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# New Homozygous Missense *MSMO1* Mutation in Two Siblings with SC4MOL Deficiency Presenting with Psoriasiform Dermatitis

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**Abstract**
Sterol-C4-methyl oxidase (SC4MOL) deficiency was recently described as an autosomal recessive cholesterol biosynthesis disorder caused by mutations in the *MSMO1* (sometimes also referred to as *SC4MOL*) gene. To date, 5 patients from 4 unrelated families with SC4MOL deficiency have been reported. Diagnosis can be challenging as the biochemical accumulation of methylsterols can affect global development and cause skin and ocular pathology. Herein, we describe 2 siblings from a consanguineous Turkish family with SC4MOL deficiency presenting with psoriasiform dermatitis, ocular abnormalities (nystagmus, optic hypoplasia, myopia, and strabismus), severe intellectual disability, and growth and motor delay. We undertook whole-exome sequencing and identified a new homozygous missense mutation c.81A>C; p.Asn27Thr in *MSMO1*. Segregation analysis in all available family members confirmed recessive inheritance of the mutation. The siblings were treated with a combination of oral and topical statin and cholesterol which resulted in clinical improvement. This study demonstrates how genomics-based diagnosis and therapy can be helpful in clinical practice.


## Introduction

Cholesterol is fundamentally linked to several important cellular functions as a key component of cell membranes, lipid rafts and the precursors of steroids, vitamin D, and bile acids [Herman and Kratz, 2012]. Underscoring the importance of cholesterol homeostasis is the discovery of a number of inherited disorders that affect cholesterol biosynthesis [Debets et al., 1996; Herman, 2003]. Clinically, disrupting cholesterol biochemistry results in abnormal morphogenesis, growth delay, and psychomotor disabilities [Herman, 2003]. Early and accurate diagnosis of these disorders is important for genetic counseling and therapeutic intervention. Within the portfolio of inherited disorders of cholesterol is sterol-C4-methyl oxidase (SC4MOL) deficiency in which mutations in the

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*MSMO1* gene lead to an accumulation of methylsterols [He et al., 2011]. This condition has previously been reported in only 5 patients so far [He et al. 2011, 2014; Frisso et al., 2017] with affected individuals variably displaying microcephaly, congenital cataracts, growth delay, psoriasiform dermatitis, intellectual disability, and immune dysfunction. Here, we report 2 siblings with SC4MOL deficiency from a consanguineous Turkish family who presented with treatment resistant psoriasiform dermatitis, motor and growth delay, intellectual disability, and ocular findings including nystagmus, optic hypoplasia, myopia, and strabismus.

## Clinical Reports

The first patient is the older male sibling (VI.10) who was diagnosed at the age of 9 years with recalcitrant severe psoriasiform dermatitis. He had well-demarcated erythematous plaques with yellow lamellar scales over almost all of his body which have been present since 18 months of age (Fig. 1a, b). His skin was normal at birth with dermatitis first noted around the diaper area at 2 months of age which subsequently became generalized. He also had nystagmus, a dysmorphic appearance, and axial hypotonia. Skin biopsy revealed characteristic features of psoriasis with psoriasiform hyperplasia, neutrophils in the epidermis, loss of the granular layer, and dilated capillaries in the dermal papillae. Based on a diagnosis of psoriasis, he was then treated with moisturizers, topical corticosteroids, and topical calcipotriene as well as systemic acitretin and methotrexate. However, none of these therapies resulted in any sustained improvement, although the distribution of the persistent skin lesions changed somewhat, becoming mostly localized to his head and neck, trunk, upper extremities, and anogenital region (Fig. 1c, d). During dermatological follow-up, he was also evaluated by many medical departments, with noting of optic hypoplasia, myopia, strabismus and nystagmus, growth delay (his weight and head circumference was <3rd percentile), motor delay, and severe intellectual disability with lack of speech. Diffusion-weighted magnetic resonance imaging (MRI) of the brain confirmed bilateral optic hypoplasia and showed lateral ventricular enlargement. He also had atrioventricular septal defect and unilateral cryptorchidism.

