

Monogenic Human Skin Disorders

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Key Words

Human genodermatoses · Monogenic human skin disorders · Tabular database

Abstract

Human genodermatoses represent a broad and partly confusing spectrum of countless rare diseases with confluent and overlapping phenotypes often impeding a precise diagnosis in an affected individual. High-throughput sequencing techniques have expedited the identification of novel genes and have dramatically simplified the establishment of genetic diagnoses in such heterogeneous disorders. The precise genetic diagnosis of a skin disorder is crucial for the appropriate counselling of patients and their relatives regarding the course of the disease, prognosis and recurrence risks. Understanding the underlying pathophysiology is a prerequisite to understanding the disease and developing specific, targeted or individualized therapeutic approaches. We aimed to create a comprehensive overview of human genodermatoses and their respective genetic aetiology known to date. We hope this may represent a use-

ful tool in guiding dermatologists towards genetic diagnoses, providing patients with individual knowledge on the respective disorder and applying novel research findings to clinical practice.

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Introduction

The number of known genodermatoses has constantly risen in the past years. In 1991, Moss [1] described 90 regionally assigned cutaneous traits, and one and a half decades later this number increased to 580 [2]. Due to significant technical improvements over the past years and novel sequencing techniques, this number has further augmented.

Similar to other monogenetic disorders, a certain genodermatosis can sometimes be caused by genetic defects in several genes (genetic heterogeneity), and on the other hand, different disorders sometimes share similar underlying genetic aberrations (allelic variants). However, more than 80% of genetic skin disorders seem to be

Table 1. Inherited ichthyoses/generalized Mendelian disorders of cornification

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
ABCA12	607800	Ichthyosis, autosomal recessive 4B (harlequin) Ichthyosis, congenital, autosomal recessive 4A	242500 601277	AR AR
ABHD5	604780	Chanarin-Dorfman syndrome	275630	AR
ALDH3A2	609523	Sjögren-Larsson syndrome	270200	AR
ALOX12B	603741	Ichthyosis, congenital, autosomal recessive 2	242100	AR
ALOXE3	607206	Ichthyosis, congenital, autosomal recessive 3	606545	AR
AP1S1	603531	MEDNIK syndrome	609313	AR
AQP5	600442	Palmoplantar keratoderma, Bothnian type	600231	AD
ATP2A2	108740	Acrokeratosis verruciformis Darier disease	101900 124200	AD AD
ATP2C1	604384	Hailey-Hailey disease	169600	AD
CDSN	602593	Ichthyosis-hypotrichosis	146520	AD/AR
CERS3	615276	Autosomal recessive congenital ichthyosis	615023	AR
CLDN1	603718	ILVASC	607626	AR
COL14A1	120324	Keratoderma, palmoplantar, punctate type IB	614936	AD
CSTA	184600	Exfoliative ichthyosis	607936	AR
CTSC	602365	Papillon-Lefèvre syndrome	245000	AR
CYP4F22	611495	Ichthyosis, congenital, autosomal recessive 5	604777	AR
DKC1	300126	Dyskeratosis congenita	305000	XL
DSG1	125670	Striate palmoplantar keratoderma (PPKS1)	148700	AD
DSP	125647	Striate palmoplantar keratoderma (PPKS2)	612908	AD
EBP	300205	Chondrodysplasia punctata, X-linked dominant	302960	XL
ELOVL4	605512	Ichthyosis, spastic quadriplegia and mental retardation	614457	AR
ENPP1	173335	Cole disease		AD
ERCC2	126340	Trichothiodystrophy	601675	AR
ERCC3	133510	Trichothiodystrophy	601675	AR
FLG	135940	Ichthyosis vulgaris	146700	AD
GJB2	121011	KID syndrome	148210	AD
GJB3	603324	Erythrokeratoderma variabilis et progressiva	133200	AD
GJB4	605425	Erythrokeratoderma variabilis with erythema gyratum repens	133200	AD
GJB6	604418	Ectodermal dysplasia, Clouston type	129500	AD
GTF2H5	608780	Trichothiodystrophy	601675	AR
JUP	173325	Naxos disease	601214	AR
KRT1	139350	Ichthyosis, cyclic, with epidermolytic hyperkeratosis	607602	AD
KRT10	148080	Ichthyosis, cyclic, with epidermolytic hyperkeratosis	607602	AD
KRT16	148067	Pachyonychia congenita type I (Jadassohn-Lewandowsky syndrome)	148067	AD
KRT17	148069	Pachyonychia congenita type II (Jackson-Lawler syndrome)	167210	AD
KRT2	600194	Ichthyosis bullosa of Siemens	146800	AD
KRT6A	148041	Pachyonychia congenita type I (Jadassohn-Lewandowsky syndrome)	167200	AD
KRT6B	148042	Pachyonychia congenita type II (Jackson-Lawler syndrome)	167210	AD
KRT9	607606	Epidermolytic palmoplantar keratoderma	144200	AD
KRT9	607606	Epidermolytic palmoplantar keratoderma	144200	AD
LIPN	613924	Ichthyosis, congenital, autosomal recessive 8	613943	AR
LOR	152445	Vohwinkel syndrome (ichthyotic variant)	604117	AD
MBTPS2	300294	IFAP syndrome with or without BRESHECK syndrome	308205	XL
MBTPS2	300294	Keratosis follicularis spinulosa decalvans, X-linked	308800	XL
MPLKIP	609188	Trichothiodystrophy, non-photosensitive 1	234050	AR
NHP2	606470	Dyskeratosis congenita, autosomal recessive 2	613987	AR
NIPAL4	609383	Ichthyosis, congenital, autosomal recessive 6	612281	AR
NOP10	606471	Dyskeratosis congenita, autosomal recessive 1	224230	AR
NSDHL	300275	CHILD syndrome	308050	XL
PKP1	601975	Ectodermal dysplasia/skin fragility syndrome	604536	AR
PNPLA1	612121	Ichthyosis, congenital, autosomal recessive 10	615024	AR
POMP	613386	Keratosis linearis with ichthyosis congenita and sclerosing keratoderma	601952	AR

