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TITLE PAGE

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Genetic mosaicism in dermatology: Clinical utility of genetic testing of skin lesions

Mosaicism is defined as the existence of two or more distinct clonal cell populations within one individual, which is the product of a single fertilised egg.[1] Mosaicism is an acquired mutation during embryonic development and can be classified according to reproductive risk: *somatic* mosaicism is limited to non-reproductive cells; *gonadal* mosaicism is found only in reproductive cells and can be expressed constitutionally in future generations and *gonosomal* mosaicism is in both.[1,2] Mosaic presentations of genetic disorders are often observable in a segmental form in the skin, due to postzygotic *de novo* mutations.[1] Thus, cutaneous mosaic disorders offer a unique opportunity to investigate genetic mosaicism.

Genetic investigation has been enhanced by next generation sequencing, which sequences nucleotides faster and cheaper than traditional Sanger sequencing.[3] Mosaicism can be determined by testing constitutional DNA from peripheral blood lymphocytes and comparing to somatic DNA derived from a biopsy of affected skin. The clinical value of confirming somatic mosaicism is twofold; it may infer prognosis or outcome, whilst potentially providing a risk assessment to future offspring. We illustrate the clinical utility of genetic testing in suspected mosaicism, presenting a case series of patients seen in the multidisciplinary Genodermatoses Clinic at the Royal Melbourne Hospital.

Case 1:Proteus Syndrome

A 47-year-old female was noted at 12-months of age to have hypertrophy of the right thumb and index finger (Fig. 1). A clinical diagnosis of Proteus Syndrome was made, before

genetic testing was feasible. She later developed epidermal naevi on her chest and right leg. DNA extracted from a naevus biopsy exhibited a pathogenic missense variant, *AKT1* c.49G>A(p.Glu17Lys). This variant which was absent from peripheral blood DNA, confirmed a diagnosis of Proteus syndrome with segmental overgrowth due to activation of the PI3K/AKT/mTOR pathway.[4] The variant causes an increased risk of meningiomas and reproductive malignancies.[4,5]

Case 2:*Segmental Darier Disease*

A 35-year-old man had a 15-month history of keratotic papules across his left chest and flank in a Blaschkoid distribution. Histopathology showed focal acantholytic dyskeratosis, clinically consistent with a diagnosis of segmental Darier disease. He sought reproductive advice given his diagnosis. The c.2249G>A(p.Arg75OGln) variant was found in the *ATP2A2* gene in the skin biopsy, but not peripheral blood, suggesting a likely pathogenic R750Q mosaic variant.[6] While there is a low likelihood that he will produce offspring with Darier disease, he was counselled regarding his option of prenatal testing or preimplantation genetic diagnosis because of the location of his lesions.

Case 3:Epidermal naevus

A 37-year-old female had keratinocytic epidermal naevi in a Blashkoid distribution over her left shoulder and mid-back (Fig. 2). The naevi were present from birth. She was undergoing *in vitro fertilisation* pregnancy. Given the concern of systematisation in her future children, she was considering preimplantation genetic diagnosis, if genetic testing confirmed a germline mutation. A heterozygous pathogenic variant c.742C>T(p.Arg248Cys) of the *FGFR3* gene was found in affected skin, but not in peripheral blood; indicating a *de novo* somatic mutation. Genetic counselling was provided and given the low likelihood of inheritance, preimplantation genetic diagnosis was not requested.

Case 4:Segmental Neurofibromatosis Type 1

A 38-year-old male sought advice following a clinical diagnosis of Neurofibromatosis Type 1 in his infant son, confirmed by the NF1:c.1756_1759del pathogenic variant. Examination of the patient revealed café au lait macules in a Blashkoid distribution overlying his left lower abdomen, raising the possibility of segmental Neurofibromatosis Type 1 affecting gonadal tissue (Fig. 3). DNA testing of peripheral blood and lesional skin did not reveal the mutation evident in his son's DNA. Genetic counselling includes a potential risk of 50:50 to future children.[5]

Case 5 and 6(Published):

Case 5 demonstrated phacomatosis pigmentokeratotica with a pathogenic heterozygous variant in the *HRAS* gene,c.37G>C(p.Gly13Arg) in DNA extracted from a sebaceous naevus of a 22-year-old male.[7] Case 6 demonstrated X-linked dominant chondrodysplasia punctata(CDPX2) with a post-zygotic variant in the *EBP* gene,c.10_20del(p.Asn4fs) of a 25-year-old male, with longstanding cicatricial alopecia and Blaschkoid ichthyosis.[8]

Mosaicism of single gene disorders explains segmental skin lesions in a range of heritable skin disorders. A mutation was identified in DNA derived from skin biopsies, which was not present in peripheral blood DNA in five of these six cases. Where lesional skin was in close proximity to gonadal tissue, patients were counselled to the possibility of gonadal mosaicism.[5] In cases of mosaicism not involving gonadal tissue, it is reasonable to reassure the patients that the likelihood of disease being passed on to offspring is low. We validate the clinical utility of genetic testing, and the unique opportunity it provides to diagnose and manage potential risks associated with somatic mosaicism.

