

# Mutation and expression of *ABCA12* in keratosis pilaris and nevus comedonicus

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Received June 22, 2017; Accepted April 17, 2018

DOI: 10.3892/mmr.2018.9342

**Abstract.** Keratosis pilaris (KP) and nevus comedonicus (NC) are congenital keratinized dermatoses; however, the exact etiology of these two diseases is unclear. The objective of the present study was to identify the disease-causing genes and their association with functional alterations in the development of KP and NC. Peripheral blood samples of one KP family, two NC families and 100 unrelated healthy controls were collected. The genomic sequences of 147 genes associated with 143 genetic skin diseases were initially analyzed from the KP proband using a custom-designed GeneChip. A novel heterozygous missense mutation in the ATP-binding cassette sub-family A member 12 (*ABCA12*) gene, designated c.6694G>T (p.Asp2232Tyr), was identified in the KP proband and confirmed by Sanger sequencing. The same mutation was also present in the affected family members but not in the healthy family members, the two patients with NC or population-matched controls. The predictions provided by PolyPhen-2 and SIFT analyses suggested that the mutation may produce a damaged protein. The region surrounding the mutation is the extra-membrane domain, which is conserved among particular species, as suggested by ClustalX; however, no *ABCA12* mutations were reported in the patients with NC. As observed by immunofluorescence, *ABCA12* expression was upregulated in the sebaceous glands of the patients with NC compared with that of normal controls. In summary, *ABCA12*-associated mutations or alterations in expression may exhibit causative or contributive effects to the development of keratinized dermatoses, including KP and NC.

## Introduction

Keratosis pilaris (KP; OMIM #604093), also known as lichen pilaris, is a benign genodermatosis that is estimated to affect ~40% of the population (1). KP is characterized by the presence of symmetric, asymptomatic and grouped keratotic follicular papules with varying degrees of perifollicular erythema. KP lesions often involve the proximal and extended parts of extremities, the cheeks and the buttocks (2). Cases may be generalized or unilateral (2). Most patients develop KP in their childhood, with a peak in incidence during adolescence (3). The incidence of KP subsequently decreases with age in 35% of those affected, but can persist in adulthood within 43%, and worsen in 22% of patients (4). KP can exist as an independent condition or in association with other diseases, such as xerosis, ichthyosis, atopic dermatitis and various conditions, including keratitis-ichthyosis-deafness syndrome, Noonan syndrome and cardiofaciocutaneous syndrome (4-6). Genetic epidemiology surveys have indicated that KP is an autosomal dominant-inherited disease (4). A study reported a deletion of the short arm of chromosome 18 may be associated with KP (7). Brown *et al* (8), Mevorah *et al* (9) and Sandilands *et al* (10) identified mutations in the filaggrin (*FLG*) gene associated with atopic dermatitis and ichthyosis vulgaris in KP. Gruber *et al* (3) revealed that only 35% of patients with KP have mutations in *FLG*, suggesting that *FLG* mutations only partially result in the KP phenotype. Other genes may be the causative genetic factor contributing to the development of KP; however, further investigation is required.

Nevus comedonicus (NC) is a rare skin disorder caused by abnormal development of the pilosebaceous unit. The prevalence of NC has been estimated to occur in 1/45,000 to 1/100,000 individuals, with no gender or racial association (11). The pathogenesis of NC is yet to be investigated. Genetic studies have revealed that the fibroblast growth factor (FGF) and FGF receptor-2 signaling pathways, and somatic mutations of tyrosine kinase receptors or never in mitosis gene A-related kinase 9 (12) may be associated with the development of NC (13). The clinical features of NC include grouped, dilated hair follicles with a dark, firm hyperkeratotic plug at the center. NC can present with open or closed comedo, which primarily occur on the face, neck and upper trunk, and may

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**Key words:** keratosis pilaris, nevus comedonicus, ATP-binding cassette sub-family A member 12, missense mutation

be linear, interrupted, unilateral, bilateral or segmental (14). Clinically, there are two types of NC: Noninflammatory and inflammatory, with the formation of cysts, fistulas, and pustules (15).

In the present study, a novel heterozygous missense mutation was identified in ATP-binding cassette sub-family A member 12 (*ABCA12*) within a family afflicted with KP. In addition, upregulated *ABCA12* expression levels in the sebaceous glands of patients with NC were investigated.

