sebire N,J, Hargrave D, Slater O. Melanoma in congenital melanocytic naevi. *British Journal of Dermatology* 2017; **In press**.

50 Ramaswamy V, Delaney H, Haque S *et al.* Spectrum of central nervous system abnormalities in neurocutaneous melanocytosis. *Developmental medicine and child neurology* 2012; **54**: 563-8.

51 Waelchli R, Aylett SE, Atherton D *et al.* Classification of neurological abnormalities in children with congenital melanocytic naevus syndrome identifies MRI as the best predictor of clinical outcome. *The British journal of dermatology* 2015.

52 Waelchli R, Williams J, Cole T *et al.* Growth and hormone profiling in children with congenital melanocytic naevi. *The British journal of dermatology* 2015; **173**: 1471-8.

53 Kinsler V, Shaw AC, Merks JH *et al.* The face in congenital melanocytic nevus syndrome. *American journal of medical genetics. Part A* 2012; **158A**: 1014-9.

54 Frascari F, Dreyfus I, Rodriguez L *et al.* Prevalence and risk factors of vitamin D deficiency in inherited ichthyosis: a French prospective observational study performed in a reference center. *Orphanet J Rare Dis* 2014; **9**: 127.

55 Boon LM, Vikkula M. Multiple Cutaneous and Mucosal Venous Malformations. In: *GeneReviews((R))* (Adam MP, Ardinger HH, Pagon RA et al., eds). Seattle (WA). 1993.

56 Mazoyer E, Enjolras O, Laurian C *et al.* Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach-Merritt syndrome. *Clin Lab Haematol* 2002; **24**: 243-51.

57 Redondo P, Aguado L, Marquina M *et al.* Angiogenic and prothrombotic markers in extensive slow-flow vascular malformations: implications for antiangiogenic/antithrombotic strategies. *The British journal of dermatology* 2010; **162**: 350-6.

58 Lee BB, Baumgartner I, Berlien P *et al.* Guideline. Diagnosis and treatment of venous malformations. consensus document of the international union of phlebology (iup): updated-2013. *Int Angiol* 2014.

59 Keppler-Noreuil KM, Lozier JN, Sapp JC *et al.* Characterization of thrombosis in patients with Proteus syndrome. *American journal of medical genetics. Part A* 2017; **173**: 2359-65.

60 Johnson EF, Davis DM, Tollefson MM *et al.* Vascular Tumors in Infants: Case Report and Review of Clinical, Histopathologic, and Immunohistochemical Characteristics of Infantile Hemangioma, Pyogenic Granuloma, Noninvoluting Congenital Hemangioma, Tufted Angioma, and Kaposiform Hemangioendothelioma. *The American Journal of dermatopathology* 2018; **40**: 231-9.

61 Keppler-Noreuil KM, Baker EH, Sapp JC *et al.* Somatic AKT1 mutations cause meningiomas colocalizing with a characteristic pattern of cranial hyperostosis. *American journal of medical genetics. Part A* 2016; **170**: 2605-10.

62 Gripp KW, Baker L, Kandula V *et al.* Nephroblastomatosis or Wilms tumor in a fourth patient with a somatic PIK3CA mutation. *American journal of medical genetics. Part A* 2016; **170**: 2559-69.

63 Polubothu S, et al. Genotype-phenotype cohort study of the GNAQ/GNA11 mosaic disorders – cutaneous phenotype but not genotype is correlated with adverse outcomes. *British Journal of Dermatology* 2018; **under review**.

64 Maertens O, De Schepper S, Vandesompele J *et al.* Molecular dissection of isolated disease features in mosaic neurofibromatosis type 1. *American journal of human genetics* 2007; **81**: 243-51.

65 Kim IS, Kim ER, Nam HJ *et al.* Activating mutation of GS alpha in McCune-Albright syndrome causes skin pigmentation by tyrosinase gene activation on affected melanocytes. *Hormone research* 1999; **52**: 235-40.

66 Do H, Dobrovic A. Sequence artifacts in DNA from formalin-fixed tissues: causes and strategies for minimization. *Clinical chemistry* 2015; **61**: 64-71.

67 Riviere JB, Mirzaa GM, O'Roak BJ *et al.* De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. *Nature genetics* 2012; **44**: 934-40.

