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Seborrhea-like dermatitis with psoriasiform elements caused by a mutation in *ZNF750*, encoding a putative C2H2 zinc finger protein

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We describe an Israeli Jewish Moroccan family presenting with autosomal dominant seborrhea-like dermatosis with psoriasiform elements, including enhanced keratinocyte proliferation, parakeratosis, follicular plugging, *Pityrosporum ovale* overgrowth and dermal CD4 lymphocyte infiltrate. We mapped the disease gene to a 0.5-cM region overlapping the PSORS2 locus (17q25) and identified a frameshift mutation in *ZNF750*, which encodes a putative C2H2 zinc finger protein. *ZNF750* is normally expressed in keratinocytes but not in fibroblasts and is barely detectable in CD4 lymphocytes.

Seborrheic dermatitis and psoriasis, each affecting 2–3% of the population worldwide, are distinct chronic papulosquamous dermatoses[1–3]. Psoriasis is characterized by red, scaly skin patches most commonly found on the elbows and knees and may be associated with arthritis[3]. Clinical manifestations of seborrheic dermatitis vary from common dandruffs to eczematous or psoriasiform plaques with predilection for sebaceous follicle-rich areas on the scalp, face and trunk[1,2]. Both diseases present with increased epidermal proliferation of keratinocytes and a sparse dermal perivascular infiltration of inflammatory cells[1–4]. Follicular plugging by orthokeratosis and parakeratosis may be noted, as well as overgrowth of the saprophyte *Pityrosporum ovale*[1–5]. Occasionally, distinguishing between the two entities can be obscured by overlapping clinical and histopathological features[1–3]. The molecular basis of both diseases is yet unclear[1–3,6].

A Jewish Israeli family of Moroccan descent presented with an apparently autosomal dominant form of seborrhea-like dermatosis with psoriasiform elements (**Fig. 1**), affecting 44 individuals in five generations (**Fig. 2a**). All affected family members presented by 10 years of age with a similar phenotype (**Fig. 1** and **Supplementary Fig. 1** and **Supplementary Table 1** online): a chronic fine diffuse scaly erythematous rash on the face, particularly on the chin, nasolabial