## Materials and methods

**High-throughput sequencing.** Written informed consent was obtained from patients and individuals involved in the present study. The present study was approved by the ethics committee of Nanfang Hospital of Southern Medical University (Guangzhou, China). A total of 5 ml of peripheral blood was obtained from one KP and two NC probands, family members and 100 unrelated healthy controls (aged 18-28 years old, 44 males and 56 females, recruited in December 2015). The KP proband was a 12-year-old female (recruited August 2013). The NC probands were an 8-year-old male (recruited May 2014) and a 17-year-old male (recruited December 2015). Genomic DNA was extracted using the Blood DNA Mini kit (cat. no. 3001050; Hangzhou Simgen Biotechnology Co., Ltd., Hangzhou, China) according to the manufacturer's protocol. The genomic sequences of 147 genes associated with 143 skin diseases were initially analyzed in the KP proband using a custom-designed GeneChip [Skin single-gene genetic disease detection package, Illumina High-throughput sequencing platform (Illumina, Inc., San Diego, CA, USA), Beijing Genomics Institute, Guangdong, China] ( $P < 0.05$ ). The details of the gene and skin disease analysis were not presented.

**Polymerase chain reaction (PCR) and Sanger sequencing.** Specific primers for the *ABCA12* gene were designed using the web-based tool Primer 3 (<http://primer3.ut.ee/>; *ABCA12* primer sequences available on reasonable request). All exons and exon-intron boundaries of the *ABCA12* gene were amplified using PCR with a 20  $\mu$ l total reaction volume containing 1  $\mu$ l genomic DNA with a final concentration of 30 ng/ $\mu$ l, 10  $\mu$ l 2X Taq PCR StarMix (Taq DNA polymerase,  $Mg^{2+}$ , dNTPs and reaction buffer solution; cat. no. A112-05, GenStar Biosolutions Co., Ltd.), 1  $\mu$ l (10  $\mu$ M) forward and reverse primers, and 7  $\mu$ l ddH<sub>2</sub>O. The thermocycling conditions were as follows: Initial denaturation at 94°C for 5 min, 35 cycles of 94°C for 30 sec, annealing at 57°C for 30 sec and 72°C for 15 sec, followed by a final extension at 72°C for 15 sec. PCR products were confirmed using 1% agarose gel electrophoresis and sequenced. The sequencing results were analyzed on an ABI 3130 genetic analyzer (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). The functional alterations in the protein were predicted by web-based tools PolyPhen-2 ([genetics.bwh.harvard.edu/pph2/](http://genetics.bwh.harvard.edu/pph2/)) and SIFT release 63 ([sift.jcvi.org/](http://sift.jcvi.org/)). Sequence conservation surrounding the mutated region was verified using ClustalX version 2.1 (<http://www.clustal.org/>).

**Immunofluorescence.** Skin lesions from two patients with NC and the patient with KP were collected (one per patient;

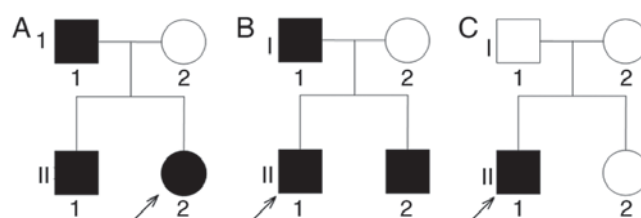


Figure 1. Family trees. (A) Family with keratosis pilaris. (B) First NC pedigree. (C) Second NC pedigree. NC, nevus comedonicus. The arrows indicate the proband.