The younger female sibling (VI.11) was diagnosed at the age of 7 years. She presented with well-demarcated plaques with yellow-brown colored lamellar scales restricted to perioral and anogenital regions when she was 3 years old (Fig. 1e, f). Skin biopsy revealed acanthosis, hyperkeratosis, and loss of granular layer in the epidermis with superficial perivascular inflammation. She also had nystagmus, optic hypoplasia, myopia, hypopigmented fundus, and milder intellectual disability as well as motor/growth delay compared to her brother. Optic hypoplasia, dysgenesis of corpus callosum (rostrum agenesis), hypoplasia of inferior vermis, enlarged cisterna magna, and asymmetrical and slightly enlarged lateral ventricles were noted in the brain MRI report.

The siblings were born at full-term after uneventful pregnancies. Their parents were consanguineous, but the family history was unremarkable. Both children showed similar morphological findings such as microcephaly, broad forehead, prominent metopic suture, hypertelorism, wide nose, short smooth philtrum, high palate, dry and brittle hair, and sparse eyebrows and eyelashes (Fig. 1c, e). Karyotype analyses of the siblings were normal.

## Methods and Results

Following informed consent approval, we undertook whole-exome sequencing using DNA extracted from peripheral blood obtained from the 2 affected siblings. SureSelect Human All Exon V6 capture kit (Agilent) was used for whole-exome sequencing. More than 3.7 Gb of sequence were generated per sample, such that >91% of the target exome was present at >20-fold coverage, and >98% present at 5-fold coverage. Because of the consanguinity, a model of rare autosomal recessive inheritance was followed by focusing on homozygous predicted protein-altering substitutions and indels that were shared by both siblings, with a minor allele frequency of less than 0.5% in each of the 1000 Genomes Project, Exome Aggregation Consortium (ExAC), National Heart, Lung, and Blood Institute Exome Variant Server (NHLBI EVS) and our in-house database of more than 6,000 exomes. This analysis revealed 9 homozygous variants, of which 4 were novel, including a missense variant, c.81A>C; p.Asn27Thr, in the *MSMO1* gene (online suppl. Table 1; see http://www.karger.com/doi/10.1159/511126). Two of the other novel variants were splicing variants with no predicted effect on the transcript or the protein, whereas the *ADGRV1* gene is associated with Usher syndrome and Febrile seizures, familial, 4, both of which are clinically irrelevant. Considering that our patients' phenotype matched to previous reports with mutations in *MSMO1,* we focused on the *MSMO1* variant. The c.81A>C variant has not been re-