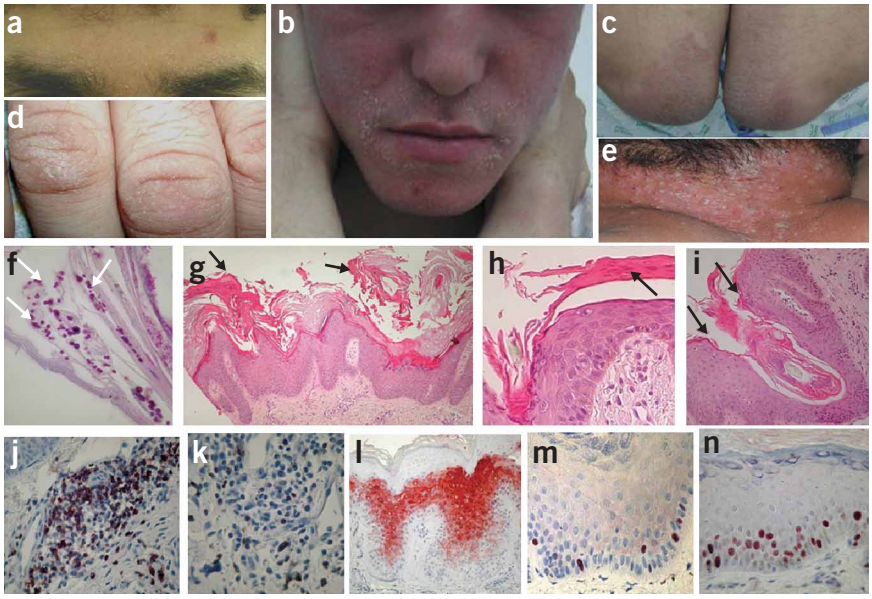

Figure 1 Disease phenotype. (**a**,**b**) Seborrhea-like facial erythema and scaling accentuated in supraorbital and perioral areas, with marked erythema and scaling of face. (**c**) Hyperkeratotic hyperpigmented plaques over elbows. (**d**) Hyperkeratotic erythematous plaques over knuckles and proximal interphalangeal joints. (**e**) Pustules on the nape. (**f**) Enlarged follicular ostium showing yeasts of *Pityrosporum ovale* (white arrows) (periodic acid–Schiff (PAS) staining; 400×). (**g**,**h**) Papillomatosis, acanthosis, hyperkeratosis and mounds of parakeratosis (arrows) and few ectatic blood vessels with mild perivascular mononuclear cell infiltrate (hematoxylin and eosin (H&E) stain;100×, 400×). (**i**) Hair follicle showing keratin plugs and mounds of parakeratosis (arrows) on either side of the follicular ostium (H&E; 200×). (**j**,**k**) Perivascular lymphocyte infiltrate: most cells are CD4 (**j**), and only few are CD8-positive (**k**) (immunohistochemistry; 400×). (**l**) Keratin 16 in affected skin (immunohistochemistry; 200×). (**m**,**n**) Ki67 staining of normal (**m**) versus affected (**n**) skin (immunohistochemistry; 400×). The histological findings were observed in four of four affected individuals studied.

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folds and eyebrows, around earlobes and over the scalp. The rash exacerbated in the winter, with emotional stress and after strenuous physical activity. Hyperkeratosis of skin over the elbows, knees, palms, soles and metacarpophalangeal joints was evident. There was no arthralgia, arthritis or neurological disorders.

Skin biopsies (**Fig. 1f–n**) demonstrated mild psoriasiform thickening (acanthosis) of the epidermis, hyperkeratosis, focal and shouldering parakeratosis, scale crusts, follicular hyperkeratotic plugs and overgrowth of *Pityrosporum ovale*. There were few ectatic blood vessels in the dermis, with mild perivascular mononuclear cell infiltrates consisting mostly of CD4 lymphocytes. However, there was no significant spongiosis typical of seborrheic dermatitis, and no evidence of clusters of neutrophils in parakeratotic layers as seen in psoriasis[3]. Immunohistochemistry demonstrated increased keratinocyte proliferation (Ki67 staining) and upregulation of keratin 16 in affected skin, as found in psoriasis.

Genome-wide linkage analysis of 18 family members (12 affected, six unaffected) using 400 microsatellite markers identified three loci with lod scores higher than 2 (D4S1534, D11S908, D17S928). Fine mapping using all 54 (19 affected, 35 unaffected) family members available for analysis ruled out loci D4S1534 and D11S908 (data not shown) but showed linkage to a 0.5-Mb segment at the telomeric end

