A novel homozygous frameshift mutation in *DSG1* gene in an Indian consanguineous family with severe dermatitis, multiple allergies and metabolic wasting syndrome

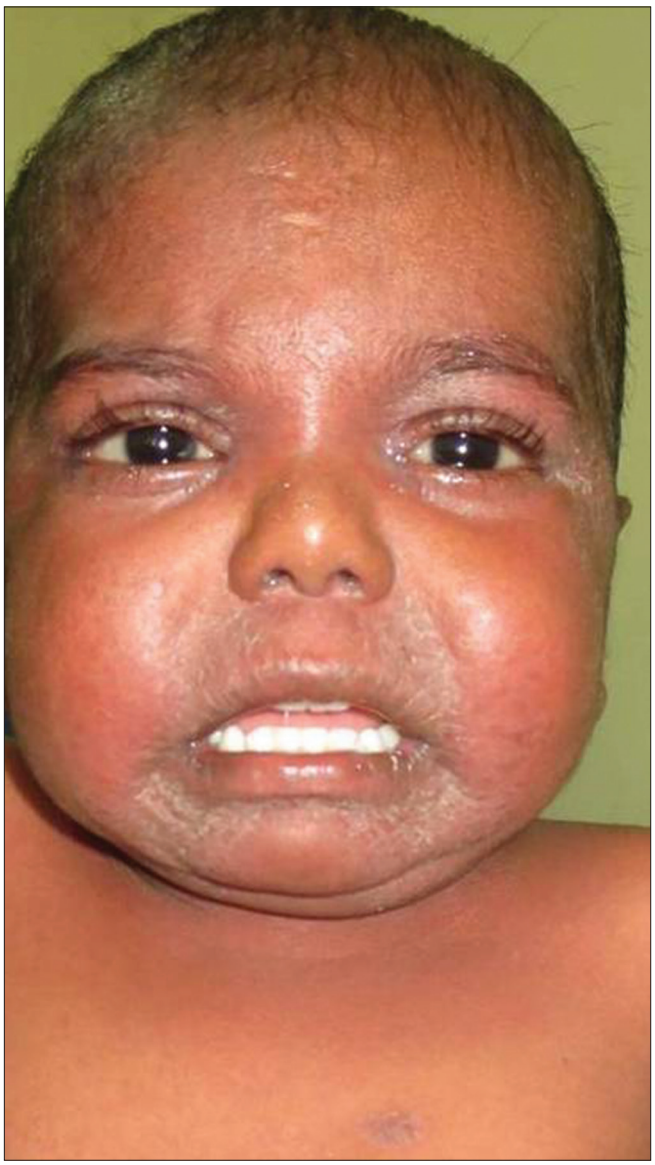

Figure 1a: Diffuse erythema with scaling on face and chest along with scant hair on the scalp

Sir,

Severe dermatitis, multiple allergies and metabolic wasting syndrome (OMIM #615508), also known as congenital erythroderma with palmoplantar keratoderma, hypotrichosis and hyper-immunoglobulin E, is a recently recognized autosomal recessive genodermatosis caused by homozygous or compound heterozygous loss of function mutation in desmoglein1 gene (*DSG1*) or heterozygous missense mutation in desmoplakin gene (*DSP*). [1,2] It was first described in 2013 by Samuelov *et al*.[1] It is clinically characterized by congenital ichthyosiform erythroderma, palmoplantar keratoderma, failure to thrive, multiple allergies, increased serum immunoglobulin E levels, hypotrichosis, recurrent infections and other systemic abnormalities like metabolic wasting, malabsorption, esophagitis, cardiac defects, microcephaly and developmental delay. Till date, approximately 14 cases of severe dermatitis, multiple allergies and metabolic wasting syndrome from 10 families have been reported in literature with varying phenotypes. Herein, we describe a rare case of severe dermatitis, multiple

