Case Report/Case Series

The Phenotypic and Genotypic Spectra of Ichthyosis With Confetti Plus Novel Genetic Variation in the 3′ End of *KRT10*

From Disease to a Syndrome

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IMPORTANCE Ichthyosis with confetti (IWC) is a genodermatosis caused by dominant negative mutations in the gene encoding keratin 10 (*KRT10*). We investigated clinical and genetic details of a substantial number of patients with IWC in order to define major and minor criteria for diagnosis of this rare disorder.

OBSERVATIONS Parallel clinical investigation of 6 patients with IWC revealed a novel spectrum of phenotypes. We found several features that qualify as major criteria for diagnosis, which are clearly and consistently associated with the condition. These included malformation of ears, hypoplasia of mammillae, and dorsal acral hypertrichosis. Genetic analysis of patients revealed several different frameshift mutations in intron 6 or exon 7 of *KRT10*. Analysis of this locus in 17 unrelated control individuals revealed 2 novel polymorphisms of *KRT10*.

CONCLUSIONS AND RELEVANCE We present for the first time to our knowledge the spectrum of clinical variability of IWC in 6 patients with confirmed mutations in *KRT10*. From this, we have extracted major and minor criteria to aid early and correct clinical diagnosis. Ectodermal malformations, present in all patients, suggest a novel classification of IWC as a syndrome. There is remarkable genetic variation at the IWC disease locus within control individuals from the general population.

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Ichthyosis with confetti (IWC) (OMIM 609165), also referred to as congenital reticular ichthyosiform erythroderma or ichthyosis variegata,[1] is a genodermatosis, first described as ichthyose en confetti in 1984.[2] It is a rare disease, with only 9 and 13 patients being clinically and genetically documented to date, respectively (cited in Burger et al[3]).[4] Patients are first noticed as collodion babies or as having a generalized extensive erythema. Histological findings are epidermal thickening in the ichthyotic skin and a disordered differentiation of keratinocytes with parakeratosis; ultrastructure shows perinuclear shells.[5,6] The ichthyotic phenotype persists throughout life. During childhood, however, numerous confetti-like patches of pale, healthy-appearing skin begin to form, increasing in size and number with age.[3] Histological examination confirms that the skin in these spots is indeed normal.[4,5] Appearance of healthy skin spots often suggests the correct diagnosis. The adult cutaneous manifestation of IWC is a generalized scaly erythroderma interspersed with hundreds to thousands of confetti-like patches of healthy skin, palmoplantar keratoderma, and dorsal acral hypertrichosis (cited in Burger et al[3] and Diociaiuti et al[7]).

The ichthyotic phenotype appears to result from dominant mutations in the gene encoding keratin 10 (*KRT10*).[4] Individuals affected by IWC all carry small heterozygous deletions, insertions, or duplications toward the 3′ end of *KRT10*. This produces a frameshift, and consequently mutated proteins in such patients contain an arginine-rich *C*-terminus. In the patches of healthy skin, however, the disease-causing mutation has reverted to the wild-type sequence through copy-neutral loss of heterozygosity.[3,4] The size of the healthy patches suggests that loss of heterozygosity occurs in the progenitor cells of an epidermal stem cell unit during early embryonic development; however, its exact mechanism and timing is unknown.

Herein, we present clinical data from 6 unrelated patients, together with details of their individual mutations in *KRT10*. Genetic data were also obtained from a seventh individual, the twin sister of one of the patients, who was not studied clinically. We observed several ectodermal malformations, which are clearly associated with the disease and underline its syndromic nature. The aim of the clinical investigations was to determine novel major and minor criteria for

diagnosis of IWC, both before and after the appearance of healthy skin spots. An analysis of the disease locus in 17 control individuals was conducted to identify novel genetic polymorphisms in the general population.

Methods

No concern was raised by the Ethikommission beider Basel, Basel, Switzerland, and the Ethical Committee Fondazione IRCCS Cà Granda, Milan, Italy.