Table 1 (continued)

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
RHBDF2	614404	Tylosis with oesophageal cancer	148500	AD
SAT1	313020	Keratosis follicularis spinulosa decalvans	308800	XL
SERPINB7	603357	Palmoplantar keratosis, Nagashima type		AR
SLC27A4	604194	Ichthyosis prematurity syndrome	608649	AR
SLURP1	606119	Mal de Meleda	248300	AR
SMARCAD1	612761	Adermatoglyphia	136000	AD
SNAP29	604202	CEDNIK syndrome	609528	AR
SPINK5	605010	Netherton syndrome	256500	AR
ST14	606797	Ichthyosis with hypotrichosis	610765	AR
STS	300747	Ichthyosis, X-linked	308100	XL
SUMF1	607939	Multiple sulphatase deficiency	272200	AR
TAT	613018	Richner-Hanhart syndrome, tyrosinaemia, type II	276600	AR
TERC	602322	Dyskeratosis congenita, autosomal dominant 1	127550	AD
TERT	187270	Dyskeratosis congenita, autosomal recessive 4	613989	AR
TGM1	190195	Ichthyosis, congenital, autosomal recessive 1	242300	AR
TGM5	603805	Peeling skin syndrome, acral type	609796	AR
TINF2	604319	Dyskeratosis congenita, autosomal dominant 3	613990	AD
WRAP53	612661	Dyskeratosis congenita, autosomal recessive 3	613988	AR

AR = Autosomal recessive; AD = autosomal dominant; XL = X-linked; MEDNIK = mental retardation, enteropathy, deafness, neuropathy, ichthyosis and keratoderma; ILVASC = ichthyosis, leucocyte vacuoles, alopecia and sclerosing cholangitis; KID = keratitis, ichthyosis and deafness; IFAP = ichthyosis follicularis, alopecia and photophobia; BRESHECK = brain anomalies, retarda-

tion, ectodermal dysplasia, skeletal malformations, Hirschsprung disease, ear/eye anomalies, cleft palate/cryptorchidism and kidney dysplasia/hypoplasia; CHILD = congenital hemidysplasia with ichthyosiform erythroderma and limb defects; CEDNIK = cerebral dysgenesis, neuropathy, ichthyosis and keratoderma.

caused by a single gene defect, and more than 80% of gene defects cause only one condition [3].

