

# Genotype-phenotype spectrum and correlations in Chinese patients with keratinocytic epidermal naevus: A retrospective study of 22 cases

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## Abstract

**Background:** Keratinocytic epidermal naevus is characterised by hyperkeratotic lesions arranged along Blaschko's lines. So far, multiple genes have been implicated, but there is no detailed data or genotype-phenotype correlation studies of keratinocytic epidermal naevi in Chinese patients.

**Objective:** To evaluate the clinical, histopathological and genetic features, genotype-phenotype correlations of keratinocytic epidermal naevus in the Chinese population.

**Methods:** A retrospective study of patients with keratinocytic epidermal naevi referred to the Department of Dermatology, West China Hospital, in the last four years. Medical history, clinical data, histopathological characteristics, and evidence of genetic mutations were collected from 22 unrelated Chinese patients with this problem.

**Results:** The distribution of the keratinocytic epidermal naevi exhibited right-side dominance. Non-epidermolytic epidermis naevus was much more common. Eight reported missense mutations were found in this study, which were detected in five genes, including *HRAS*, *KRT10*, *FGFR3*, *GJB2*, and *PIK3CA*. *HRAS* was the most commonly affected gene (9/22, 40.91%) in this study, with the c.37G>C (6/22, 27.27%) substitution representing a possible hotspot mutation. Mutation allele loads were higher in the affected lesions than blood samples. Epidermolytic epidermal naevus was found in three patients exclusively carrying *KRT10* mutations. Inflammatory epidermal naevi were caused by mutations of *KRT10* and *PIK3CA*. Most of the mosaic mutations detected in keratinocytic epidermal naevi patients were the same as germline mutations identified in systemic diseases caused by these genes.

**Limitations:** The retrospective nature of the study.

**Conclusion:** Our findings reveal the genotype-phenotype spectrum and their correlation amongst Chinese patients with keratinocytic epidermal naevi. In addition, our data underscores the importance of genetic testing in lesional skin to help characterise and categorise keratinocytic epidermal naevi, decide on a therapeutic strategy, and offer genetic counselling and prenatal diagnosis.

**Key words:** Keratinocytic epidermal naevus, somatic mosaicism, deep next-generation sequencing, genotype-phenotype correlation, Chinese

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## Introduction

Epidermal naevus is a relatively common cutaneous mosaic disorder, typically seen at birth or developing in early childhood and evolving during puberty. Keratinocytic epidermal naevus is usually characterised clinically by gray-brown papules or plaques distributed in a linear pattern, following the lines of Blaschko and histologically by hyperplasia of epidermal keratinocytes. Clinically, keratinocytic epidermal naevus can be classified into localised or generalised variants, and inflammatory linear verrucous epidermal naevus.<sup>1</sup> Inflammatory linear verrucous epidermal naevus could be localised or generalised. Histopathologically, keratinocytic epidermal naevus can be categorised into many distinct types, such as epidermolytic epidermal naevus, non-epidermolytic epidermal naevus, and inflammatory epidermal naevus.<sup>2</sup> Inflammatory epidermal naevus could overlap with the other two subtypes. Herein, we describe the clinical, histopathological, and genetic features of 22 unrelated patients with keratinocytic epidermal naevi in the Chinese population.

## Methods

We retrospectively reviewed the clinical, pathological, and genetic features of patients referred to our department for keratinocytic epidermal naevus between 2021 and 2024. Clinical information and medical history was collected. All patients underwent a complete physical examination at their first visit and every 12 months thereafter, in order to detect any transition towards epidermal naevus syndrome. Skin biopsies were performed for histopathological examination. Peripheral blood and lesional skin samples were obtained for the whole exome sequencing. Subsequently, targeted deep sequencing was carried out with an average coverage depth reaching  $\times 20,000$ .