Seven patients with IWC from Italy and Switzerland were included in this study. Patients, or parents of minor patients, provided written informed consent for all investigations. All patients were clinically investigated, with the exception of patient 7, the monozygotic twin sister of patient 6; according to her family, the phenotype of patient 7 is very similar to that of her sister. Clinical examination of all patients was by 2 dermatologists (G.T. and P.H.I.), both experts in genodermatoses. Patient 3 has previously been described clinically,[2,8,9] and patient 4 has been described clinically and genetically.[3,6]

All 7 patients with IWC and some of their parents or siblings were analyzed genetically, as well as 17 unrelated control subjects from the general population. Genetic mutations were identified by direct sequencing of *KRT10* from genomic DNA extracted from whole blood, as previously described.[3]

Clinical features that were clearly and consistently associated with the condition were defined as major criteria. Clinical features, which were not obligatory present in every patient, were defined as minor criteria.

Results

The individuals described in this study include 7 patients with IWC, 6 female and 1 male, from 6 unrelated families. Patients ranged from children to adults. We characterized the following major criteria, which are apparent clinical diagnostic features of the disease (**Table 1**; **Figure 1** and **Figure 2**; and eFigure 1 in the Supplement). All patients had a history of erythroderma from birth, with the appearance of healthy skin spots during childhood. Four patients showed hyperpigmentation within these spots, which seems to be independent of sun exposure (Table 1 and eFigure 1G in the Supplement). Furthermore, all patients showed epidermal scaling and dorsal acral hypertrichosis, limited to the areas of ichthyotic skin (Table 1; Figure 1A; and eFigure 1A in the Supplement). Affected hairs were dark (which had turned white in 1 patient) and relatively thick in all patients, irrespective of skin type. Two female patients reported an unusually fast growth of these hairs. Further major criteria included several ectodermal malformations. Hypoplasia of mammillae was observed in all patients, and malformed ears were observed in 5 patients (Table 1; Figure 1C; and eFigure 1B, C, and G in the Supplement). Unfortunately, because this last feature was not immediately apparent, it was not investigated in 1 patient who could not be recalled to the clinic within the time frame of this study.

Minor criteria (Table 1; Figure 1 and Figure 2; and eFigure 1 in the Supplement) were not present in all of the 6 patients investigated clinically. Nevertheless, they may give important hints for correct diagnosis in future patients. All but 2 patients were born as collodion babies. Lunulae were notably large and the nail plates were elongated in 5 patients (Table 1; Figure 1E; and eFigure 1F in the Supplement). Malformation of nails (unguis inflexus), palmoplantar hyperkeratosis, and ectropion of the eyelids were present in 4 patients (Table 1; Figure 1D; and eFigure 1D and F in the Supplement). Decreased finger length relative to palms and joint contractions of the fingers were apparent in 3 patients (Table 1; Figure 1D; and eFigure 1D and E in the Supplement). Although scalp hair was normal in all patients, 3 patients had reduced eyebrows and eyelashes. Strabismus was present in 3 patients and nystagmus in 2 patients. Teeth were normal in all patients, and none reported increased or reduced sweating or blistering. All patients had a small height and weight relative to their age. The relevance of this remains to be verified, however, by normalization of patient parameters with parental height and weight. In the absence of this significant information, we listed this feature as a minor criterion.

Findings from a detailed investigation of the skin pattern showed that healthy spots were not distributed equally across the skin but followed a gradient, being largest and at greatest density in the neck, décolleté, and scapula regions; fewer and smaller on arms and legs; and almost absent from the face. In 1 adult patient, the skin on the legs showed a patchy, dark brown hyperpigmentation and a verrucous appearance (Figure 1B); these features have been reported in another study of an elderly female patient.[5]

The general impression at clinical assessment was that patients are affected in very individual ways. Generally, skin problems seem to improve with age. All patients but one are receiving long-term systemic acitretin (retinoic acid) treatment.

Patients' parents and siblings were not affected by IWC, with the exception of patient 7, the monozygotic twin of patient 6. Sequencing of *KRT10* from each patient revealed different, heterozygous mutations, which are causative for IWC (**Table 2** and eFigure 2 in the Supplement). Two unrelated patients carried different, single base-pair (bp) mutations in the intron 6 splice acceptor site of *KRT10*; both are predicted to produce an alternative splice site (http://www.umd.be/HSF/) similar to previously described cases of IWC causing mutations[4,7] and, consequently, a frameshift in the DNA sequence. Four patients carried small insertions and deletions within exon 7. Consistent with previous reports, all mutations reported herein caused a frameshift in the sequence predicted to be translated into mutant proteins with an arginine-rich *C*-terminus. Alignment of predicted protein sequences revealed that the arginine-rich sequence varied in length between different patients and contained a consensus sequence of 55 amino acids (eFigure 3 in the Supplement). Consequently, the aberrant keratin 10 protein (K10) is localized in the nucleus (data previously published[3]).