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FIGURE LEGENDS:

Figure 1: Asymmetric and disproportionate over growth of right-hand fingers with macrodactyly in a 47-year-old female with Proteus syndrome.

Figure 2: A. Scattered epidermal naevi located over the left chest, shoulder and **B.** lower back of a 37-year-old female with somatic epidermal naevi.

Figure 3: A. A streak of café au lait macules overlying the left lower abdomen in a 38-year-old male, raising the possibility of segmental Neurofibromatosis Type 1. **B.** Magnified image of left lower abdomen showing scattered macules in a linear, Blashkoid pattern.

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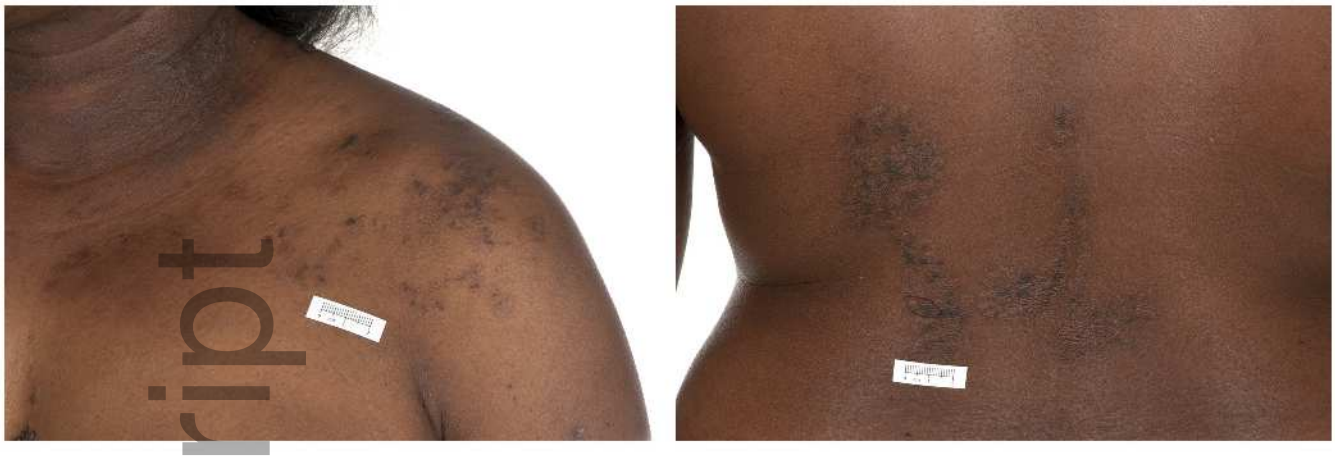

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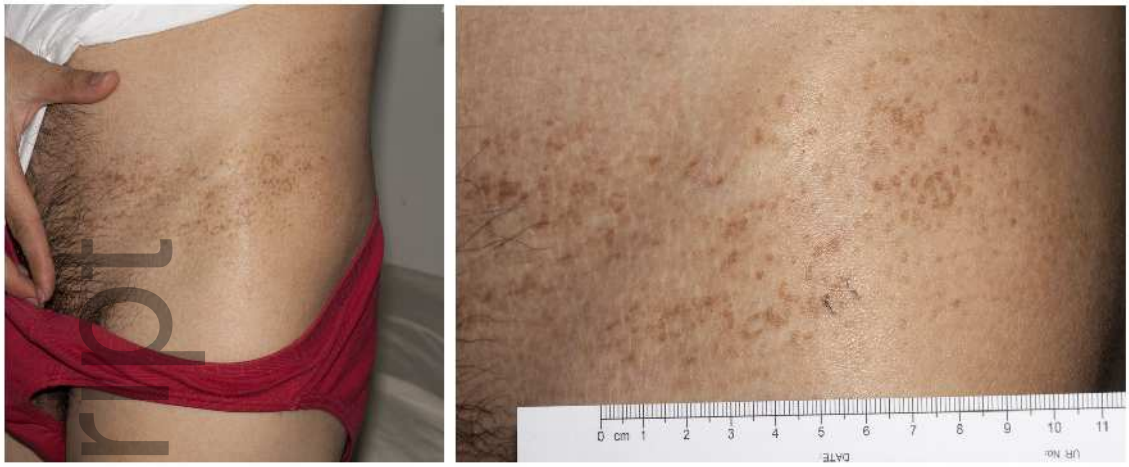

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