68 Wali GN, Felton SJ, McPherson T. Management of naevus sebaceous: a national survey of UK dermatologists and plastic surgeons. *Clinical and experimental dermatology* 2018; **43**: 589-91.

69 Hsu MC, Liau JY, Hong JL *et al.* Secondary neoplasms arising from nevus sebaceus: A retrospective study of 450 cases in Taiwan. *The Journal of dermatology* 2016; **43**: 175-80.

70 Santibanez-Gallerani A, Marshall D, Duarte AM *et al.* Should nevus sebaceus of Jadassohn in children be excised? A study of 757 cases, and literature review. *J Craniofac Surg* 2003; **14**:

658-60.

71 Neuhold JC, Friesenhahn J, Gerdes N *et al.* Case reports of fatal or metastasizing melanoma in children and adolescents: a systematic analysis of the literature. *Pediatric dermatology* 2015; **32**: 13-22.

72 Hale EK, Stein J, Ben-Porat L *et al.* Association of melanoma and neurocutaneous melanocytosis with large congenital melanocytic naevi--results from the NYU-LCMN registry. *The British journal of dermatology* 2005; **152**: 512-7.

73 Pilarski R, Burt R, Kohlman W *et al.* Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *Journal of the National Cancer Institute* 2013; **105**: 1607-16.

74 Bubien V, Bonnet F, Brouste V *et al.* High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. *Journal of medical genetics* 2013; **50**: 255-63.

75 (ERN-Skin) ERN. European Reference Network for Rare Skin Diseases (ERN-Skin). In. 2018.

76 Tinschert S, Naumann I, Stegmann E *et al.* Segmental neurofibromatosis is caused by somatic mutation of the neurofibromatosis type 1 (NF1) gene. *Eur J Hum Genet* 2000; **8**: 455-9.

77 Zlotogora J. Mutations in von Recklinghausen neurofibromatosis: an hypothesis. *American journal of medical genetics* 1993; **46**: 182-4.

78 Rasmussen SA, Colman SD, Ho VT *et al.* Constitutional and mosaic large NF1 gene deletions in neurofibromatosis type 1. *Journal of medical genetics* 1998; **35**: 468-71.

79 Nomura K, Umeki K, Hatayama I *et al.* Phenotypic heterogeneity in bullous congenital ichthyosiform erythroderma: possible somatic mosaicism for keratin gene mutation in the mildly affected mother of the proband. *Archives of dermatology* 2001; **137**: 1192-5.

80 van den Akker PC, Pasmooij AM, Meijer R *et al.* Somatic mosaicism for the COL7A1 mutation p.Gly2034Arg in the unaffected mother of a patient with dystrophic epidermolysis bullosa pruriginosa. *The British journal of dermatology* 2015; **172**: 778-81.

81 Levinsohn JL, McNiff JM, Antaya RJ *et al.* A Somatic p.G45E GJB2 Mutation Causing Porokeratotic Eccrine Ostial and Dermal Duct Nevus. *JAMA dermatology* 2015; **151**: 638-41.

82 Bygum A, Fagerberg CR, Clemmensen OJ *et al.* Systemic epidermal nevus with involvement of the oral mucosa due to FGFR3 mutation. *BMC medical genetics* 2011; **12**: 79.

83 Sol-Church K, Stabley DL, Demmer LA *et al.* Male-to-male transmission of Costello syndrome: G12S HRAS germline mutation inherited from a father with somatic mosaicism. *American journal of medical genetics. Part A* 2009; **149A**: 315-21.

84 Adams DM, Trenor CC, 3rd, Hammill AM *et al.* Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. *Pediatrics* 2016; **137**: e20153257.

85 Parker VER, Keppler-Noreuil KM, Faivre L *et al.* Safety and efficacy of low-dose sirolimus in

the PIK3CA-related overgrowth spectrum. *Genetics in medicine : official journal of the American College of Medical Genetics* 2018.

86 Venot Q, Blanc T, Rabia SH *et al.* Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature* 2018; **558**: 540-6.

87 Lindhurst MJ, Yourick MR, Yu Y *et al.* Repression of AKT signaling by ARQ 092 in cells and tissues from patients with Proteus syndrome. *Sci Rep* 2015; **5**: 17162.

