Congenital Reticular Ichthyosiform Erythroderma

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Ichthyosis with confetti (IWC) (OMIM 609165), also known as congenital reticular ichthyosiform erythroderma, is a rare autosomal dominant ichthyosis caused by heterozygous mutations in the *keratin 10* (*KRT10*) gene.¹ Affected individuals present with erythroderma and scaling at birth but gradually develop multiple characteristic confetti-like clear areas of normal skin throughout their childhood. Diagnosis of IWC is therefore often delayed until early adolescence when areas of normal appearing skin become larger and more numerous.

A female infant was born via spontaneous vaginal delivery at 36 weeks gestation to non-consanguineous parents. Erythroderma with scaling was noted at birth in the absence of bullae or collodion membrane. The baby had low set small ears, small nares and normal nails. Skin biopsy from the abdomen showed mild parakeratosis and acanthosis, increased basal and parabasal mitotic activity and non-specific spongiosis. Hair analysis was normal on light and electron microscopy. The overall clinical picture was felt to be consistent with congenital ichthyosiform erythroderma (CIE). Her family then moved abroad and the patient was followed in a different dermatology institution. Her early course was complicated by recurrent *Staphylococcus aureus* infections. The ichthyosis was managed with 0.5mg/kg of oral etretinate between the ages 2 - 4 and a trial of topical tretinoin aged 5. Bilateral ear canal impaction with squamous debris required repeated suctioning and the patient also underwent successful release of bilateral cryptotia age 4. Excessive hair growth on the dorsal part of limbs as well as pubic area was investigated at age 3 with no underlying hormonal abnormality identified at the time.

The patient subsequently returned for follow up with our service at the age of 9. Clinical examination revealed short stature, ichthyosis, erythroderma and multiple confetti areas of normal skin predominantly on trunk and face (Fig.1) Palmoplantar keratoderma was now more obvious and the patient also developed bilateral ectropion and flexion contractures of her neck and elbows(Fig.2). Recurrent skin infections, both bacterial and fungal in origin, continued to complicate her course. The patient is now 21 years old and recently underwent successful correction of a right eye ectropion with skin graft from inner thigh area. Recent DEXA scan showed osteopaenia and repeat thyroid function tests revealed subclinical hypothyroidism with mildly elevated TSH and patient was commenced on low dose levothyroxine and dietary calcium supplements. Her ichthyosis and palmoplantar keratoderma are managed only with emollients at present.

In light of recent reports^{1,2} we then screened the patients genomic DNA extracted from PBMCs for mutations in the coding sequence of *KRT10* gene and identified a heterozygous c.1374-1G>C mutation at the acceptor splice site of exon 7. This splice site mutation has previously been reported³ and is predicted to result in aberrant keratin 10, most likely by the use of an alternative cryptic acceptor splice site within exon 7 resulting in a frameshift and an arginine-rich tail domain. Previously reported mutations causing IWC were shown to create frameshifts in intron 6 or exon 7 of *KRT10* resulting in arginine rich tails.^{1,2}

The first report of the genetic basis for IWC¹ identified heterozygous frameshift mutations in the *KRT10* gene resulting in arginine-rich C-terminal peptide as the cause of IWC. This premature stop is predicted to result in mislocalisation of keratin 10 to the nucleolus, disrupting the keratin network and leading to loss of barrier function. This mutation was lost due to correction through revertant mosaicism in

confetti-like areas of normal skin. Another disorder associated with mutations in keratin 10 gene is epidermolytic ichthyosis (EI), previously known as epidermolytic hyperkeratosis. *KRT10* mutations reported in EI however do not result in arginine – rich tail as is the case in IWC. Our case further confirms that specific *KRT10* gene defects affecting the keratin 10 tail cause IWC and also highlights the typical initial presentation with erythroderma and scaling resembling CIE with gradual development of areas of healthy skin within ichthyotic skin during childhood and early adolescence. Further clinical features present in our patient and similar to other reports of IWC include prominent palmoplantar keratoderma, hypertrichosis affecting dorsal limbs^{2,3,4,5}, ectropion^{2,3,4,5}, short stature^{3,5}, but also contraction neck deformity and cryptotia³.

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Figure 1 (a) Chest and (b) back confetti-like areas of normal skin.

Figure 2 (a) dorsal and (b) ventral side of arm with hyperkeratotic palm, elbow contracture and cofetti – like areas of normal skin.