Incontinentia Pigmenti Type II (IP2)

47

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Contents

MIM Number
308310

Synonyms
Bloch-Sulzberger syndrome

47.1 Definition

Incontinentia pigmenti is a multisystem X-linked condition that is male lethal and therefore only affects girls. The condition is characterised by a vesicular erythematous skin rash and affects ectodermal structures (i.e. the skin, hair, teeth and nails). In addition the condition, in about 1/5 of patients, is associated with ocular abnormalities, which resemble exudative vitreoretinopathy and can cause neovascularisation and tractional retinal detachment [1].

47.2 Inheritance

IP is a male lethal X-linked condition, which affects girls. (This is sometimes termed X-linked dominant inheritance.) The condition is caused by mutation of the *IKBKG* (Inhibitor Of Kappa Light Polypeptide Gene Enhancer In B Cells, Kinase Of, Gamma) gene on Xq28, which has also been termed *NEMO* (NF-Kappa-B Essential Modulator) [2].

About 80 % of mutations result an intragenic recombination that leads to deletion of exons 4–10 of *NEMO* [3]. For affected females, this will either be a de novo event or is inherited from the mother. In addition, missense mutations, frameshift mutations and nonsense mutations have been described although there is no genotype: phenotype correlation. Because these mutations are cell lethal – and hence lethal to males – they cause 100 % skewing of X-inactivation in the blood of females. *NEMO* is required for activation by cytokines of the transcription factor nuclear factor kappa B (NFKB). NFKB activation is implicated in inflammation,

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autoimmunity as well as for the inhibition of apoptosis. *NEMO* is thus essential in the modulation of immune, inflammatory and apoptotic responses.

47.3 Epidemiology

The disease is extremely rare with no estimates of prevalence although it is proposed that around 1,000 cases have undergone molecular genetic testing.

47.4 Clinical Features

Skin: Affected females have an erythematous, blistering rash that manifests at, or soon after, birth. This changes over time to become pigmented. It then fades to leave patchy hypopigmentation in adulthood (Figs. 47.5, 47.7 and 47.8). The areas of pigmentation and depigmentation are linear, following Blaschko's lines, the paths of embryonic dermal cell migration (Fig. 47.8). The skin eruptions may lead to patchy alopecia.