Still, the current genetic knowledge has only marginally found its way into clinical practice. This may partly be due to (1) the enormous amount of genetic data that may sometimes appear to be difficult to access, interpret and filter for relevant information, (2) inconsistencies in nomenclature of entities termed after phenotypic versus genotypic aspects, (3) a considerable challenge in establishing a clear clinical diagnosis due to often non-specific and overlapping phenotypes, and (4) the expected lack of direct therapeutic consequences after genetic testing in many cases.

However, a precise genetic diagnosis can be of great help in counselling the patient and his family regarding prognosis and recurrence risks, and in some cases it may even guide therapy. Understanding the underlying genetic defect and its consecutive pathomechanisms is a first step in understanding the disease, enabling the development of individualized therapeutic approaches targeting the actual molecular defect. Beyond that, even the knowl-

edge of a currently incurable and maybe fatal diagnosis can help in preventing unnecessary and often stressful diagnostic procedures as well as futile therapeutic attempts. Thus, the knowledge of the patient's genotype is becoming increasingly important with respect to therapeutic decisions and is superior to a purely clinical alignment of the phenotype.

Methods

We aimed to create a comprehensive overview of human genodermatoses and their respective genetic aetiology known to date. We searched the literature using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and OMIM (<http://www.ncbi.nlm.nih.gov/omim/>) for information regarding genodermatoses. Only entities with a known monogenetic aetiology were included, entities with only linkage loci or complex or unknown genetic origin were disregarded. Furthermore, we excluded entities where skin manifestations are very rare, secondary (e.g. caused by haematological or immunological problems) or represent only a minor or insignificant symptom compared to other features of the disorder.

Table 2. Genetic epidermolyses and blistering disorders

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
COL17A1	113811	Epidermolysis bullosa, junctional, non-Herlitz type	226650	AR
COL7A1	120120	Epidermolysis bullosa dystrophica, autosomal recessive	226600	AR
		Epidermolysis bullosa dystrophica, Bart type	132000	AD
		Epidermolysis bullosa dystrophica, localisata variant		AR
		Epidermolysis bullosa dystrophica, autosomal dominant	131750	AD
		Epidermolysis bullosa dystrophica, autosomal recessive	226600	AR
		Epidermolysis bullosa pruriginosa	604129	AD/AR
		Epidermolysis bullosa, pretibial	131850	AD
		Toenail dystrophy, isolated	607523	AD
		Transient bullous epidermolysis of the newborn	131705	AD/AR
DSP	125647	Epidermolysis bullosa, lethal acantholytic	609638	AR
EXPH5	612878	Epidermolysis bullosa, non-specific, autosomal recessive	615028	AR
FERMT1	607900	Kindler syndrome	173650	AR
ITGA3	605025	Interstitial lung disease, nephritic syndrome and epidermolysis bullosa, congenital	614748	AR
ITGA6	147556	Epidermolysis bullosa, junctional, with pyloric stenosis	226730	AR
ITGB4	147557	Epidermolysis bullosa of hands and feet	131800	AR
		Epidermolysis bullosa, junctional, non-Herlitz type	226650	AR
		Epidermolysis bullosa, junctional, with pyloric atresia	226730	AR
KRT1	139350	Ichthyosis, cyclic, with epidermolytic hyperkeratosis	607602	AD
KRT10	148080	Ichthyosis, cyclic, with epidermolytic hyperkeratosis	607602	AD
KRT5	148040	Dowling-Degos disease 1	179850	AD
		Epidermolysis bullosa simplex with migratory circinate erythema	609352	AD
		Epidermolysis bullosa simplex with mottled pigmentation	131960	AD
		Epidermolysis bullosa simplex, Dowling-Meara type	131760	AD
		Epidermolysis bullosa simplex, Koebner type	131900	AD
		Epidermolysis bullosa simplex, Weber-Cockayne type	131800	AD
KRT14	148066	Dermatopathia pigmentosa reticularis	125595	AD
		Epidermolysis bullosa simplex, Dowling-Meara type	131760	AD
		Epidermolysis bullosa simplex, Koebner type	131900	AD
		Epidermolysis bullosa simplex, recessive 1	601001	AR
		Epidermolysis bullosa simplex, Weber-Cockayne type	131800	AD
LAMA3	600805	Naegeli-Franceschetti-Jadassohn syndrome	161000	AD
		Epidermolysis bullosa, generalized atrophic benign	226650	AR
		Epidermolysis bullosa, junctional, Herlitz type	226700	AR
LAMB3	150310	Laryngo-onychocutaneous syndrome	245660	AR
		Epidermolysis bullosa, junctional, Herlitz type	226700	AR
LAMC2	150292	Epidermolysis bullosa, junctional, non-Herlitz type	226650	AR
		Epidermolysis bullosa, junctional, Herlitz type	226700	AR
PLEC1	601282	Epidermolysis bullosa simplex with pyloric atresia	612138	AR
		Epidermolysis bullosa simplex, Ogna type	131950	AD
		Muscular dystrophy with epidermolysis bullosa simplex	226670	AR
POFUT1	607491	Dowling-Degos disease 1	615327	AD
POGLUT1	515618	Dowling-Degos disease		AD

