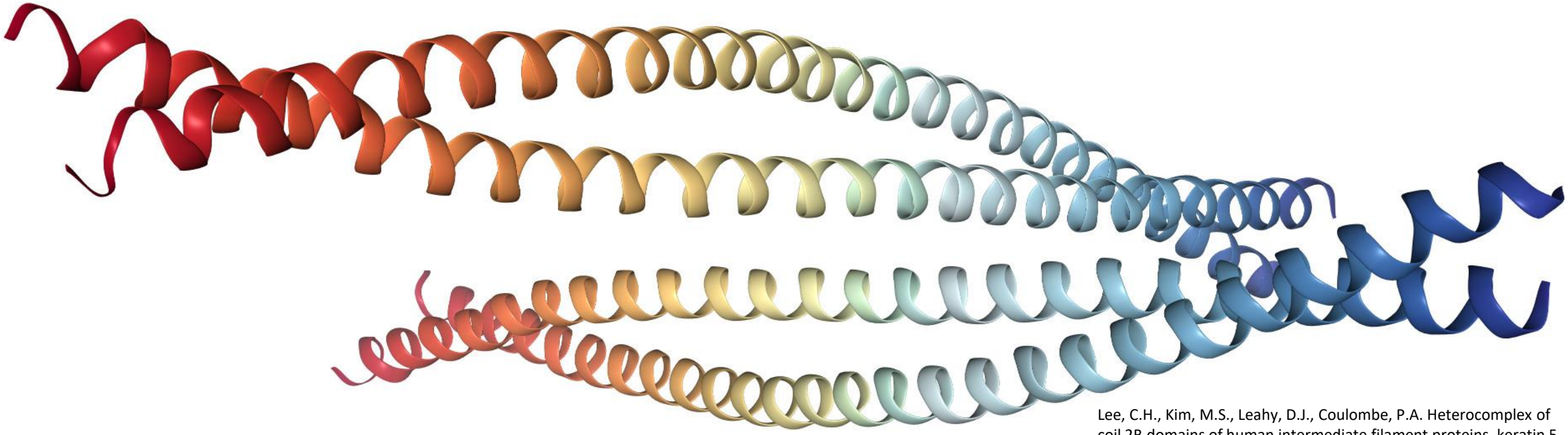
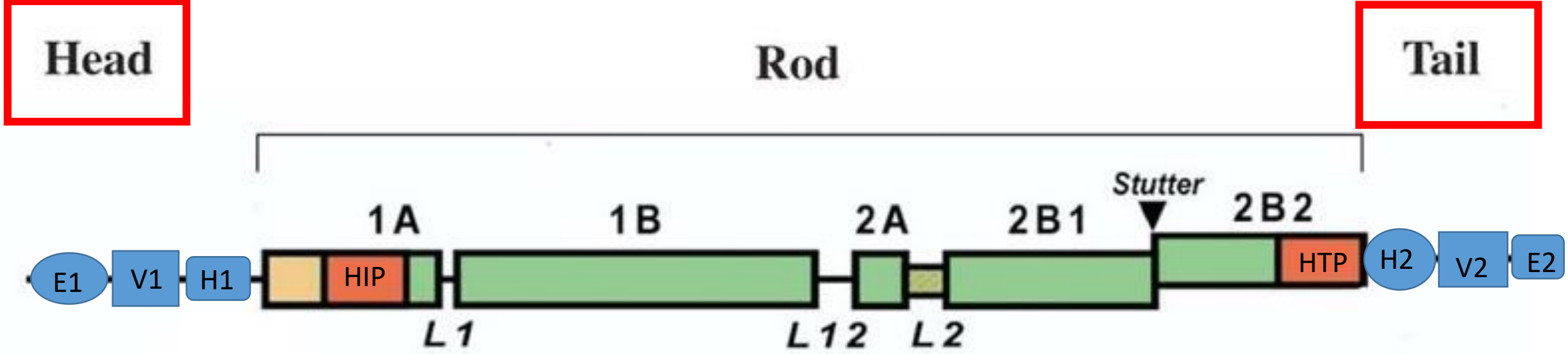
Genotype–phenotype correlations in EBS with KRT5 and KRT14 mutations



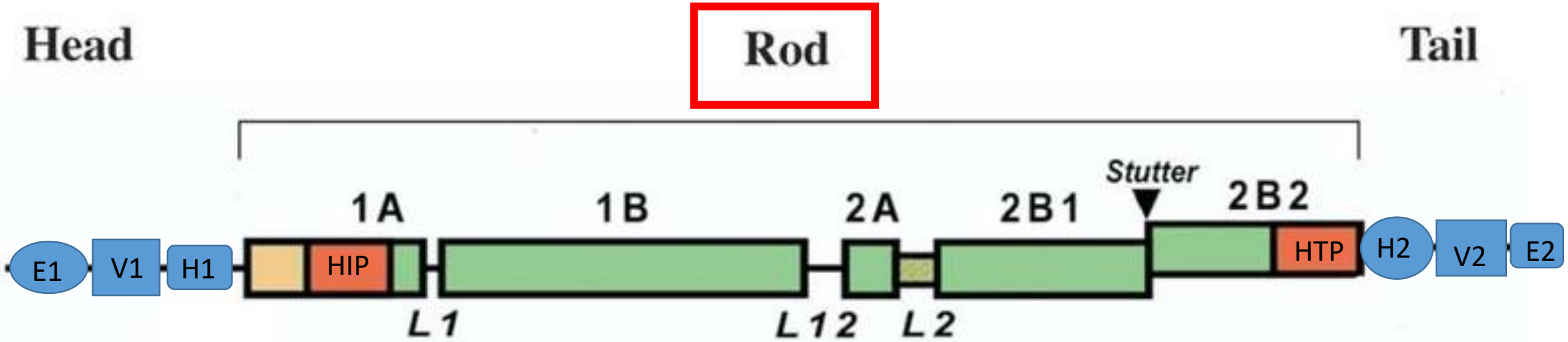
Lee, C.H., Kim, M.S., Leahy, D.J., Coulombe, P.A. Heterocomplex of coil 2B domains of human intermediate filament proteins, keratin 5 (KRT5) and keratin 14 (KRT14). 2012

What are the keratins?

- The predominant subtype of intermediate filament (IF) proteins in epithelial cells
- 54 different keratin proteins demarcated from:
  - 28 type I (smaller and acidic)
  - 26 type II (larger and basic-neutral)
  - that function as a pair in tissue-specific mode



- Globular structure
- Positive charge
- Role in
  - Interaction with other molecules
  - Polymerisation of keratins
  - Post traductional modifications



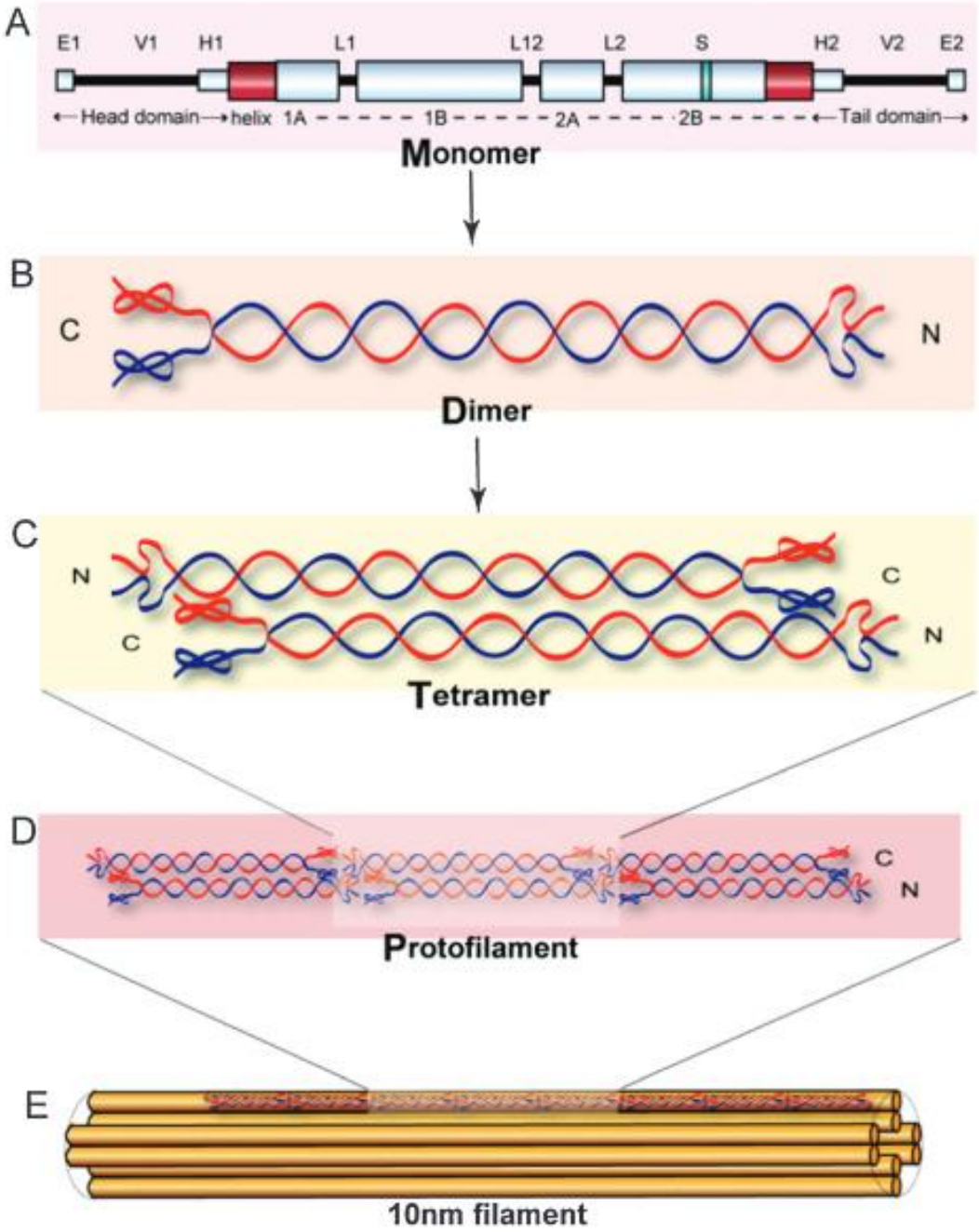
- Characteristic of IF proteins
- Four α-helical subdomains separated by non-helical 'linker' regions
- Composed of repeats of seven amino acids in positions labeled a–g (heptad) mandatory in the formation of the α-helix and coiled-coil heterodimer (1 heptad = 1 turn of α helix).

a b c d e f g

hydrophobic apolar charged polar

- The first amino acid residues at the N-terminal end of the rod domain and the last ones at the C-terminal end form an helix-initiating /terminating motif, which initiates/terminates the formation of the α-helix.

IF polymerisation



What are the functions of keratins?

- Protection of epithelial cells and tissue from mechanical stress
- Other functions
  - Protection against apoptosis
  - Regulation of epithelial tissue growth
  - Regulation of epithelial cell migration
  - ….

Which phenotypes?

Table 3 Epidermolysis bullosa simplex (EBS) clinical subtypes

Most common EBS clinical subtypes	Targeted protein(s)
Autosomal dominant EBS	
Localized	Keratin 5, keratin 14
Intermediate	Keratin 5, keratin 14
Severe	Keratin 5, keratin 14
With mottled pigmentation	Keratin 5[a]
Migratory circinate erythema	Keratin 5
Autosomal recessive EBS	
Intermediate or severe	Keratin 14, keratin 5

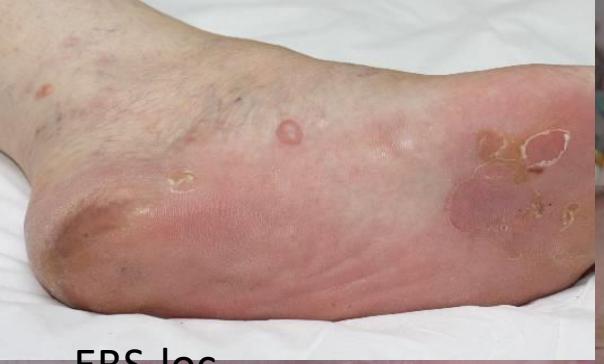
[a]Typical recurrent mutation in keratin 5, but cases with other keratin 5, keratin 14 or exophilin-5 mutations have been reported; **bold**, syndromic EBS subtypes.