## Results

### Clinical data

The series consisted of 22 cases, 10 males and 12 females, from 22 unrelated families [Table 1]. Seventeen patients (17/22, 77.27%) were aged  $< 18$  years while the remaining five (5/22, 22.73%) were adults. Lesions were observed in a majority of the patients since birth (21/22, 95.45%) with only one (1/22, 4.55%) developing lesions after the age of two. Unilateral distribution of the lesions was observed in most patients (17/22, 77.27%). Right-sided involvement (15/17, 88.24%) was much more common than the left-sided one (2/17, 11.76%). Fourteen patients had generalised epidermal naevus (14/22, 63.64%) while eight had the localised variant (8/22, 36.36%) [Figures 1a–1c]. All three patients with inflammatory linear verrucous epidermal naevus were female, with the lesions in all of them presenting on the right side of the body. Extracutaneous abnormalities were not documented in our patients.

### Histopathological findings

Haematoxylin-eosin staining was performed in all the 22 patients [Table 1]. Nineteen patients were affected with non-epidermolytic epidermal naevus (19/22, 86.36%) and the remaining three had epidermolytic epidermal naevus (3/22, 13.64%). Among them, two of epidermolytic epidermal naevus (2/3, 66.67%) and one of non-epidermolytic epidermal naevus (1/3, 33.33%) overlapped with inflammatory epidermal naevus. Compared to the non-inflammatory epidermal naevus (19/22, 86.36%), inflammatory epidermal naevus (3/22, 13.64%) was rarer [Figures 2a–2c].

### Genotype-phenotype correlation

Whole exome sequencing followed by targeted deep sequencing were performed using lesional skin and peripheral blood samples from all 22 patients [Table 1]. Seventeen patients (17/22, 77.27%) were found to carry mutations in five



**Figure 1:** Phenotypic spectrum of keratinocytic epidermal naevus (a) Patient 12 with generalised epidermal naevus, (b) Patient 11 with localised epidermal naevus, and (c) Patient 18 with inflammatory linear verrucous epidermal naevus.

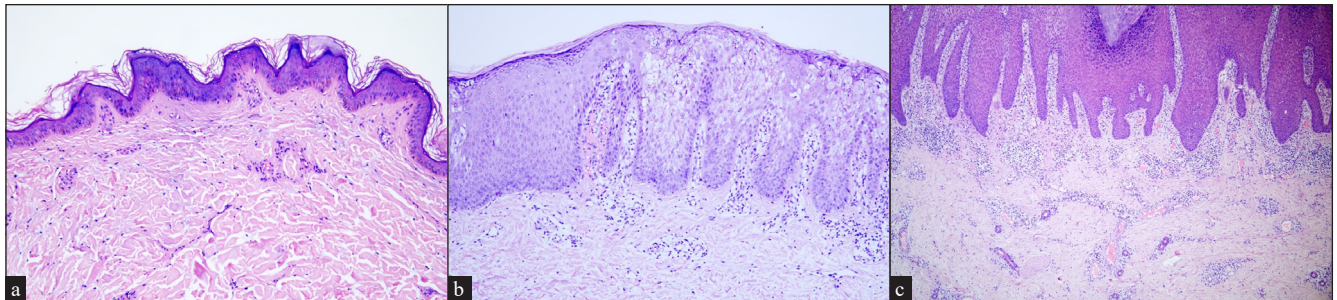
Table 1: Clinical, histopathological and molecular features of 22 cases with keratinocytic epidermal naevus in our study