For abbreviations, see table 1.

Table 3. Nuclear excision repair disorders

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
DDB2	600811	Xeroderma pigmentosum, group E, DDB-negative subtype	278740	AR
ERCC1	126380	Xeroderma pigmentosum		AR
ERCC2	126340	Xeroderma pigmentosum, group D Trichothiodystrophy	278730 601675	AR AR
ERCC3	133510	Xeroderma pigmentosum, group B Trichothiodystrophy	610651 601675	AR AR
ERCC4	133520	Xeroderma pigmentosum, group F	278760	AR
ERCC5	133530	Xeroderma pigmentosum, group G	278780	AR
ERCC6	609413	Cockayne syndrome, type B UV-sensitive syndrome 1	133540 600630	AR AR
ERCC8	609412	Cockayne syndrome, type A UV-sensitive syndrome 2	216400 614621	AR AR
GTF2H5	608780	Trichothiodystrophy	601675	AR
MPLKIP	609188	Trichothiodystrophy	234050	AR
POLH	603968	Xeroderma pigmentosum, variant type	278750	AR
RECQL4	603780	Rothmund-Thompson syndrome	268400	AR
WRN	604611	Werner syndrome	277700	AR
XPA	611153	Xeroderma pigmentosum, group A	278700	AR
XPC	613208	Xeroderma pigmentosum, group C	278720	AR

DDB = Damage-specific DNA-binding protein; AR = autosomal recessive.

Table 4. Genetic disorders with hypo-and hyperpigmentations

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
ADAM10	602192	Reticulate acropigmentation of Kitamura		AD
ADAR	146920	Dyschromatosis symmetrica hereditaria	127400	AD
AP3B1	603401	Hermansky-Pudlak syndrome 2	608233	AR
BLM	604610	Bloom syndrome	210900	AR
BLOC1S3	609762	Hermansky-Pudlak syndrome 8	614077	AR
BLOC1S6	604310	Hermansky-Pudlak syndrome 9	614171	AR
BRAF	164757	Cardiofaciocutaneous syndrome	115150	AD
C10ORF11	614537	Albinism, oculocutaneous, type VII	615579	AR
DTNBP1	607145	Hermansky-Pudlak syndrome 7	614076	AR
EDN3	131242	Waardenburg syndrome, type 4B	613265	AR
EDNRB	131244	Waardenburg syndrome, type 4A	277580	AR
ENPP1	173335	Cole disease		AD
HPS1	604982	Hermansky-Pudlak syndrome 1	203300	AR
HPS3	606118	Hermansky-Pudlak syndrome 3	614072	AR
HPS4	606682	Hermansky-Pudlak syndrome 4	614073	AR
HPS5	607521	Hermansky-Pudlak syndrome 5	614074	AR
HPS6	607522	Hermansky-Pudlak syndrome 6	614075	AR
KIT	164920	Piebaldism	172800	AD
MAP2K1	176872	Cardiofaciocutaneous syndrome	115150	AD
MAP2K2	601263	Cardiofaciocutaneous syndrome	115150	AD
MC1R	155555	Oculocutaneous albinism, type II, modifier of	203200	AD
MITF	156845	Tietz albinism-deafness syndrome Waardenburg syndrome, type 2A	103500 193510	AD AD
MLH1	120436	MMR deficiency syndrome (Turcot syndrome)	276300	AR
MLPH	606526	Griselli syndrome, type 3	609227	AR
MSH2	609309	MMR deficiency syndrome (Turcot syndrome)	276300	AR
MSH6	600678	MMR deficiency syndrome (Turcot syndrome)	276300	AR