We sequenced the same locus from unaffected parents or siblings of patients and from 17 unrelated control individuals from the general population. We did not detect the

Table 1. Summary of Clinical Findings in Patients With Ichthyosis With Confetti[a]

	Patients, No./Total No. (%)	Patient No.					
		1	2	3	4	5	6
Pathological mutation		c.1374-1G>A	c.1374-1G>C	c.1506_1507delAA	c.1546_1551delinsT	c.1557_1558delCG	c.1573_1574dupA
Age at clinical examination		Child	Young adult	Adult	Adult	Child	Young adult
Sex		Female	Male	Female	Female	Female	Female
Major Criteria							
Erythroderma since birth[b]	6/6 (100)	+	+	+	+	+	+
Current IWC (Figure 1 and eFigure 1 in the Supplement)	6/6 (100)	+	+	+	+	+	+
Scaling with changing severity[b]	6/6 (100)	+	+	+	+	+	+
Appearance of healthy spots, age, y[b]	6/6 (100)	7	12-13	10	10-12	7	12-14
Dorsal acral hypertrichosis (Figure 1A and eFigure 1A in the Supplement)[b]	6/6 (100)	+	+	+	+	+	+
Hypoplasia of mammillae (eFigure 1G in the Supplement)	6/6 (100)	+	+	+	+	+	+
Malformation of ears (Figure 1C and eFigure 1B and C in the Supplement)[b]	5/5 (100)	+	+	+	+	+	Not investigated
Minor Criteria							
Collodion baby[b]	4/6 (80)	+	+	–	–	+	+
Unguis inflexus (eFigure 1F in the Supplement)[b]	5/6 (83)	+	–	+	+	–	+
Large lunulae/long nail plates (Figure 1E and eFigure 1F in the Supplement)[b]	5/6 (83)	+	+	+	+	–	+
Palmoplantar hyperkeratosis (Figure 1D and eFigure 1D in the Supplement)[b]	4/6 (67)	+	–	–	+	+	+
Hyperpigmentation in healthy spots (eFigure 1G in the Supplement)	4/6 (67)	–	+	+	+	–	+
Ectropion of eyelids[b]	4/6 (67)	+	+	+	+	–	–
Strabismus	3/6 (50)	–	+	+	+	–	–
Reduced eyebrows and lashes	3/6 (50)	+	+	–	+	–	–
Decreased finger length relative to palm (Figure 1D and eFigure 1D and E in the Supplement)	3/6 (50)	–	–	+	+	–	+
Nystagmus	2/6 (33)	–	+	–	+	–	–
Pruritus[b]	2/6 (33)	+	–	+	–	–	–
Involvement of scalp[b]	2/6 (33)	Scaling alopecia	Strong scaling	–	–	–	–
Joint contractions (eFigure 1E in the Supplement)[b]	2/6 (33)	–	–	+	+	–	–
Short stature relative to age[b]	6/6 (100)	109 cm (below −3 SD)	170 cm (15th percentile)	160 cm (25th percentile)	153 cm (fourth percentile)	137 cm (37th percentile)	158 cm (20th percentile)
Low weight relative to age[b]	5/5 (100)	16 kg (below third percentile)	58 kg (10th percentile)	48 kg (18th percentile)	45 kg (10th percentile	28 kg (10th percentile)	Not investigated

Abbreviations: +, present; –, absent.

[a] Patients are numbered according to the position of their pathological mutation. Data concerning normal weight and size, used to provide a comparison, were obtained from recent percentile tables from patients' countries of origin.

