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Identification of Distinct Mutations in *AAGAB* in Families with Type 1 Punctate Palmoplantar Keratoderma

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TO THE EDITOR

Our understanding of skin biology has been greatly enhanced by studying genodermatoses, as this has guided the discovery of key genes responsible for skin function (Chamcheu *et al.*, 2011). Palmoplantar keratodermas (PPKs) are a group of rare, heterogeneous hereditary diseases characterized by epidermal hyperkeratosis of palmoplantar skin. They are typically classified according to their mode of inheritance or morphologic features of the disease. However, the clinical picture is often complicated by significant interfamilial and intra-familiar variation in lesional appearance (Kelsell and Stevens, 1999).

Within this study, we focused on punctate palmoplantar keratoderma type 1 (PPKP1), also known as punctate PPK, or Buschke-Fischer-Brauer (OMIM 148600). Inheritance of punctate PPK is commonly autosomal dominant, however, sometimes it presents as an

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acquired disease (Emmert *et al.*, 2003). Onset of punctate PPK is usually observed between 10 and 45 years of age, with the number and severity of lesions increasing with advancing age. Lesions present as multiple small yellow hyperkeratotic papules with central indentation and are irregularly distributed. Typically, there is an increased confluence of lesions over areas of high pressure, such as on the soles of the feet, while the punctate morphology is more evident on the palms (Figure 1a). There is an absence of inflammatory changes, and only rare nail findings in punctate PPK. Notably, punctate PPK has been reported to be associated with an increased incidence of squamous cell carcinomas, as well as early- and late-onset malignancies, such as Hodgkin's disease, renal, breast, pancreatic and colonic adenocarcinomas (Bennion and Patterson, 1984; Kelsell and Stevens, 1999).

Ten years ago, mutations in more than 15 genes had been identified in different forms of PPK; however, the pathogenic mutations underlying punctate PPK were unknown. We previously reported three large pedigrees from both Israel and Mexico, who presented with punctate PPK, and mapped the affected *locus* to Chromosome 15q22-24 using linkage analysis (Martinez-Mir *et al.*, 2003).

Recently, two groups simultaneously identified several loss of function mutations in a single gene, *AAGAB*, in multiple families of different ancestries with punctate PPK (Giehl *et al.*, 2012; Pohler *et al.*, 2012). *AAGAB* encodes the alpha and gamma adaptin binding protein p34, and is located on chromosome 15q.22, within our previously identified linkage region (Martinez-Mir *et al.*, 2003). Since this finding, four subsequent studies have described mutations in *AAGAB* that underlie punctate PPK in several new families (Cui *et al.*, 2013; Kiritsi *et al.*, 2013; Li *et al.*, 2013; Pohler *et al.*, 2013), revealing nine new and two recurrent mutations. In light of these recent findings, we sequenced the whole *AAGAB* gene in our cohort of 11 families presenting with punctate PPK lesions (Supplementary Figures 1–11). The pedigrees of PPK01-PPK03 were previously documented, when we performed linkage on all three families (Martinez-Mir *et al.*, 2003). We sequenced PPK01 and PPK02, who are of Israeli and Arab-Israeli origin, for mutations in *AAGAB.* In addition to PPK01 and PPK02, we sequenced *AAGAB* in an additional 9 new families who presented with punctate PPK, which were designated PPK04-PPK12. Of these, two were from Israel, one was from Canada and six were from Slovenia. In Slovenia, the incidence of punctate PPK is 3.3/100,000 inhabitants, making it of extremely high prevalence in this population (Miljkovic and Kansky, 2009), especially compared with the two-fold lower incidence of 1.17/100,000 in the neighboring Croatian population (Stanimirovic *et al.*, 1993).