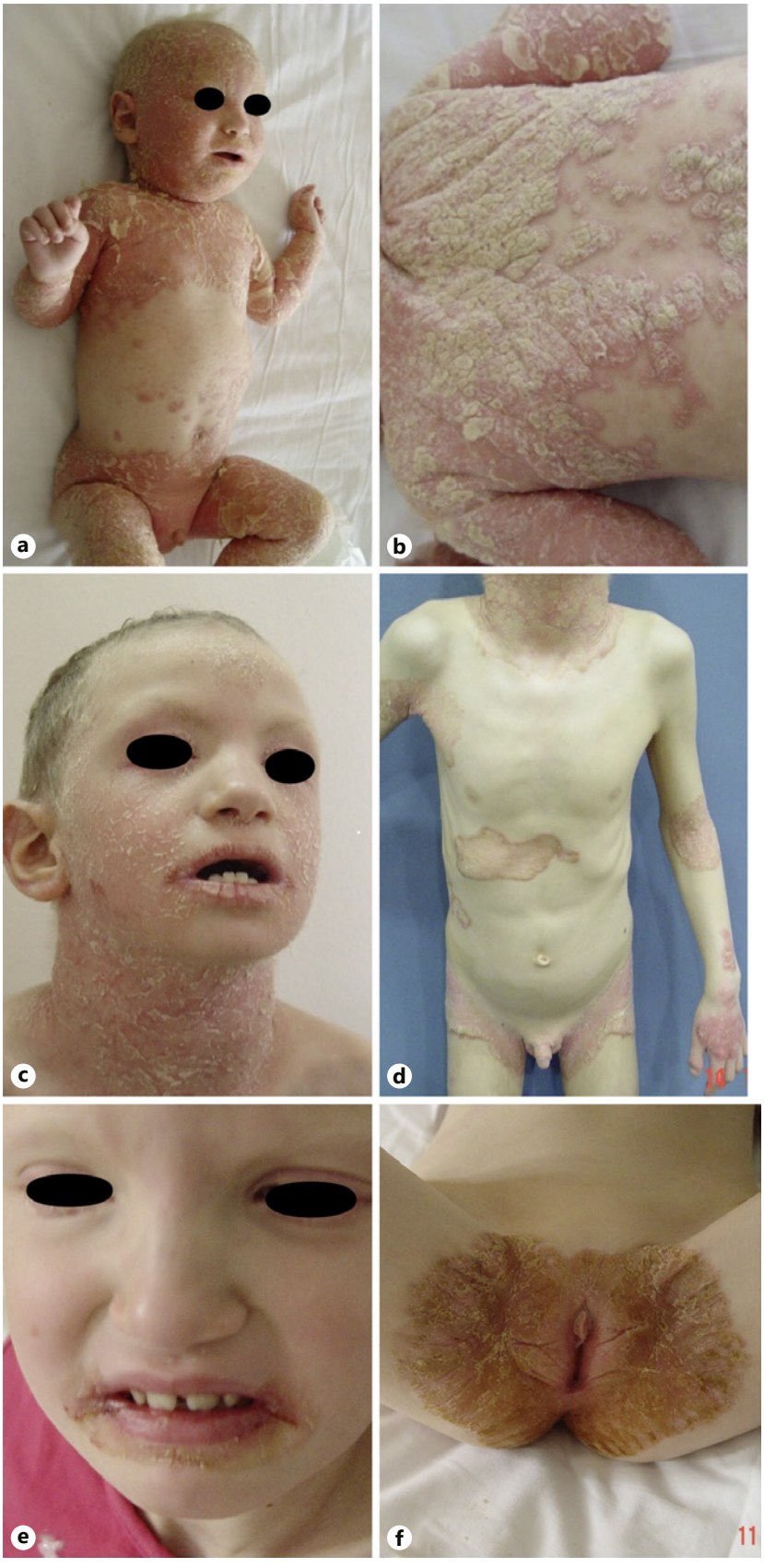


**Fig. 1.** Clinical manifestations in patients VI.10 and VI.11. **a**, **b** Clinical appearance of the brother at 18 months of age on first admission characterized by erythematous plaques with yellowish lamellar scales on entire body, sparing some areas on trunk and back, and palms and soles. **c**, **d** At 9 years of age, well-demarcated erythematous scaly plaques mimicking psoriasis on face and neck, trunk, upper extremities, and gluteal region. **e**, **f** The sister with well-demarcated plaques with yellow-brown lamellar scales on perioral and anogenital region.

