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Incontinentia pigmenti in a father and daughter

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Incontinentia pigmenti (IP) is a rare multi-system X-linked dominant genetic disorder caused by mutations in *IKBKG*, encoding inhibitor of nuclear factor kappa-B kinase subunit gamma (IKK- γ). Functionally, the encoded IKK- γ protein participates in nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) signalling to regulate inflammatory and immune responses and prevent

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apoptosis. Loss-of-function mutations in *IKBKG*, as occurs in IP, leave mutant cells vulnerable to apoptosis when exposed to tumour necrosis factor alpha.[1] Females with IP who inherit germline mutations in *IKBKG* usually survive because of skewed X-inactivation favouring expression of the wild-type allele, whereas most males with IP die *in utero*. However, possible explanations for rare examples of male IP survival include: Klinefelter syndrome (47XXY), hypomorphic *IKBKG* mutations, and post-zygotic mutations in *IKBKG* leading to somatic mosaicism.[2] Here, we describe an adult male with IP, with survival being attributed to tissue mosaicism, who then fathered a female child with IP affecting her germline.

A 29-year-old Kuwaiti man was born with severe linear blistering followed by hyperpigmentation and hyperkeratotic plaques in a Blaschkoid distribution on the head, trunk, upper and lower limbs (Figure 1a and b). He had linear facial asymmetry and blindness of the left eye. His dentition was abnormal, necessitating dentures. The rest of his neurological examination was unremarkable. His one-year-old daughter was born at term via normal vaginal delivery. There was no history of consanguinity in the family. Soon after birth she had linear, streaky erythema and vesicles, with subsequent hyperpigmentation and hyperkeratotic plaques; lesions were noted on the upper and lower limbs along lines of Blaschko (Figure 1c). Other systemic abnormalities were excluded on clinical examination and developmental parameters were normal. No neurological abnormalities have been noted during her first 12 months.

Following informed consent, a three-primer PCR protocol was used to screen for the most common recurrent pathogenic mutation in *IKBKG* that underlies ~80% of IP cases worldwide, an intragenic deletion from within intron 3 to within intron 10 that removes all of exons 4-10.[1] Such a PCR protocol is necessary because of a non-functional copy of *IKBKG* running in the opposite

direction. We used a recently reported method,[3] that represents an improvement over other protocols because of its capacity to non-preferentially amplify both wild-type and deletion mutant *IKBKG* alleles (c.f. some other protocols that favour amplification of the wild-type allele because of GC nucleotide mismatch).

This PCR protocol (Figure 2) failed to demonstrate presence of the common deletion in *IKBKG* in the father's genomic DNA extracted from his peripheral blood. However, the deletion was clearly identified in his lesional skin DNA and, to a much lesser extent, in his non-lesional skin DNA. In contrast to the father, the deletion was present in peripheral blood genomic DNA from his daughter. Presence of all deletions was confirmed by Sanger sequencing (data not shown). The clinical phenotype in this family infers that the father must be a tissue mosaic for the IP deletion mutation that has unexpectedly also affected the gonads and hence been transmitted to his daughter as a germline abnormality. Her clinical signs reflect skewed X-inactivation, resulting in survival, as is the case for most affected females.

To our knowledge, there are only three previous reports of father-to-daughter transmission of IP. Two cases were similar to ours, with a history of probable tissue mosaicism in the fathers,[4,5] although the clinical descriptions predated the discovery of *IKBKG* mutations in IP and thus neither of these cases had supportive molecular pathology. One other report described a clinically unaffected father having two daughters with IP (born to different mothers).[6] The lack of clinical abnormalities in the father in that case is consistent with gonadal mosaicism, although again the report was published before the discovery of *IKBKG* as the IP gene. Thus our fourth case represents the first example of father to daughter transmission of IP in which a pathogenic mutation in *IKBKG* has been demonstrated.

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Figure legends

Figure 1. Clinical features (a) Blaschkoid distribution of hyperpigmentation with hyperkeratotic plaques, with some pallor and atrophy, affecting the abdomen in the father; (b) Similar Blaschko-linear changes are evident on his right leg; (c) Lower limbs of his daughter showing Blaschko-linear vesicles and early verrucous inflammatory plaques.

Figure 2. A modified PCR amplification method identifies the recurrent intragenic deletion of *IKBKG* in the DNA samples from the father's affected skin and the proband's blood, but not from the father's blood (see ref. 1 for detailed methodology). Only a very faint band was detected in the DNA from the father's unaffected skin. For these specific PCR conditions, the upper 1045-bp band indicates the presence of the deletion, whereas the 733-bp band is wild-type. C = control DNA; MW = molecular weight ladder.