**Genetic Report**

These should report a dermatological case involving genetics or a genodermatosis that has made an impact on the author.

**Requirements for submission**

Genetic Reports should include:

* no more than 600 words,
* no more than two clinical figures including a histological figure or an electrophoretogram
* up to 2 tables and 6 references,
* 2 multiple choice questions (MCQs) that test the knowledge of the reader. Detailed guidelines for authors for writing MCQs are provided [here](https://www.onlinelibrary.wiley.com/pb-assets/assets/13652230/mcq_guidelines-1509469139000.pdf).

**Total word count: 622**

**Title: Pigmentary anomaly caused by mosaic 3q22.2q29 duplication**

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A 39-year-old with a life-long history of linear hyperpigmentation affecting her limbs sought advice regarding the potential risks to her offspring. As she had been given a possible diagnosis of Incontinentia Pigmenti (IP), she was referred to our dermatology department by the genetics team for further evaluation. The skin changes appeared spontaneously during infancy, without any preceding vesicular or inflammatory changes, and have remained static since. She had no other medical problems.

On examination she had linear, sharply defined hyperpigmentation along the lines of Blaschko affecting both upper and lower limbs (Figure 1a and 1b). In addition, she had linear skin-coloured papules on her left palm (Figure 1c) also in a Blaschkoid distribution, and streaks of lighter- coloured hair on her scalp. There were no abnormalities noted on her nails. Ophthalmoscopy revealed hypopigmented spots in the macular region of the retina in each eye (Figure 2a). Optical coherent tomography demonstrated these were due to focal areas of depigmentation of the retinal pigment epithelium. The patient had been reviewed annually in the ophthalmology clinic for over 10 years with no significant progression of these hypopigmented lesions.

The characteristic clinical stages evolving in IP were not seen in our patient and sequencing of the *IKBKG* gene did not reveal any mutation found in 80% of patients with IP1. Skin biopsies from a palmar papule and a hyperpigmented streak on her leg showed only mild acanthosis, not diagnostic of any known condition. Karyotype was performed on biopsy with no evidence of mosaicism, only moderate X-inactivation skewing on all analysed DNA from her peripheral blood lymphocytes and dark and light skin biopsies. We carried out an array comparative genomic hybridization (array-CGH) on DNA extracted from a punch biopsy of a papule on her hand, which revealed a 63.4 Mb duplication on the long arm (q) of chromosome 3: arr[GRCh37] 3q22.2q29(134212001\_197837069)x3 (Figure 2b). This mutation affected an estimated 40% of the analysed cells and had not been found on a previous array-CGH performed on her blood. Since fibroblast culture was not possible from the skin biopsy, it remains unconfirmed whether this extra material is present as an interstitial duplication or as a supernumerary marker chromosome.

The region of the duplication contained the *HPS3* gene, which appears to be the only known gene in this duplication to be involved in the pigmentary pathway2. In our patient, this mosaic genetic anomaly did not result in any additional developmental abnormalities Conversely, Gimelli et al3 presented a case with Blaschkoid hyperpigmentation with duplication similar in magnitude and cytogenetic location, with more profound debilitating anomalies including mental retardation and ambiguous genitalia. As they reported increased *HPS3* gene expression, we hypothesise this to be the cause of increased pigmentation in our patient3.

The Blaschko lines, first described by Alfred Blaschko in 1901, are known to represent the pathways of epidermal cell migration during embryonic development4. Various pigmentary abnormalities have been described along these lines.

These presentations are thought to be a result of different phenotypes within an individual resulting from epigenetic or genetic mosaicism4,5. In a high proportion of cases, Blaschkoid dyspigmentation can be accompanied by extra-cutaneous manifestations, most commonly of the neurological type6.

Our case is an example of genetic mosaicism resulting from a *de novo* genetic defect arising at some point in embryonic development. In our case, there were no apparent abnormalities apart from the skin and hair, but another reported case was much more severely affected. The readily available genetic and cytogenetic tests will enable us to further characterise the aetiology and potential risks in these patients, in particular relating to the risks posed to their unborn offspring given the possible involvement of gametes. Non-invasive pre-natal testing may play a role in the future for screeningthe more severe cases.