[b] Clinical features, already reported in different patients than the ones described here.

heterozygous frameshift mutations responsible for IWC in any of these individuals; however, we found 6 common in-frame sequence variants that occurred independently of IWC. Two of these were novel (**Table 3**): an in-frame deletion of 15 bp (c.1521_1535del15) and a triplication of 30 bp (c.1654_1683tri30). These variants occurred independently of each other in the heterozygous state in 1 of 17 control individuals (minor allele frequency [MAF] = 0.029/1). Of 17 control individuals, 8 (MAF = 0.235/8) were heterozygous for a different, recently published variant (c.1468_1479del12).[7]

Discussion

The skin pattern of IWC directly reflects a process of self-healing resulting from the spontaneous loss of a dominant pathological mutation during mitosis.[3,4] The clinical spectrum of symptoms and the features and development of the disease give important insight into its underlying mechanisms. As patients are born with severe skin symptoms, K10 may be important during prenatal skin development. Alternatively, mutant K10 might execute a dominant negative effect, as suggested by the effect of autosomal dominant mutations in *Krt10* in a mouse model for epidermolytic ichthyosis. Although mice heterozygous for a targeted mutation in *Krt10* were clearly affected,[10,11] *Krt10* (−/−) mice had an essentially normal epidermis,[11] suggesting that loss of a given keratin is less detrimental than the presence of a mutant one.

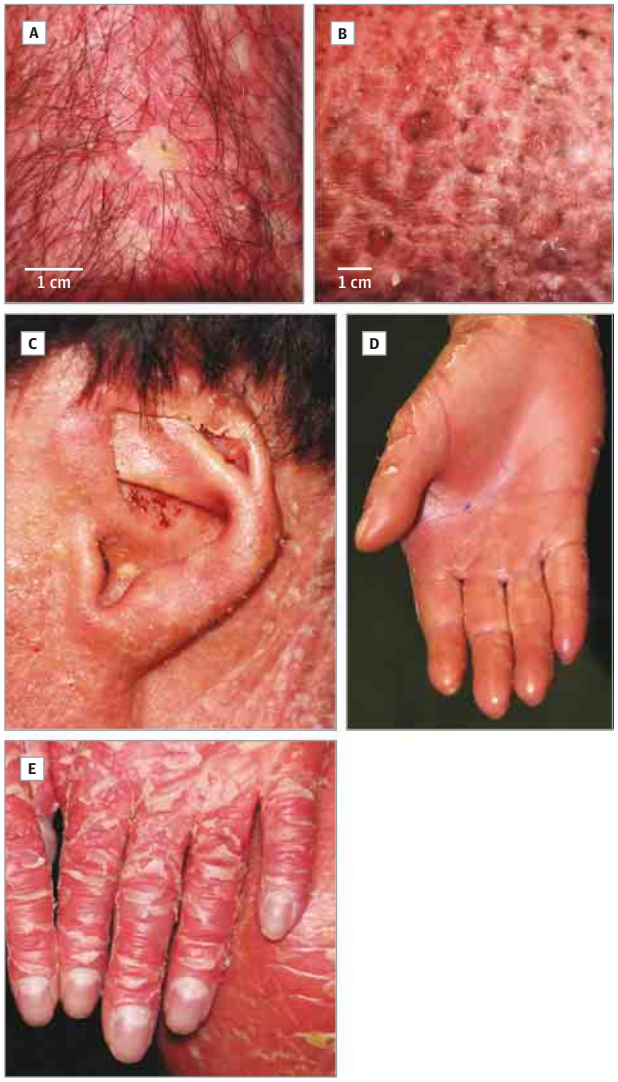
Evidence for prenatal expression of K10 in humans is scarce. Dale et al[12] found expression of K10 in the fetal intermediate skin layer from week 9 of fetal development. Malformation of the ears, present in 5 patients described in this study and mentioned by Elbaum et al[13] and Diociaiuti et al,[7] might indicate an influence of K10 or mutant K10 from around week 6 of development, when formation of the ear is initiated. Alternatively, aberrant cornification might disturb auricle formation, as it is observed in some collodion babies and other severe disorders of cornification (eg, Harlequin fetus). In the context of scaling erythema, malformation of the ears may represent a key sign of IWC, allowing correct diagnosis before the characteristic skin pattern has evolved (Figure 2). Hypoplasia of mammillae is also strongly connected to the disease (Table 1 and eFigures 1 and 2 in the Supplement). Although this major feature has not been previously noted, it is visible on published pictures of other patients with IWC.[5,14]

An association between different ichthyoses and hypertrichosis has been only sporadically reported; thus, hypertrichosis appears to be a specific phenotype of IWC. It is limited to areas of ichthyotic skin, and thus may be triggered by inflammation and hyperemia, as has been hypothesized, for example, in postcast hypertrichosis.

