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Mosaic Neurocutaneous Disorders and Their Causes

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Neurocutaneous disorders are a heterogeneous group of conditions (mainly) affecting the skin [with pigmentary/vascular abnormalities and/or cutaneous tumours] and the central and peripheral nervous system [with congenital abnormalities and/or tumours]. In a number of such disorders, the skin abnormalities can assume a mosaic patterning (usually arranged in archetypical patterns). Alternating segments of affected and unaffected skin or segmentally arranged patterns of abnormal skin often mirror similar phenomena occurring in extra-cutaneous organs/tissues [eg, eye, bone, heart/vessels, lung, kidney and gut]. In some neurocutaneous syndromes the abnormal mosaic patterning involve mainly the skin and the nervous system configuring a (true) mosaic neurocutaneous disorder; or an ordinary trait of a neurocutaneous disorder is sometimes superimposed by a pronounced linear or otherwise segmental involvement; or, lastly, a neurocutaneous disorder can occur solely in a mosaic pattern. Recently, the molecular genetic and cellular bases of an increasing number of neurocutaneous disorders have been unravelled, shedding light on the interplays between common intra- and extra-neuronal signalling pathways encompassing receptor-protein and protein-to-protein cascades (eg, RAS, MAPK, mTOR, PI3K/AKT and GNAQ pathways), which are often responsible of the mosaic distribution of cutaneous and extra-cutaneous features. In this article we will focus on the well known, and less defined mosaic neurocutaneous phenotypes and their related molecular/genetic bases, including the mosaic neurofibromatoses and their related forms (ie, spinal neurofibromatosis and schwannomatosis); Legius syndrome; segmental arrangements in tuberous sclerosis; Sturge-Weber and Klippel-Trenaunay syndromes; microcephaly/megalencephaly-capillary malformation; blue rubber bleb nevus syndrome; Wyburn-Mason syndrome; mixed vascular nevus syndrome; PHACE syndrome; Incontinentia pigmenti; pigmentary mosaicism of the Ito type; neurocutaneous melanosis; cutis tricolor; speckled lentiginous syndrome; epidermal nevus syndromes; Becker's nevus syndrome; phacomatosis pigmentovascularis and pigmentokeratotica; Proteus syndrome; and encephalocraniocutaneous lipomatosis.
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Introduction

Since ancient times, the term *mosaic* defines the art of creating a picture or an image with an assemblage of small pieces of (colored) glass, stone, or other materials.[1] The earliest known examples of mosaics made by placing different materials in a pattern creating an artwork, can be likely traced back in the east as far as the colored clay cones ("*cone mosaic*") pressed tightly together and used for wall (coated) decoration by the Sumerians at *Uruk-Warka* in the fourth millennium BC (late Ubaid to early or late Uruk period)[2]; other ancient artworks were found at a temple building in *Abra*, Mesopotamia, and are dated to the second half of 3000 BC.[3]; they consisted of pieces of colored stones, shells, and ivory.

In modern biology, the term *mosaic* is used in a metaphoric way, it means an organism that is composed of 2 or more genetically different cell lines originating from one homogeneous zygote.[1,4] Mosaicism can occur in all pluricellular living organisms.[1] During the first half of the 20th century, mosaic patterning was first described in the vegetable[5] and animal[6] kingdoms. Today it is clear that every human being represents, to some degree, a mosaic.[1]

Mosaicism can involve all organs but is most easily noted in the skin because this organ is right before our eyes.[1] In a number of human diseases the abnormally patterning skin merely represents the tip of the iceberg of an underlying

