A novel EVER1 polymorphism of epidermodysplasia verruciformis: Homozygous TMC6 c.718del

To the Editor: We recently published an interesting case of a 9-year-old girl with epidermodysplasia verruciformis (EV) titled "Diffuse skin-colored papules in a child" in *JAAD Case Reports*. Genetic testing had not been completed at the time of publication and we write to discuss these fascinating results. A previously unreported genetic variation was discovered using next generation sequencing and thought to be the most likely pathologic cause of EV in our patient. Specifically, our patient was found to be homozygous in the TMC6 gene (transmembrane channel gene 6) for a sequence variant defined as c.718del, which is predicted to result in a frameshift and premature protein termination (p.Gln240serfs*76).

EV can present with a spectrum of cutaneous morphologies, various genetic mutations (eg, TMC6 [EVER1] and TMC8 [EVER2], RHOH, MST-1, CORO1A, and interleukin 7 genes), and multiple inheritance patterns (eg, autosomal recessive, autosomal dominant, X-linked, and sporadic).[1] The most common genetic aberrations associated with EV are mutations of the TMC6 and TMC8 genes; approximately 11% of these cases are associated with consanguinity, and 10% from multiplex families.[2] Our patient lacked a suspect family history and immunosuppression. Novel to our case is the identification of the specific variant of TMC6, c.718del, which has not previously been reported in the literature. Other chain-terminating variants of TMC6 have been documented upstream and downstream of c.718 to be disease causing, and, similarly, we believe this to be an additional pathogenic variant of TMC6 associated with EV.[3,4]

The TMC6 and TMC8 genes belong to the TMC family of proteins involved in zinc homeostasis and downstream signaling cascades important to the immune system. It has been suggested that through these mechanisms, TMC6 and TMC8 gene products provide resistance against human papillomavirus (HPV) infection.[1] These genes are expressed in keratinocytes as well as some immune system cells.[1] It is not surprising then to note that most patients with EV have been reported to have impaired cell-mediated immunity, and HPV subtypes are invariably identified in EV cells. In addition to our patient's unremarkable family history, laboratory investigations with normal results at the time of dermatologic examination included HIV screening, serum protein electrophoresis, and complete blood count.

This case of EV presented with a novel genetic variant of the TMC6 gene as well as characteristic age of onset, cutaneous morphology, and histologic findings. EV skin lesions develop as a result of the cumulative cocarcinogenic effects of genetic, HPV, and UV radiation factors. Infection with specific types of HPV (namely HPV-5, HPV-8, and HPV-14) have been associated with higher oncogenic potential of nonmelanoma skin cancer, which is typically observed approximately 20-30 years after the formation of benign lesions. Identification of this variant of TMC6 in our patient adds to the genetic athenaeum associated with EV, demystifies otherwise classic EV phenotypes with no apparent origin, as well as guides clinical management, including regular yearly skin examinations and counseling patients on sun protection methods.

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Conflicts of interest

None disclosed.

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