Autosomal dominant

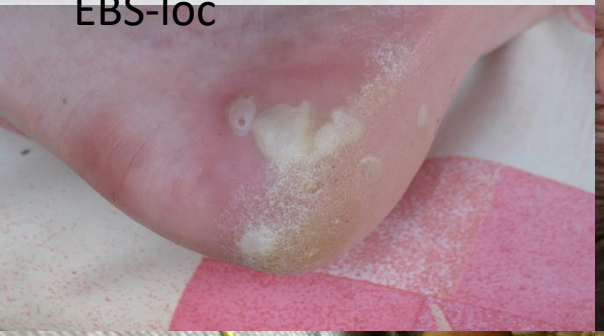
Galli-Galli disease/ Dowling Degos disease	Keratin 5
Naegeli-Franceschetti-Jadassohn syndrome/ dermatopathia pigmentosa reticularis	Keratin 14

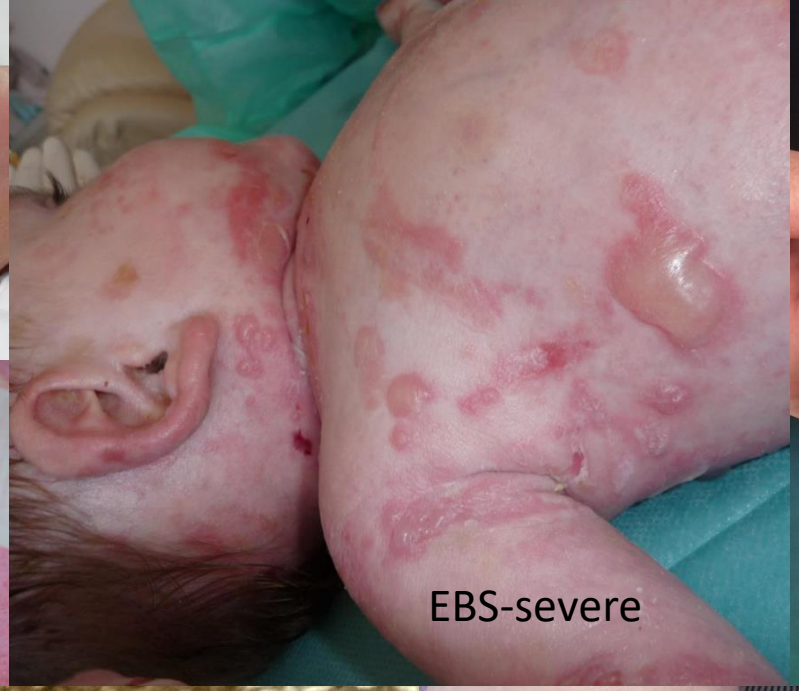
Polymorphism

Gene susceptibility to basal cell carcinoma	Keratin 5

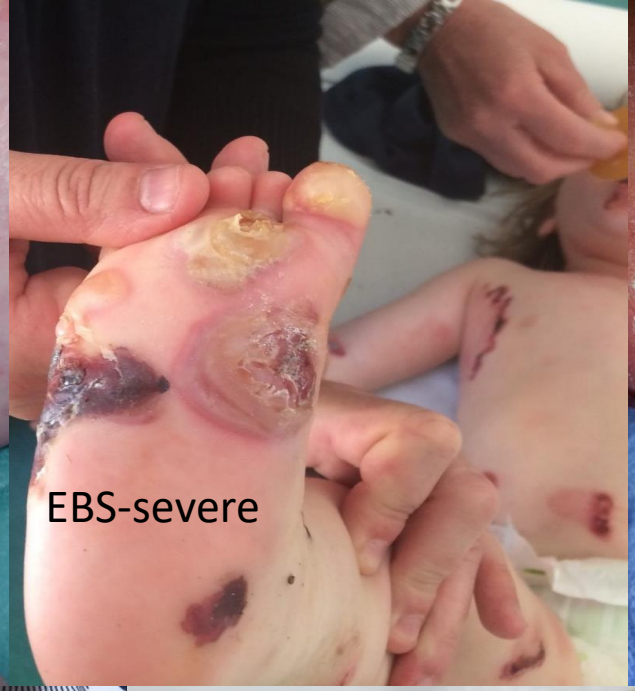


EBS-loc

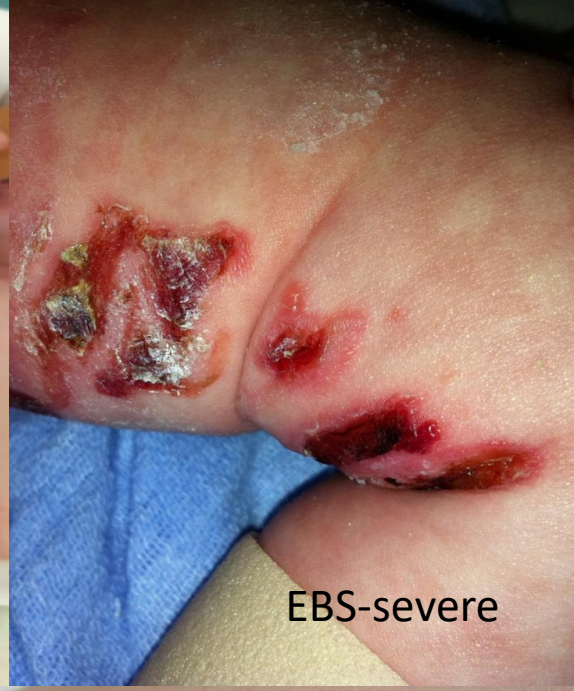




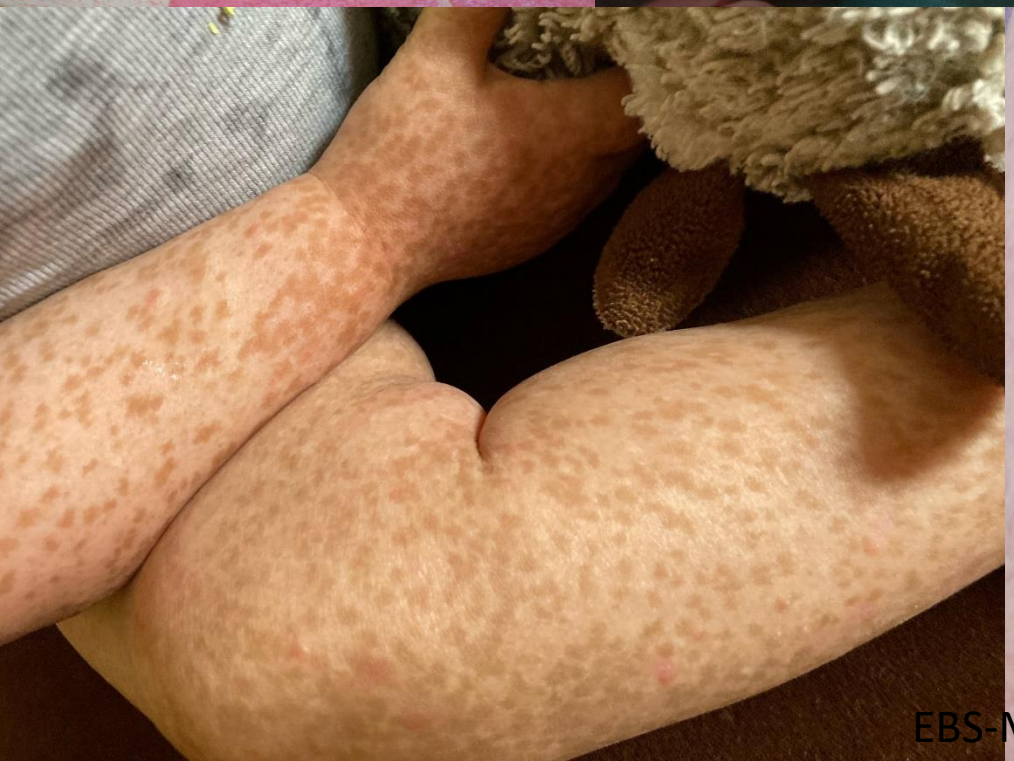
EBS-severe



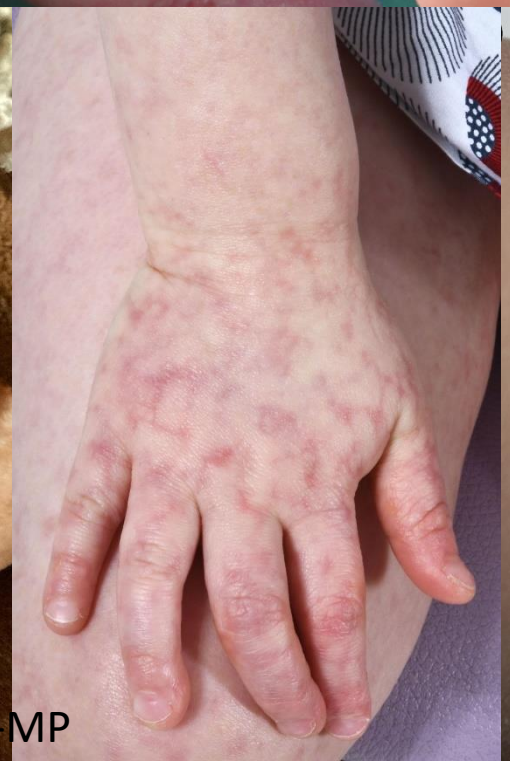
EBS-severe

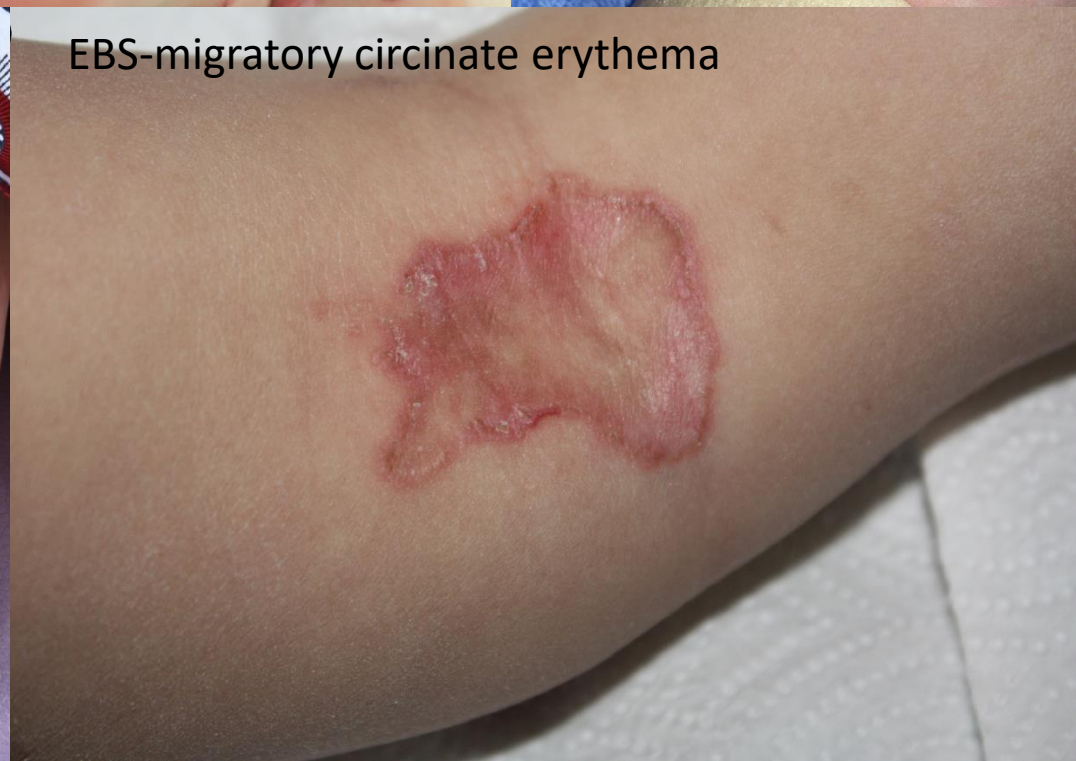


EBS-severe



EBS-MP



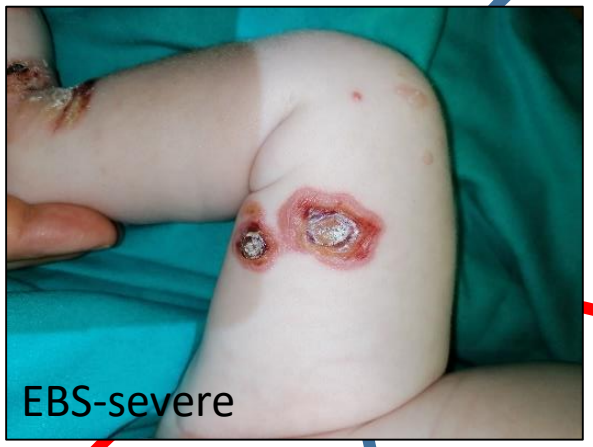


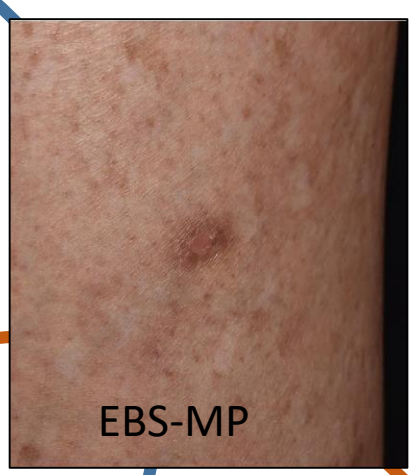
EBS-migratory circinate erythema

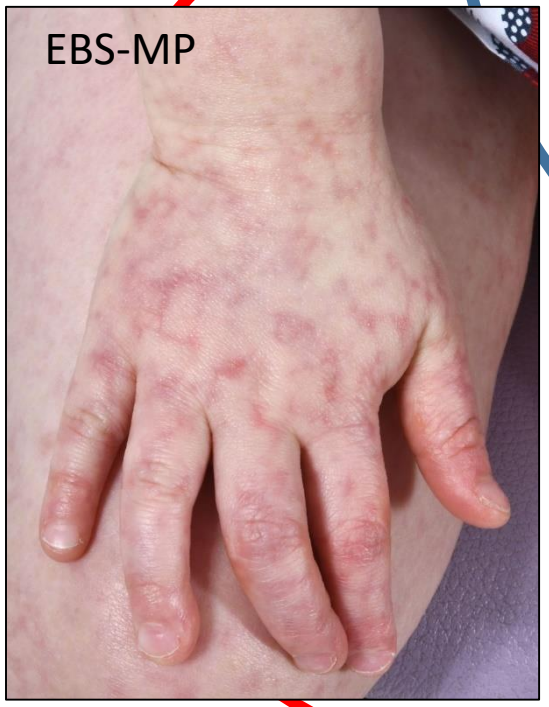
SKIN FRAGILITY

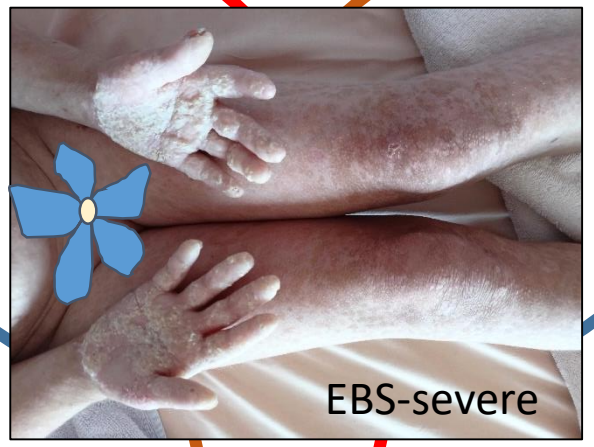
INFLAMMATION

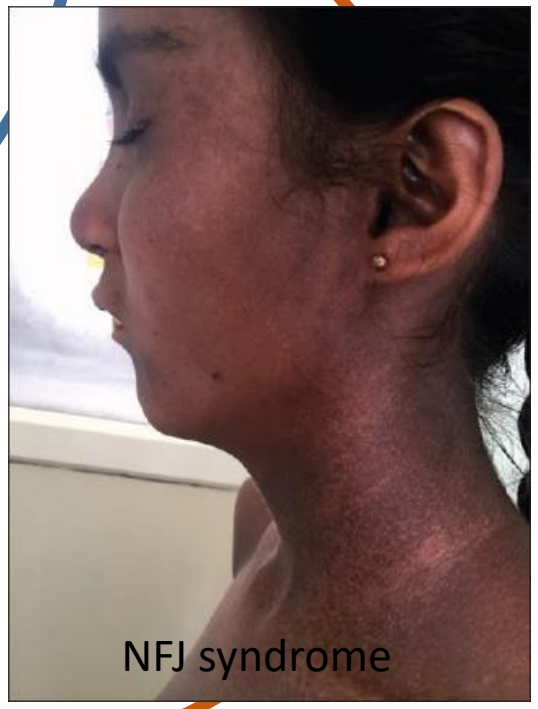
PIGMENTATION

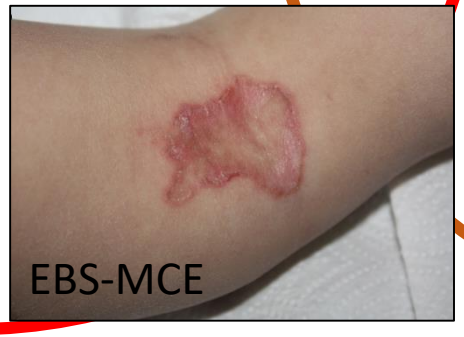


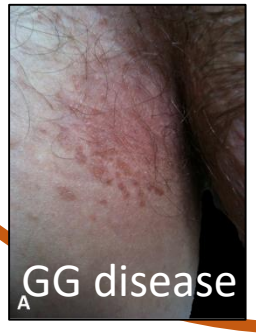




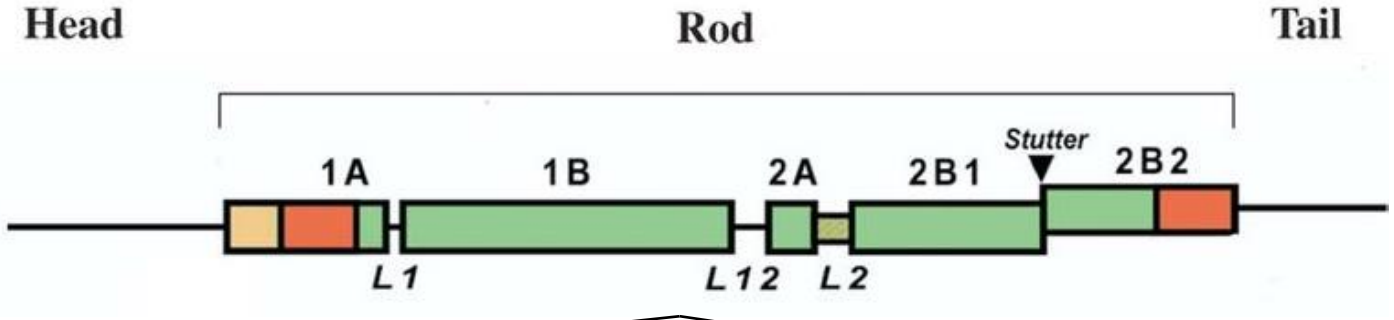








Consequences of KRT5 and 14 mutations



Absence of keratin
AR-EBS

Keratin dysfunction

Keratin polymerization

Protein interaction

Post traductional modifications

Molecular BioSystems

ROYAL SOCIETY OF CHEMISTRY

PAPER

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View Journal

In silico analysis of all point mutations on the 2B domain of K5/K14 causing epidermolysis bullosa simplex: a genotype–phenotype correlation†

Cite this: DOI: 10.1039/c4mb00138a

2nd July 2014

Santasree Banerjee,‡[ab] Qian Wu,‡[ab] Ping Yu,[ab] Ming Qi*[abc] and Chen Li*[ab]

Review series

The Journal of Clinical Investigation July 2009

Epidermolysis bullosa simplex: a paradigm for disorders of tissue fragility

Pierre A. Coulombe,[1,2,3] Michelle L. Kerns,[2] and Elaine Fuchs[4,5]

[1]Department of Biochemistry and Molecular Biology, Bloomberg School of Public Health, and [2]Department of Biological Chemistry and [3]Department of Dermatology, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA. [4]Laboratory of Mammalian Cell Biology and Development and [5]Howard Hughes Medical Institute, Rockefeller University, New York, New York, USA.