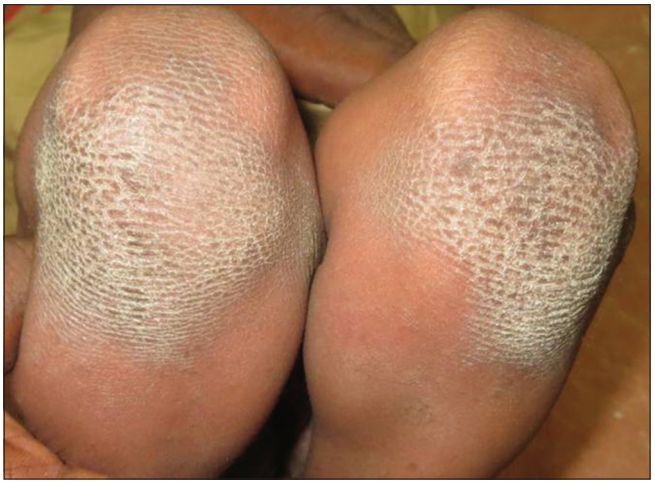

Figure 1b: Well-defined hyperkeratotic plaques present on the knee joint

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allergies and metabolic wasting syndrome in an Indian consanguineous family with a novel homozygous frameshift mutation, in exon 15 of *DSG1*gene and identical mutation in a heterozygous state in the parents.