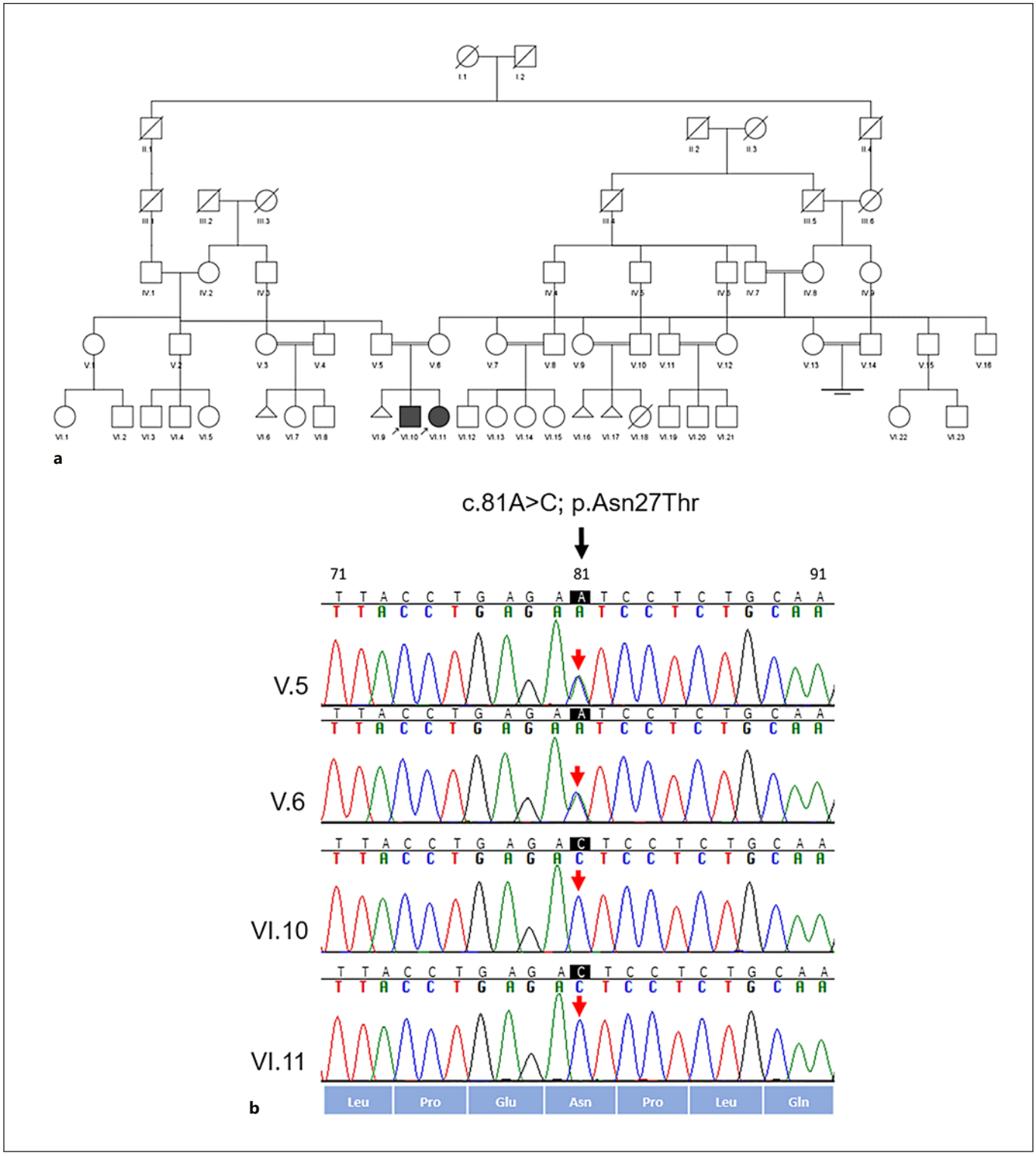


**Fig. 2.** Mutation analysis. **a** Pedigree structure. **b** Sanger sequencing chromatograms of the **c**.81A>C; p.Asn27Thr *MSMO1* mutation.