CONCISE COMMUNICATION

2010 162, pp1365–1369

BJD British Journal of Dermatology

Identification of novel and known *KRT5* and *KRT14* mutations in 53 patients with epidermolysis bullosa simplex: correlation between genotype and phenotype

M.J. Arin, G. Grimberg, H. Schumann,* H. de Almeida Jr,† Y.-R. Chang,* G. Tadini,‡ J. Kohlhase,§ T. Krieg, L. Bruckner-Tuderman*¶ and C. Has*

Novel and recurrent mutations in Keratin 5 and 14 in Korean patients with *Epidermolysis bullosa* simplex

Tae-Won Kang, Jeong Seon Lee, Song-Ee Kim, Se-Woong Oh, Soo-Chan Kim *

Journal of Dermatological Science 57 (2010) 90–94

Epidermolysis Bullosa Simplex in Scotland Caused by a Spectrum of Keratin Mutations

Elizabeth L. Rugg[1,4], Helen M. Horn[2], Frances J. Smith[1,3], Neil J. Wilson[1], Alison J.M. Hill[1], Gareth J. Magee[1], Carrie S. Shemanko[1,5], David U. Baty[3], Michael J. Tidman[2] and E. Birgitte Lane[1]

Journal of Investigative Dermatology (2007) 127, 574–580

2010 162, pp1004–1013

CLINICAL AND LABORATORY INVESTIGATIONS

BJD British Journal of Dermatology

Keratin mutations in patients with epidermolysis bullosa simplex: correlations between phenotype severity and disturbance of intermediate filament molecular structure

B. Jeřábková,*† J. Marek,† H. Bučková,‡ L. Kopečková,* K. Veselý,§ J. Valíčková,‡ J. Fajkus†¶ and L. Fajkusová*†

Epidermolysis Bullosa Simplex: Recurrent and *De Novo* Mutations in the KRT5 and KRT14 Genes, Phenotype/Genotype Correlations, and Implications for Genetic Counseling and Prenatal Diagnosis

J Invest Dermatol 125:239 –243, 2005

Ellen G. Pfendner, Sara G. Sadowski, and Jouni Uitto

Department of Dermatology and Cutaneous Biology, Jefferson Medical College, Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania

J Appl Genetics (2016) 57:175–181
DOI 10.1007/s13353-015-0310-9

HUMAN GENETICS • ORIGINAL PAPER

Novel sporadic and recurrent mutations in *KRT5* and *KRT14* genes in Polish epidermolysis bullosa simplex patients: further insights into epidemiology and genotype–phenotype correlation

Skin fragility

Is genotype able to predict if EBS will be localized, intermediate or severe?

