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The sterol-C4-methyl oxidase deficiency in cholesterol biosynthesis and the juvenile psoriasis form dermatitis: A new case in a teenager Italian male

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Inborn defects of cholesterol biosynthesis are metabolic disorders presenting with multi-organ and tissues anomalies. Recently, a new autosomal recessive defect in four patients involving the demethylating enzyme C4-methylsterols (SC4MOL) has been described. In infancy, all showed microcephaly, congenital cataracts, growth delay, psoriasiform dermatitis, immune dysfunction and intellectual disability. Herein, we describe a new case of SC4MOL deficiency, showing bilateral congenital cataracts, psychomotor and development delay and learning disabilities in the early life. At 15 years, he showed small stature and behavioral disorder. His skin never demonstrated a marked psoriasiform rash, but only abundant dandruff of scalp. Despite numerous biochemical and genetic examinations, the diagnosis was missed until 19 years. Based on clinical evidences, such as congenital cataracts, microcephaly and developmental delay, a cholesterol biosynthesis defect was suspected. Blood C4-monomethyl- and C4-dimethylsterols levels were significantly higher than controls, suggesting a true deficiency of SC4MOL. SC4MOL gene sequencing showed mutations in both alleles (1st variant: c.731A>G, p.Y244C, already known; 2nd one: c.605G>A, p.G202E, new variant). Both mutations are absent in both EXAC database and healthy controls. His parents are found heterozygous. Finally, integrating clinical, metabolic, and genetic tests, we diagnosed the SC4MOL deficiency definitively. Notably, the interactions of multi-field skills are fruitful to diagnose a new defect of cholesterol biosynthesis. Therefore, we suggest that plasma sterol profile should be taken early into account for all undiagnosed patients showing clinical signs overlapping that of patient presented here.

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Association with genetic variants in the IL-23 and NF-κB pathways discriminates mild and severe psoriasis skin disease

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Psoriasis is clinically heterogeneous and symptoms can vary from mild almost cosmetic symptoms to severe disease requiring systemic therapy. Biomarkers predicting disease development are lacking. Herein, we explored the genetic background in two polarized cohorts of carefully phenotyped patients with long-term follow-up; consistent mild phenotype (n=696) and severe disease course requiring systemic therapy (n=715). All patients were treated at the same dermatology department ensuring homogenous assessment. Genotyping included known psoriasis associated variants with special focus on the IL-23 and NF-B pathways. A case study comparing severe and mild psoriasis phenotypes, controlling for age at disease onset and gender, revealed significant differences between the two groups for SNPs in IL23R, NFKB1, IL21, IL12B, NFKBIL1 and IL23A. HLA-C*06 associated equally in the mild and severe disease cohorts. Strong additive effects when combining HLA-C*06 with IL23A, IL23R, IL12B, NFKB1 or TNIP1, were restricted to the severe cohort indicating that activation of these pathways may influence disease severity in psoriasis. No protective gene was identified in the mild cohort, suggesting that current screens have primarily identified psoriasis variants associated with a more severe phenotype. These results demonstrate the importance of careful phenotyping and long-term clinical follow-up in genetic studies.

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