88 Kusters-Vandevelde HV, Willemsen AE, Groenen PJ *et al.* Experimental treatment of NRAS-mutated neurocutaneous melanocytosis with MEK162, a MEK-inhibitor. *Acta neuropathologica communications* 2014; **2**: 41.

89 Kinsler VA, O'Hare P, Jacques T *et al.* MEK inhibition appears to improve symptom control in primary NRAS-driven CNS melanoma in children. *British journal of cancer* 2017; **116**: 990-3.

90 Bavle A, Shah R, Gross N *et al.* Encephalocraniocutaneous Lipomatosis. *J Pediatr Hematol Oncol* 2018.

91 Couto JA, Huang AY, Konczyk DJ *et al.* Somatic MAP2K1 Mutations Are Associated with Extracranial Arteriovenous Malformation. *American journal of human genetics* 2017; **100**: 546-54.

92 Cai ED, Sun BK, Chiang A *et al.* Postzygotic Mutations in Beta-Actin Are Associated with Becker's Nevus and Becker's Nevus Syndrome. *The Journal of investigative dermatology* 2017; **137**: 1795-8.

93 Soblet J, Kangas J, Natynki M *et al.* Blue Rubber Bleb Nevus (BRBN) Syndrome Is Caused by Somatic TEK (TIE2) Mutations. *The Journal of investigative dermatology* 2017; **137**: 207-16.

94 Ayturk UM, Couto JA, Hann S *et al.* Somatic Activating Mutations in GNAQ and GNA11 Are Associated with Congenital Hemangioma. *American journal of human genetics* 2016; **98**: 789-95.

95 Rodriguez-Laguna L, Ibanez K, Gordo G *et al.* CLAPO syndrome: identification of somatic activating PIK3CA mutations and delineation of the natural history and phenotype. *Genetics in medicine : official journal of the American College of Medical Genetics* 2018.

96 Kurek KC, Luks VL, Ayturk UM *et al.* Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. *American journal of human genetics* 2012; **90**: 1108-15.

97 Twigg SR, Hufnagel RB, Miller KA *et al.* A Recurrent Mosaic Mutation in SMO, Encoding the Hedgehog Signal Transducer Smoothened, Is the Major Cause of Curry-Jones Syndrome. *American journal of human genetics* 2016; **98**: 1256-65.

98 Bieser S, Reis M, Guzman M *et al.* Grade II pilocytic astrocytoma in a 3-month-old patient with encephalocraniocutaneous lipomatosis (ECCL): case report and literature review of low grade gliomas in ECCL. *American journal of medical genetics. Part A* 2015; **167A**: 878-81.

99 Han JY, Yum MS, Kim EH *et al.* A rare case of dysembryoplastic neuroepithelial tumor

combined with encephalocraniocutaneous lipomatosis and intractable seizures. *Korean J Pediatr* 2016; **59**: S139-S44.

100 Damar C, Yaman A, Ali Ikidag M *et al.* Encephalocraniocutaneous lipomatosis with Wilms' tumor. *Pediatrics international : official journal of the Japan Pediatric Society* 2017; **59**: 835-6.

101 Boppudi S, Bogershausen N, Hove HB *et al.* Specific mosaic KRAS mutations affecting codon 146 cause oculoectodermal syndrome and encephalocraniocutaneous lipomatosis. *Clinical genetics* 2016; **90**: 334-42.

102 Bennett JT, Tan TY, Alcantara D *et al.* Mosaic Activating Mutations in FGFR1 Cause Encephalocraniocutaneous Lipomatosis. *American journal of human genetics* 2016; **98**: 579-87.

103 Levene A. Disseminated dermal melanocytosis terminating in melanoma. A human condition resembling equine melanotic disease. *The British journal of dermatology* 1979; **101**: 197-205.

104 Teekhasaenee C, Ritch R, Rutnin U *et al.* Ocular findings in oculodermal melanocytosis. *Archives of ophthalmology* 1990; **108**: 1114-20.

105 Singh AD, De Potter P, Fijal BA *et al.* Lifetime prevalence of uveal melanoma in white patients with oculo(dermal) melanocytosis. *Ophthalmology* 1998; **105**: 195-8.