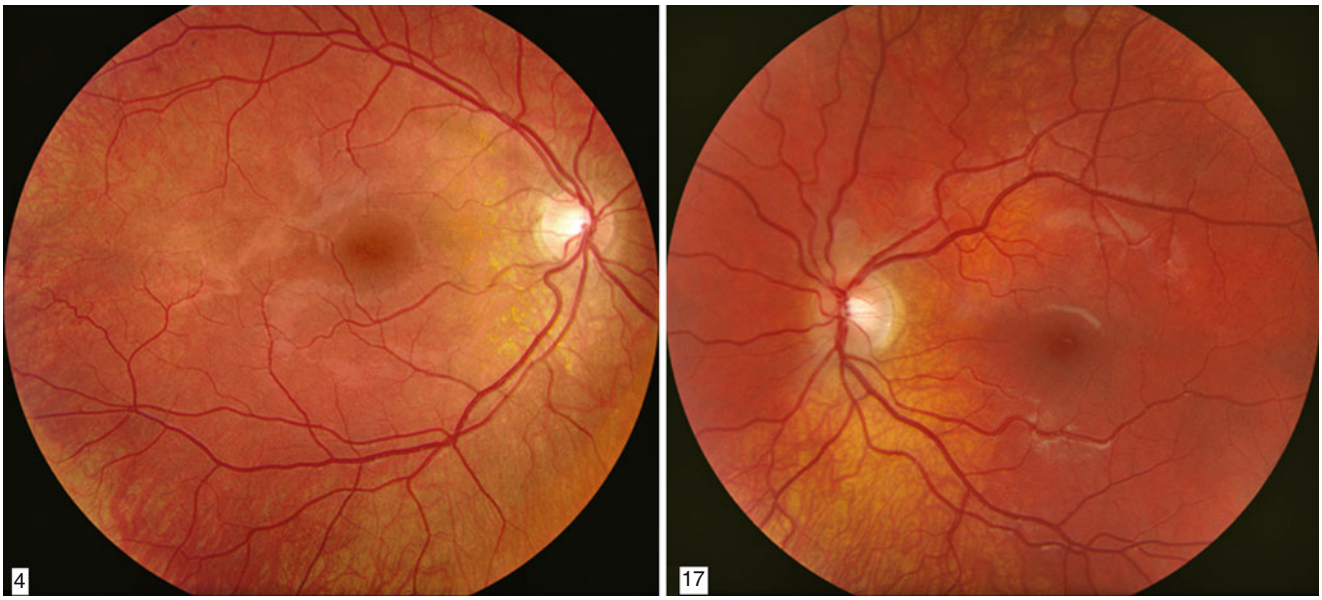

Fig. 47.1 Fundus colour photographs of the posterior pole in an 8-year-old girl. VA 20/20 OU. The left eye of her mother was enucleated after repeated retinal detachment surgery, whereas the functionally normal right eye presented retinal new vessels and retinal ischaemia in the temporal periphery. An elder sister of the patient presented skin lesions, hypodontia and arteriovenous anastomoses in the fundus periphery of the right eye. In the sister's left eye, no fundus lesions were seen

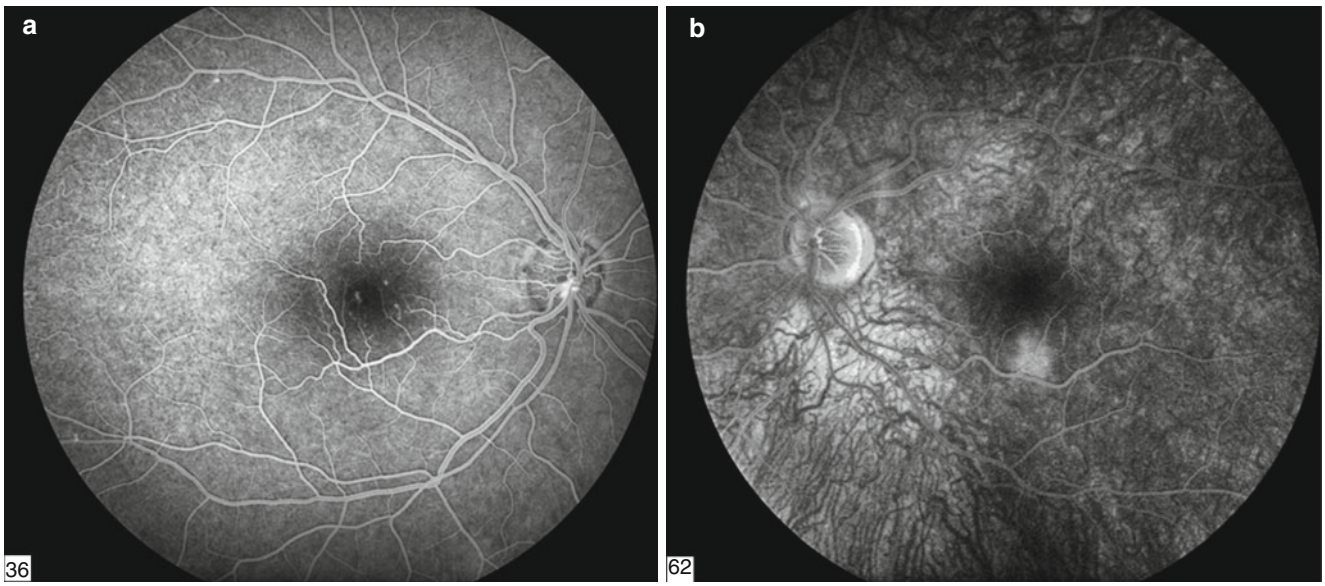

Fig. 47.2 Fluorescein angiography of the posterior pole of the patient in Fig. 47.1. (**a**) Right eye: capillary anomalies close to the fovea and discrete prepapillary new vessels on the optic disc. (**b**) Localised diffusion under the left fovea

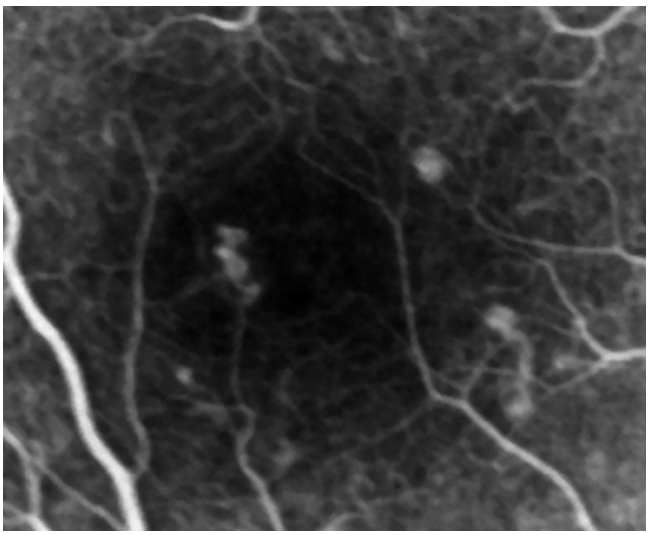

Fig. 47.3 Enlargement of the fluorescein angiography of the right macula, highlighting the capillary changes