~0.8x1 cm). The lesion from the KP proband was obtained from the left leg. NC samples were obtained from the waist and neck. Samples were fixed at room temperature by immersion in 10% formalin solution and, after 12 h the samples were processed into paraffin blocks. Sections (~3-4  $\mu$ m) were obtained, and the prepared paraffin sections were placed on adhesive slides and incubated overnight at 37°C. Immunofluorescence staining was performed as described below. The slides were de-waxed in 100% dimethylbenzene twice and subsequently dehydrated via a descending alcohol (100, 95, 85 and 70%) gradient. The antigen was retrieved via incubation in a water bath (95°C) for 6 min and then cooled to room temperature. The samples were blocked with 3% peroxide-methanol for 20 min at room temperature to quench endogenous peroxidase activity and then rinsed in PBS three times. The following steps were conducted in a moisture chamber: i) Samples were incubated with rabbit anti-ABCA12 antibody (cat. no. bs-11906R; BIOSS, Beijing, China) diluted 1:50 in antibody diluent (cat. no. IH0340; Beijing Leagene Biotech Co., Ltd., Beijing, China) at 37°C for 1 h and then 4°C overnight. ii) Following rinsing with PBS three times, DyLight goat anti-rabbit green fluorescent protein (cat. no. 4412; CST Biological Reagents Co., Ltd., Shanghai, China) diluted 1:500 in antibody diluent was applied; the samples were then incubated at room temperature without light for 90 min. iii) Following three rinses with PBS, the slides were stained with DAPI at room temperature for 10 min. iv) After washing with PBS for 5 min, the slides were sealed with glycerin. v) The slides were allowed to dry naturally and then visualized under a fluorescence microscope at 360 and 488 nm (magnification, x200). A total of 5 samples of normal skin were also analyzed which was obtained from a normal skin biopsy. Immunohistochemistry was conducted in the Central Laboratory of Nanfang Hospital of the Southern Medical University.

## Results

**Familial background.** The familial association between the proband in a family with KP was presented in Fig. 1A; that of the two NC families were presented in Fig. 1B and C.

### Clinical and histopathological findings

**KP family.** A Chinese pedigree family with three members afflicted with KP across two generations (Fig. 1A) were employed in the present study. The proband, a 12-year-old female, presented symmetric, asymptomatic and rough keratotic follicular papules, and mild perifollicular erythema at the cheek. The extensor of the upper arms and anterior thighs

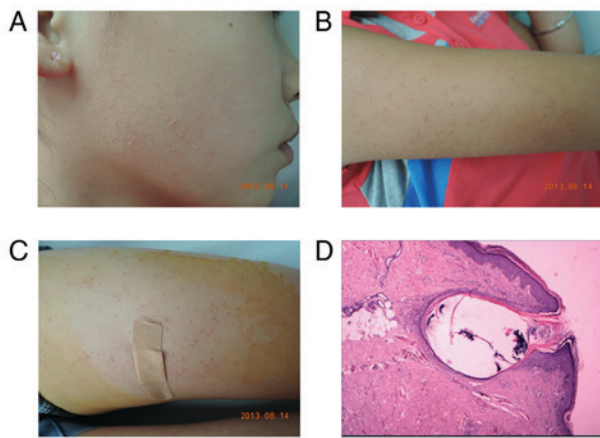


Figure 2. Clinical and pathological features of keratosis pilaris. (A-C) Clinical images of the proband: Symmetric, rough keratotic follicular papule and mild perifollicular erythema on the cheek, extensor of the upper arms and the anterior thighs. (D) Histopathology of a skin biopsy of the right thigh of the proband revealed that the follicular orifice was distended by a keratin plug; mild infiltration of mononuclear cells in the superficial dermis was observed (hematoxylin and eosin, magnification, x200).