**MCQs-** Interpretation of Blaschkoid hyperpigmentation

**Question 1**

Pigmentary anomalies with a linear pattern on patients' limbs are described as having a Blaschkoid distribution. Why do these patterns arise?

1. It is an autosomal dominant genetic disorder
2. It is an X-linked genetic disorder
3. It is a result of genetic mosaicism
4. It is a sporadic presentation of unknown origin
5. It is a recessive genetic disorder

Answers to question 1

1. Incorrect. Although some familial cases have been described, Blaschkoid dyspigmentation is not a specific disorder but rather a pattern seen in patients who have cell lines with different phenotypes resulting from mosaicism of genetic or epigenetic origin, such as that which occurs in females with Incontinentia Pigmenti.
2. Incorrect. Blaschkoid dyspigmentation does not have a specific pattern of inheritance but rather depends on the underlying aetiology.
3. Correct. Blaschkoid dyspigmentation is a result of mosaicism. The pattern seen relates to the migratory pathways of keratinocytes and melanocytes during embryonic development.
4. Incorrect. The aetiology of Blaschkoid distribution of disease has been understood for a long time and the advent of genetic studies has allowed further characterisation of these presentations.
5. Incorrect. As above there it is not an individual genetic disorder but rather a pattern of presentation applicable to genetic anomalies.

**Question 2**

You are reviewing a 2-year-old child in your paediatric Dermatology clinic who presents with Blaschkoid hyperpigmentation in a linear and whorled pattern. You cannot find any obvious extra-cutaneous involvement in your examination. Can you reassure the child´s mother about this presentation?

1. Yes, the patient has got Linear Whorled Naevoid Hyperpigmentation and can be discharged from Dermatology
2. Yes, the absence of any congenital deformities guarantees this disorder is limited to the skin
3. No, cutaneous hyperpigmentation in this distribution is always associated with neurological abnormalities
4. Yes, but you should explain that her grandchildren might have similar pigmentary changes on their skin as it is autosomal dominant
5. Not at this stage. This type of presentation can have associated extra-cutaneous changes which might not become apparent until later on in childhood. The child should be followed-up and have input from an ophthalmologist, paediatrician, and neurologist.

Answers to question 2

1. Incorrect. Although this type of presentation could be referred to as Linear Whorled Naevoid Hyperpigmentation, it can be associated with extra-cutaneous manifestations not apparent on dermatological examination and the child should not be discharged from secondary care.
2. Incorrect. In some cases of mosaic dyspigmentation there may be congenital deformities as well as other extracutaneous features, but these are not mutually exclusive and therefore the absence of one does not rule out the other.
3. Incorrect. There are cases in which abnormalities can be limited to the skin.
4. Incorrect. Although some cases of familial Blaschkoid dyspigmentation have been described, a mosaic genetic mutation passed on to offspring would affect all cells from the first stage of embryonic development and therefore not have a Blaschkoid distribution.
5. Correct. Although on initial assessment only skin changes might be apparent, the presence of neurological abnormalities, such as epilepsy or intellectual impairment requiring referral to neurologist for further investigations, may not present until later in childhood. The right level of counselling and support should be offered to the parents and children should be evaluated closely to ensure all the developmental milestones are met.

**References:**

1. Conte MI, Pescatore A, Paciolla M, Esposito E, Miano MG et al. Insight into IKBKG/NEMO locus: report of new mutations and complex genomic rearrangements leading to incontinentia pigmenti disease. Hum Mutat. 2014;35(2):165-77.
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3. Gimelli G, Giorda R, Beri S, Gimelli S, Zuffardi O. A large analphoid invdup(3)(q22.3qter) marker chromosome characterized by array-CGH in a child with malformations, mental retardation, ambiguous genitalia and Blaschko's lines. Eur J Med Genet. 2007;50(4):264-73
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6. Salas-Labadía C, Gómez-Carmona S, Cruz-Alcívar R. *et al.* Genetic and clinical characterization of 73 Pigmentary Mosaicism patients: revealing the genetic basis of clinical manifestations. Orphanet J Rare Dis. 2019;14(1):259.