Table 4 (continued)

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
MYO5A	160777	Griselli syndrome, type 1	214450	AR
NF1	613113	Neurofibromatosis, type 1	162200	AD
NF2	607379	Neurofibromatosis, type 2	101000	AD
OCA2	611409	Albinism, oculocutaneous, type II	203200	AR
		Albinism, brown oculocutaneous	203200	AR
PAX3	606597	Waardenburg syndrome, type 1	193500	AD
		Waardenburg syndrome, type 3	148820	AD/AR
PMS2	600259	MMR deficiency syndrome (Turcot syndrome)	276300	AR
PRKAR1A	188830	Carney complex type I	160980	AD
PTPN11	176876	Leopard syndrome	151100	AD
RAB27A	603868	Griselli syndrome, type 2	607624	AR
RECQL4	603780	Rothmund-Thompson syndrome	268400	AR
SLC45A2	606202	Oculocutaneous albinism, type IV	606574	AR
SNAI2	602150	Waardenburg syndrome, type 2D	608890	AR
		Piebaldism	172800	AR
SOX10	602229	Waardenburg syndrome, type 4C	613266	AR
SPRED1	609291	Legius syndrome	611431	AD
STK11	602216	Peutz-Jeghers syndrome	175200	AD
TYR	606933	Albinism, oculocutaneous, type IA	203100	AR
		Albinism, oculocutaneous, type IB	606952	AR
TYRP1	115501	Albinism, oculocutaneous, type III	203290	AR

AD = Autosomal dominant; AR = autosomal recessive; MMR = mismatch repair.

Table 5. Disorders of ectodermal appendages including ectodermal dysplasia

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
ABCC9	601439	Cantú syndrome	239850	AD
ALMS1	606844	Alström syndrome	203800	AR
APCDD1	607479	Hypotrichosis simplex	605389	AD
ARHGAP31	610911	Adams-Oliver syndrome	100300	AD
AXIN2	604025	Ectodermal dysplasia and neoplastic syndrome	608615	AD
BANF1	603811	Nestor-Guillermo progeria syndrome	614008	AR
BCS1L	603647	Björnstad syndrome	262000	AR
CDH3	114021	Hypotrichosis with juvenile macular dystrophy	601553	AR
CYP26C1	608428	Focal facial dermal dysplasia 4	614974	AR
DDX59	615464	Orofaciodigital syndrome V	174300	AR
DLX3	600525	Trichodento-osseous syndrome	190320	AD
DOCK6	614194	Adams-Oliver syndrome	614219	AR
DSC3	600271	Hypotrichosis and recurrent skin vesicles	613102	AR
DSG4	607892	Hypotrichosis	607903	AR
DSP	125647	Skin fragility-woolly hair syndrome	607655	AR
EDA	300451	X-linked hypohidrotic ectodermal dysplasia (ED1)	305100	XL
EDAR	604095	Ectodermal dysplasia, hypohidrotic	224900	AD
EDARADD	606603	Ectodermal dysplasia, hypohidrotic	614941	AD
EFNB1	300035	Craniofrontonasal dysplasia	304110	XL
ERCC2	126340	Trichothiodystrophy	601675	AR
ERCC3	133510	Trichothiodystrophy	601675	AR
FOXP1	600838	T-cell immunodeficiency, congenital alopecia and nail dystrophy	601705	AR
GJB6	604418	Ectodermal dysplasia 2, Clouston type	129500	AR

Table 5 (continued)