The unequal distribution of healthy spots across the integument indicates an additional, unknown influence in their development, possibly a factor involved in growth or blood circulation.

An intriguingly similar pattern of ichthyotic and healthy skin is observed in patients with pityriasis rubra pilaris. Pityriasis rubra pilaris usually occurs sporadically, being triggered by some unknown factor. Hypothetically, there is a common underlying mechanism for the 2 diseases; as in IWC, the induced erythema might unmask skin areas with a different genetic composition.

Figure 1. Clinical Appearance of Patients With Ichthyosis With Confetti

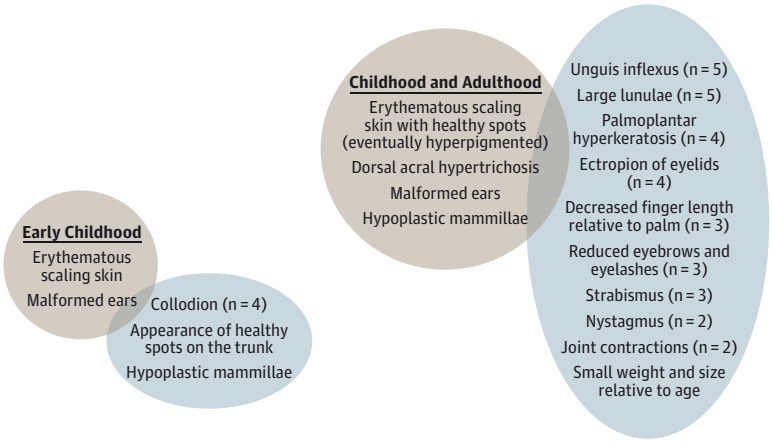


A, Hypertrichosis on the lower arm limited to ichthyotic skin. B, Dark brown hyperpigmentation and verrucous skin on the lower legs of a patient. C, Microtia and angulation of upper helix. D, Decreased finger length relative to palms. E, Large lunulae and elongated nail plates.

Systemic acitretin improves disease symptoms in most patients with IWC. Systemic retinoids decrease cell proliferation while increasing cell differentiation. Interestingly, they have been shown to down-regulate *KRT10* expression.[15]

Sequencing of *KRT10* from patients with IWC revealed that the intron 6 splice acceptor site was affected in 6 of the 15 genetically described kindreds (eFigure 2 in the Supplement). Moreover, this locus is highly repetitive and showed considerable genetic variation in 17 disease-free individuals, pointing to increased plasticity in this DNA region. The sequence variants are all in-frame and not related to overt disease; however, we did not test whether any of these polymorphisms were

Figure 2. Diagnosis of Ichthyosis With Confetti in Early Childhood and Later in Life



Major criteria, considered central to diagnosis are within circles; minor criteria and developing features of the disease are within ovals. For minor criteria, the number of affected patients of the 6 patients in the present study is indicated.

Table 2. Sequence Changes in Exon 6-7 of *KRT10* Detected in Patients With IWC[a]

Patient No.	cDNA	Predicted Protein
1	c.[**1374-1G>A**;1459C>T];[1459C>T; 1654_1683dupAGCTCCGGCGGCGGATACGGCGGCGGCAGC]	p.[**Ser458Argfs*120**;His487Tyr];[His487Tyr; Ser552_Ser561dup]
2	c.[**1374-1G>C**;1459C>T];[1468_1479delGGCCACGGCGGC]	p.[**Ser458Argfs*120**;His487Tyr];[Gly490_Gly493del]
3	c.[1459C>T];[1459C>T;**1506_1507delAA**; 1654_1683tripAGCTCCGGCGGCGGATACGGCGGCGGCAGC]	p.[His487Tyr];[His487Tyr;**Gly502Glyfs*78**;Ser552_Ser561trip]
4	c.[1459C>T;**1546_1551delinsT**];[1468_1479delGGCCACGGCGGC]	p.[His487Tyr;**Gly516Phefs*63**];[Gly490_Gly493del]
5	c.[**1557_1558delCG**]	p.[**Ser519Argfs*61**]
6 + 7	c.[1459C>T];[1468_1479delGGCCACGGCGGC;**1573_1574dupA**]	p.[His487Tyr];[Gly490_Gly493del;**Ser525Lysfs*56**]

Abbreviation: cDNA, complementary DNA; IWC, ichthyosis with confetti.