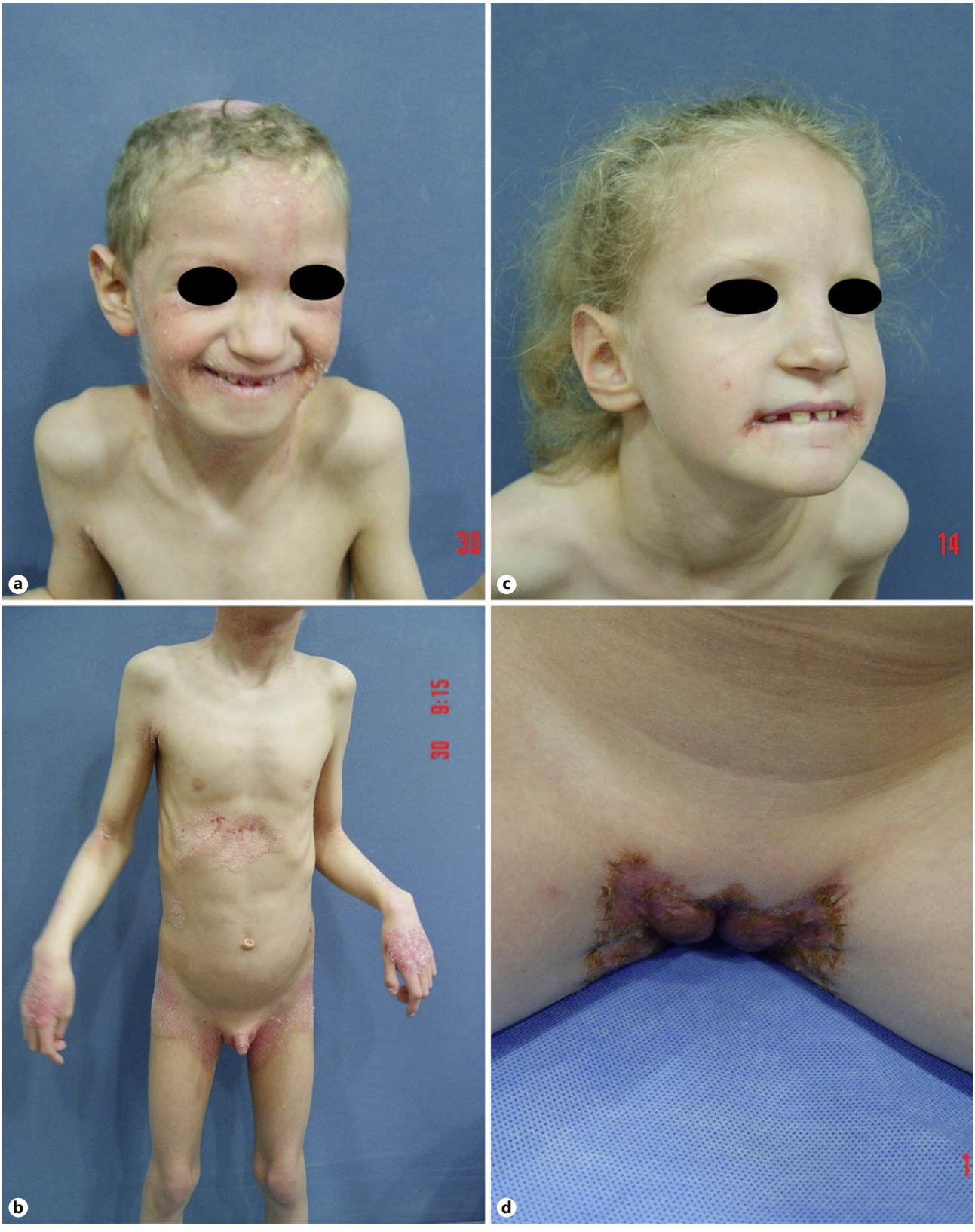


**Fig. 3.** Clinical improvement of psoriasiform skin lesions after 3 months of therapy in the brother (**a**, **b**) and in the sister (**c**, **d**).

ported before in the genome aggregation database (gnomAD) and was predicted to be deleterious with a Combined Annotation Dependent Depletion (CADD) score of 29. Segregation analysis of the c.81A>C substitution in all available members of the pedigree, including the 2 unaffected parents, confirmed the recessive inheritance of the mutation (Fig. 2). Therefore, the c.81A>C mutation is classified as "likely pathogenic" according to the ACMG criteria [Richards et al., 2015].

The levels of total cholesterol and triglycerides in plasma samples of the patients were within normal limit; however, we were not able to determine levels of methylsterols. In flow cytometric analyses of the patients, decreased expression of CD16 on granulocytes in the affected male child and increased ratio of nonclassical monocytes in the female child were detected. Based on a genetic diagnosis of SC4MOL deficiency, we started cholesterol/statin therapy. Rosuvastatin (5 mg/day) and cholesterol (10 mg/kg/day) supplementation were given orally and topical vaseline containing 1% rosuvastatin and 10% cholesterol was applied to skin lesions. Skin findings of the patients were improved within 8 weeks after beginning therapy (Fig. 3). Over the first 3 months of treatment, we did not observe any improvement in the patients' growth or neurological/ophthalmological abnormalities; further treatment and follow-up are ongoing.