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
HOXC13	142976	Ectodermal dysplasia 9, hair/nail type	614931	AR
HR	602302	Atrichia with 2 ocular lesions, also called congenital alopecia universalis	209500	AR
HVEC	600644	Cleft lip/palate-ectodermal dysplasia syndrome	225060	AR
IFT122	606045	Cranio-ectodermal dysplasia 1	218330	AR
IFT43	614068	Sensenbrenner syndrome	614099	AR
IKBKG	300248	Anhidrotic ectodermal dysplasia with immune deficiency	300291	XL
JUP	173325	Naxos disease	601214	AR
KCTD1	613420	Scalp-ear-nipple syndrome	181270	AD
KRT17	148069	Steatocystoma multiplex Pachyonychia congenita, Jackson-Lawler type	184500	AD
KRT74	608248	Woolly hair	194300	AD
KRT75	609025	Pseudofolliculitis barbae	612318	AD
KRT81	602153	Monilethrix	158000	AD
KRT83	602765	Monilethrix	158000	AD
KRT85	602767	Ectodermal dysplasia 4, hair/nail type	602032	AR
KRT86	601928	Monilethrix	158000	AD
LIPH	607365	Woolly hair	604379	AR
LMNA	150330	Hutchinson-Gilford progeria	176670	AD
LMX1B	602575	Nail-patella syndrome	161200	AD
LPAR6	609239	Woolly hair Hypotrichosis 8	278150	AR
MSX1	142983	Ectodermal dysplasia 3, Witkop type	189500	AD
PKP1	601975	Ectodermal dysplasia/skin fragility syndrome	604536	AR
POC1A	614783	Short stature, onychodysplasia, facial dysmorphism and hypotrichosis syndrome	614813	AR
PORCN	300651	Focal dermal hypoplasia	305600	XL
PVRL1	600644	Margarita Island type of ectodermal dysplasia (ED4)	225060	AR
RBM28	612074	Alopecia, neurological defects and endocrinopathy syndrome	612079	AR
RBpj	147183	Adams-Oliver syndrome	614814	AD
RMRP	157660	Cartilage hair hypoplasia	250250	AR
SNRPE	128260	Hypotrichosis	615059	AD
SOX18	601618	Hypotrichosis-lymphoedema-telangiectasia syndrome	607823	AD
TP63	603273	Ankyloblepharon-ectodermal defects-cleft lip/palate syndrome	106260	AD
TRPS1	604386	Trichorhinophalangeal syndrome, type I	190350	AD
TWIST2	607556	Focal facial dermal dysplasia 3, Setleis type	227260	AR
WDR35	613602	Cranio-ectodermal dysplasia 2	613610	AR

For abbreviations, see table 1.

Results

We summarized the genes according to their phenotypic spectra in tables 1–9.

Discussion

Historically, the classification of genodermatoses was based on clinical experience and a broad phenotypic knowledge of the treating physician. The OMIM database

is an important tool listing and describing phenotypes of Mendelian disorders as well as their known underlying genetic causes [3]. However, with respect to genodermatoses, its structure is often of limited use for diagnostic clinical purposes.

Modern molecular genetics with novel high-throughput sequencing techniques have not only expedited the identification of countless disease-causing genes, it has also led to a widening of the associated phenotypes in various entities [4, 5]. We learned that the phenotypic spectrum of an individual disorder might go far beyond what

Table 6. Vascular disorders

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
ACVRL1	601284	Telangiectasia, hereditary haemorrhagic, type 2	600376	AD
C1NH	606860	Angio-oedema, hereditary, types I and II	106100	AD
C7ORF22	607929	Cerebral cavernous malformations	603284	AD
ENG	131195	Telangiectasia, hereditary haemorrhagic, type 1	187300	AD
FLT4	136352	Hereditary lymphoedema type I	153100	AD
FOXC2	602402	Lymphoedema-distichiasis syndrome	153400	AD
GDF2	605520	Telangiectasia, hereditary haemorrhagic, type 5	615506	AD
GLMN	601749	Glomuvenous malformations (glomangiomas)	138000	AD
GNAQ	600998	Sturge-Weber syndrome	185300	mosaic
		Capillary malformations, congenital, 1, somatic, mosaic	163000	mosaic
KRIT1	604214	Cerebral cavernous malformations	116860	AD
PDCD10	609118	Cerebral cavernous malformations	603285	AD
RASA1	139150	Capillary malformation-arteriovenous malformation	608354	AD
		Parkes Weber syndrome	608355	AD
TEK	600221	Venous malformations, multiple cutaneous and mucosal	600195	AD

AD = Autosomal dominant.