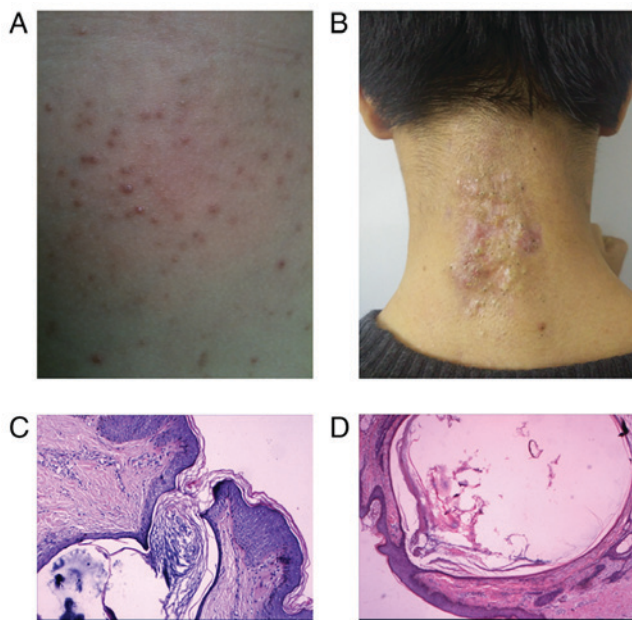


Figure 3. Clinical and pathological features of two patients with NC. (A) Clinical features of the first patient with NC: Numerous keratotic papules and comedo-like lesions on the waist and blackheads on parts of the lesions. (B) Clinical manifestation of the second patient: Aggregated, dilated hair follicles, blackheads with cysts, fistulas and abscesses on the neck. (C and D) Histopathology images of the two patients with NC; dilated follicular ostia filled with keratin layers were observed (hematoxylin and eosin, magnification, x200). NC, nevus comedonicus.

(Fig. 2A-C) were analyzed. The patient had no notable medical or family history and no mental retardation. The father and younger brother of the proband presented similar phenotypes.

**Histopathology of skin biopsies.** Samples were fixed at room temperature by immersion in 10% formalin solution (at room temperature) and after 12 h the samples were processed into paraffin blocks. Sections (~3-4  $\mu$ m) were obtained, and the prepared paraffin sections were placed on adhesive slides

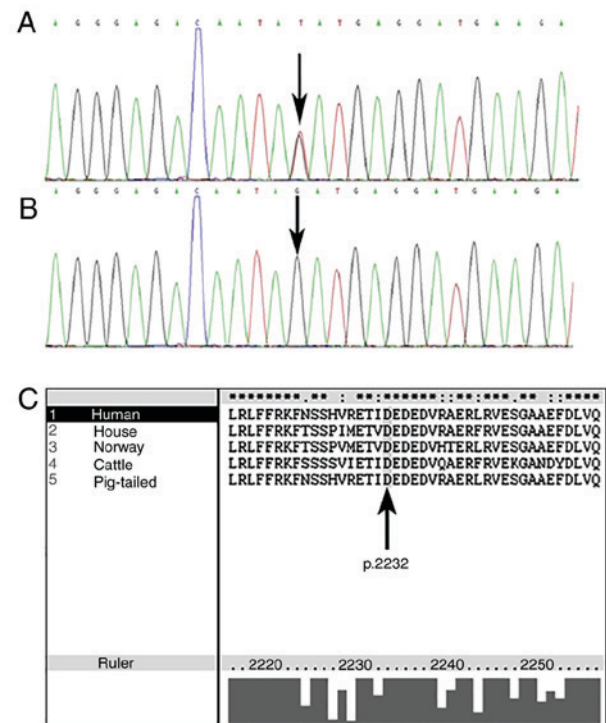


Figure 4. (A) Heterozygous missense c.6694G>T (p.Asp2232Tyr) mutation in *ABCA12* in the proband of the keratosis pilaris family, the proband's father and younger brother. (B) No mutations of *ABCA12* were detected in the mother or the control group. (C) Amino acid sequence of the region surrounding the mutation revealed highly conserved residues. The aspartic acid 'D' residue at position 2232 (arrow) presented high conservation among human, horse, Norway rat, cattle, and pig *ABCA12* genes. *ABCA12*, ATP-binding cassette sub-family A member 12.

and incubated overnight at 37°C. The slides were de-waxed in 100% dimethylbenzene twice and subsequently dehydrated via a descending alcohol (100, 95, 85 and 70%) gradient. Then the slides were stained with hematoxylin (cat. no. DH0001; Beijing Leagene Biotech Co., Ltd., Beijing, China) for 8 min, then wash in pure water for 3 sec and finally stained with eosin (cat. no. DH0050; Beijing Leagene Biotech Co., Ltd.) for 1 min at room temperature. Finally the slides were visualized under a light microscope (magnification, x200). The samples were obtained from the left thigh of the proband and revealed that the follicular orifice was distended by a keratin plug; mild infiltration of mononuclear cells in the superficial dermis was observed (Fig. 2D), supporting a diagnosis of KP.