Localized	Intermediate	Severe
		
Blisters mainly on hands and feet	Generalized blistering but less severe	Severe and extensive blistering, with the oral mucosa affected
Infancy, early childhood, adulthood	Birth, infancy	Birth
Autosomal dominant in *KRT5* (more prevalent) and *KRT14*	Autosomal dominant in *KRT5* and *KRT14*	Autosomal dominant in *KRT5* and *KRT14*

Int. J. Mol. Sci. **2024**, 25, 9495

EBS localized vs EBS interm vs EBS sev

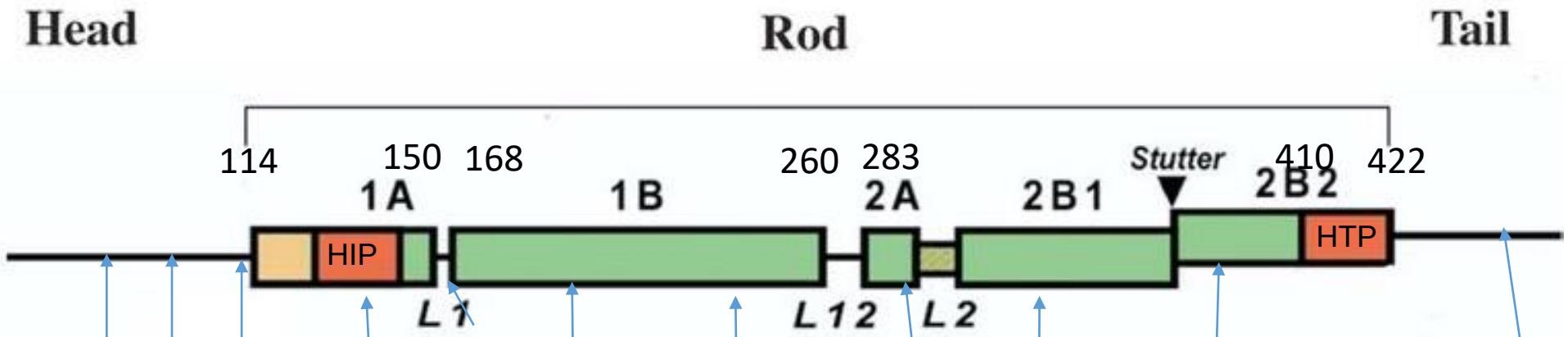
- Is the severity of skin fragility depends on:
  - Mode of inheritance?
  - Type of keratin involved KRT5 vs KRT14?
  - Type of mutation: nonsense vs missense?
  - Localization of the mutation in the keratin domain?
  - Nature of amino acid mutated?

Are autosomal recessive EBS more severe?

EBS AR

- Less than 10% of EBS with KRT5/KRT14 mutations
- Usually more severe (intermediate or severe subtype), but seems to improve with time
- KRT14 mutations
  - Are most frequent (20 mutations, some recurrent)
  - Most of published mutations are nonsense mutations, homozygous, from asymptomatic parents.
  - Absence of keratin14 staining in most cases, but keratin 5 can form a heterodimer with keratin 15.
- KRT5
  - Few reported cases (10 mutations)
  - Most mutations are missense mutations,
  - From consanguineous asymptomatic or very mild parents or non consanguineous parents whom one is symptomatic
  - Sparse staining for keratin 5 (even for non sense mutation?). Keratin14 can not form another heterodimer

KRT14



c.92delT
p.30Ter

c.129dupC
p.Ser44Ter

c.313-314delGC
p.?

p.Ala105Ter

p.Met119Ile

c.346A>T
p.Lys116Ter

p.Arg134Cys

p.Glu144Ala

c. 427delC
p.Leu143Ter

c.460C>T,
p.Gln154Ter

c.612T>A
p.Tyr204Ter

c.744delC/insAG
p.Tyr248Ter

c.749delA
p.Lys250Ter8

c.827delC
p.Pro276Ter4

c.915G>A
p. Trp305Ter

c.1120C>T
p.Gln374Ter

c.1163G>A
p. Arg388His

c.1174G > T
p.Glu392Ter

c.1186C>T
p. Gln396Ter

c.1194del
p.Tyr398Ter

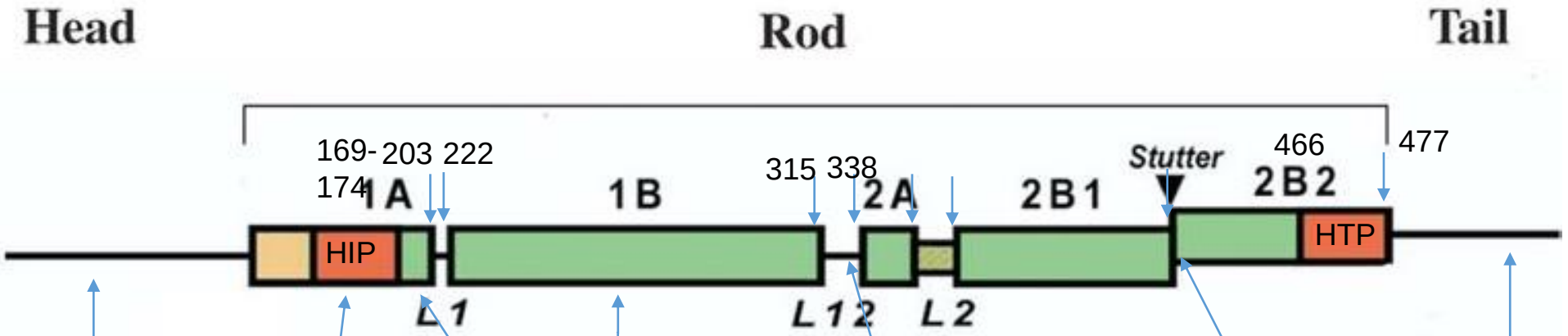
c.1840A > C
p.?

EBS-loc

EBS-interm

EBS-sev

KRT5



c.472G>A,
p.Asp158Asn

c.508G>A,
p.Glu170Lys

c.521G>C,
p.Lys173Asn

c.817delG
p.Val273Ter

p.Gly476Asp +
p.Gly183Glu

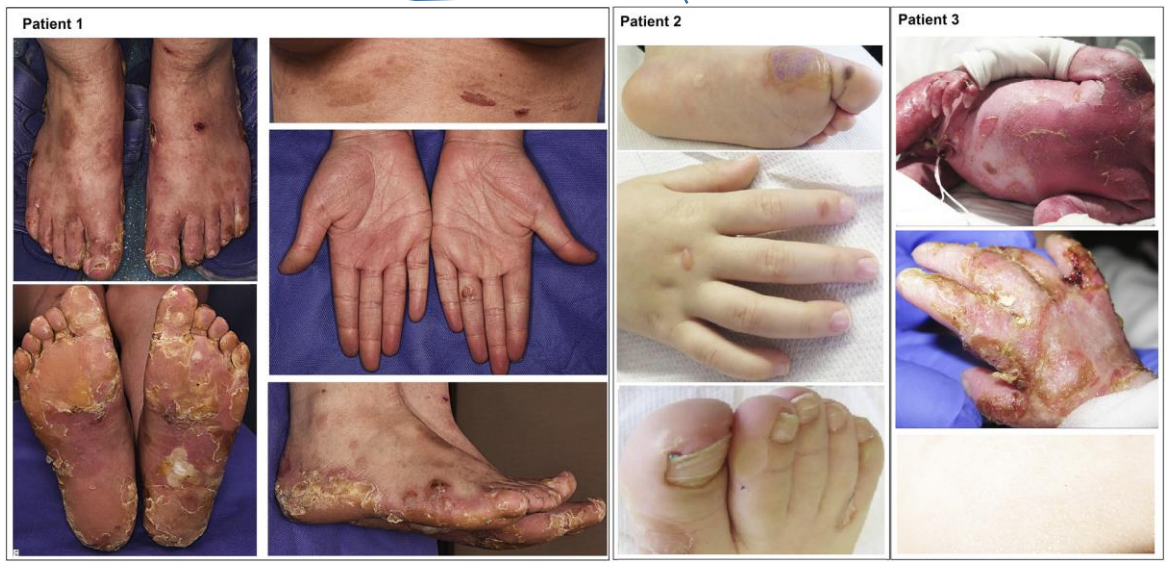
c.991C>T
p.Arg331Cys

c. 1675C>T
p.Arg559Ter

c.1440-1G>A
p.?

p.Glu170Lys +
p.Val143Ala

p.Glu170Lys +
p.Glu418Lys



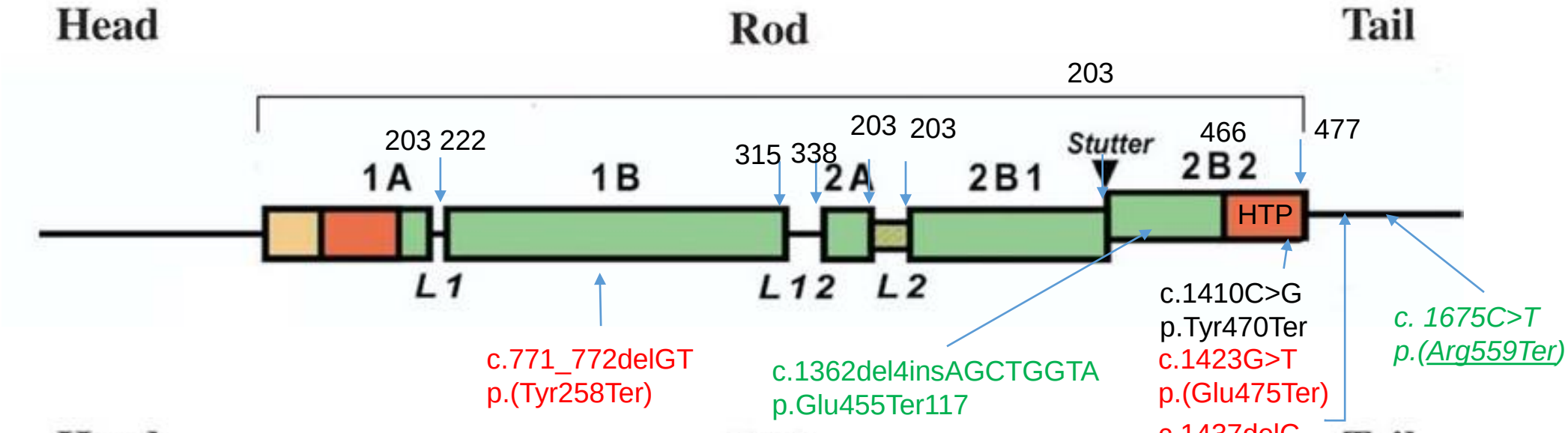
Are autosomal recessive EBS more severe? YES

Are nonsense mutations less severe in AD forms?

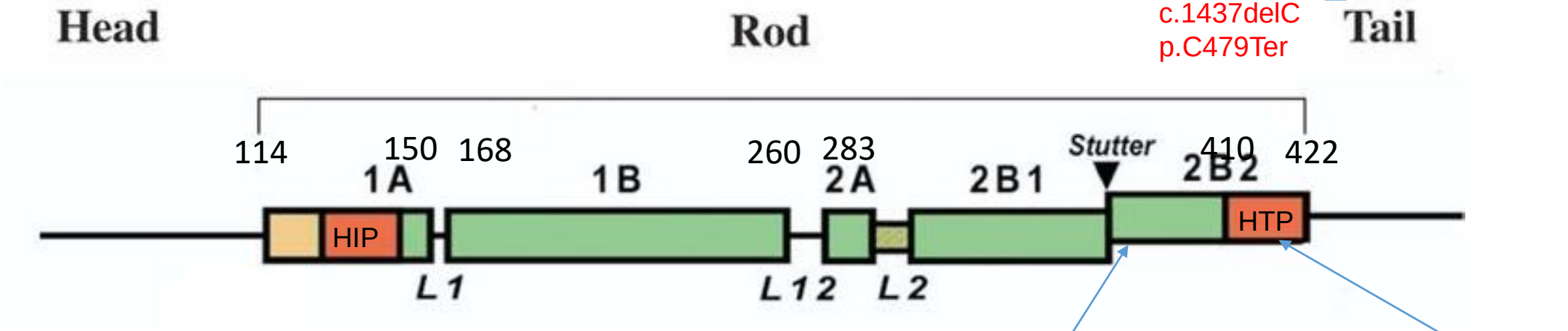
Nonsense mutations

- Rare
- Most of reported mutations are localized in the α-helix domain 2B and the tail of keratin 5/14 which can lead to an expression of truncated protein and can exert a dominant negative effect.
- Mutation severity is variable, but involvement of HTP domain usually results in a more severe phenotype.