Table 7. Connective tissue defects

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
ABCC6	603234	Pseudoxanthoma elasticum	264800	AR
ADAMTS2	604539	Ehlers-Danlos syndrome, type VIIC	225410	AR
ALDH18A1	138250	Cutis laxa	219150	AR
ATP6V0A2	611716	Cutis laxa	219200	AR
ATP7A	300011	Menkes disease	309400	XL
B3GALT6	615291	Ehlers-Danlos syndrome, progeroid type 2	615349	AR
B4GALT7	604327	Ehlers-Danlos syndrome, progeroid type 1	130070	AD
COL1A1	120150	Ehlers-Danlos syndrome, type I	130000	AD
		Ehlers-Danlos syndrome, type VIIA	130060	AD
COL1A2	120160	Ehlers-Danlos syndrome, type VIIB	130060	AD
COL3A1	120180	Ehlers-Danlos syndrome, type IV	130050	AD
COL5A1	120215	Ehlers-Danlos syndrome, type II	130010	AD
		Ehlers-Danlos syndrome, type I	130000	AD
COL5A2	120190	Ehlers-Danlos syndrome, type I	130000	AD
EFEMP2	604633	Cutis laxa	614437	AR
ELN	130160	Cutis laxa	123700	AD
FBLN5	604580	Cutis laxa	614434	AD/AR
FBN1	134797	Marfan syndrome	154700	AD
FBN2	612570	Contractural arachnodactyly, congenital	121050	AD
LTBP4	604710	Cutis laxa	613177	AR
PLOD1	153454	Ehlers-Danlos syndrome, type VI	225400	AR
PYCR1	179035	Cutis laxa	614438	AR
SMAD3	603109	Loeys-Dietz syndrome	613795	AD
TGFB2	190220	Loeys-Dietz syndrome	608967	AD
TGFBR1	190181	Loeys-Dietz syndrome	609192	AD
TGFBR2	190182	Loeys-Dietz syndrome	608967	AD
TNXB	600985	Ehlers-Danlos syndrome, autosomal dominant, hypermobility type	130020	AD
		Ehlers-Danlos syndrome, autosomal recessive, due to tenascin-X deficiency	606408	AR
ZMPSTE24	606480	Restrictive dermopathy, lethal	275210	AR

For abbreviations, see table 1.

Table 8. Dermal mosaics

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
AKT1	164730	Proteus syndrome	176920	mosaic
BRAF	164757	Cardiofaciocutaneous syndrome	115150	mosaic
FGFR3	134934	Naevus, epidermal, somatic	162900	mosaic
GNAQ	600998	Sturge-Weber syndrome	185300	mosaic
		Capillary malformations, congenital, 1, somatic, mosaic	163000	mosaic
GNAS	139320	McCune-Albright syndrome	174800	mosaic
HRAS	190020	Naevus, epidermal, somatic	162900	mosaic
		Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic	163200	mosaic
IDH1	147700	Ollier disease/Maffucci syndrome		mosaic
IDH2	147650	Ollier disease/Maffucci syndrome		mosaic
KRAS	190070	Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic	163200	mosaic
MAP2K1	176872	Cardiofaciocutaneous syndrome	615279	mosaic
MAP2K2	601263	Cardiofaciocutaneous syndrome	615280	mosaic
NRAS	164790	Naevus, epidermal, somatic	162900	mosaic
PIK3CA	171834	Naevus, epidermal, somatic	162900	mosaic
PORCN	300651	Focal dermal hypoplasia	305600	mosaic
PTEN	601728	Linear PTEN naevus	158350	mosaic
PTPN11	176876	Leopard syndrome	151100	mosaic
SOX10	602229	Giant melanocytic naevus		mosaic
SPRED1	609291	Legius syndrome	611431	mosaic
TSC1	605284	Tuberous sclerosis complex	191100	mosaic
TSC2	191092	Tuberous sclerosis complex	613254	mosaic

PTEN = Phosphatase and tensin homologue.

