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A novel candidate gene in autosomal dominant facial pruritus

Dear Editor, Pruritus is a common and often debilitating symptom that is associated with dermatological conditions including eczema, allergic contact dermatitis, urticaria, some drug eruptions and less commonly systemic diseases and neuropathic causes[1]. We report here an unusual familial centrofacial pruritus without any history or clinical findings of a rash, affecting three siblings and their father.

The index patient (II-1; Figure 1a) was a 62-year-old female with a 20-year history of severe localised pruritus of the nose. Her predominant symptom was debilitating itch on the surface of the skin around her nasal bridge, nasal septum and the nasal alae. She had no associated nasal congestion, rhinorrhea, skin changes nor rash and there was no relation to seasons, being outdoors, time of day, occupation, or food intake. Possible triggers included a warm environment and exercise. The pruritus would last for several hours and responded only to the antihistamine pheniramine, but not to others. Nortriptyline and pregabalin had also been tried and led to an improvement in her symptoms for two weeks before becoming ineffective.

Her past medical history was unremarkable, however she described occasionally waking in the night as a child with intense widespread pruritus and showering was required to relieve her symptoms. Extensive laboratory studies and skin prick testing had ruled out any allergic causes and other systemic disorders.

The proband underwent clinical exome sequencing at the Royal Melbourne Hospital. Analysis was undertaken starting with genes associated with nociception channelopathies (*SCN9A*, *SCN10A, SCN11A, TRPA1*), where no pathogenic

variants were identified. Further genes associated with Mendelian disorders were analysed. A heterozygous variant of uncertain significance was detected in the *TRPM3* gene (NM_001007471.4:c.3187+1G>A p.?; Figure 1b). This sequence change is rare in the population (2/251,242 alleles, 0 homozygotes in gnomAD v2.1)[2]. There was no phenotype information available for the two heterozygotes identified in the genome aggregation database (gnomAD), and it is plausible that they could be affected with pruritus. The variant alters the canonical donor splice site in intron 21 and is expected to disrupt RNA splicing. The predicted outcomes include, exon skipping that likely results in an absent or disrupted protein product, or cryptic donor activation that would lead to in-frame 36 nucleotide intron inclusion[3]. There is a reported alternative transcript with cryptic donor activation (ENST00000396285), but it is not expressed in any tissues in the Genotype-Tissue Expression (GTEx) database. RNA studies are required to determine the splice impact of this variant, and whether loss of expression of the allele would occur. The variant was detected in the DNA of both symptomatic brothers (II-2 and II-4, Figure 1a) and not in the asymptomatic sister (II-3, Figure 1a). Thus, there is a 1 in 8 probability of the variant being present by chance.

The sensation of itch is transmitted from the skin to the spinal cord by specific subsets of cutaneous sensory neurons which are distinct from those that convey nociception. There has been longstanding investigation of the differences between pain and itch, as well as their commonality as unpleasant sensations, with responses which are somatosensory. The selectivity theory of itch suggests that a subpopulation of nociceptor fibres which innervate the skin can be activated by a range of substances which create the sensation of itch, as compared to a more general activation of nociceptors in the genesis of pain[4].

Transient receptor potential (TRP) ion channels have roles in nociception and itch[5]. The TRPM3 ion channel is thermosensitive and has been described as mediating nociception but not itch, evoked by using endogenous pruritogenic mediators in animal studies[6]. Recently, gain-of-function missense variants in *TRPM3* have been associated with intellectual disability and epilepsy[7]. However, it is unknown if loss of function is a mechanism of disease for this gene. TRPM3-deficient mice exhibited clear deficits in their avoidance responses to noxious heat and in the development of inflammatory heat hyperalgesia[8]. But there are currently no studies associating TRPM3 with itch or investigating putative loss of function variants in this gene.

The clear segregation of the *TRPM3* variant in this family is highly suggestive of a causal relationship. Furthermore, the physiological role of TRPM3 suggests it could be a plausible candidate for pruritus. Further functional studies and the identification of additional families with similar variant types are required to determine whether the reported variant or gene is associated with pruritus.

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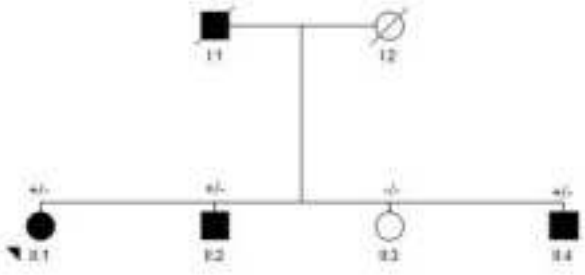
Figure Legend

Figure 1. Pedigree and segregation data for a family with facial pruritus and a variant in *TRPM3*. (a) Pedigree of the family; clinically affected individuals are shaded and the index patient is indicated by the arrow. *TRPM3* variant genotype is indicated as +/- for heterozygous status and -/- for non-carrier. (b) The index patient's (II-1) aligned sequence reads showing the heterozygous *TRPM3* canonical splice site variant (NM_001007471.4:c.3187+1G>A) in integrative genomics viewer.



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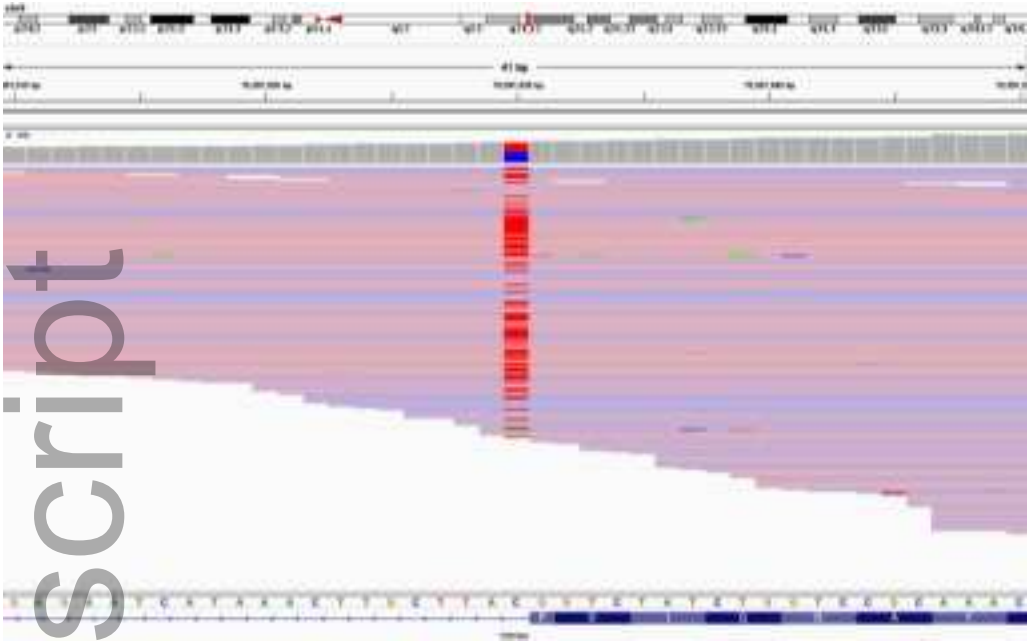

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