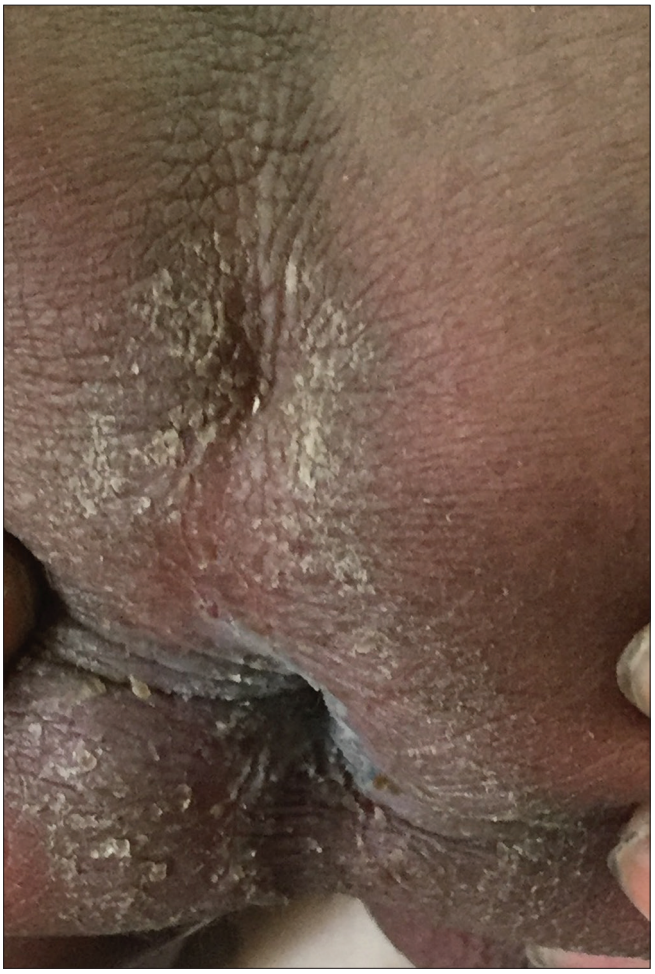

Figure 1c: Perianal scaling with hyperkeratosis

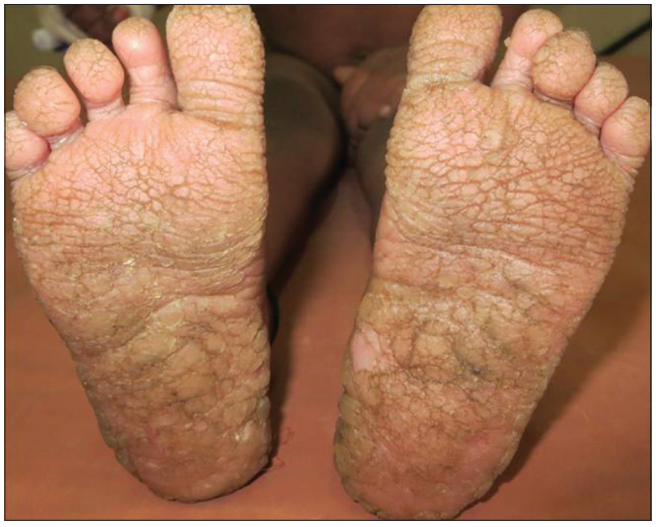

Figure 2b: Diffuse plantar keratoderma

A 4-year-old term boy, first born to a second degree consanguineously married couple of Indian origin, presented with erythema and scaling all over the body from 7thday of life with recurrent respiratory infections, failure to thrive, metabolic wasting and developmental delay. Both the parents had mild palmoplantar keratoderma. He had Cushingoid features, short stature with height less than 3rd percentile (69.6cm) and bone age of 2 years along with infantile face, voice and microphallus with a stretch penile length of 2.5 cm (<2 standard deviation for age) which were suggestive of growth hormone deficiency. Cutaneous examination showed diffuse erythema with scaling all over the body [Figure 1a]. Well-defined hyperkeratotic scaly plaques were present on the extensor aspect of both the knee joints, upper and lower limbs [Figure 1b]. Ill-defined hyperkeratosis with accentuation was present on the flexures and perianal region [Figure 1c]. Scalp showed mild scaling and hypotrichosis [Figure 1a]. Diffuse palmoplantar keratoderma was present [Figures 2a and b]. Investigations revealed increased serum immunoglobulin

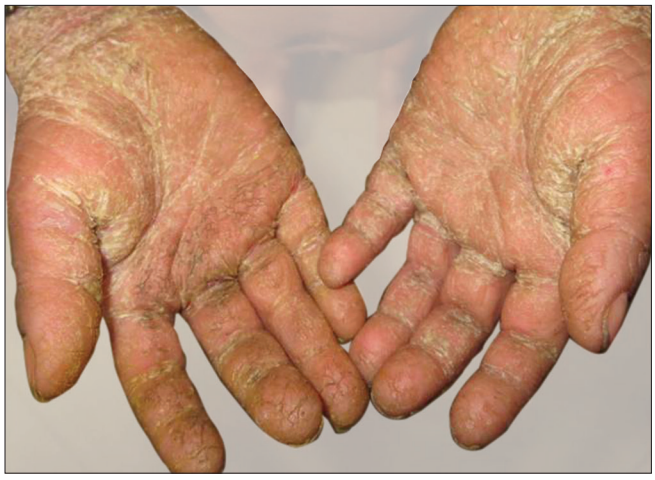

Figure 2a: Diffuse keratoderma present on palms

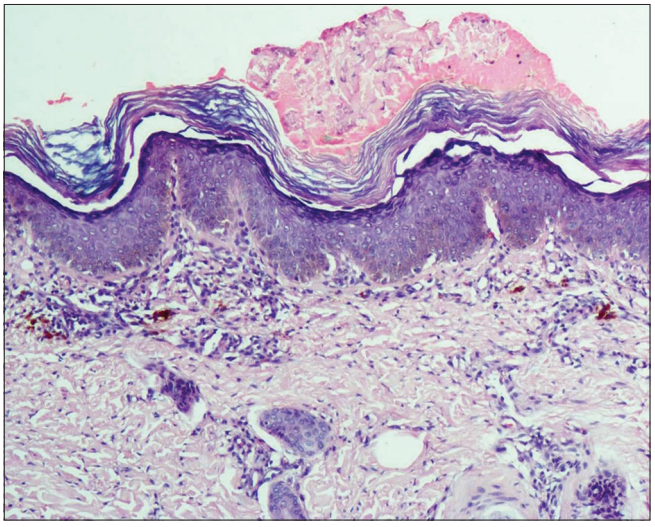

Figure 3: Epidermis showing orthokeratosis, hypergranulosis, subtle acantholysis and a few scattered dyskeratotic cells (H and E,×100)