Table 9. Genodermatoses with tumour predisposition

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
AKT1	164730	Cowden syndrome	615109	AD
APC	611731	Gardner syndrome	175100	AD
ATM	607585	Ataxia-telangiectasia	208900	AR
AXIN2	604025	Ectodermal dysplasia and neoplastic syndrome	608615	AD
BLM	604610	Bloom syndrome	210900	AR
CYLD	605018	Tricho-epithelioma, multiple familial	601606	AD
DDB2	600811	Xeroderma pigmentosum, group E, DDB-negative subtype	278740	AR
DKC1	300126	Dyskeratosis congenita	305000	XR
ERCC2	126340	Xeroderma pigmentosum, group D	278730	AR
ERCC3	133510	Xeroderma pigmentosum, group B	610651	AR
ERCC4	133520	Xeroderma pigmentosum, group F	278760	AR
ERCC5	133530	Xeroderma pigmentosum, group G	278780	AR
FERMT1	607900	Kindler syndrome	173650	AR
FH	136850	Leiomyomatosis with or without renal cell cancer	150800	AD
FLCN	607273	Birt-Hogg-Dubé syndrome	135150	AD
GTF2H5	608780	Trichothiodystrophy	601675	AR
MLH1	120436	MMR deficiency syndrome (Turcot syndrome)	276300	AR
MPLKIP	609188	Trichothiodystrophy	234050	AR
MSH2	609309	MMR deficiency syndrome (Turcot syndrome)	276300	AR
MSH6	600678	MMR deficiency syndrome (Turcot syndrome)	276300	AR
NF1	613113	Neurofibromatosis, type 1	162200	AD
NF2	607379	Neurofibromatosis, type 2	101000	AD
NHP2	606470	Dyskeratosis congenita, autosomal recessive 2	613987	AR

Table 9 (continued)

Gene	Gene MIM No.	Disease	Phenotype MIM No.	Inheritance
NOP10	606471	Dyskeratosis congenita, autosomal recessive 1	224230	AR
NOTCH3	600276	Myofibromatosis, infantile, 2	615293	AD
PDGFRB	173410	Myofibromatosis, infantile, 1	228550	AD
PIK3CA	171834	Cowden syndrome	615108	AD
PMS2	600259	MMR deficiency syndrome (Turcot syndrome)	276300	AR
POLH	603968	Xeroderma pigmentosum, variant type	278750	AR
PRKAR1A	188830	Carney complex type I	160980	AD
PTCH1	601309	Naevoid basal cell carcinoma syndrome (Gorlin syndrome)	109400	AD
PTCH2	603673	Familial basal cell carcinoma	605462	AD
PTEN	601728	Cowden syndrome	158350	AD
RECQL4	603780	Rothmund-Thompson syndrome	268400	AR
RHBDF2	614404	Tylosis with oesophageal cancer	148500	AD
STK11	602216	Peutz-Jeghers syndrome	175200	AD
TERC	602322	Dyskeratosis congenita, autosomal dominant 1	127550	AD
TERT	187270	Dyskeratosis congenita, autosomal recessive 4	613989	AR
TINF2	604319	Dyskeratosis congenita, autosomal dominant 3	613990	AD
TSC1	605284	Tuberous sclerosis complex	191100	AD
TSC2	191092	Tuberous sclerosis complex	613254	AD
WRAP53	612661	Dyskeratosis congenita, autosomal recessive 3	613988	AR
WRN	604611	Werner syndrome	277700	AR
XPA	611153	Xeroderma pigmentosum, group A	278700	AR
XPC	613208	Xeroderma pigmentosum, group C	278720	AR

AD = Autosomal dominant; AR = autosomal recessive; DDB = damage-specific DNA-binding protein; XR = X-chromosomal recessive; MMR = mismatch repair.

is apparent to us and what is considered to meet current diagnostic criteria. On the other hand, oligosymptomatic or overlapping phenotypes may not fit into current classification schemes. In addition, the borders of 'clinically affected' and 'subclinical carrier' of a genetic disease may sometimes be blurred.

Due to sometimes extensive heterogeneity of disorders as well as little specificity of phenotypic features, we believe that novel sequencing approaches such as targeted next-generation sequencing will help to simplify genotype-phenotype correlations and possibly revolutionize our understanding of phenotypes in human skin disorders towards a more gene-based classification.

Previous work on genodermatoses databases has been an important step in this direction [1, 2]. We hope the provided overview represents a useful current and slightly modified update of this previous work comprehensively summarizing the existing knowledge on genotype-phenotype correlations of monogenic skin disorders. We hope our tables make the current genetic data more accessible to dermatologists and may arouse interest in the

genetics of human skin disorders or even serve as templates for the design of novel targeted next-generation sequencing tools.

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