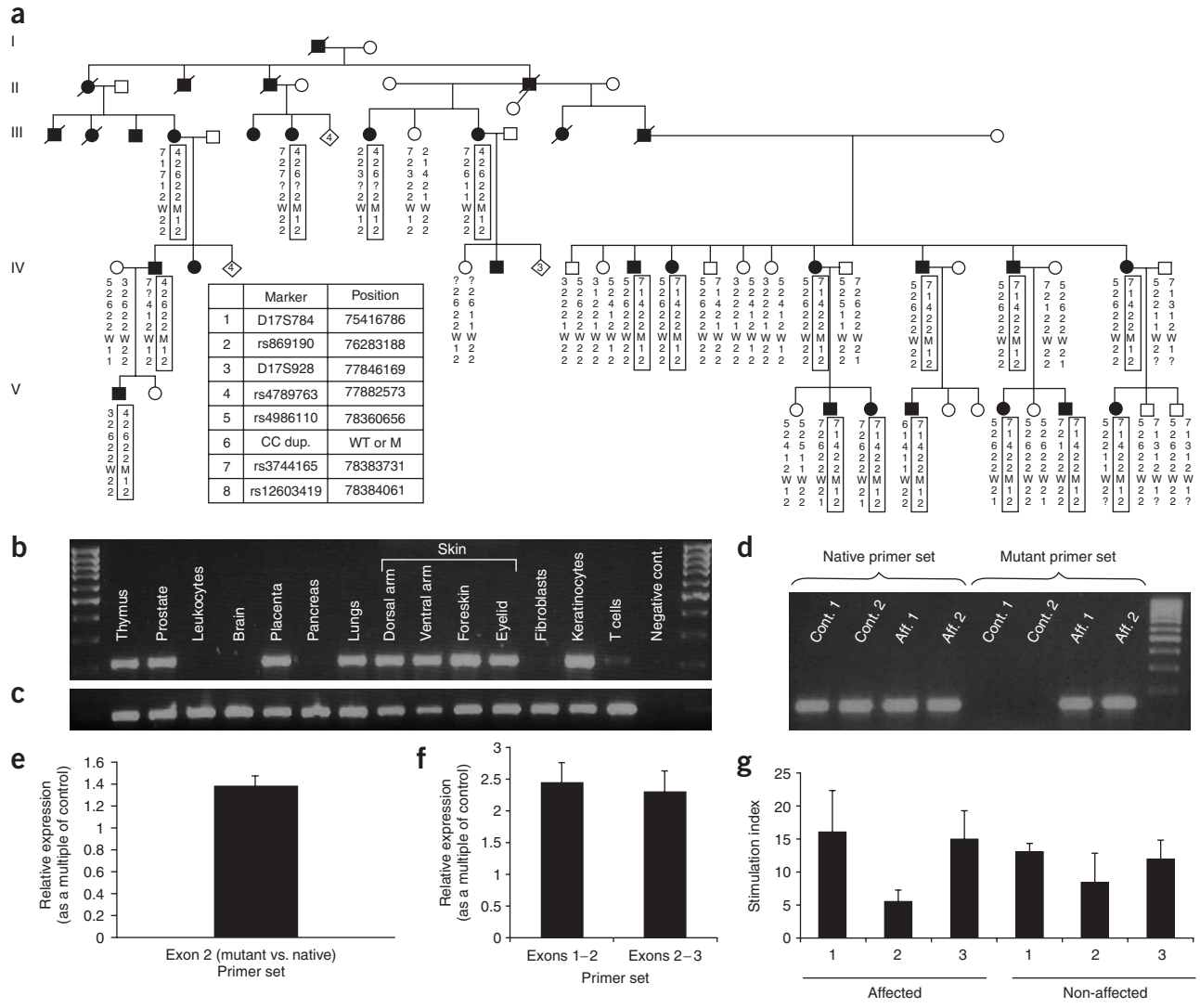

Figure 2 Genetic mapping, mutation identification and expression analysis. (**a**) Fine mapping. Genomic location of the *ZNF750* CC duplication (wild-type versus mutant alleles) is depicted. (**b**,**c**) *ZNF750* expression in human tissues and cells. RT-PCR products of (**b**) *ZNF750* exons 1–2 (210 bp) and (**c**) reference gene *GAPDH* (200 bp). RT-PCR amplification of *ZNF750* from activated and non-activated T cells was minimal (visible amplification product achieved only after two sequential rounds of RT-PCR). Real-time quantitative RT-PCR showed near-zero copy number of *ZNF750* transcripts in both activated and non-activated CD4 cells (data not shown). (**d**) RT-PCR from mRNA of keratinocytes of affected (Aff. 1, Aff. 2) and unaffected (Cont. 1, Cont. 2) individuals, using primers specific to the normal allele and to the mutant allele. Amplicons were of expected sizes, and sequences were verified. (**e**,**f**) Real-time quantitative RT-PCR amplification of *ZNF750* mRNA, using primer sets unique (**e**) or common (**f**) to mutant and wild-type *ZNF750* alleles. Results were normalized to an internal housekeeping control gene (*GAPDH*) shown not to vary between samples. (**e**) Keratinocytes of affected individuals harbor nearly equal levels of *ZNF750* wild-type and mutant transcripts. Shown are levels of mutant transcripts divided by levels of native transcripts (mean ± s.e.m.; $n = 3$). (**f**) Keratinocytes of affected individuals harbor nearly double the levels of *ZNF750* transcripts as compared with unaffected individuals. Shown are levels of *ZNF750* transcripts in keratinocytes of three affected individuals divided by the levels in keratinocytes of three controls (mean ± s.e.m.). (**g**) Peripheral blood CD4 T lymphocyte proliferation assay[15] in affected versus unaffected individuals (mean ± s.e.m. for triplicates of each sample, $n = 6$).

of chromosome 17q25 (**Fig. 2a**) with a maximum multipoint lod score[7] of 8.79 at $\theta = 0$ at SNP rs3744165. We sequenced the entire coding region of all 12 genes and six ESTs within this locus (**Supplementary Methods** and **Supplementary Table 2** online) and identified only a single mutation in the coding region of *ZNF750* (zinc finger protein 750; GenBank FLJ13841; NM_024702.1), a gene harboring the SNP rs3744165 within its 5′-UTR. This previously uncharacterized three-exon gene encodes a protein with a nuclear localization site at its 5′ end, and a conserved zinc finger domain (**Supplementary Fig. 2** online) that starts at amino acid residue 25. With two histidines and two cysteines that might serve as a zinc binding domain, ZNF750 is a putative member of the C2H2 subclass of zinc finger transcription factors[8]. The mutation (56_57dupCC) causes a frameshift resulting in missense coding as of residue 19 of this 723-residue protein, leading to a putative 44-residue truncated protein, fully abrogating the zinc finger domain (**Supplementary Fig. 2**). Screening with denaturing HPLC (**Supplementary Fig. 2** and **Supplementary Table 2**) showed that all 19 affected individuals tested were heterozygous for the mutation, whereas none of 35 unaffected family members or 100 non-related individuals of Jewish Moroccan ancestry had the mutation.