**NC patients.** A total of two NC pedigrees were employed in the present study. The proband of the first family was an 8-year-old male with a 4-year medical history. The clinical manifestations of the proband constituted numerous keratotic papules and comedo-like lesions on the waist, buttocks and legs (data not shown). Physical examination revealed symmetric, light brown-colored papules 2-5 mm in size (Fig. 3A). The father and younger brother of the proband (Fig. 1B) exhibited the same symptoms. The second patient, a 17-year-old male, presented aggregated, dilated hair follicles, blackheads with cysts, fistulas and abscesses on the neck (Fig. 3B). Family disease history was not positive for the second NC family (Fig. 1C). The pathology of both patients demonstrated dilated follicular ostia filled with keratin layers (Fig. 3C and D).



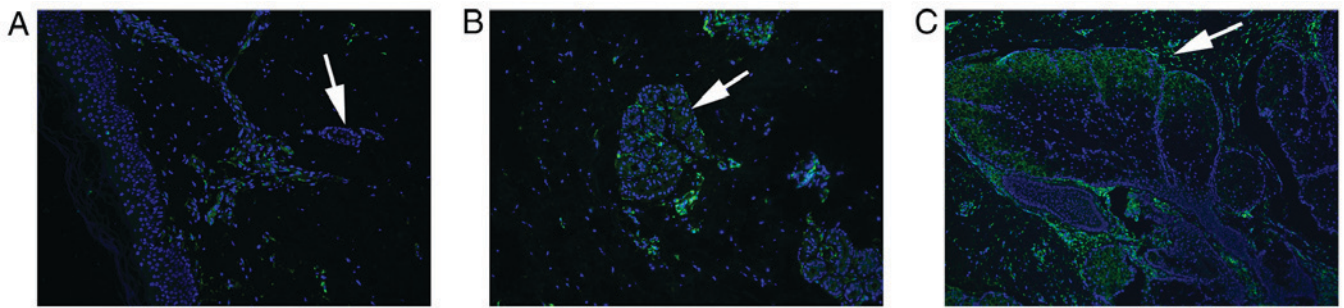


Figure 5. Immunofluorescence staining. (A) Healthy individual without NC. (B and C) The results from the two patients with NC. ATP-binding cassette sub-family A member 12 expression was observed to be stronger in the sebaceous glands of patients with NC compared with that of normal skin (white arrow). Magnification, x200. NC, nevus comedonicus.

**Mutation screening for the *ABCA12* genomic sequence.** High-throughput sequencing revealed a heterozygous missense c.6694G>T (p.Asp2232Tyr) mutation in *ABCA12* in the KP proband (Fig. 4A), and direct sequencing of all coding and exon-intron boundaries confirmed that this mutation was present in all of the affected KP family members, but not present in healthy family members, patients with NC or 100 population-matched controls (Fig. 4B). PolyPhen-2 and SIFT-based investigations suggested that this mutation may produce a damaged protein. The region surrounding this mutation is highly conserved among other species, according to ClustalX (Fig. 4C). The aforementioned results support the hypothesis that the p.Asp2232Tyr mutation in *ABCA12* may be one of the pathological factors that contribute to KP.

***ABCA12* is highly expressed in the sebaceous gland.** To understand whether *ABCA12*, which regulates lipid transport, is involved in the development of NC, the expression levels of *ABCA12* were examined using immunofluorescence. The results demonstrated that *ABCA12* expression was upregulated in the sebaceous glands of patients with NC (Fig. 5B and C) compared with in normal controls (Fig. 5A). Therefore, high expression levels of *ABCA12* in the sebaceous gland may be associated with the development of NC.

## Discussion

The putative pathogenesis of KP suggests a disorder of keratinization. The papules may arise from the excessive accumulation of keratin within the follicular orifices (6). Perifollicular erythema results from mechanical irritation from hyperkeratosis and increased skin pH, caused by a reduction in moisturizing amino acids (16). Several genetic studies have reported null mutations in the *FLG* gene of patients with KP, which has been associated with ichthyosis vulgaris and atopic dermatitis (17). *FLG*, a multifunctional protein expressed in the epidermis, not only aggregates and aligns keratin intermediate filaments within corneocytes, but also facilitates the release of a variety of amino acids, which contribute to natural moisture levels or reduced skin surface pH. Loss of function of *FLG* may lead to reduced natural moisture, resulting in epithelial barrier abnormalities (3); however, Gruber *et al* (3) reported that mutations of *FLG* may only partially result in the KP phenotype. Therefore, other genes may serve as causative genetic factors contributing to the development of KP; however, further research is required.