47.4.1 Other Extraocular Manifestations

Dental: Hypodontia and microdontia, delayed eruption of teeth (Figs. 47.5 and 47.8).

Nails: Dystrophic nails.

Breast: Abnormalities include breast aplasia, asymmetry and supernumerary nipples [4].

CNS: Although severe neurological abnormalities including seizures and developmental delay are described, they were probably overrepresented in the early literature. They may be more common in those with ophthalmic abnormalities.

Retina: The precise frequency of ocular abnormalities is unclear but is reported in around a fifth of patients [4, 5]. IP2 is associated with defective peripheral retinal vascularisation, which resembles familial exudative vitreoretinopathy or retinopathy of prematurity. Importantly the main risk of ocular complications in infancy and childhood (Figs. 47.1, 47.2, 47.3, 47.4 and 47.6) as with FEVR, the ocular and

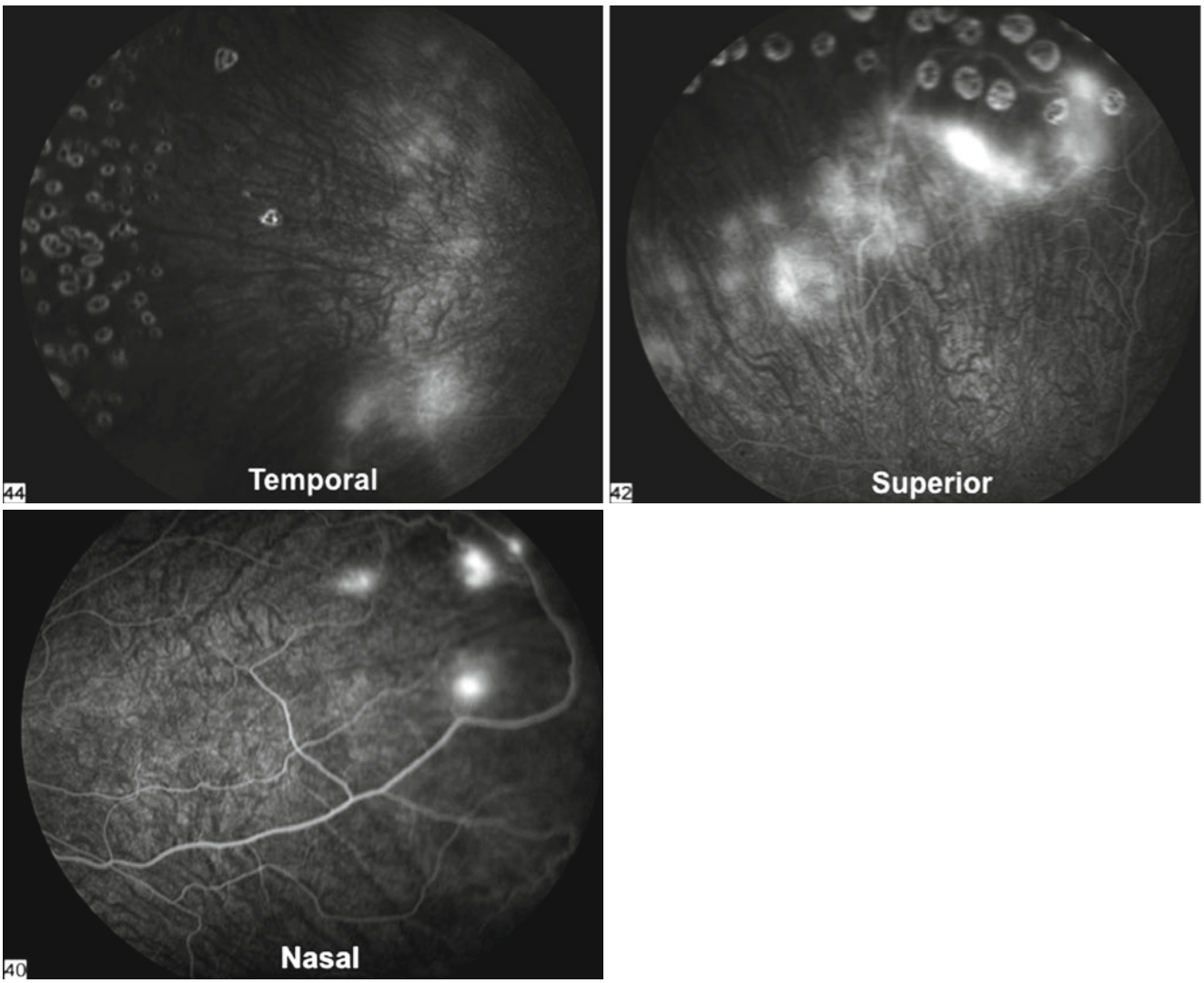

Fig. 47.4 Fluorescein angiography of the retinal periphery of the patient of Fig. 47.1. Peripheral ischaemia and retinal neovascularisation (partially treated with the laser)

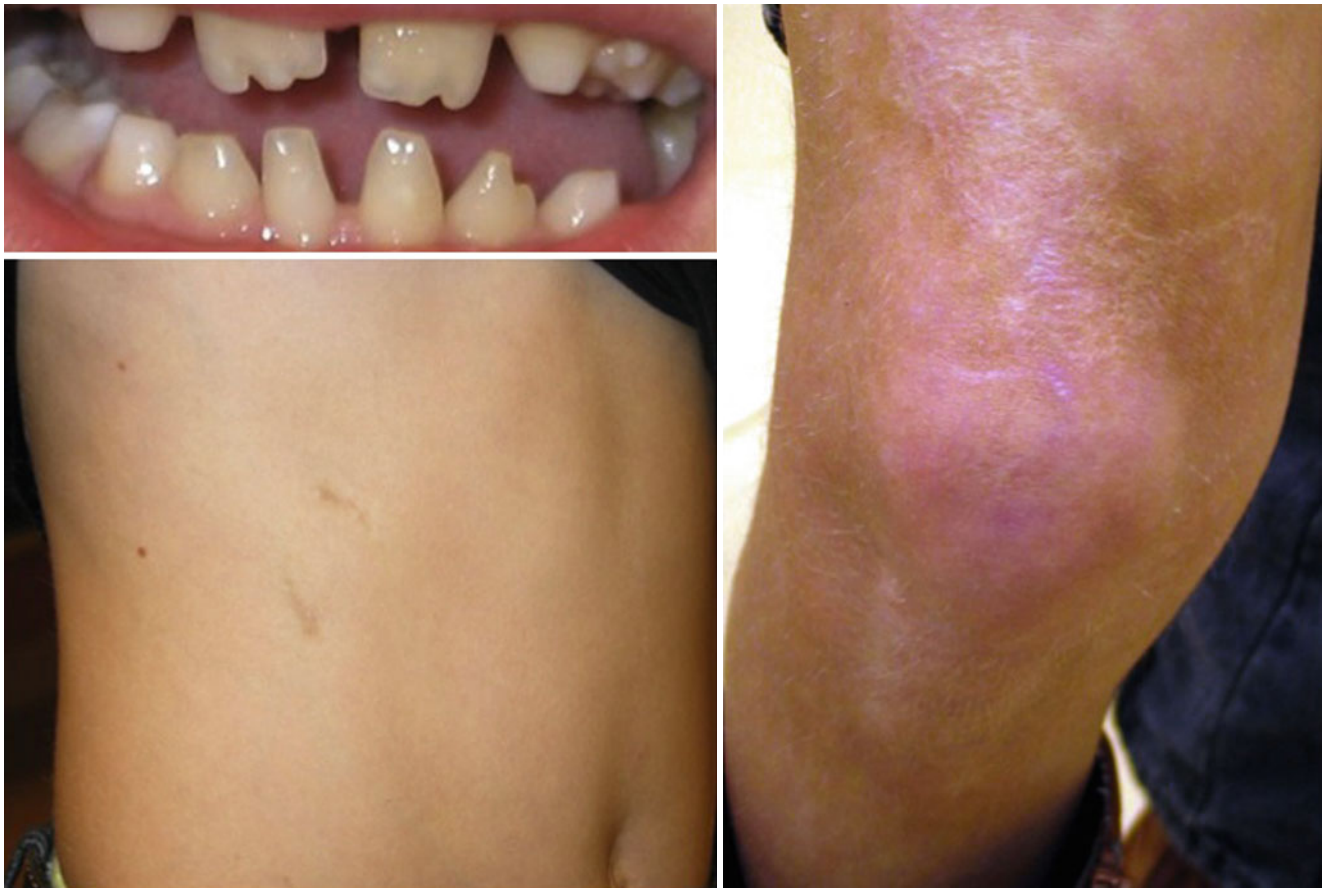

Fig. 47.5 Dental anomalies, hyperpigmented spots on the trunk and hypopigmented scars on the knee of the patient of Fig. 47.1