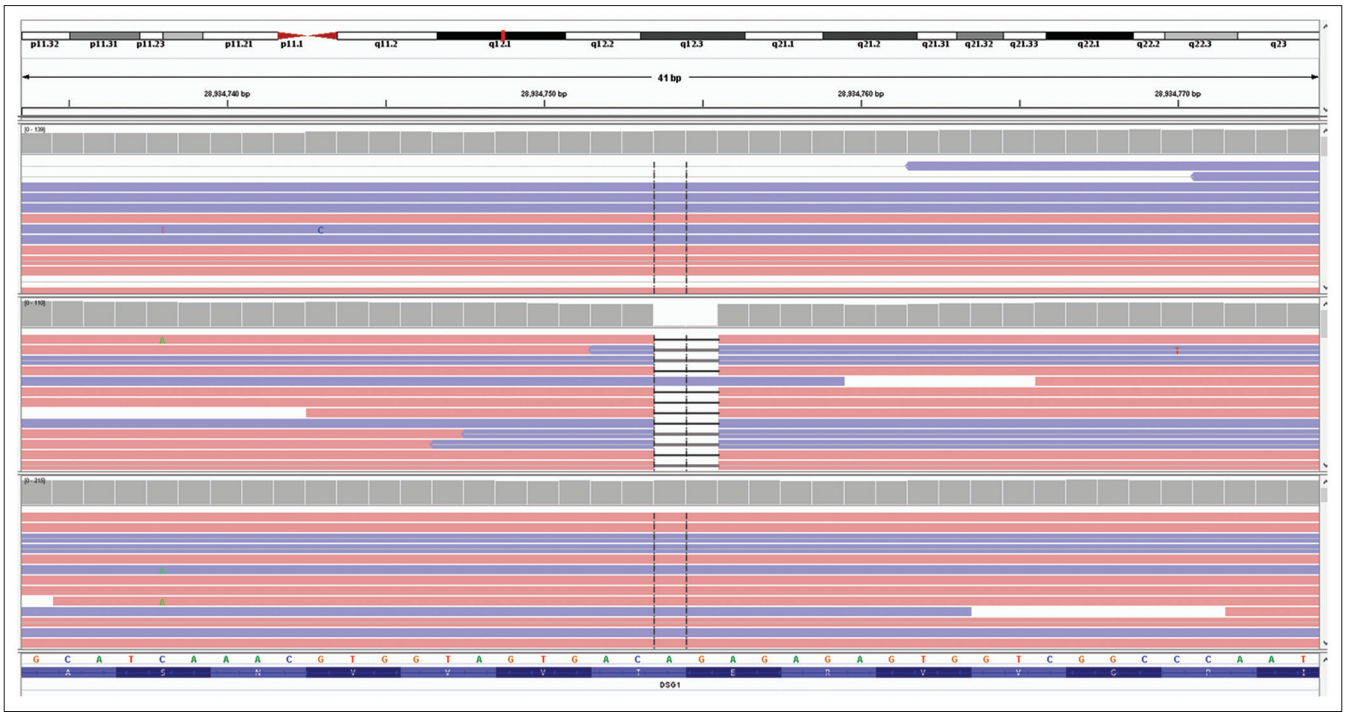

Figure 4: Excerpt of next-generation sequencing data of the proband visualized with the integrative genomic viewer showing homozygous 2 base pair deletion in exon 15 of desmoglein1 gene located on chromosome 18 compared with two control sequences

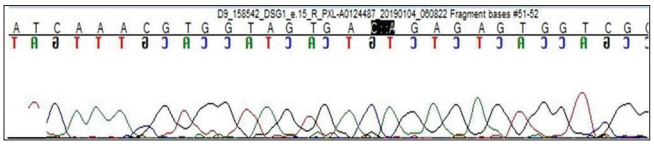

Figure 5a: Sequence chromatogram and alignment to the reference sequence showing the variation in exon 15 of the desmoglein1 gene (chr18:28934754_28934755delAG; c.2601_2602delAG; p.Arg867SerfsTer9) in the proband

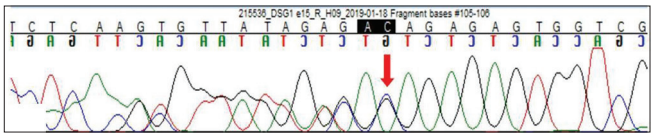

Figure 5b: Sequence chromatogram and alignment to the reference sequence showing the identical variation in heterozygous carrier father indicated by the red arrow

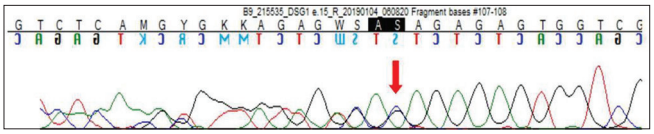

Figure 5c: Sequence chromatogram and alignment to the reference sequence showing the identical variation in heterozygous carrier mother indicated by the red arrow