Pt N*	Sex	Age of visit	Age of onset	Family history	Clinical type	Side of the involvement	Distribution	Histopathologic type	Mutation	Reference	Mutation allele load in skin lesions (reads)	Mutation allele load in peripheral blood (reads)	Germline mutation disease
1	M†	8y°	5mo§	Negative	Localised	Right	Neck	Non-epidermolytic	HRAS c.37G>C; p.Gly13Arg	4	13.12% (25,436/193,871)	0	Costello syndrome
2	F‡	1y	Birth	Negative	Generalised	Right	Scalp, face, trunk, groin, limbs	Non-epidermolytic	HRAS c.38G>T; p.Gly13Val	6	28.13% (202,230/719,040)	7.22% (66,506/921,430)	/
3	M	2y	Birth	Negative	Localised	Left	Hand, chest	Non-epidermolytic	HRAS c.37G>C; p.Gly13Arg	4	15.16% (30,047/198,200)	0	Costello syndrome
4	F	28y	1y	Negative	Generalised	Right	Trunk, leg	Non-epidermolytic	FGFR3 c.742C>T; p.Arg248Cys	7	25.71% (13,770/53,550)	0.86% (527/61,026)	Thanatophoric dysplasia
5	F	4y	1y	Negative	Generalised, ILVEN#	Right	Neck, trunk, limbs	Epidermolytic, inflammatory	KRT10 c.467G>A; p.Arg156His	3	8.74% (4653/53,234)	1.91% (1065/55,646)	EI
6	F	10y	birth	Negative	Generalised, ILVEN	Right	Trunk, arm	Epidermolytic, inflammatory	KRT10 c.466C>T; p.Arg156Cys	8	18.42% (32,005/173,715)	2.12% (3185/150,292)	EI
7	M	4y	2mo	Negative	Generalised	Left and right	Scalp, face, neck, trunk, limbs	Non-epidermolytic	HRAS c.34G>A; p.Gly12Ser	9	37.11% (88,706/239,059)	2.12% (5598/263,832)	Costello syndrome
8	F	5y	7mo	Negative	Generalised	Left and right	Neck, trunk, limbs	Non-epidermolytic	HRAS c.34G>A; p.Gly12Ser	9	32.45% (95,228/293,464)	4.56% (10,934/239,863)	Costello syndrome
9	F	10y	Birth	Negative	Localised	Left and right	Back, hands	Non-epidermolytic	HRAS c.37G>C; p.Gly13Arg	4	17.46% (11,765/67,364)	0	Costello syndrome
10	M	4y	Birth	Negative	Localised	Right	Chest	Non-epidermolytic	HRAS c.37G>C; p.Gly13Arg	4	22.01% (36,256/164,697)	0	Costello syndrome
11	F	4y	Birth	Negative	localised	Right	Neck	Non-epidermolytic	HRAS c.37G>C; p.Gly13Arg	4	34.25% (29,269/85,461)	0	Costello syndrome
12	M	7y	Birth	Negative	Generalised	Right	Scalp, trunk, limbs	Non-epidermolytic	GJB2 c.148G>A; p.Asp50Asn	5	38.46% (108,640/282,464)	1.40% (5315/380,411)	Keratitichthyosis-deafness syndrome
13	F	4y	Birth	Negative	Generalised	Left and right	Right region of trunk, right arm, lower legs	Non-epidermolytic	Not identified	/	0	0	/
14	M	19y	12y	Negative	Generalised	Right	Trunk, leg	Non-epidermolytic	Not identified	/	0	0	/
15	M	13y	Birth	Negative	Generalised	Right	Trunk, groin, leg	Non-epidermolytic	Not identified	/	0	0	/
16	M	3y	Birth	Negative	Generalised	Right	Trunk, limbs	Non-epidermolytic	Not identified	/	0	0	/
17	F	5y	Birth	Negative	Localised	Right	Leg	Non-epidermolytic	Not identified	/	0	0	/
18	F	47y	Birth	Negative	Localised, ILVEN	Right	Arm	Non-epidermolytic, inflammatory	PIK3CA c.1633G>A; p.Glu545Lys	10	20.43% (18,657/91,309)	0	/
19	M	33y	Birth	Yes (daughter suffers from EI‡)	Generalised	Left and right	Trunk, limbs	Epidermolytic	KRT10 c.467G>A; p.Arg156His	3	25.08% (163,778/652,937)	0	EI
20	M	13y	Birth	Negative	Localised	Left	Neck, face	Non-epidermolytic	HRAS c.37G>C; p.Gly13Arg	4	27.27% (47,256/173,272)	0	Costello syndrome