KRT5



KRT14



EBS-loc

EBS-interm

EBS-sev

c.1120C>T
p.(Gln374Ter)

c.1131dup
p.(Gly378TrpfsTer105)

c.1151_1154dup
p.(Gln386GlyfsTer98)

c.1186C>T
p.Gln396Ter

c.1228C>T
p.Gln410Ter

c.1231G>T
p.Glu411Ter

c.1234del
p.(Ile412Ter30)

c.1243_1246delTACC
p.(Tyr415Ter26)

c.1256_1274+163 del182insA
p.Leu419Ter41

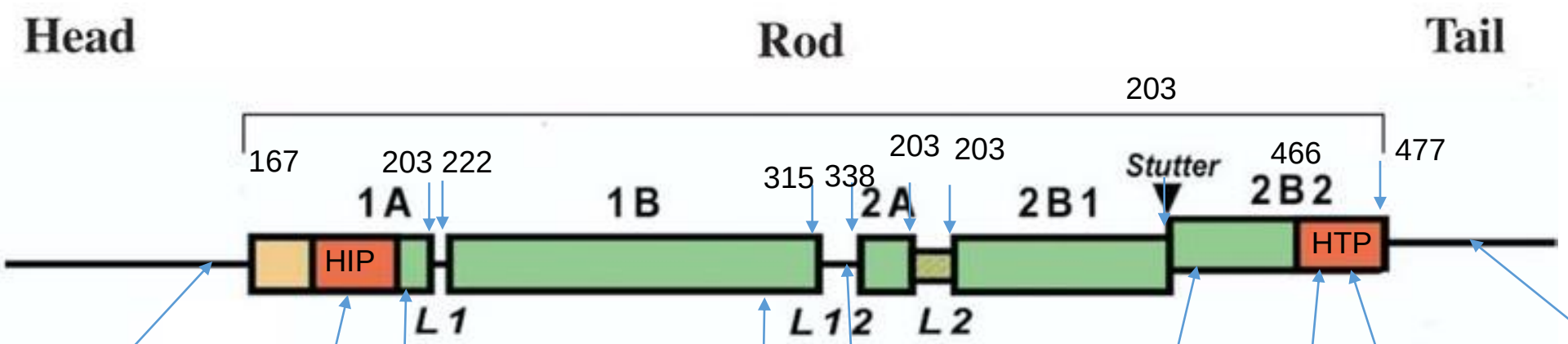
Are nonsense mutations less severe in AD forms? NO

Role of localization of missense mutation in keratin’s domains?

Localization of substitued amino acid

- Mutations in the HIP and HTP domain usually result in a more severe phenotype.
- Some hotspot mutations always lead to a severe phenotype.
- The same mutation can cause different phenotypes
  - In a population specific manner or not
  - Even in the same family!
- Mutations localized in the same amino acid or the same domain can cause different phenotypes

KRT5



c.455C>T
p.(Pro152Leu)
c.473A>G
p.(Asp158Gly)

c.472G>C
p.(Asp158His)

*c.593C>G
p.(Thr198Ser)
*c.593C>A
p.(Thr198Asn)

c.605T>C
p.(Leu202Pro)

c.587T>C
p.(Leu196Pro)
c.587T>C
p.(Leu196Pro)

c.927+1G>A
c.927+1G>C
c.927+1G>T
c.927+2T>C
p.(?)

c.1283C>T
p.(Ala428Val)

c.1269_1273dupGGCCCT
p.(Ala424_Leu425dup)

c.1474+1G>C
c.1474+2T>C
p.(?)

c.1418T>G
p.(Leu473Arg)

c.528C>A
c.528
p.(Asn176Lys)
p.(Asn176Ser)

c.536T>A
p.(Phe179Tyr)

c.548T>A
p.(Ile183Asn)

c.991C>T
p.(Arg331Cys)

c.992G>T
p.(Arg331Leu)

c.968T>C
p.(Val323Ala)

c.1397A>G
p.(Glu466Gly)

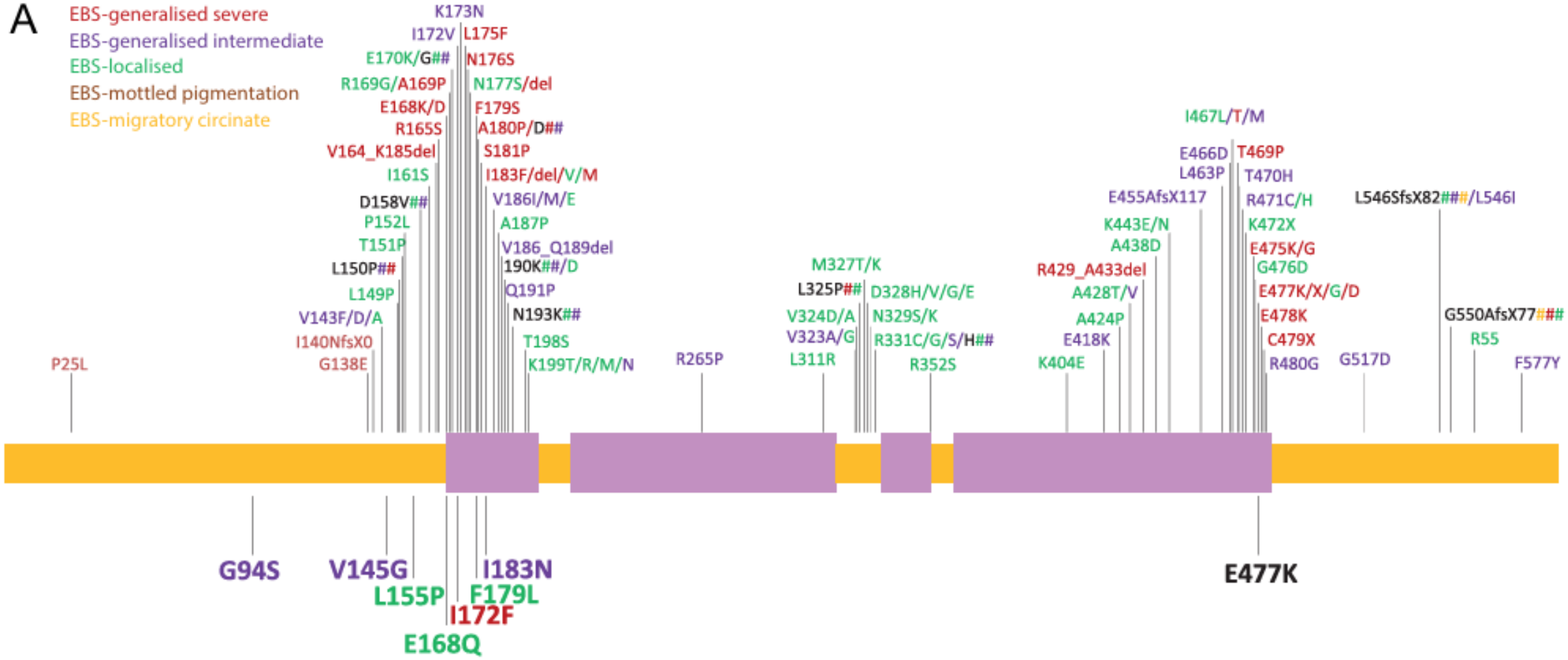
c.1401 C>G
p.(Ile467Met)

c.1427G>A
p.(Gly476Asp)

c.1429G>A
p.(Glu477Lys)

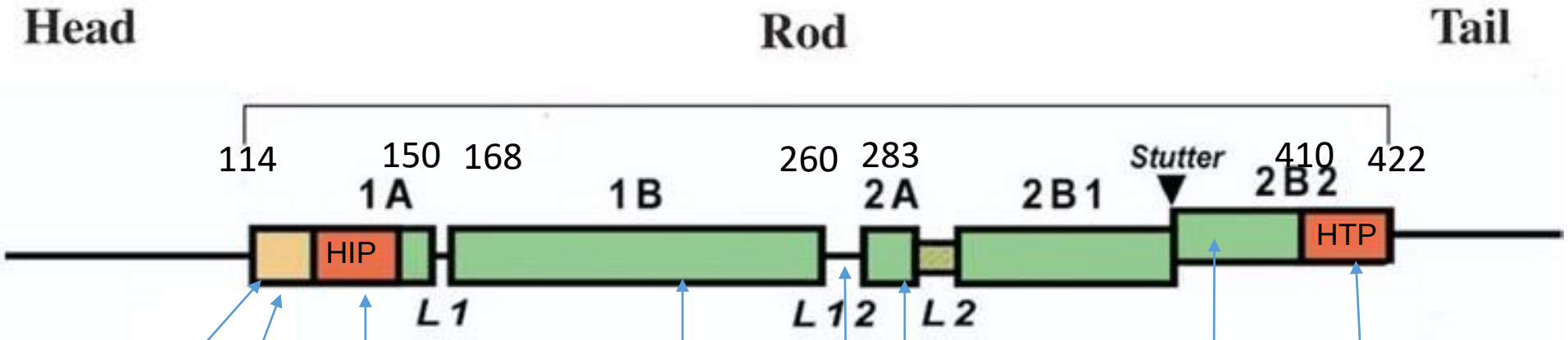
EBS-loc
EBS-interm
EBS-sev

Pediatric Dermatology. 2019;36:132–138



Acta Derm Venereol 2017; 97: 1114–1119

KRT14



*c.348G>T
p.(Lys116Asn)
c.346A>G
p.(Lys116Glu)

c.356T>C
p.(Met119Thr)

*c.373C>T
p.(Arg125Cys)
*c.374G>A
p.(Arg125His)
*c.374G>A
p.(Arg125His)
c.373 C>A
p.(Arg125Ser)

c.581G>A
p.(Arg194His)

c.397G>T
(p.Val133Leu)
c.398T>C
p.(Val133Ala)

c.783_842del
p.(Arg261_Leu280del)

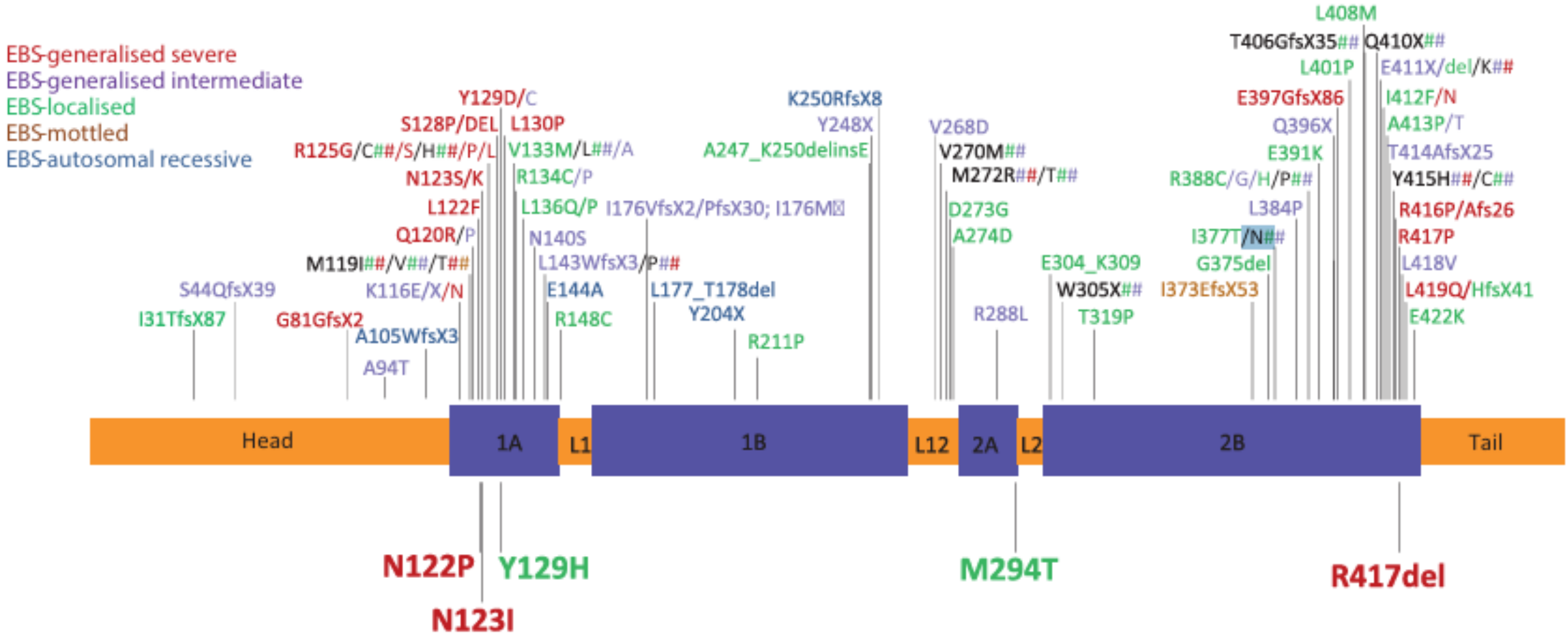
c.863G>T
p.(Arg288Leu)

c.1069_1080del
p.(Asn357_Glu360del)