## Discussion

*MSMO1* encodes a sterol-C4-methyl oxidase (SMO) that catalyzes demethylation of C4-methylsterols in the cholesterol synthesis pathway. C4 methylsterols are also known as meiosis-activating sterols which are linked to cell overproliferation, cholesterol homeostasis, immune regulation in skin and blood, and in the pathogenesis of psoriasiform skin disease [He et al., 2014]. The homozygous mutation, c.81A>C (p.Asn27Thr), in *MSMO1* identified in our patients is a novel variant. Previously, the reported pathogenic mutations comprise: c.343 G>A (p.Gly115Arg), c.519T>A (p.His173Gln), c.605G>A (p.Gly202Glu), and c.731A>G (p.Tyr244Cys) [He et al., 2011; Frisso et al., 2017].

Of the 5 previously reported patients with SC4MOL deficiency (see Table 1 for clinical and molecular details), 3 of them presented with psoriasiform skin lesions [He et al., 2014]. Similar to the children in our study, the first patient described by He et al. [2011] had severe psoriasiform dermatitis, treated as psoriasis for years until a more accurate diagnosis was confirmed. The other 2 patients were siblings presenting with psoriasiform dermatitis in early infancy with normal cholesterol levels, although full clinical details of these cases are lacking [He et al., 2014]. Psoriasiform skin lesions were features in 5 of the 7 reported individuals with SC4MOL deficiency.

There are several possible explanations why SC4MOL deficiency might result in a psoriasiform dermatitis. Disruption of cholesterol biosynthesis accelerates DNA synthesis and generates epidermal hyperplasia [Wolf et al., 2012]. Moreover, accumulation of sterol intermediates in impacts on cell cycle activation with increased S-G2-M to G0-G1 ratio [He et al., 2014]. Epidermal growth factor receptor signaling is reduced in SC4MOL deficiency, which can also generate dermatitis [He et al., 2014]. Furthermore, immunological abnormalities may contribute: SC4MOL deficiency can lead to increased numbers of TLR-$2^+$, TLR-$4^-$ granulocytes, a higher proportion of $CD8^{dim}$ T cells that are also $CD28^-CD56^+$, downregulated expression of the granulocyte-specific CD16b isoform, and constitutive production of IL-6 [Debets et al., 1996; Begon et al., 2007]. SC4MOL is also situated within the psoriasis susceptibility locus *PSORS9* and may be a direct genetic risk factor [He et al., 2014]. Taken together, psoriasiform dermatitis may be explained by multiple molecular and immunological alterations in SC4MOL deficiency.

Nevertheless, there is clearly some variability in the clinical manifestations resulting from SC4MOL deficiency, not only for the psoriasiform dermatitis but also in growth delay, intellectual disability, immunopathology, ocular findings, and onset age of clinical anomalies.The development of the blood-brain barrier, likely around 12–18 weeks of human gestation, makes the developing embryonic/fetal brain dependent on endogenous cholesterol synthesis [Virgintino et al., 2008]. As a result, cholesterol biosynthesis pathway defects lead to neurodevelopmental and behavioral findings along with central nervous system structural anomalies [Kanungo et al., 2013]. Overall, the high phenotypic and clinical variability might be explained by the variable accumulation of diverse noncholesterol sterols in cells and tissues of affected patients [Rossi et al., 2007; Herman and Kratz, 2012; Di Taranto et al., 2016].