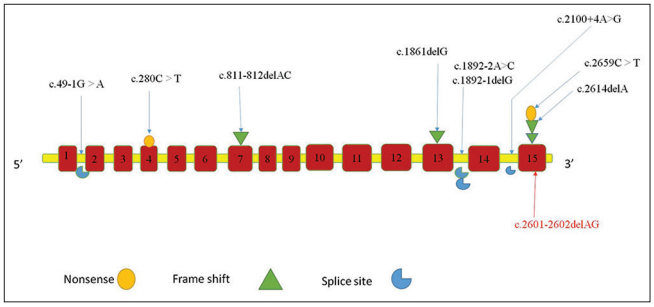

Figure 6: Mutation spectrum of recessive mutations in the desmoglein1gene causing severe dermatitis, multiple allergies and metabolic wasting syndrome as described in literature till date.The novel mutation in our study is represented in red

E levels (>2000 IU/mL) and growth hormone stimulation test confirmed severe growth hormone deficiency. Light microscopy of the hair shaft was normal. Histopathological examination revealed orthokeratosis, hypergranulosis, subtle acantholysis and a few scattered dyskeratotic cells in the epidermis [Figure 3]. Differential diagnoses considered were Netherton syndrome, non-bullous ichthyosiform erythroderma, trichothiodystrophy, ichthyosis hypotrichosis syndrome and epidermal growth factor receptor deficiency.

Genetic testing was done in the proband and his parents after taking written informed consent. Clinical exome sequencing report of the proband revealed homozygous 2 base pair (AG) deletion in exon 15 of *DSG1* gene located on chromosome 18,c.2601_2602delAG (NM_001942.3:g. 28934754_28934755delAG) where amino acid arginine was replaced by serine at 867th codon position that resulted in a frameshift mutation and premature truncation of protein 9 amino acids downstream to codon 867 (p.Arg867Serfs*9;

Table 1: Phenotype and genotype of all 10 reported families of severe dermatitis, multiple allergies and metabolic wasting syndrome

Study	Samuelov L, *et al.*			Has C, *et al.*	McAleer MA, *et al.*	Cheng R, *et al.*	
	Year						
	2013			2015	2015	2016	
	Case1 (family 1)	Case2 (family 1)	Case3 (family 2)	Case4 (family 3)	Case5 (family 4)	Case 6 (family 5)	Case 7 (family 5)
Age/sex	7 years/female	3 years/female	9 months/female	17 years/female	6 years/male	13 years/female	7 years/male
Consanguinity	+	+	+	−	−	+	+
Congenital erythroderma	+	+	+	+	+	+	+
PPK	+	+	+	+	+	+	+
Hair/nails	Hypotrichosis	Hypotrichosis	Hypotrichosis	Curly hair	Hypotrichosis	Curly hair	N
Multiple allergies	+	+	+	+	+	−	−
Metabolic wasting	+	+	+	−	−	−	+
Other Systemic involvement	Hypernatremia, recurrent infections, eosinophilic esophagitis, GERD, malabsorption, microcephaly, VSD, PS	Hypernatremia, recurrent infections, eosinophilic esophagitis, GERD, malabsorption, microcephaly, VSD, PS	Recurrent infections, growth retardation	−	Macrocephaly, developmental delay, nystagmus, keratitis	−	Recurrent infections, growth retardation
Family history	PPK in parents	PPK in parents	PPK in parents/2 siblings death	Focal PPK in parents	N	PPK in parents/ sibling death	PPK in parents/ sibling death
Ig E levels	Raised	Raised	Raised	Raised	Raised	Raised	N
Gene/mutation	HOM/DSG1/c. 49-1G>A	HOM/DSG1/c. 49-1G >A	HOM/DSG1/ C.1861delG	HOM/DSG1/c. 2659C>T	HET/DSP/c. 6208G>A	HOM/DSG1/c. 1892-1delG	HOM/DSG1/c. 1892-1delG

Study	Schlipf NA *et al.*		Danescu S, *et al.*	JYW Lee, *et al.*	Shahar Taiber *et al.*			Present case
	Year							
	2016		2016	2017	2018			2019
	Case 8 (family 6)	Case 9 (family 6)	Case 10 (family 7)	Case 11 (family 8)	Case 12 (family 9)	Case 13 (family 10)	Case 14 (family 10)	Case 15 (family 11)
Age/sex	27 years/male	11 years/male	2 years/female	19 years/female	2.5 years/male	2 months/female	17 years/female	4 years/male
Consanguinity	−	−	−	+	+	+	+	+
Congenital erythroderma	+	+	+	+	+	+	+	+
PPK	+	+	+	+	+	+	+	+
Hair/nails	N	N	Curly	N	Hypotrichosis	N	N	Hypotrichosis
Multiple allergies	+	+	+	−	−	+	+	−
Metabolic wasting	−	−	−	−	−	−	−	+

Contd...