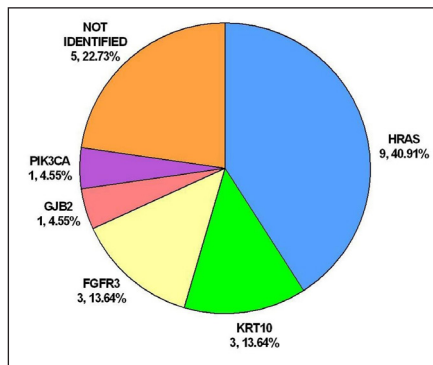
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Pt N*	Sex	Age of visit	Age of onset	Family history	Clinical type	Side of the involvement	Distribution	Histopathologic type	Mutation	Reference	Mutation allele load in skin lesions (reads)	Mutation allele load in peripheral blood (reads)	Germline mutation disease
21	F	27y	Birth	Negative	Generalised	Right	Trunk, arm, buttock	Non-epidermolytic	FGFR3 c.742C>T; p.Arg248Cys	7	28.66% (18,485/ 64,495)	0	Thanatophoric dysplasia
22	F	6y	Birth	Negative	Generalised	Right	Neck, trunk, limbs	Non-epidermolytic	FGFR3 c.742C>T; p.Arg248Cys	7	24.47% (16,468/ 67,304)	0	Thanatophoric dysplasia

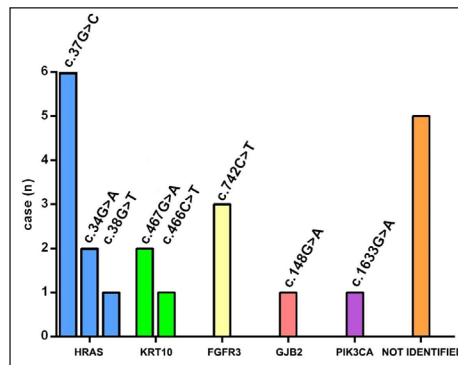
\*Pt N: patient number; †M: male; ‡F: female; §y: year; ||mo: month; \*\*EI: epidermolytic ichthyosis; ††ILVEN: inflammatory linear verrucous epidermal naevus



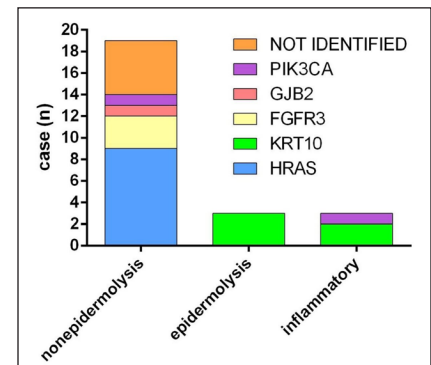
**Figure 2:** Histopathological features of keratinocytic epidermal naevus. (a) Hyperkeratosis, verrucous acanthosis and papillomatosis in non-epidermolytic epidermal naevus (Haematoxylin and eosin, 100x), (b) Hyperkeratosis, keratinocyte vacuolisation and keratohyalin granules in epidermolytic epidermal naevus (Haematoxylin and eosin, 100x), and (c) Psoriasiform epidermal hyperplasia, orthokeratosis, parakeratosis, marked lymphocyte infiltration in the dermis in inflammatory epidermal naevus (Haematoxylin and eosin, 40x).



**Figure 3a:** Genotypic spectrum of keratinocytic epidermal naevus in this study. Pie chart showing the genotypic spectrum of the 22 cases studied.



**Figure 3b:** Genotypic spectrum of keratinocytic epidermal naevus in this study. Distribution of mutation sites according to the gene involved.



**Figure 3c:** Genotypic spectrum of keratinocytic epidermal naevus in this study. Distribution of genes according to the pathological types.

genes related to keratinocytic epidermal naevus, including *HRAS*, *KRT10*, *FGFR3*, *GJB2*, and *PIK3CA*. Mutations of *HRAS* were mostly prevalent with an incidence of 40.91% (9/22). Mutations of *KRT10*, *FGFR3*, *GJB2*, and *PIK3CA* were identified in 3/22 (13.64%), 3/22 (13.64%), 1/22 (4.55%) and 1/22 (4.55%), respectively [Figure 3a]. A total of eight missense mutations were identified in our study, which were classified as pathogenic/likely pathogenic variants in the ClinVar database and were previously reported in epidermis naevus or epidermis naevus-related syndrome.<sup>3-10</sup> The c.37G>C substitution in *HRAS* represented a possible hotspot mutation (6/22, 27.27%) [Figure 3b].