Genomic DNA was obtained from blood samples collected following informed consent in accordance with IRB regulations at Columbia University and the Declaration of Helsinki Principles. We used Sanger Sequencing to sequence the *AAGAB* gene in patients from each of our families, using primers previously described for this gene (Pohler *et al.*, 2012). Pedigrees, sequencing results, and photographs of each family can be found in the Supplemental results. We found 7 distinct pathogenic mutations within the 11 families, of which 5 are previously unreported to our knowledge (Figure 1b). These were all heterozygous, consistent with an autosomal dominant pattern of inheritance. Mutations segregated with the disease phenotype in all but one individual where a heterozygous mutation was observed, but the patient had no visible PPK lesions (Supplemental Figure 4).

Of our seven identified mutations (Table 1), we found one, c.481C>T: p.R161X, in four of our families (three from Slovenia, one from Israel). This mutation was previously described as a founder mutation in families of Croatian origin (Giehl *et al.*, 2012), and was found within Scottish and Chinese families (Cui *et al.*, 2013; Kiritsi *et al.*, 2013; Pohler *et al.*, 2012). Moreover, the mutation in our Canadian family, c.472delG; p.G158Efs*1, was previously found in 5 families of Scottish origin (Pohler *et al.*, 2012). The other 5 mutations identified in this study have not been reported elsewhere to our knowledge. Of these, one c.566C>G, p.S189X, was found in two families of Slovenian origin, while the remaining 4 mutations, which were all predicted to cause frameshifts in the protein, were each unique to a single family. Substantial phenotypic variability was noted between patients who carried the same mutation, ranging from very mild, to extensively hyperkeratotic presentations of the disease. While this indicates that environmental factors and personal skin care regimens may affect the degree of hyperkeratosis, it is common for dominantly inherited diseases to have such variable expressivity and may simply reflect stochastic physiological processes.

AAGAB consists of 10 exons with a coding sequence of 945 nucleotides, and codes for the α- and γ- adaptin-binding protein p34 (Pohler *et al.*, 2012). p34 plays a role in membrane trafficking, and as a result of *AAGAB* mutations, deficiencies in p34 lead to impaired endocytic recycling of EGFR proteins, which leads to cellular hyperproliferation (Pohler *et al.*, 2012). This cellular hyperproliferation is postulated to be at least one cause of the hyperkeratotic lesions observed in punctate PPK.

In summary, we have identified five mutations previously unreported to our knowledge and two recurrent mutations of the *AAGAB* gene which underlie punctate PPK. There are now a total of twenty-two mutations in *AAGAB* that have been identified in patients with punctate PPK. Although PPK is a rare disorder, diseases characterized by hyperkeratosis and hyperproliferation are common, and identification of the underlying cellular mechanisms in this keratoderma may contribute to our future ability to understand and treat the more prevalent hyperkeratotic diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations used