Table 1: Contd..

Study	Schlipf NA *et al.*		Danescu S, *et al.*	JYW Lee, *et al.*	Shahar Taiber *et al.*			Present case
Year	2016		2016	2017	2018			2019
	Case 8 (family 6)	Case 9 (family 6)	Case 10 (family 7)	Case 11 (family 8)	Case 12 (family 9)	Case 13 (family 10)	Case 14 (family 10)	Case 15 (family 11)
Other Systemic involvement	–	–	–	–	–	–	–	Recurrent respiratory infections, failure to thrive, metabolic wasting, short stature, developmental delay, growth hormone deficiency
Family history	Mother - PPK	Mother- PPK	Father- PPK	N	Plantar keratoderma in parents	PPK in parents	PPK in parents	PPK in parents
Ig E levels	Raised	Raised	Raised	Raised	N	Raised	Raised	Raised
Gene/mutation	HOM/DSG1/c. 2614delA	HOM/DSG1/c. 2614delA	Compound HET/DSG1/c. 811_812delAC	HOM/DSG1/c. 1892-2A>C	HOM/DSG1/c. 280C>T	HOM/DSG1/c. 2659C>T	HOM/DSG1/c. 2659C>T	HOM/DSG1/c. 2601-2602delAG

+: Present, -: Absent, N: Normal, GERD: Gastroesophageal reflux disease, VSD: Ventricular septal defect, PS: Pulmonary stenosis, GH: Growth hormone deficiency, HOM: Homozygous, HET: Heterozygous, DSG: Desmoglein, DSP: Desmoplakin, PPK: Palmoplantar keratoderma

ENST00000257192.4) [Figure 4]. This *DSG1* variant has not been reported in Human Gene Mutation Database Professional 2018.4, Single Nucleotide Polymorphism Database, 1000 genomes, Exome Aggregation Consortium and our internal databases. We also excluded it from 300 normal healthy Indians.The in-silico prediction of the variant is damaging by MutationTaster (www.mutationtaster.org). Protein Variation Effect Analyzer, (http://provean.jcvi.org) predicted it to be deleterious with a score of -4.3. This variant is not associated with nonsense-mediated mRNA decay and it is highly conserved across species.[3] This mutant variant of the index case was validated by Sanger sequencing [Figure 5a].The Sanger sequence report of both father and mother revealed an identical mutation in a heterozygous state [Figures 5b and c]. Fortunately, his asymptomatic sister did not have the mutation.

Desmosomal cadherin *DSG1* is a component of intercellular desmosome junctions; it has a central role in the pathogenesis of pemphigus foliaceus, bullous impetigo, staphylococcal scalded skin syndrome and an inherited skin disorder – striate palmoplantar keratoderma (OMIM #148700).[1] Monoallelic *DSG1* mutation results in striate palmoplantar keratoderma whereas biallelic loss of function mutation results in severe life-threatening severe dermatitis, multiple allergies and metabolic wasting syndrome.[4] This mutation results in complete loss of protein function by the cytoplasmic accumulation of the abnormal protein which cannot be transported to the cell surface. Heritable barrier abnormality with subsequent immune cascade is a possible cause.This results in increased expression of various genes coding for cytokines associated with allergic diseases.[5] The role of atopy and allergies in the pathogenesis of severe dermatitis, multiple allergies and metabolic wasting syndrome is not well-established. Hence, further investigations are required to know the exact etiology and pathomechanism in producing this phenotypic heterogeneity.

The clinical phenotype and genotype of all 10 families reported in the literature have been described in Table 1.[1,2,4-7] Currently, 10 pathogenic variants in 14 cases in two genes *DSG1* and *DSP* have been described in literature: homozygous nonsense-2, splice site-4 and frameshift mutations-3 in *DSG1* gene and heterozygous missense-1 in *DSP* gene [Figure 6].[1,2,4-7] Cardiac abnormality, food allergies, hypoalbuminemia, microcephaly and esophageal abnormalities were not seen in our case. The differential diagnosis of severe dermatitis, multiple allergies and metabolic wasting syndrome with salient features has been tabulated in Table 2. Several therapeutic approaches like topical corticosteroids, topical tacrolimus and oral retinoids (acitretin 0.5mg/kg) have been tried with partial improvement of ichthyosis and palmoplantar keratoderma. Our case was treated with bland emollients and wet wrap therapy. Parents were not willing to start oral retinoids. Long-term prognosis depends on the systemic involvement.