In lesional skin samples of the 17 patients with somatic mutations, the mutation allele load ranged from 8.74% to 38.46%. Only seven patients (7/22, 31.82%) were found carrying mutations in the peripheral blood, with the mutation allele load ranging from 0.86% to 7.22%. Mutations were identified in half of the blood samples in generalised epidermal naevus (7/14, 50%), while none of the mutations was observed in the blood samples in localised epidermal naevus. On the whole, in terms of mutation allele load, it was much lower in the blood ( $0.92 \pm 1.82\%$ ) than in the lesional skin ( $18.95 \pm 12.82\%$ ). In addition, compared to the localised epidermis naevus, the mutation allele load was

**Table 2: Mutation allele load analysis of patients with keratinocytic epidermal naevus included in this study**

	Localised EN* (PN <sup>‡</sup> , MAL <sup>‡</sup> )	Generalised EN (PN, MAL)	Total EN (PN, MAL)	p-value (Localised vs. Generalised)
Total (N)	8	14	22	/
Blood	0, 0	7, 1.44 ± 2.13%	7, 0.92 ± 1.82%	0.0730
Lesional skin	7, 18.71 ± 10.17%	10, 19.09 ± 14.48%	17, 18.95 ± 12.82%	0.9492
p-value (Blood vs. Lesional skin)	0.0001	0.0001	< 0.0001	/

\*EN: Epidermal naevus; †PN: Positive detection patient number; ‡MAL: Mutation allele load

significantly higher in generalised epidermal naevus, either in the peripheral blood ( $1.44 \pm 2.13\%$  vs. 0) or lesional skin ( $19.09 \pm 14.48\%$  vs.  $18.71 \pm 10.17\%$ ) [Table 2].

In our study, 14 patients (14/22, 63.64%) had generalised epidermal naevus, seven of whom were identified with mutations in *HRAS* (3/14, 21.43%), *KRT10* (2/14, 14.29%), *FGFR3* (1/14, 7.14%) and *GJB2* (1/14, 7.14%). Eight patients (8/22, 36.36%) presented with localised epidermal naevus. Mutations in *HRAS* (6/8, 75.00%) and *PIK3CA* (1/8, 12.50%) were found in seven of them. *HRAS* mutations occurred most frequently, including c.34G>A, c.38G>T, and c.37G>C. The c.34G>A and c.38G>T mutations were found in generalised epidermal naevus, while all the c.37G>C mutations were identified in localised epidermal naevus. Of note, acantholysis (epidermolytic epidermal naevus) was found in three patients (3/22, 13.64%) exclusively carrying *KRT10* mutations. Inflammatory epidermal naevus (3/22, 13.64%) was caused by mutations in *KRT10* (2/3, 66.67%) and *PIK3CA* (1/3, 33.33%) [Figure 3c].

## Discussion

Clinically, no gender predilection was observed in the study and a majority of the patients developed keratinocytic epidermal naevus at birth. Unilateral distribution of the lesions was found in most patients, with right-sided involvement being much more common. Histopathologically, non-epidermolytic epidermal naevus was found more commonly.

Inflammatory linear verrucous epidermal naevus is a rare inflammatory epidermal naevus characterised with pruritic erythematous scaly papules and plaques occurring along Blaschko's lines.<sup>11</sup> In this study, three female cases of inflammatory linear verrucous epidermal naevus were included. Unlike a previous report from India<sup>12</sup> that, the left-sided inflammatory linear verrucous epidermal naevus was more common, in our study, all the patients with this variant exhibited right-sided involvement, suggesting clinical heterogeneity in different populations. Inflammatory linear verrucous epidermal naevus was reported to be caused by mosaic mutations in *GJAI*, *CARD14*, *HRAS*, and *KRT10*.<sup>13</sup>

In our study, intriguingly, except for two patients with generalised inflammatory linear verrucous epidermal naevus caused by *KRT10* mutations, a localised inflammatory linear verrucous epidermal naevus patient was found to carry a *PIK3CA* mutation (c.1633G>A), which has not been reported in this type previously. We speculate that compared to the *PIK3CA* mutation, *KRT10* mutations seemingly lead to more extensive skin lesions in inflammatory linear verrucous epidermal naevus patients.