In the present study, a heterozygous missense c.6694G>T (p.Asp2232Tyr) mutation within *ABCA12* of the KP proband was identified. At present, no mutations in *ABCA12* have been reported to be associated with the onset of KP. Mutations of *ABCA12* have been considered to be a major cause of harlequin ichthyosis (18,19). *ABCA12*, located on chromosome 2q35, encodes a protein constituting 2595 amino acids, including two ATP nucleotide binding sites between residues 1370-1554 and 2282-2467, and two transmembrane domains (amino acid residues 1063-1271 and 1987-2293), each comprising six hydrophobic membrane spanning helices (20,21). *ABCA12* belongs to the ATP-binding cassette (ABC) transmembrane transporter protein superfamily, which bind and hydrolyze ATP for the transport of lipids in lamellar granules to granular layer keratinocytes (22). The main molecular function of *ABCA12* is yet to be investigated. Akiyama (19) demonstrated that a lack of *ABCA12* function disrupted glucosylceramide and ganglioside transport, leading to intracellular accumulation of these substances; this phenomenon was recovered by *in vitro* via *ABCA12*-corrective gene transfer (19). Investigations conducted by Wang *et al* (23) and Sun *et al* (24) indicated that increases in the production of gangliosides may result in keratinocyte apoptosis rather than the formation of epidermal stratification. Jiang *et al* (25) reported that ceramides, the precursors of glucosylceramides, stimulate *ABCA12* expression via the PPAR-mediated signaling pathway, subsequently regulating this lipid transporter. Conversely, Zuo *et al* (26) reported a lack of desquamation of the skin cells and rapid water loss from the skin in *ABCA12*<sup>-/-</sup> mice rather than enhanced proliferation of basal layer keratinocytes. Therefore, the mutations of *ABCA12* may affect lipid transport and skin cell desquamation, which may lead to the development of solid and dry lesions associated with KP.

NC is an epidermal nevus involving the pilosebaceous unit (27); the etiology of NC requires further investigation. Recently, the underlying signaling pathways associated with acne and the somatic mutations of tyrosine kinase receptors have been identified, and may serve a role in the development of NC (11,13). The present study revealed that the typical histopathology of NC was associated with large dilated follicular ostia filled with keratinous layers, similar to that of KP. Therefore, the present study aimed to investigate whether patients with NC also possessed mutations in *ABCA12*, which may affect lipid transport, resulting in the accumulation of keratin. Following sequencing, no *ABCA12*

mutations were identified in the two NC pedigrees employed in the present study; however, immunofluorescence analysis revealed that the ABCA12 protein was highly expressed in the sebaceous glands of patients with NC compared with in normal skin. Under normal conditions, ABCA12 protein is expressed and localized in epidermal keratinocytes (28). Conversely, ABCA12 expression was identified within the sebaceous glands of the two patients NC in the present study. The findings of the present study were supported by the presence of abnormal sebaceous glands. In conclusion, a novel missense mutation c.6694G>T in ABCA12 was identified in a KP family, and it was demonstrated that ABCA12 expression was upregulated in the sebaceous glands of NC patients without ABCA12 mutation. Therefore, it was inferred that ABCA12 mutations or expression changes may be causative or contributive factors to disease development of congenital keratinized dermatoses, such as KP and NC. ABCA12 may be considered as a therapeutic target for the treatment of NC. There remained limitations to the present study; for example, further investigations are needed to clarify the genetic background of the previous generations of the probands.

#### Acknowledgements

Not applicable.

#### Funding

The present study was supported by grants from National Natural Science Foundation of China (grant no. 81371724) to YHL.

#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

FL and YY performed the experiments and wrote this article. YZ collected blood and skin samples. YHL and KZ designed the experiments. All authors read and approved the final manuscript.

#### Ethics approval and consent to participate

The present study was approved by the ethics committee of Nanfang Hospital of Southern Medical University (Guangzhou, China).

#### Patient consent for publication

Written informed consent was obtained from patients and individuals involved in the present study.

#### Competing interests

The authors declare that they have no competing interests.

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