Table 2: Differential diagnosis of severe dermatitis, multiple allergies and metabolic wasting syndrome

Disorder	Gene	Mode of inheritance	Clinical features
Atopic dermatitis	*FLG*	AD	Pruritus, eczematous reactions along with characteristic distribution, erythroderma in childhood, features of diagnostic criteria by Hanifin and Rajka. No systemic involvement
Hyperimmunoglobulinemia E syndrome	*STAT3/DOCK8*	AD/AR	Atopic dermatitis/erythroderma, cutaneous staphylococcal infections, severe viral infections, sinopulmonary abscess, recurrent bronchitis, pneumonia, emphysema, bronchiectasis, abscess, coarse facies, dental and skeletal abnormalities
Netherton syndrome	*SPINK 5*	AR	Generalized scaling, erythroderma, ichthyosis linearis circumflexa, failure to thrive, diarrhea, atopic features, trichorrhexis invaginata
Nonbullous ichthyosiform erythroderma	*TGM1/ABCA 12, ALOXE3, ALOX12B, CYP4F22*	AR	At birth as collodion membrane, generalized erythema, scaling, ectropion, alopecia, rarely intrauterine growth retardation and failure to thrive
Trichothiodystrophy	*ERCC2, ERCC3, GTF2H5, C7Orf11*	AR	Congenital ichthyosiform erythroderma, brittle hair, impaired intelligence, short stature, decreased fertility, photosensitivity, "tiger tail" hair shaft defect on polarized microscopy
Ichthyosis hypotrichosis syndrome	*ST14*	AR	Generalized ichthyosis with sparing of face, palms and soles, alopecia of scalp, eyebrows and eyelashes, follicular atrophoderma, photophobia, hypohidrosis, dental abnormalities
EGFR deficiency	*EGFR*	AR	Generalized erythema with scaling, pustules, alopecia, failure to thrive, diarrhea, high IgE, hypernatremia, recurrent bronchiolitis
ADAM17 deficiency	*ADAM17*	AR	Erythroderma, failure to thrive, short stature, malabsorption, recurrent infections, cardiomyopathy
NISCH syndrome	*CLDN1*	AR	Generalized scaling, sparing of skin folds, palms and soles, curly hair, frontotemporal cicatricial alopecia, sclerosing cholangitis, hepatomegaly, oligodontia

AD: Autosomal dominant, AR: Autosomal recessive, *FLG*: Filaggrin, *STAT3* gene: Signal transducer and activator of transcription 3, *DOCK8*: Dedicator of cytokinesis, *SPINK5*: Serine Peptidase Inhibitor Kazal Type 5, TGM1: Transglutaminase 1, *ALOXE3*: Archidonate Lipoxygenase 3, *CYP4F22*: Cytochrome P450 Family 4 Subfamily F Member 22, *GTF2H5*: General Transcription Factor IIH Subunit 5, *ST14*: Suppressor of Tumorigenicity 14 protein, *EGFR*: Epidermal growth factor receptor gene, NISCH: Neonatal ichthyosis-sclerosing cholangitis, *CLDN1*: Claudin 1

In conclusion, our described case of severe dermatitis, multiple allergies and metabolic wasting syndrome of Indian origin presented with characteristic clinical features with a novel homozygous frameshift mutation in the *DSG1*gene. Growth hormone deficiency with microphallus was unique in our case. This study expands the spectrum of the *DSG1* mutation database and emphasizes the important role played by *DSG1* in maintaining epidermal integrity, signal transduction pathways and keratinocyte differentiation. *DSG1* mutation screening needs to be done in all suspected cases of severe dermatitis, multiple allergies and metabolic wasting syndrome.

Limitations of the study: Functional assays have not been done due to logistic reasons. Further studies need to be done to understand the exact pathogenesis of severe dermatitis, multiple allergies and metabolic wasting syndrome. Change in a phenotypic presentation in our case may be due to the different position of the mutation loci and epigenetic modifiers with multiple environmental factors.