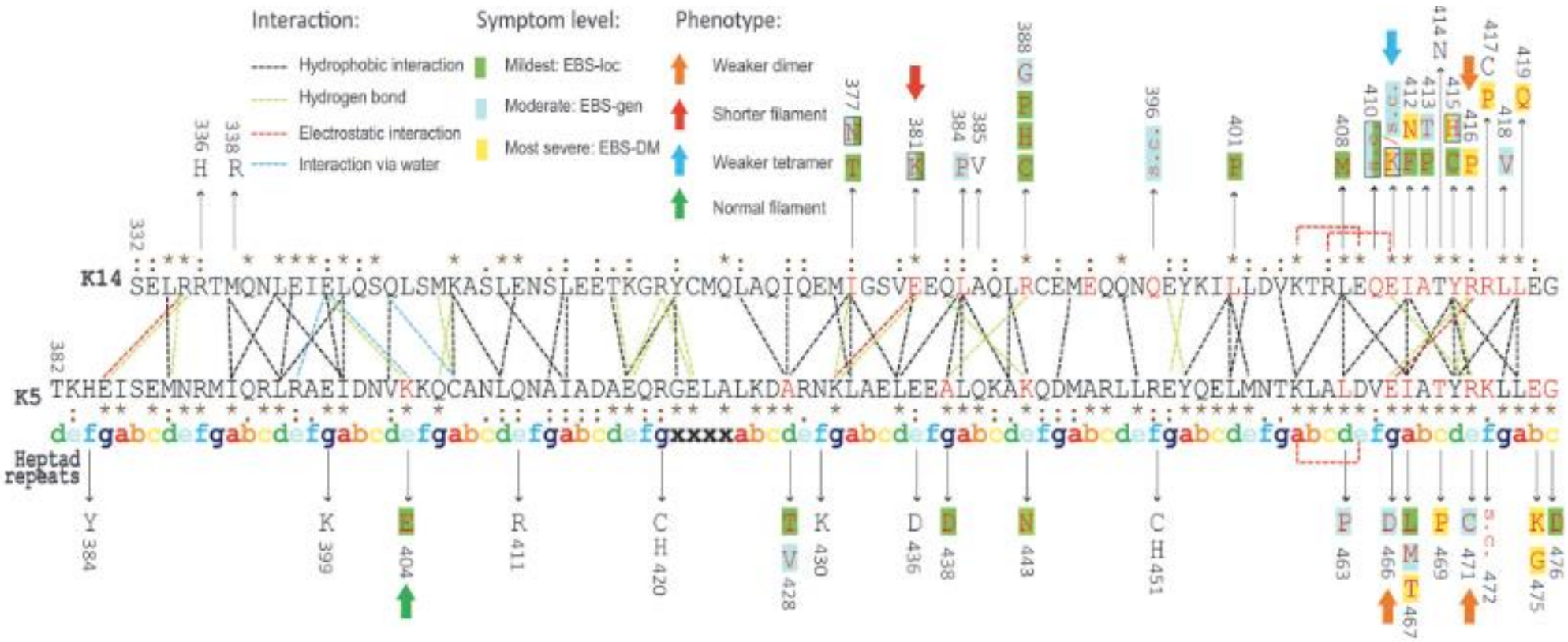
*c.1162C>T
p.(Arg388Cys)

c.1231_1233del
p.(Glu411del)

EBS-loc
EBS-interm
EBS-sev



Acta Derm Venereol 2017; 97: 1114–1119



The position in the heptad of the mutated amino acid is not predictive of the phenotype

Table 4 All mutations of different phenotypes occurred on each position of the heptad repeat

Position on heptad repeat	SNP (%)		EBS-loc (%)		EBS-gen (%)		EBS-DM (%)		Total (pathogenic)
a (hydrophobic)	1	7	4	25	3	23	3	30	10
b (polar)	1	7	1	6	1	8	2	20	4
c (polar)	1	7	1	6	0	0	1	10	2
d (hydrophobic)	0	0	3	19	3	23	1	10	7
e (charged)	2	14	6	38	3	23	1	10	10
f (polar)	6	43	0	0	0	0	1	10	1
g (charged)	3	21	1	6	3	23	1	10	5
Total	14		16		13		10		

Mol. BioSyst. 2014

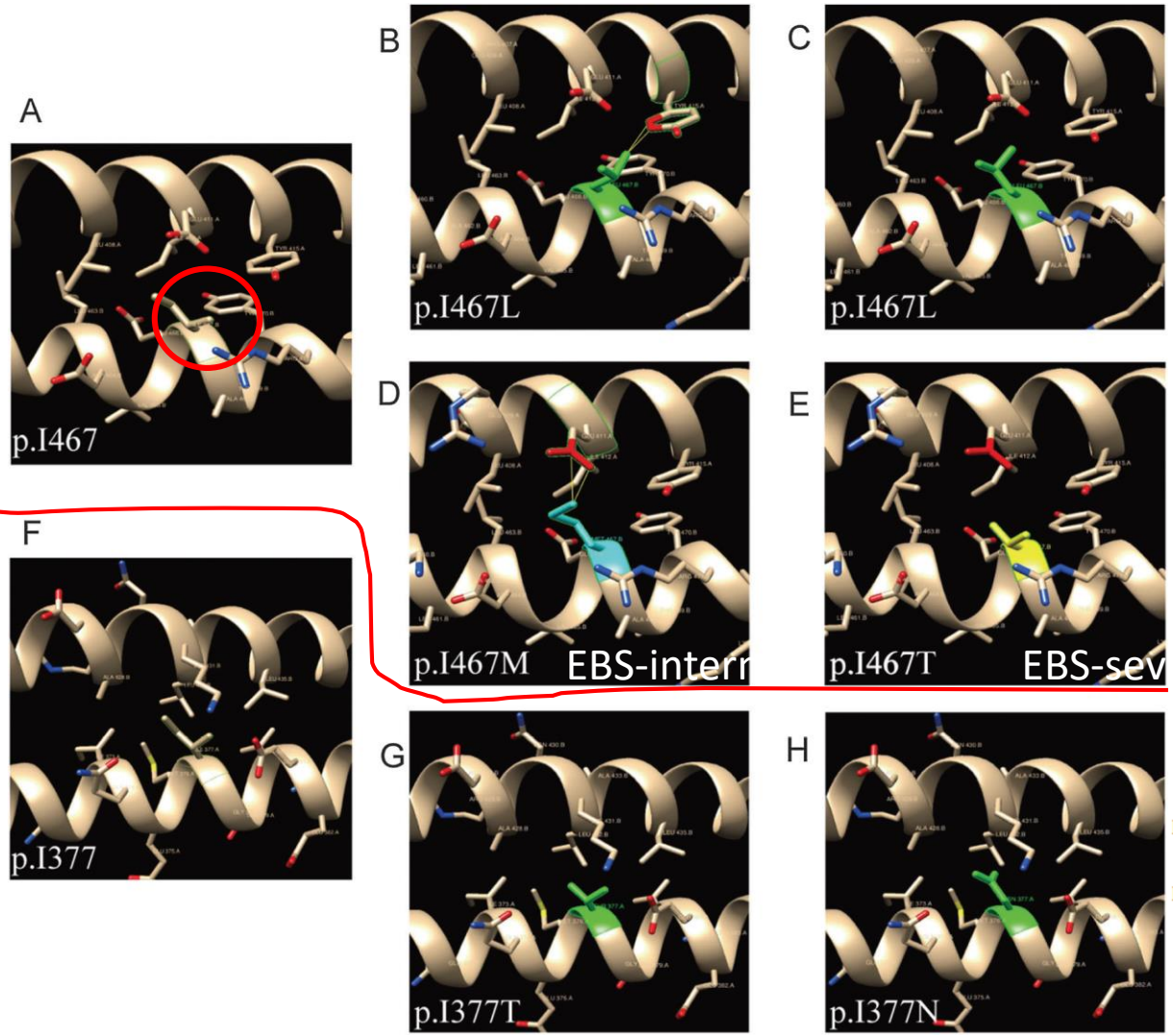
Role of localization of missense mutation in keratin’s domains?

Mutations in the HIP and HTP domain usually result in a more severe phenotype.

The position in the heptad of the mutated amino acid is not predictive of the phenotype

What is the role of the nature of the mutated amino acid in the severity of the phenotype?

EBS-loc



p.I467L	a	EBS-	Aliphatic, Hydrophobic, Neutral	Aliphatic, Hydrophobic, Neutral	Loss of hydrophobic interaction with K14 L408, I412, Y415	
p.I467M	a	EBS-gen	***Aliphatic***, Hydrophobic, Neutral	Hydrophobic, Neutral	Loss of hydrophobic interaction with K14 L408, I412, Y415	
p.I467T	a	EBS-DM	***Aliphatic***, Hydrophobic, Neutral	***Polar***, Hydrophilic, Neutral	Loss of hydrophobic interaction with K14 L408, I412, Y415	
p.I377N	a	EBS-loc/ gen	***Aliphatic***, Hydrophobic, Neutral	***Polar***, Hydrophilic, Neutral	Loss of hydrophobic interaction with K5 A428, L432, L435	Hydrogen bond is broken with K5 K431
p.I377T	a	EBS-loc	***Aliphatic***, Hydrophobic, Neutral	***Polar***, Hydrophilic, Neutral	Loss of hydrophobic interaction with K5 A428, L432, L435	Hydrogen bond is broken with K5 K431

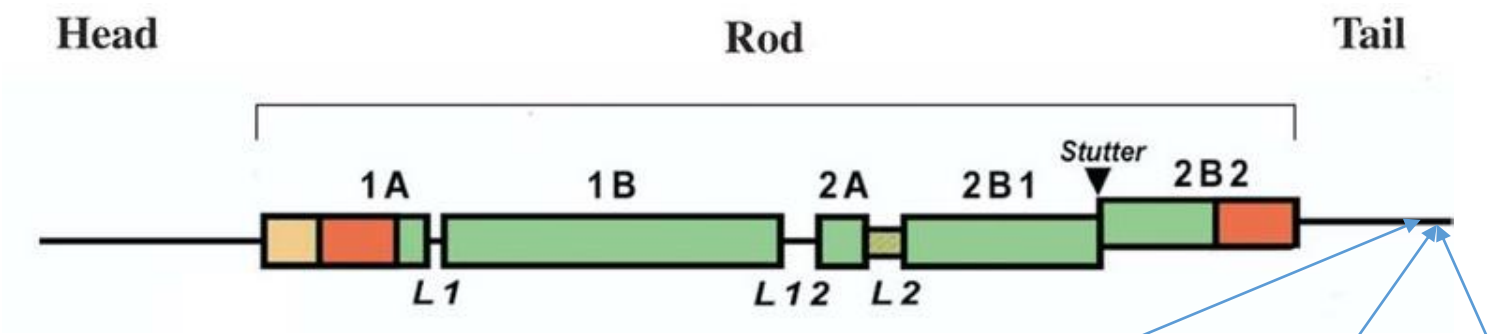
EBS-loc

What is the role of the nature of the mutated amino acid in the severity of the phenotype?

Substitution by an amino acid with different properties leads usually to a more severe phenotype.