PPK/PPKP1	palmoplantar keratoderma/palmoplantar keratoderma, punctate, type 1

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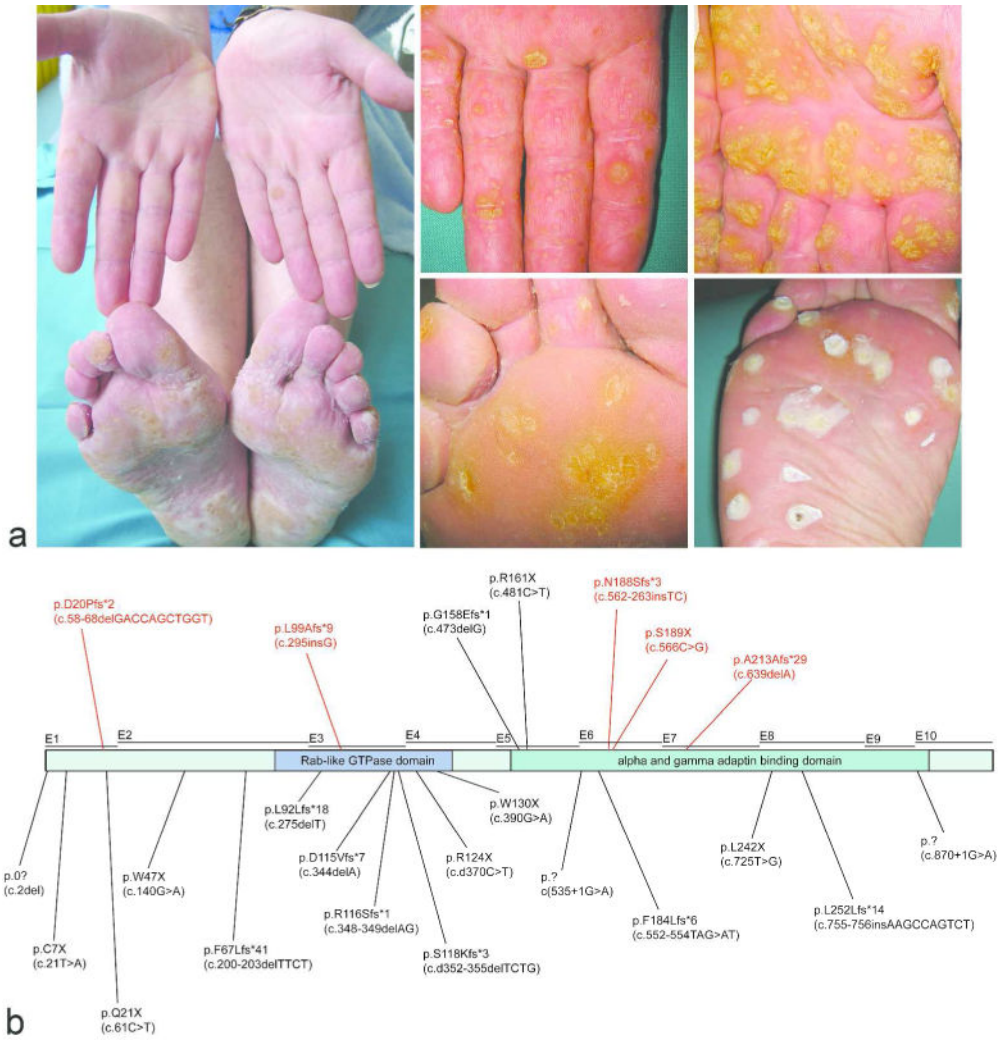

Figure 1. Mutations in *AAGAB* underlie punctate PPK

(a) Representative photographs of patients with punctate PPK. Note the disproportionate involvement of the soles over the palms, and the high degree of phenotypic variability between patients. (b) Summary and location of *AAGAB* mutations identified within this and previous studies. Mutations on the top half of the diagram are those identified within this study (red indicates novel mutations, while black indicates mutations that have been previously described). On the bottom half of the diagram are mutations that have been identified in previous studies. Within the *AAGAB* protein, the locations of the GTPase and adaptin binding domains are indicated, as are the locations of the 10 exons.

Table 1

Summary of mutations in *AAGAB* gene found in 11 families with punctate PPK

DNA mutation	Consequence to Protein	Families	Ancestry
c.481C>T[1]	p.R161X	PPK04 PPK07 PPK08 PPK09	Slovenian and Arab-Israeli
c.566C>G	p.S189X	PPK05 PPK06	Slovenian
c.58-68delGACCAGCTGGT	p.D20Pfs*2	PPK02	Israeli
c.472delG[2]	p.G158Efs*1	PPK11	Canadian
c.562-563insTC	p.N188Sfs*3	PPK01	Israeli
c.295insG	p.L99Afs*9	PPK12	Israeli
c.639delA	pA213Afs*29	PPK10	Slovenian

[1] Mutation previously reported by Pohler *et al.* 2012, Giehl *et al.* 2012, Cui *et al.* 2013, and Kiritsi *et al.* 2013.

[2] Mutation previously reported by Pohler *et al.* 2012 and Pohler *et al.* 2013.