To verify the size of the normal *ZNF750* mRNA, we amplified the predicted cDNA segments by RT-PCR from mRNA prepared from skin biopsies of normal individuals. Comparison of the cDNA sequences to the databases (National Center for Biotechnology Information, University of California Santa Cruz) indicated that there are no alternative splicing variants. *ZNF750* is expressed in the skin, prostate, lungs placenta and thymus, and minimally in T cells, but not in peripheral blood leukocytes, pancreas and brain (**Fig. 2b**,**c**). It is clearly expressed in primary human keratinocytes but not in fibroblasts (**Fig. 2b**,**c**).

The mutant transcript is expressed in affected individuals and not in normal controls (**Fig. 2d**). Real-time PCR using primer sets specific to mutant and wild-type *ZNF750* transcripts showed that, in affected keratinocytes, the mutant transcript is not lost to editing (**Fig. 2e**). Notably, real-time PCR using primers common to the mutant and wild-type *ZNF750* transcripts showed that keratinocytes of affected individuals have a (roughly twofold) higher level of *ZNF750* transcripts than those of normal controls (**Fig. 2f**), perhaps in an attempt to compensate for lack of ZNF750 function. Based on these data, we argue that a gene dosage effect is unlikely. Members of the zinc finger proteins have been shown to form both homodimers and heterodimers[8]. Thus, while we have yet to determine the mechanism by which abrogation of a single copy of the gene causes disease, a dominant-negative effect is plausible.

ZNF750 is expressed in keratinocytes and not in fibroblasts, suggesting a primary defect in keratinocytes, the major skin cell type affected both in seborrheic dermatitis and in psoriasis[1–3]. As in seborrheic dermatitis and psoriasis[1–4,6], we found infiltrates of CD4 cells, with only minimal CD8 cells, in skin biopsies of affected individuals (**Fig. 1j**,**k**). Although *ZNF750* is transcribed in human thymus, it is not expressed in human peripheral blood leukocytes, and its expression in CD4 lymphocytes is minimal, independent of lymphocyte activation (**Fig. 2b**,**c**). Moreover, phorbol 12-myristate 13-acetate (PMA)-induced and ionomycin-induced T cell proliferation rates of peripheral blood CD4 cells of affected and unaffected individuals were similar (**Fig. 2g**). Thus, evidence for a primary role of *ZNF750* in direct modulation of the immune system in this disorder is limited. However, as keratinocytes secrete cytokines and adhesion molecules[9], keratinocyte-mediated immunomodulation by ZNF750 is plausible.

Seborrheic dermatitis has been associated with various neurological abnormalities, and emotional stress has been shown to aggravate the disease[1,2]. Although emotional stress aggravated the skin lesions in affected individuals in this kindred, no neurological symptoms were evident, in line with *ZNF750* not being transcribed in brain.

Zinc binding is essential for folding and activity of C2H2 proteins[8]. Although seborrheic dermatitis does not respond to supplementary zinc therapy, extreme zinc deficiency in patients with acrodermatitis enteropathica and acrodermatitis enteropathica–like conditions may be accompanied by dermatitis mimicking seborrheic dermatitis of the face[1–3]. Thus, a possible role for *ZNF750* in the seborrheic dermatitis–like presentation of extreme zinc deficiency should be considered.

Pityrosporum ovale overgrowth, found in affected individuals here, is thought to be associated with seborrheic dermatitis and has also been implicated in psoriasis[4]. *Malassezia* yeast species can differentially induce human cytokine production by means of keratinocytes[9], suggesting a possible mechanism of involvement of *Pityrosporum ovale* in seborrheic dermatitis and psoriasis.

Psoriasis is thought to be a complex genetic disease, caused in most cases by the interaction of several common disease alleles[6]. Autosomal dominant, highly penetrant and mostly non-arthritic psoriasis has been associated with the PSORS2 locus[10–14] harboring *ZNF750*. The non-arthritic psoriasiform elements in the phenotype described here suggest that *ZNF750* mutations or polymorphisms might underlie variants of psoriasis. Seborrheic dermatitis and psoriasis have many similar clinical and pathological elements[1–3]. Identification of *ZNF750* might open new insights to molecular pathways through which enhanced keratinocyte proliferation, CD4 infiltrates and *Pityrosporum ovale* overgrowth evolve in those common diseases.

Note: Supplementary information is available on the Nature Genetics website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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