106 Patel BC, Egan CA, Lucius RW *et al.* Cutaneous malignant melanoma and oculodermal melanocytosis (nevus of Ota): report of a case and review of the literature. *Journal of the American Academy of Dermatology* 1998; **38**: 862-5.

107 Sorlin A, Maruani A, Aubriot-Lorton MH *et al.* Mosaicism for a KITLG Mutation in Linear and Whorled Nevoid Hypermelanosis. *The Journal of investigative dermatology* 2017; **137**: 1575-8.

108 Xu F, De Las Casas LE, Dobbs LJ, Jr. Primary meningeal rhabdomyosarcoma in a child with hypomelanosis of Ito. *Archives of pathology & laboratory medicine* 2000; **124**: 762-5.

109 Ruggieri M, Magro G, Ruggieri M *et al.* Tumors and hypomelanosis of Ito. *Archives of pathology & laboratory medicine* 2001; **125**: 599-601.

110 Morigaki R, Pooh KH, Shouno K *et al.* Choroid plexus papilloma in a girl with hypomelanosis of Ito. *Journal of neurosurgery. Pediatrics* 2012; **10**: 182-5.

111 Mirzaa GM, Campbell CD, Solovieff N *et al.* Association of MTOR Mutations With Developmental Brain Disorders, Including Megalencephaly, Focal Cortical Dysplasia, and Pigmentary Mosaicism. *JAMA Neurol* 2016; **73**: 836-45.

112 Lim YH, Bacchiocchi A, Qiu J *et al.* GNA14 Somatic Mutation Causes Congenital and Sporadic Vascular Tumors by MAPK Activation. *American journal of human genetics* 2016; **99**: 443-50.

113 Collin B, Taylor IB, Wilkie AO *et al.* Fibroblast growth factor receptor 3 (FGFR3) mutation in a

verrucous epidermal naevus associated with mild facial dysmorphism. *The British journal of dermatology* 2007; **156**: 1353-6.

114 Bourdeaut F, Herault A, Gentien D *et al.* Mosaicism for oncogenic G12D KRAS mutation associated with epidermal nevus, polycystic kidneys and rhabdomyosarcoma. *Journal of medical genetics* 2010; **47**: 859-62.

115 Munro CS, Wilkie AO. Epidermal mosaicism producing localised acne: somatic mutation in FGFR2. *Lancet* 1998; **352**: 704-5.

116 Watanabe Y, Shido K, Niihori T *et al.* Somatic BRAF c.1799T>A p.V600E Mosaicism syndrome characterized by a linear syringocystadenoma papilliferum, anaplastic astrocytoma, and ocular abnormalities. *American journal of medical genetics. Part A* 2016; **170A**: 189-94.

117 Luks VL, Kamitaki N, Vivero MP *et al.* Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *The Journal of pediatrics* 2015; **166**: 1048-54 e1-5.

118 Manevitz-Mendelson E, Leichner GS, Barel O *et al.* Somatic NRAS mutation in patient with generalized lymphatic anomaly. *Angiogenesis* 2018; **21**: 287-98.

119 Dumitrescu CE, Collins MT. McCune-Albright syndrome. *Orphanet J Rare Dis* 2008; **3**: 12.

120 Jobling RK, Lara-Corrales I, Hsiao MC *et al.* Mosaicism for a SPRED1 deletion revealed in a patient with clinically suspected mosaic NF. *The British journal of dermatology* 2016.

121 Vazquez-Osorio I, Duat-Rodriguez A, Garcia-Martinez FJ *et al.* Cutaneous and Systemic Findings in Mosaic Neurofibromatosis Type 1. *Pediatric dermatology* 2017; **34**: 271-6.

122 Colman SD, Rasmussen SA, Ho VT *et al.* Somatic mosaicism in a patient with neurofibromatosis type 1. *American journal of human genetics* 1996; **58**: 484-90.

123 Kinsler VA, Thomas AC, Ishida M *et al.* Multiple congenital melanocytic nevi and neurocutaneous melanosis are caused by postzygotic mutations in codon 61 of NRAS. *The Journal of investigative dermatology* 2013; **133**: 2229-36.