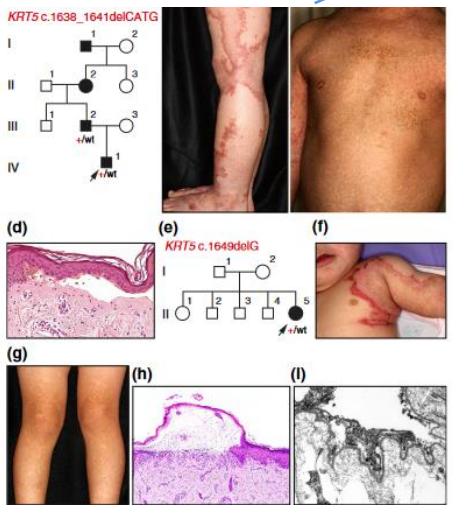
Inflammation

EBS migratory circinate erythema: KRT5



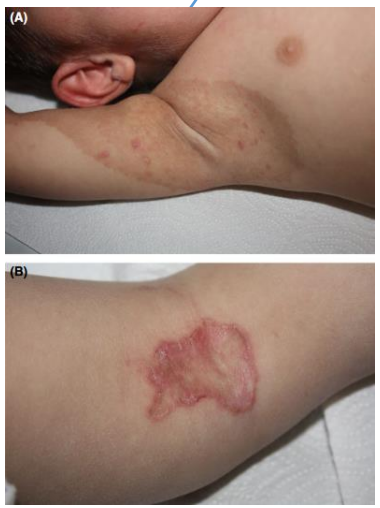
c.1321_1332del12
p.Lys441_Gln444del

Eur J Dermatol. 2018;28(1):123-125.



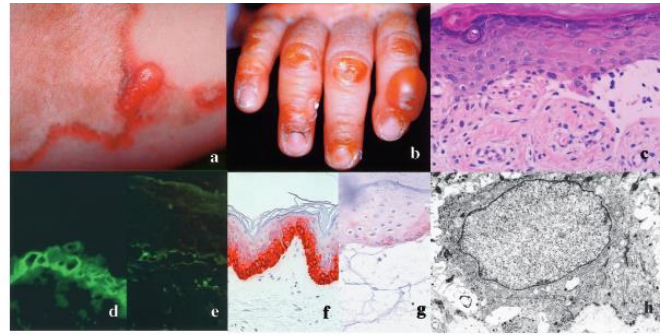
c.1637del4
p.Leu546Ter82

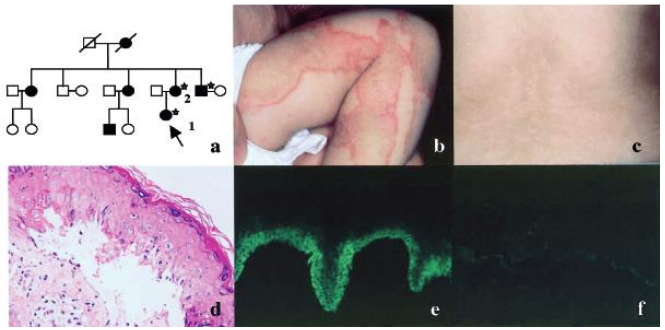
Journal of Dermatological Science 72 (2013)
JEADV 2017, 31, e224–e272
Japon



c.1650delC
p.Gly550Ter

Pediatric Dermatology. 2020;37:358–361.turquie



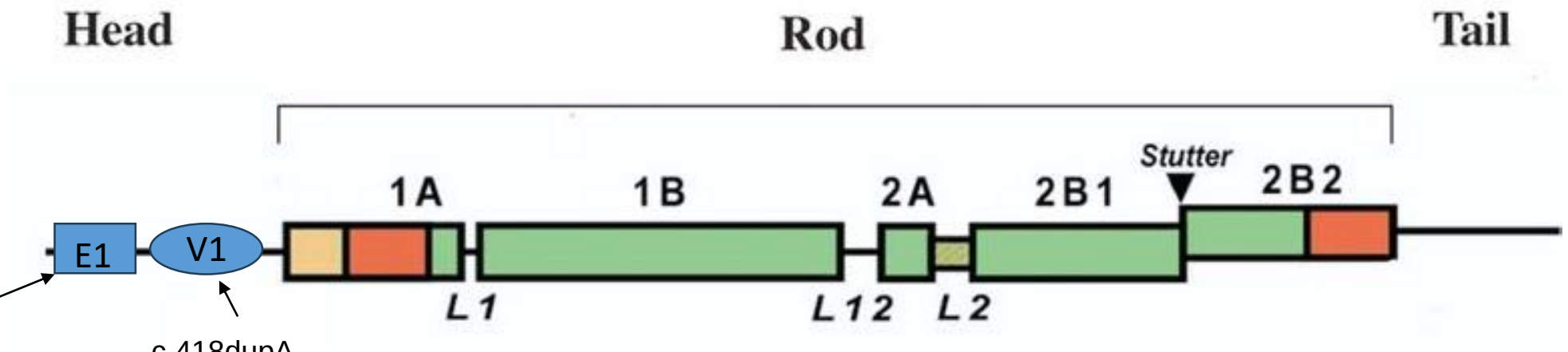


c.1649delG
p.Gly550Ter77

J Invest Dermatol. 2003 Sep;121(3):482-5
JEADV 2017, 31, e224–e272
Acta Derm Venereol 2014; 94: 307–311
Clin Genet. 2004 Sep;66(3):236-8.
Japon/Corée/europe

Pigmentary anomalies

Galli-Galli /Dowling Degos disease: KRT5



c.38dupG
p.(Ser14Ter3)

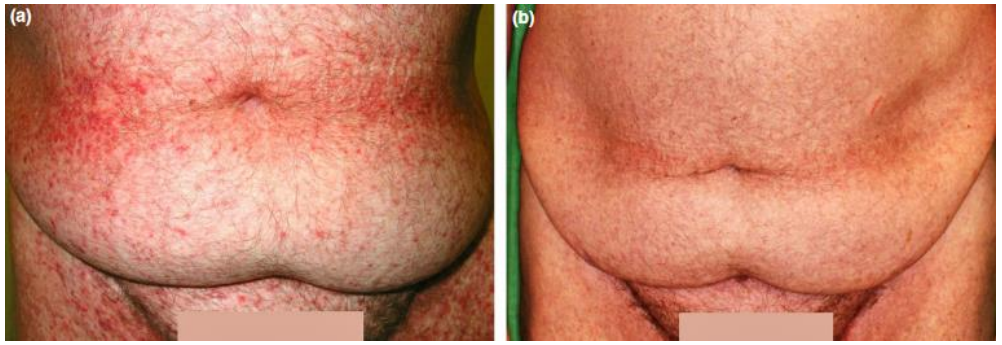
c.14C>A
p.(Ser5Ter)

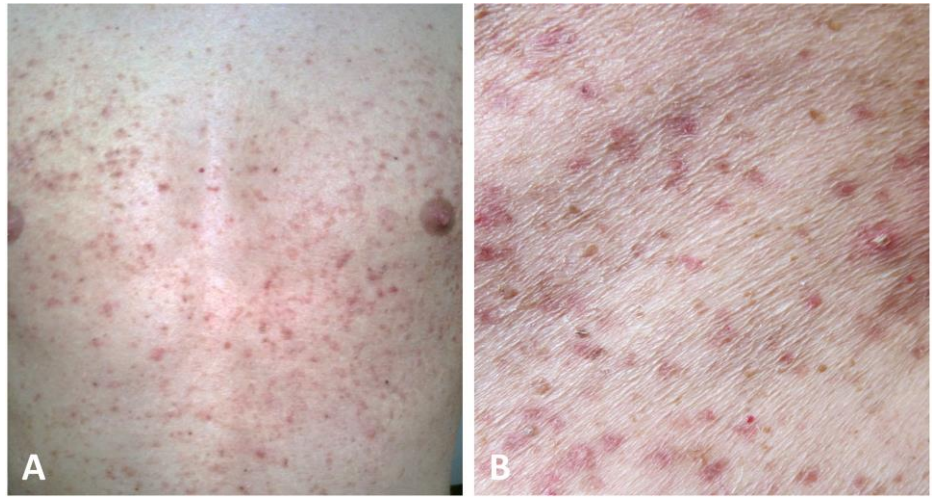
c. 10C>T
p.(Gln4Ter)

c.2T>C
p.(Met1?)

c.418dupA
p.(Ile140Ter39)

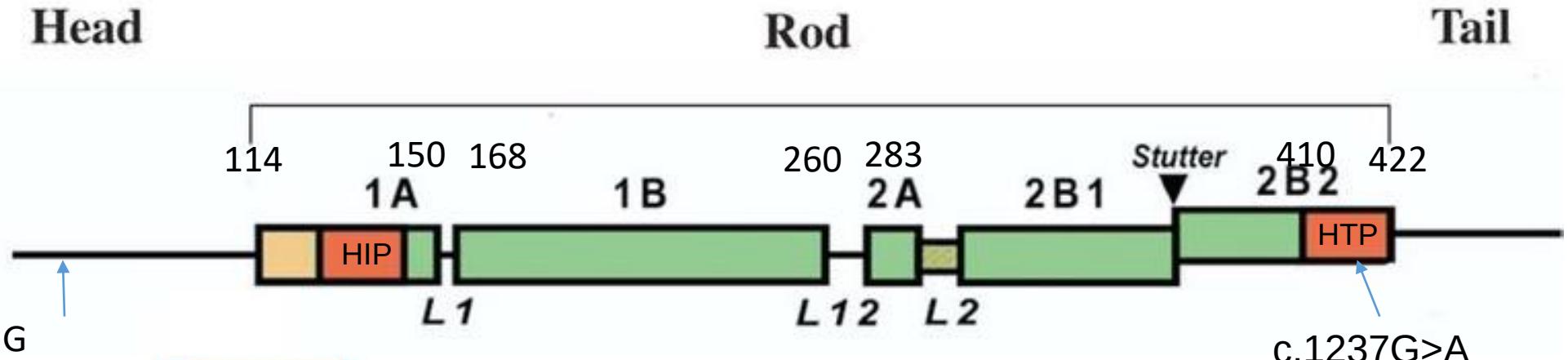
c.476C>T
p.(Pro159Leu)





J Dermatol. 2022;49:e63–e64.