[a] Pathological mutations are indicated in boldface.

Table 3. Variability in the 3′ End of *KRT10*[a]

Variation	cDNA	Protein	Official Denotation	Official MAF (NCBI)	MAF
1	wt	wt	wt	Unknown	C=0.059/2
2	c.1459C>T	p.H487T	rs17855579	C=0.342/746	C=0.324/11
3	c.1468_1479del12	p.490_493delGHGG	Unknown	Unknown	del=0.235/8
4	c.1521_1535del15	p.508_512delSSGGG	Unknown	Unknown	del=0.029/1
5	c.1632C>A	p.G544G	rs368733857	Unknown	A=0.029/1
6	c.1654_1683dup30	p.552_562dupSSGGGYGGGS	Unknown	Unknown	dup=0.088/3
7	c.1654_1683tri30	p.552_562triSSGGGYGGGS	Unknown	Unknown	tri=0.029/1

Abbreviations: A, adenosine; C, cytosine; cDNA, complementary DNA; del, deletion; dup, duplication; MAF, minor allele frequency; NCBI, National Center for Biotechnology Information; tri, triplication; wt, wild type.

[a] The listed variations in exon 7 of *KRT10* occurred independently in 17 unrelated, disease-free control individuals from the general population.

correlated with subclinical phenotypes, such as, for example, a tendency for dry skin. These results suggest a mutation hot spot in this particular section of DNA.

Alignment of the predicted proteins produced by mutated *KRT10* showed an arginine-rich consensus sequence of 55 amino acids (eFigure 3 in the Supplement). Because nuclear localization signals frequently contain clusters of basic amino acid residues, this might underlie the observed mislocalization of mutated protein into the nucleus.[3,4]

Conclusions

A detailed clinical investigation of several patients with IWC enabled us to identify major and minor disease criteria for the first time. Among these are ectodermal malformations, which point to an influence of K10 during prenatal development and suggest reclassification of IWC as a genetic syndrome.

ARTICLE INFORMATION

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Study concept and design: Spoerri, Itin, Burger.
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Statistical analysis: Brena.
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NOTABLE NOTES

Dermatologic Etymology
Primary Morphology of Skin Lesions

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A cutaneous disease can be classified according to its primary **morphology** (Greek. *μορφη, morphē,* form + *-λογία, -logia*, a discourse, science, the study of).[1,2]

Macule (Latin. *macula*, spot)[1]

Patch (French. *pieche*, piece)[1,2]

Papule (Latin. *papula*, swelling)[1,2]

Plaque (Dutch. *plak*<*plakken*, tablet or plate)[1,2]

Nodules (Latin. *nodulus*<*nodus*, knot)[1,2]

Vesicle (Latin. *vesicula*<*vesica*, little bladder or blister)[1]

Bulla (Latin. *bulla*, bubble)[1-3]

Pustule (Latin. *pustula*, pimple)[1,2]

Abscess (Latin. *ab*, away from + *cedere*, to go).[1-3] Note: *abscessus*, a departure, perfect participle of *abscedere*, to go away from.[3] It was thought that evil humors within the body gathered in a mass and departed through **suppuration** (Latin. *suppuratio*>*suppurare*. to discharge pus)[1]

Petechiae (Latin. *petigo* scab, eruption)[1]

Ecchymosis (Greek. *ἐκχύμωσις, ekkhumōsis* < *ekkhumonathai*, escape of blood)[1,2]

Purpura (Greek. *πορφύρα, porphyra*, purple pigment)[3]

Telangiectasia (Greek. *τέλος, télos*, end + *ἀγγεῖον, angeion*, vessel + *ἔκτασις. ektasis*, dilatation)[1,2]

Erythroderma (Greek. *ἐρυθρός, eruthrós*, red + *δέρμα, derma*, skin or hide)[1,2]

Milium (Latin. *milium*, millet, a small seed)[2,3]

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