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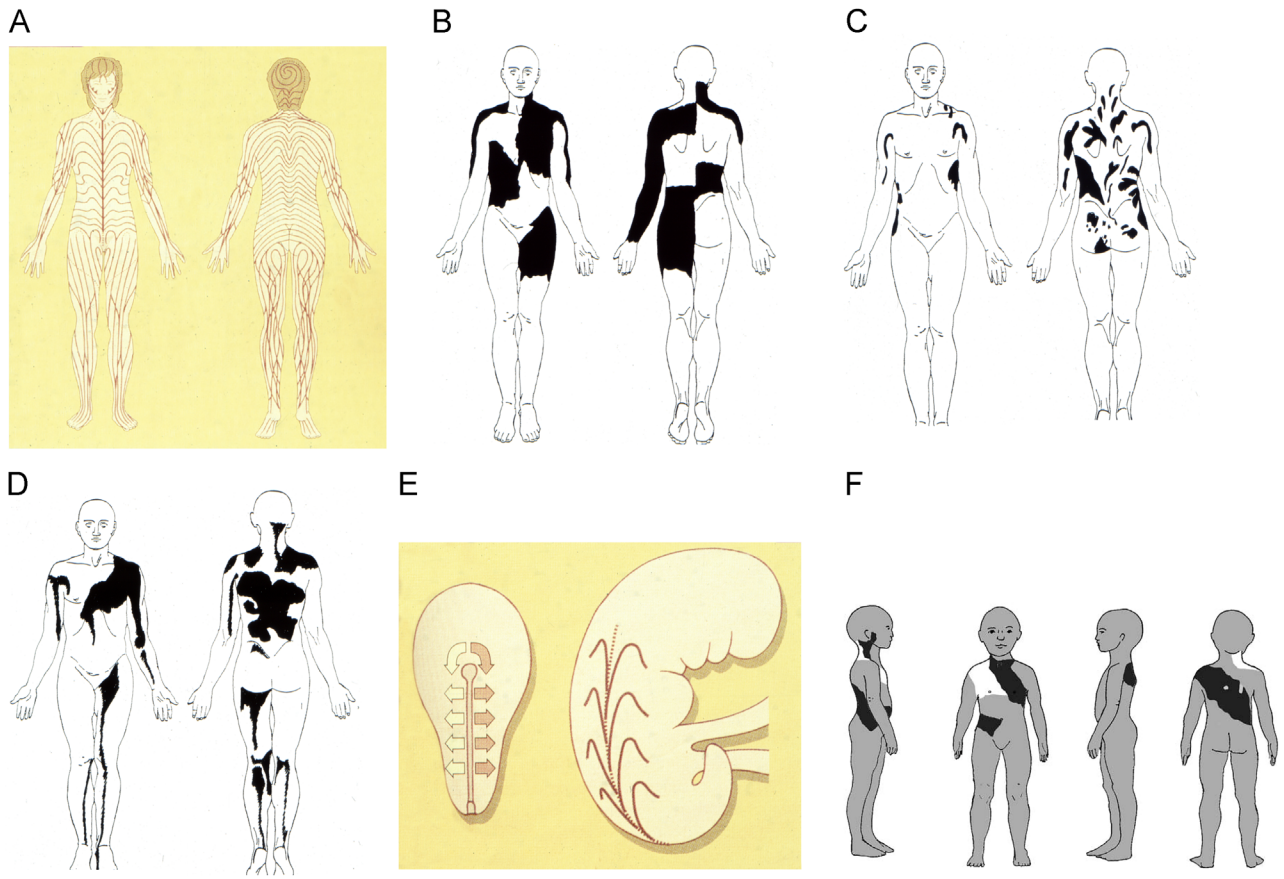

Figure 1 Ideograms showing examples of archetypical patterns of cutaneous mosaicism. (A) Type 1 "along the *lines of Blaschko*" in narrow or large bands; (B) type 2 "*checkerboard*" pattern; (C) type 3 "*phylloid*" pattern; (D) type 4 "*patchy pattern without midline separation*"; (E) type 5 "*lateralisation*" pattern; and (F) type 6 "*sash-like*" pattern. (Color version of figure is available online.)

(systemic and single organ or tissue) involvement[7,8]; alternating segments of affected and unaffected skin or segmentally arranged patterns of abnormal skin mirror similar phenomena occurring in extracutaneous organs or tissues configuring complex mosaic malformation syndromes.[9-12] In some of such syndromes the abnormal mosaic or segmental patterning involve mainly the skin and the nervous system configuring a (true) mosaic neurocutaneous disorder[7,8,11,12] or a well-known neurocutaneous disorder is sometimes superimposed by a pronounced linear or otherwise segmental involvement[11,12] or, lastly, a well-known neurocutaneous disorder can occur (sometimes or only) in a mosaic pattern.[13,14]

A classification of several patterns of cutaneous mosaicism was proposed in 1993[7,8] and expanded in 2014.[1,15]

Archetypical Patterns of Cutaneous Mosaicism

A total of 6 archetypical patterns of cutaneous mosaicism have been so far distinguished, including[1,9,10,15] (Fig. 1) (1) *type 1* "along the *lines of Blaschko*" (ie, a system of cutaneous markings distributed in linear, whorled, S-shaped, V-shaped, or fountain-like patterns and streaks) in (a) narrow or (b) large bands (Fig. 1A); (2) *type 2* "*checkerboard*" pattern (ie, alternating squares of aberrant tissues arranged in flag-like or block-like patterns) (Fig. 1B); (3) *type 3* "*phylloid*" pattern (ie, arranged in leaf-like or lef-shaped oblong macules reminiscent of the floral ornaments of a Jugendstil painting) (Fig. 1C); (4) *type 4* "*patchy pattern without midline separation*" (large patches not respecting the dorsal and ventral midline) (Fig. 1D); (5) *type 5* "*lateralisation*" pattern (ie, a unilateral diffuse involvement with a sharp midline demarcation, particularly strict on the ventral aspect of the trunk) (Fig. 1E); and (6) *type 6* "*sash-like*" pattern[1,15] (ie, large oblique macules reminiscent of a swathed sash, or large, round or flag-like areas) (Fig. 1F). *Less well-defined* or so far *unclassifiable* patterns include[1]: (a) a pattern of diffuse hypopigmentation of the trunk leaving a small area of normal skin on a unilateral aspect of the thorax and a segmental hyperpigmentation involving both arms and the trunk, apparently with a midline separation [so far recorded in cutis tricolor: see specific paragraph]; (b) the so-called "*Pallister-Killian pattern*" with streaks and spots of hypopigmentation (or, less often, hyperpigmentation) not compatible with the pattern of Blaschko's lines ["atypical" Blaschko lines so far recorded in Pallister-Killian syndrome]; and (c) the "*mesotropic facial pattern*" involving (in a square-shaped pattern) the phyltrum and the upper lip (and sometimes the forehead and lower lip) [so far recorded in