124 Tsubota A, Akiyama M, Sakai K *et al.* Keratin 1 gene mutation detected in epidermal nevus with epidermolytic hyperkeratosis. *The Journal of investigative dermatology* 2007; **127**: 1371-4.

125 Levinsohn JL, Sugarman JL, Yale Center for Mendelian G *et al.* Somatic Mutations in NEK9 Cause Nevus Comedonicus. *American journal of human genetics* 2016; **98**: 1030-7.

126 Kuentz P, Fraitag S, Gonzales M *et al.* Mosaic Activating FGFR2 Mutation in Two Foetuses with Papillomatous Pedunculated Sebaceous Naevus. *The British journal of dermatology* 2016.

127 Revencu N, Boon LM, Mulliken JB *et al.* Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Human mutation* 2008; **29**: 959-65.

128 Om A, Cathey SS, Gathings RM *et al.* Phacomatosis Pigmentokeratotica: A Mosaic RASopathy with Malignant Potential. *Pediatric dermatology* 2017; **34**: 352-5.

129 Groesser L, Herschberger E, Sagrera A *et al.* Phacomatosis pigmentokeratotica is caused by a postzygotic HRAS mutation in a multipotent progenitor cell. *The Journal of investigative dermatology* 2013; **133**: 1998-2003.

130 Kuentz P, Mignot C, St-Onge J *et al.* Postzygotic BRAF p.Lys601Asn Mutation in Phacomatosis Pigmentokeratotica with Woolly Hair Nevus and Focal Cortical Dysplasia. *The Journal of investigative dermatology* 2016.

131 Tran HV, Zografos L. Primary choroidal melanoma in phakomatosis pigmentovascularis IIa. *Ophthalmology* 2005; **112**: 1232-5.

132 Shields CL, Kligman BE, Suriano M *et al.* Phacomatosis pigmentovascularis of cesioflammea type in 7 patients: combination of ocular pigmentation (melanocytosis or melanosis) and nevus flammeus with risk for melanoma. *Archives of ophthalmology* 2011; **129**: 746-50.

133 Oiso N, Tsuruta D, Imanishi H *et al.* Phylloid hypermelanosis and melanocytic nevi with aggregated and disfigured melanosomes: causal relationship between phylloid pigment distribution and chromosome 13 abnormalities. *Dermatology* 2010; **220**: 169-72.

134 Hansen LK, Brandrup F, Rasmussen K. Pigmentary mosaicism with mosaic chromosome 5p tetrasomy. *The British journal of dermatology* 2003; **149**: 414-6.

135 Gonzalez-Ensenat MA, Vicente A, Poo P *et al.* Phylloid hypomelanosis and mosaic partial trisomy 13: two cases that provide further evidence of a distinct clinicogenetic entity. *Archives of dermatology* 2009; **145**: 576-8.

136 Coras B, Vogt T, Roesch A *et al.* Bowen's disease on porokeratotic eccrine ostial and dermal duct nevus. *Dermatol Surg* 2007; **33**: 496-9.

137 Nassiri N, Hansen J. Diffuse squamous cell carcinoma in porokeratotic eccrine ostial and dermal duct nevus. *Plastic and reconstructive surgery* 2009; **123**: 87e-8e.

138 Easton JA, Donnelly S, Kamps MA *et al.* Porokeratotic eccrine nevus may be caused by somatic connexin26 mutations. *The Journal of investigative dermatology* 2012; **132**: 2184-91.

139 Zhou XP, Marsh DJ, Hampel H *et al.* Germline and germline mosaic PTEN mutations associated with a Proteus-like syndrome of hemihypertrophy, lower limb asymmetry, arteriovenous malformations and lipomatosis. *Human molecular genetics* 2000; **9**: 765-8.

140 Lihua J, Feng G, Shanshan M *et al.* Somatic KRAS mutation in an infant with linear nevus sebaceous syndrome associated with lymphatic malformations: A case report and literature review. *Medicine (Baltimore)* 2017; **96**: e8016.

141 Levinsohn JL, Teng J, Craiglow BG *et al.* Somatic HRAS p.G12S mutation causes woolly hair and epidermal nevi. *The Journal of investigative dermatology* 2014; **134**: 1149-52.