Regarding treatment, previous studies have indicated that the blockage of methylsterol accumulation and supplementation of the end product cholesterol should be the main goal of therapy [He et al., 2011]. Moreover, concomitant use of a statin to prevent substrate entry into the metabolic pathway and supplementation of the end product is necessary for numerous cellular functions. There is

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**Table 1.** Clinical and molecular features of reported patients with SC4MOL deficiency and present cases

| | He et al. [2011, 2014] | | | Frisso et al. [2017] | Present cases | |
|---|---|---|---|---|---|---|
| | Case 1 | Case 2 | Cases 3 and 4 (siblings)* | Case 5 | VI.10 | VI.11 |
| Skin findings | Psoriasiform dermatitis | Dry skin | Psoriasiform dermatitis | – | Psoriasiform dermatitis | Psoriasiform dermatitis |
| Age at onset of skin findings | 2 years | – | Early infancy | – | 2 months | 3 years |
| Failure to thrive/growth delay | + | + | N/A | Short stature | + | – |
| Microcephaly | + | + | N/A | – | + | + |
| Neurodevelopmental findings | ID | Developmental delay | N/A | ID/learning difficulty | Severe ID | Severe ID |
| Structural brain abnormalities | – | – | N/A | Blake's cyst<br>Dysmorphic ventricles<br>Cerebellar hypoplasia | Enlarged ventricles | Enlarged ventricles<br>Corpus callosum dysgenesis<br>Hypoplastic inferior vermis<br>Enlarged cisterna magna |
| Ocular findings | Congenital cataract | Congenital cataract | N/A | Congenital cataract | Optic hypoplasia<br>Strabismus<br>Myopia<br>Nystagmus | Optic hypoplasia<br>Strabismus<br>Myopia<br>Nystagmus |
| Cholesterol levels | Low | Low | Normal | Normal | Normal | Normal |
| Miscellaneous | Chronic arthralgia<br>Delayed puberty | Joint contracture | N/A | Obesity | ASD<br>Unilateral cryptorchidism | – |
| *MSMO1* mutations | c.[519T>A]; [731A>G] | c.[G343G>A]; [G343G>A] | N/A | c.[731A>G]; [605 G>A] | c.[81A>C]; [81A>C] | c.[81A>C]; [81A>C] |

ASD, atrioventricular septal defect; ID, intellectual disability; N/A, not available; +, present; – absent. * Full clinical and molecular details of these patients are not reported.

therefore a rationale to use cholesterol/statin combination therapy for patients. Dietary (including supplemented) cholesterol is not thought to cross the blood-brain barrier, and there is no known established standard therapy for neurodevelopmental and behavioral findings [Kanungo et al., 2013]. In the first case of SC4MOL deficiency reported [He et al., 2011], treatment with oral cholesterol/statin led to biochemical, immunological and clinical (skin and growth) improvement within 3 months after beginning therapy [He et al., 2011]. A second patient also had treatment benefit, [He et al., 2011] and it was mentioned in a third but with insufficient follow-up time to comment further [Frisso et al., 2017].

Given the rarity of this syndrome, establishing the diagnosis is difficult, and it can take years until a more accurate diagnosis is confirmed. Genetic analysis for SC4MOL deficiency should be considered in patients with treatment resistant psoriasiform dermatitis accompanied by variable growth delay, intellectual disability, and ocular findings. Early diagnosis is important to improve genetic counseling and because early administration of the mechanism-based therapy may improve growth, cholesterol/sterol biochemistry, immune dysregulation, and skin lesions [He et al., 2014].


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## Statement of Ethics

Written informed consent for publication was obtained from the patients' parents. The paper is exempt from ethical committee approval. It is a retrospective study and all analysis were done as a part of the routine diagnostic procedures.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

I. Kalay Yildizhan wrote the manuscript. I. Kalay Yildizhan, P. Kocyigit and N. Kundakci did the clinical evaluation, data analysis and literature review. E. Gökpınar İli and N. Yürür Kutlay did clinical genetic evaluation of the family, cytogenetic analysis, literature review, and wrote part of the manuscript. A. Onoufriadis, E. Kesidou, M. A. Simpson, J.A. McGrath performed whole-exome sequencing, data analysis, and also wrote part of the manuscript. P. Kocyigit, N. Kundakci, N.Y. Kutlay, and J.A. McGrath revised the manuscript. All authors reviewed and approved the final version.

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