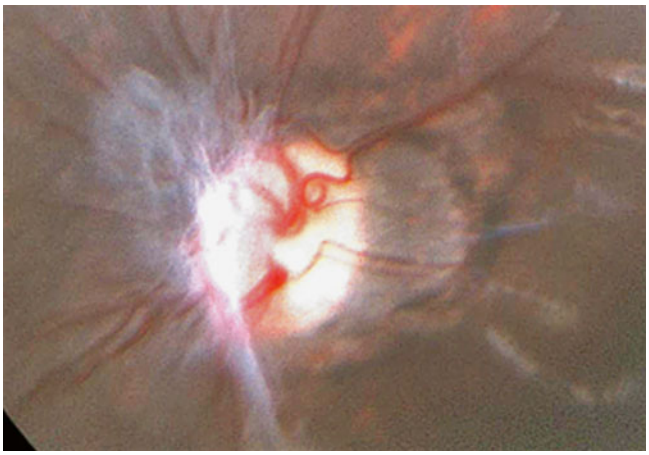

Fig. 47.6 Pale optic disc and retinitis proliferans in a newborn girl with IP2

visual complications are the result of retinal ischaemia which can lead to neovascularisation, tractional retinal detachment and in severe cases the development of a vascularised retrolental mass. IP2 is therefore one of the differential diagnoses of leucocoria. Defective foveal vascularisation can cause macular ischaemia/neovascularisation.

The variable nature of the ophthalmic abnormalities in IP2 and the real risk of bilateral disease are such that it is recommended that all affected girls are screened during early life, either being examined under anaesthesia or using indirect ophthalmoscopy. There are no official guidelines for screening although a frequent (monthly) review in the first months of life, and slightly less frequently (around 3 monthly) until around the age of three years has been proposed [6, 7]. In affected eyes there is abnormal retinal vascularisation with peripheral areas of avascularity, which may be visualised directly or with fluorescein angiography. There are no characteristic electroretinographic abnormalities.

47.5 Variants of IP2

IP is a truly monogenic condition, which is extremely rare. The condition may be distinguished from ROP and Norrie disease/FEVR on the basis of the systemic abnormalities. A small number of affected males have been described either with Klinefelter syndrome (47, XXY) or as a result of somatic mosaicism of the pathogenic mutations in *IKBKG* [8, 9].

47.6 Evolution

Like ROP and FEVR, the ocular manifestations of IP2 are highly variable. Unfortunately, the natural history can be severe and bilateral in a small but significant number of cases. Retinal ischaemia can lead to neovascularisation, retinal traction, macular ectopia, falciform retinal folds and total retinal detachment with a 'pseudoglioma' appearance. IP2 is a differential diagnosis of leucocoria.