Acknowledgment

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Melanoma arising in a giant congenital melanocytic nevus with neuroblastoma RAS mutation

Sir,

Malignant melanoma is uncommon in Asian population and pre-pubertal incidence is extremely rare. Pediatric melanoma is not a congener of adult melanoma with varying risk factors, morphology, behavior and prognosis.[1] Congenital melanocytic nevi are recognized risk factors for melanoma, directly proportional to their number.[2]

A four-year-old girl presented with a rapidly growing hyperpigmented nodule on her back, within her large congenital melanocytic nevus, for the past four months. It was extremely tender on palpation and associated with occasional bleeding following minor trauma. There were no other systemic complaints and family history was unremarkable.

Clinical examination revealed a single, large melanocytic nevus (>20 cm diameter) on her back (Fitzpatrick type 3 skin), along with multiple satellite nevi sized 0.5–8 cm. The overlying nodule (8 cm x 7 cm x 4 cm) was sessile, lobulated and erythematous to variegate hyperpigmented [Figure 1]. We noted focal areas of ulceration and superficial hemorrhages on its surface. Both nodule and surrounding skin were distinctly tender. There was no clinical lymphadenopathy or hepatosplenomegaly. Dermoscopy of the nodule showed lobulated surface with peripheral linear and curved vessels, ulceration, blue white veils, depigmented areas and yellow-orange homogenous areas with yellow-brown crusting [Figure 2].

Biopsy of the nodule revealed invasive neoplastic cells arranged in sheets. These cells contained abundant eosinophilic cytoplasm, round to oval nuclei with nuclear pleomorphism, prominent nucleoli, occasional nuclear pseudo-inclusions and multiple atypical mitoses; diagnostic of malignant melanoma [Figures 3a and b]. Immunohistochemistry showed diffuse cytoplasmic positivity

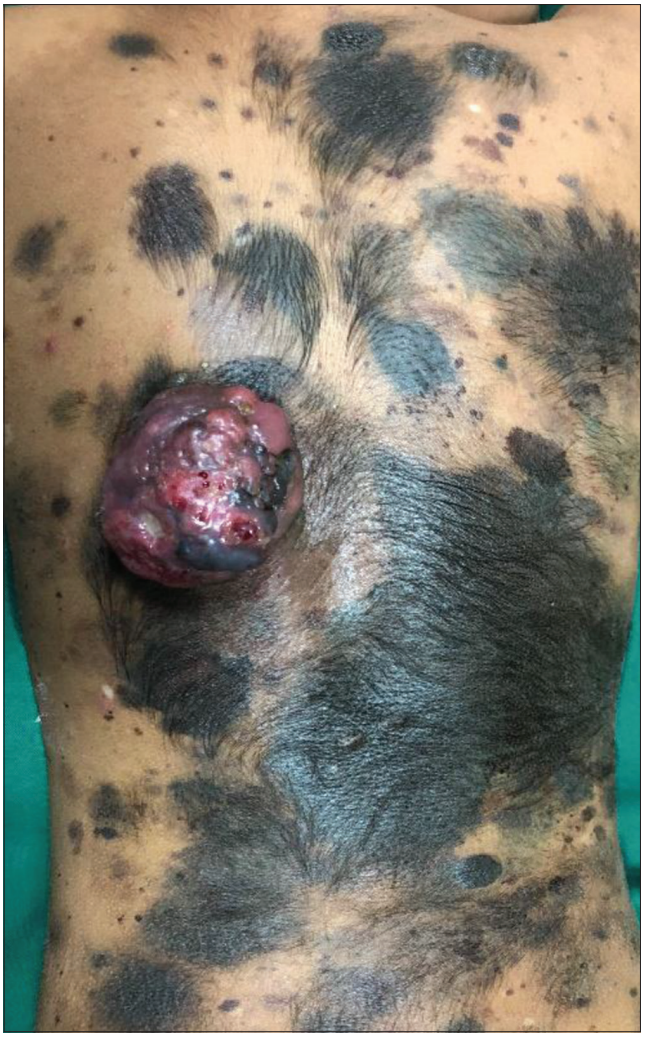

Figure 1: Ulcerated lobulated nodule of size 8 cm × 7 cm × 4 cm present over congenital melanocytic nevus of size 20 cm over the back with multiple satellite nevi of size 0.5–8 cm

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