
TO THE EDITOR

We read with great interest the recent paper by Jiang et al. (2011). The authors performed a meta-analysis of 15 case–control studies involving 6,362 subjects to examine the association between the TP53 Arg72Pro polymorphism and skin cancer risk. The meta-analysis suggests that the TP53 Arg72Pro polymorphism may have little involvement in skin cancer susceptibility. Nevertheless, I have several concerns.

First, they concluded that the TP53 Arg72Pro polymorphism may have little involvement in the pathogenesis of skin cancer, regardless of type, including melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). But their results are insufficient to support the conclusion. In the meta-analysis, only 3 (348 cases and 730 controls) of the 15 studies were conducted in non-Caucasians. In addition, although they did not observe the association between the TP53 Arg72Pro polymorphism and risk of melanoma, SCC, and BCC in the subgroup analysis according to subtypes of skin cancer, the results may be unreliable owing to the limited sample size (melanoma: 1,282 cases and 2,149 controls; SCC: 670 cases and 1,635 controls; BCC: 804 cases and 1,891 controls). Therefore, the results of the meta-analysis indicate that the TP53 Arg72Pro polymorphism may have little involvement in the pathogenesis of skin cancer, mainly in Caucasians. Further studies based on larger sample size and stratified by subtypes of skin cancer are still needed, especially in non-Caucasians.

Second, there are some problems with the methods. A meta-analysis should encompass as much information as possible. However, the authors searched only for articles in the Medline database using the PubMed engine, and results were limited to papers published in the English language. Hence, it is possible that some studies that meet the inclusion criteria were not included in the meta-analysis. Database bias, language bias, and publication bias may have distorted the results of the meta-analysis. In addition, although the genotype contrasts (Arg/Arg versus Pro/Pro, Arg/Pro versus Pro/Pro, Arg/Arg + Arg/Pro versus Pro/Pro, Arg/Arg versus Arg/Pro + Pro/Pro) were reported in the article, the allele (Arg allele versus Pro allele) contrast was not reported. It is necessary to perform the allele contrast. Finally, they should follow PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines when reporting their meta-methods research (Liberati et al., 2009).

Third, the article has other shortcomings. The quality of the studies in the meta-analysis was assessed using the predefined scale for quality assessment (Table 5 in the article). But their quality scale omitted the important factor of whether cases and controls were matched by age and gender. Lack of matching by age and gender could result in bias in case–control studies. Also, to determine the sources of the heterogeneity across studies, the authors performed the stratified analysis by subtypes of skin.
Angioid Streaks in Pseudoxanthoma Elasticum: Role of the p.R1268Q Mutation in the ABCC6 Gene

Q Li et al.
Angioid Streaks in PXE

TO THE EDITOR
Pseudoxanthoma elasticum (PXE) is an autosomal recessive disorder characterized by ectopic mineralization of soft connective tissues (Li et al., 2009a; Uitto et al., 2010). The clinical manifestations derive primarily from the involvement of three organ systems, the skin, the eyes, and the cardiovascular system. There is considerable phenotypic, both intra- and inter-familial, heterogeneity with respect to the age of onset and the severity of the disease. Furthermore, in some families the involvement of one of the organ systems predominates, so that in some families the primary manifestations are in the skin with little eye or cardiovascular involvement, whereas in others, the ocular problems are the major cause of morbidity. The eye manifestations characteristically consist of angioid streaks that are due to mineralization of an elastin-rich Bruch’s membrane behind the pigmented retina (Booij et al., 2010). Mineralization of this membrane causes ruptures of blood vessels with subsequent neovascularization, associated with bleeding to the eye, and leading to progressive loss of visual acuity and, occasionally, blindness.

Classic PXE is caused by mutations in the ABCC6 gene, which encodes a putative transmembrane transporter protein, ABCC6, expressed primarily in the baso-lateral surface of hepatocytes (Piendlner et al., 2007). ABCC6 has been shown in in vitro experiments using inside-out insect cell vesicles to function as an efflux pump, which transports anionic small molecular weight conjugates (Ilías et al., 2002). However, the physiological ligands in vivo and the precise role of ABCC6 in the pathomechanistic pathways leading to peripheral connective tissue mineralization are currently unknown.

Well over 300 distinct mutations have been identified in the ABCC6 gene, consisting of premature termination codon (PTC)-causing mutations as a result of nonsense mutations or out-of-frame small insertions or deletions (Piendlner et al., 2007). In addition, large genomic deletions resulting in loss of several exons or the entire gene, and occasionally including flanking genes as well, have been identified (Chassaing et al., 2007). Finally, a number of missense mutations, particularly those affecting the nucleotide binding folds (NBF1 and NBF2), two protein domains critical for the function of ABCC6 as a transmembrane transporter protein, have been identified. Careful examination of the mutation database in the context of phenotypic variability in PXE has not revealed any clear-cut genotype-phenotype correlations (Piendlner et al., 2007). However, specific mutations in ABCC6 have been

Abbreviations: PXE, pseudoxanthoma elasticum; PTC, premature termination codon

REFERENCES


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CONFLICT OF INTEREST
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Overall, the meta-analysis suggests that the TP53 Arg72Pro polymorphism may have little involvement in the pathogenesis of skin cancer, mainly in Caucasians. Additional studies in larger sample sizes and stratified by subtype of skin cancer are still needed, especially in non-Caucasians. Meanwhile, we believe that our remarks will contribute to more accurate elaboration and substantiation of the results presented by Jiang et al. (2010).

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