Naegeli-Franceschetti-Jadasson syndrome: KRT14



c.17delG
p.Arg6Ter8

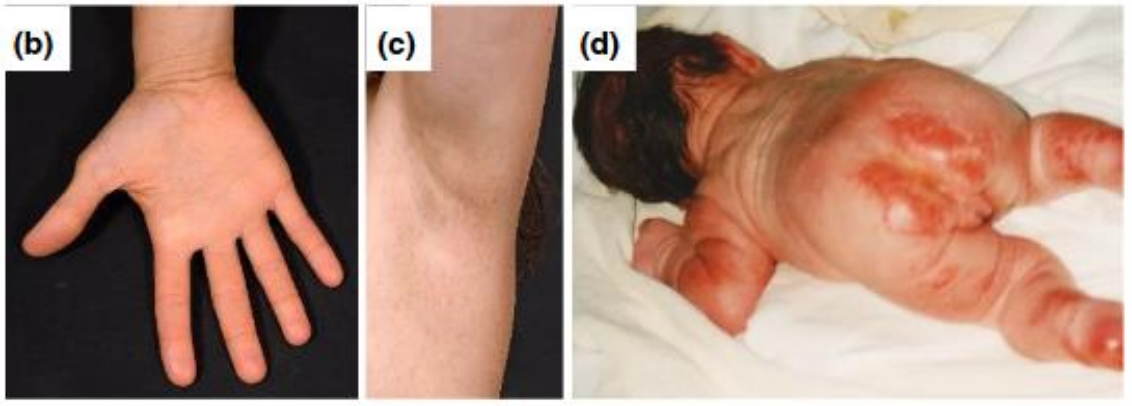
c.16_17insCT
p.Arg6Ter1

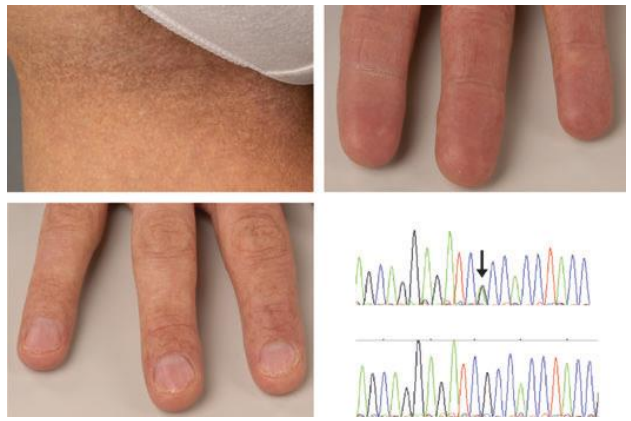
c.21C>T
p.Gln7Ter

c.29delC
p.Ser11Ter7

c.54C>A
p.Cys18Ter

c.1237G>A
p.Ala413Thr

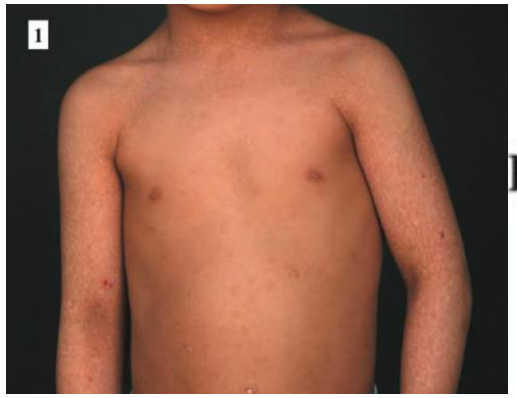


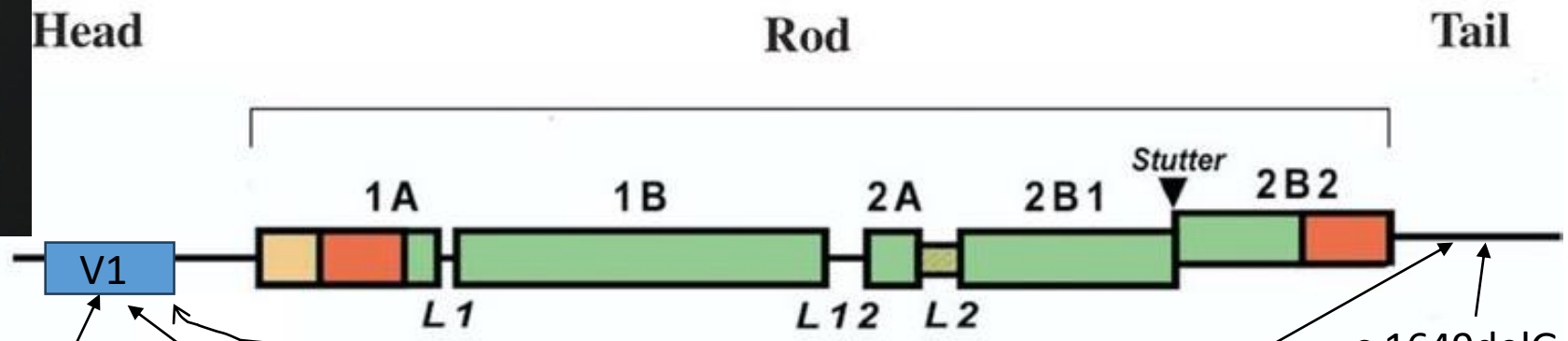


Br J Dermatol. 2019 Oct;181(4):864-866 Journal of Investigative Dermatology (2008) 128, 1517–1524; British Journal of Dermatology (2020) 183, pp754–787

JEADV 2010, 24, 1113–1121

EBS with mottle pigmentation: KRT5





c. 74C>T
p.Pro25Leu

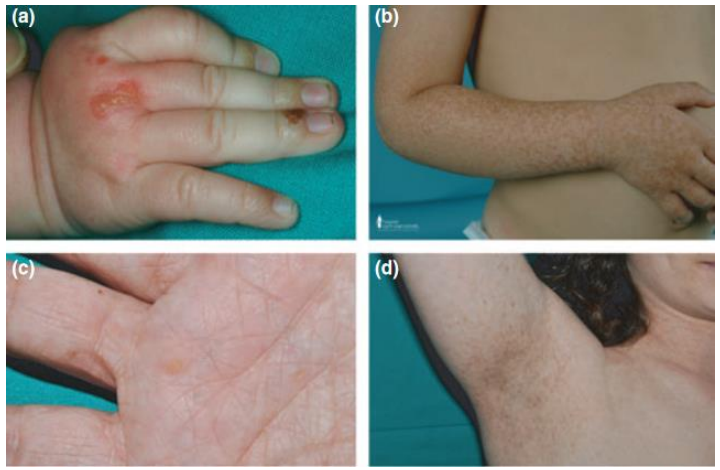
c. 237C>T
p.(Ser79=)

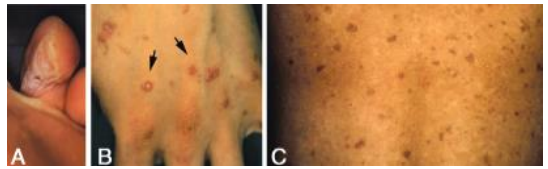
c.287G>A
p.Gly96Asp
c.289T>A
p.Phe97Ile
Med J Islam Repub Iran. 2020

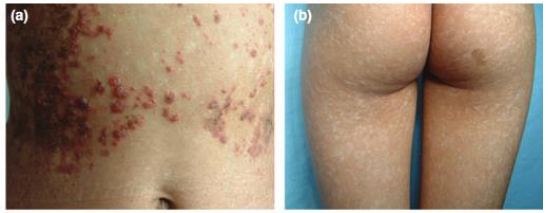
c.1440-357_1475-15del
p.Arg480Serfs*37
Journal of Investigative Dermatology (2017) 137

p.Ile140Ter
p.GlY138Glu
Acta Derm Venereol 2017; 97: 1114–1119

c.1649delG
p.(Gly550AlafsTer77)

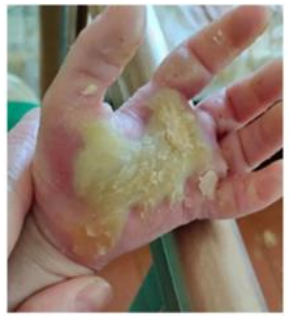


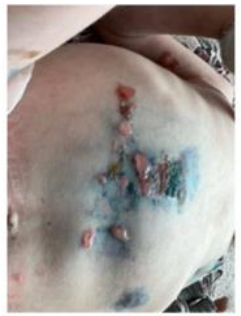


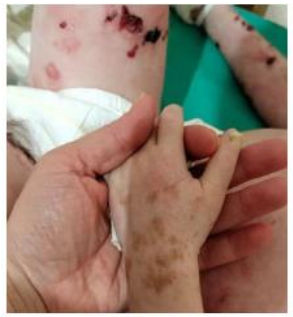


Pediatric Dermatology Vol. 2013

EBS with mottle pigmentation, KRT14?

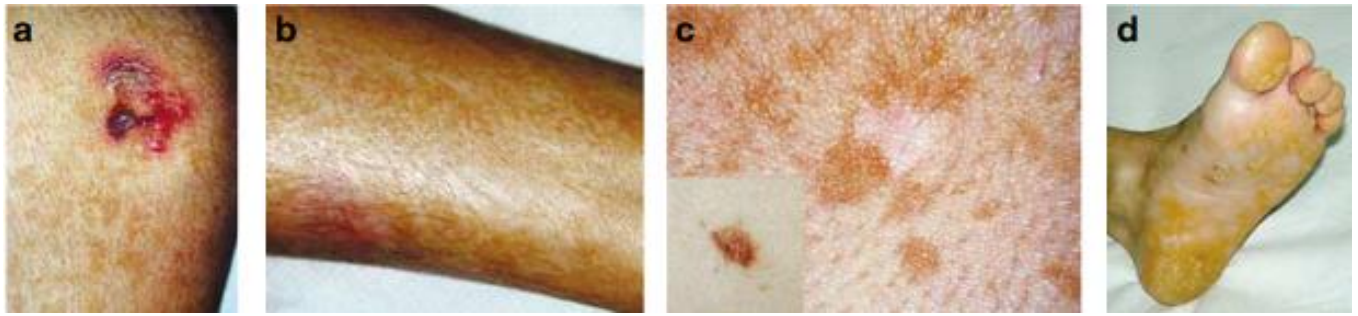






c.356T>C
p.Met119Thr

Int. J. Mol. Sci. 2024,



c.1117_1158dup
p.Ile373_Glu386dup

c.?
p.Ile373Ter53

Acta Derm Venereol 2017; 97: 1114–1119

Skin cancer

Nat Genet. 2009 August ; 41(8): 909–914. doi:10.1038/ng.412.

New common variants affecting susceptibility to basal cell carcinoma

ARTICLE

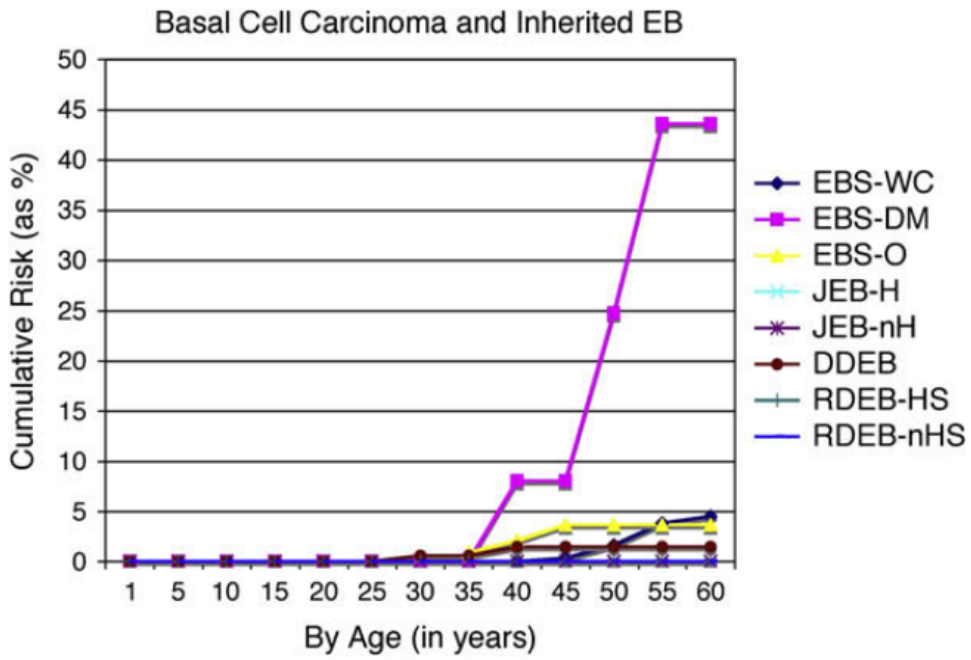
Received 20 Apr 2016 | Accepted 8 Jul 2016 | Published 19 Aug 2016 DOI: 10.1038/ncomms12510 OPEN

Genome-wide association study identifies 14 novel risk alleles associated with basal cell carcinoma

SNP rs11170164, encoding a G138E substitution in the keratin 5 (KRT5) gene, affects risk of BCC (OR = 1.35, P = 2.1 × 10−9) and rs641615 (D197E) OR of 1.21 (P = 2.2 × 10−5).

Epidermolysis bullosa and the risk of life-threatening cancers: The National EB Registry experience, 1986-2006

J AM ACAD D ERMATOL FEBRUARY 2009



Arch Dermatol Res (2017) 309:587–593
DOI 10.1007/s00403-017-1757-9

CONCISE COMMUNICATION

Keratin gene mutations influence the keratinocyte response to DNA damage and cytokine induced apoptosis

In conclusion

- AR EBS are usually more severe
- For AD EBS
  - The type of keratin (5 vs 14) involved
  - The type of mutation: nonsense vs missense
  - The localization of substituted amino acid in the heptad

  } are not predictive of severity

  - Mutations in the HIP and HTP domains are more severe
  - Drastic change in properties of the substituted amino acid is more severe
  - Some (rare) mutations always lead to the same phenotype, in particular in head and tail domain of keratins and for rare phenotypes
  - Other regulatory factors are involved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CHU de Nice