Keratinocytic epidermal naevus is a genotypically diverse mosaic disorder. Non-epidermolytic keratinocytic epidermal naevus is known to arise as a result of prenatal postzygotic mutations in either rat sarcoma/mitogen-activated protein kinase pathway (*HRAS*, *KRAS*, *NRAS*, *BRAF*) or the PI3K/AKT pathway (*PIK3CA*).<sup>4,14,15</sup> Among the growth factor receptor genes found upstream of these pathways, mutations in *FGFR2*, *FGFR3*, or *EGFR* have also been reported to cause non-epidermolytic keratinocytic epidermal naevus.<sup>14</sup> However, epidermolytic keratinocytic epidermal naevus is often associated with mutations in keratin genes, such as *KRT1*, *KRT2*, and *KRT10*.<sup>16,17</sup> In addition, mutations in *GJB2* have been found in both non-epidermolytic and epidermolytic keratinocytic epidermal naevus.<sup>5,18</sup> Similar findings were observed in our study. Mutations of *HRAS*, *GJB2*, *FGFR3* and *PIK3CA* were identified in non-epidermolytic keratinocytic epidermal naevus, while *KRT10* was associated with epidermolytic keratinocytic epidermal naevus [Figure 3c].

Clinical manifestations of keratinocytic epidermal naevi vary according to the underlying pathogenic genes. Postzygotic mutations in *HRAS* and *FGFR3* have been reported to cause systematized epidermal naevus, inducing skeletal abnormalities, thymoma, breast hypotrophy, acanthosis nigricans, and more.<sup>19,20</sup> More than half (12/22, 54.55%) of the keratinocytic epidermal naevus patients carried the *HRAS* or *FGFR3* mutations in our study. Although none of the patients in our study was found to be associated with extracutaneous symptoms, further periodical follow-up every 12 months is necessary to assess the risk of systematic involvement, especially in those who carry mutations in *HRAS* and *FGFR3*.<sup>21</sup>

*HRAS* was the most commonly affected gene, with c.37G>C substitution representing a hotspot mutation.<sup>4</sup> In our study, compared to c.38G>T and c.34G>A found in the generalised epidermal naevus, c.37G>C was only identified in the localised epidermal naevus, suggesting c.37G>C mutation may lead to a milder epidermal naevus phenotype.

As a mosaic disorder, our study showed that the mutation allele load was significantly higher in generalised epidermal naevus either in the peripheral blood or lesional skin when compared to the localised variant. Meanwhile, the mutation detection rate was much lower in the blood than lesional skin in either generalised or localised epidermal naevus. Therefore, deep next-generation sequencing of the affected lesions is necessary to detect mutations in keratinocytic

epidermal naevus. Genetic analysis performed solely in the peripheral blood could easily lead to false conclusions, particularly in localised epidermal naevus.<sup>22,23</sup>

It is worth noting that most mosaic mutations detected in our keratinocytic epidermal naevus patients were the same as the germline mutations identified in systemic diseases caused by these genes.<sup>11</sup> This means that in keratinocytic epidermal naevus, an individual carrying a somatic heterozygous mutation could have co-existing gonadal mosaicism and would be at risk of transmission of the mutation to the offspring, who usually presents much more severe phenotypes.

Treatment for epidermis naevus is challenging. Recently, sirolimus which blocks mammalian target of rapamycin signalling was found effective in the patient with epidermis naevus carrying a *FGFR3* mutation.<sup>24</sup> Based on the widespread application of gene detection, targeted therapy could be a trend in the treatment of keratinocytic epidermal naevus in the future.

### Limitations

This study is limited by its retrospective nature, the non-standardised documentation and small sample size.

### Conclusion

To the best of our knowledge, this is the largest case series of keratinocytic epidermal naevus in the Chinese population so far. Our results reveal the genotype-phenotype spectrum and its correlation in this disease. The study underscores the importance of genetic testing in characterisation and categorisation of keratinocytic epidermal naevus, having a bearing on genetic counselling as well as prenatal diagnosis. Future therapeutic strategies could also be based on these findings.

**Ethical approval:** The research/study was approved by the Institutional Review Board at the ethics committee of West China Hospital, Sichuan University, number 2019-(519), dated 10 October 2019.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent.

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**Use of artificial intelligence (AI)-assisted technology for manuscript preparation:** The authors confirm that there was no use of AI-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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