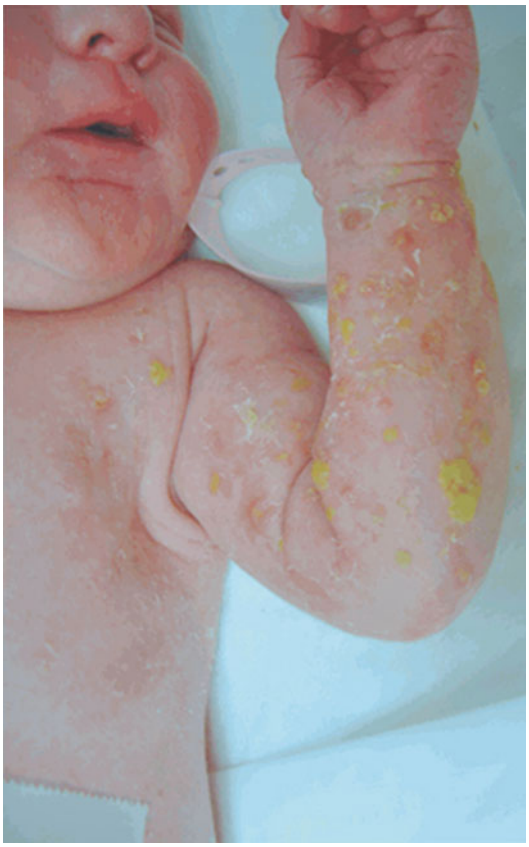

Fig. 47.7 Blisters and wart-like like skin lesions in the patient of Fig. 47.6

47.7 Diagnosis and Differential Diagnosis

A diagnosis of IP2 syndrome must be excluded in those with an appearance of FEVR/ROP. The condition may be diagnosed in young girls with a characteristic history of the typical skin rash. Therefore IP2 must, like FEVR, be suspected in those with retinal folds, exudative or tractional retinal detachment, macular ectopia or straightened retinal vessels. The differential diagnosis includes:

ROP: The retinal appearance of IP2 results from a defect in the vascularisation of the developing retinal, in particular at its periphery, and is similar to retinopathy of prematurity (ROP).

Persistent Hyperplastic Primary Vitreous (*PHPV*): At the more severe end of the spectrum severe IP2, FEVR, Norrie disease and OPPG are all are associated with a severe retinal phenotype that mimics persistent hyperplastic primary vitreous (PHPV).

47.8 Treatment

Individuals with suspected or proven IP2 require full retinal examination and screening over the first years of life. This should be undertaken using indirect ophthalmoscopy with scleral indentation. Like FEVR individuals require management of secondary complications of peripheral retinal ischaemia, for example, using laser of cryotherapy to manage neovascularisation and surgery to treat retinal detachment. The use of anti-VEGF treatments has been described.

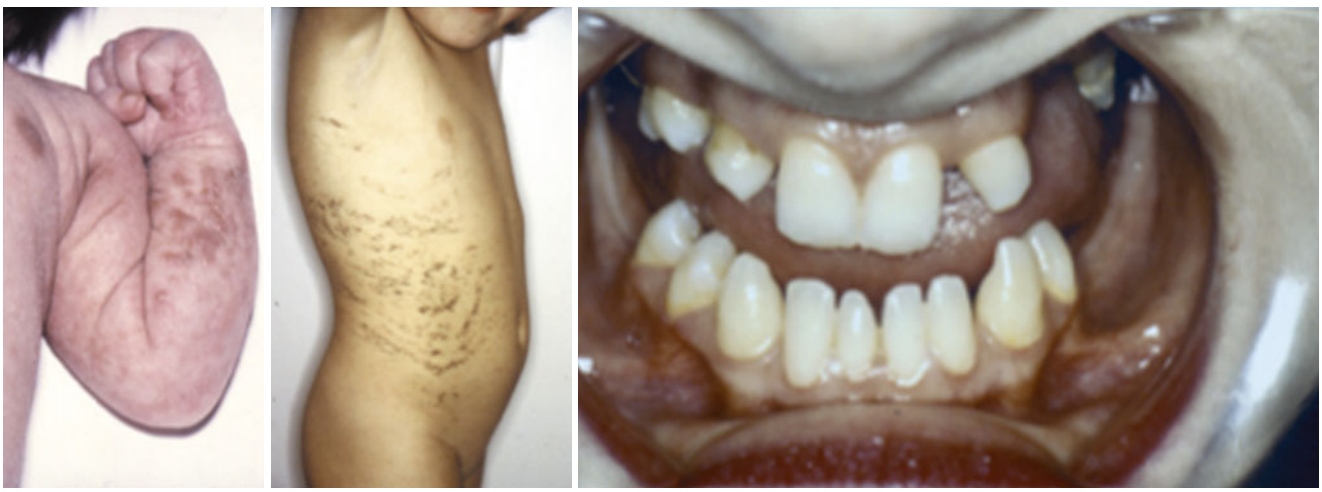

Fig. 47.8 Early blistering skin rash, linear pigmented rash following lines of Blaschko and dental anomalies in IP2

Summary for the Clinician

- IP2 is a very rare male lethal X-linked condition that affects girls.
- The condition is caused by mutations in the iIKBKG gene on Xq28.
- In around 1/5 patients, ocular complications resemble ROP or FEVR as a consequence of defective peripheral retinal vascularisation.
- All children with suspected IP2 should be screened regularly in early life.
- Like FEVR, ocular complications result from abnormal development of retinal vasculature. The secondary consequences of retinal ischaemia cause retinal damage and visual loss.

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