Reviewer's report

Title: Identification of novel mutation in cathepsin C gene causing Papillon-Lefevre Syndrome in Mexican patients.

Version: 2 Date: 21 September 2012

Reviewer: Muhammad Naeem

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Major Concern:
Report of 458T>G polymorphism as a causative mutation in this study may raise the following concerns:

1. Hart et al 2000 (Ref 48 in this manuscript) reported 458T>G variation initially as a causal mutation in compound heterozygous state along with 199-222del. There has been no functional study reported so far to demonstrate the functional effect of this mutation (458T>G variation) on the protein. Rather, later reports (Allende et al 2006 in Human Mutation and Lefèvre et al 2001 in Journal of Investigative Dermatology) documented this variation as a polymorphism due its identification in control population in high frequency.

2. The authors of the current study under review have illustrated that: 458T>G mutation was identified in normal controls; the affected amino acid Thr153 was a non-conserved residue; PolyPhen-2 software predicted a benign mutation.

3. The authors have tried to correlate 458T>G mutation with percentage of cathepsin C activity (homo and compound heterozygous patients < heterozygote carriers < normal). However, I was unable to conclude this correlation: the individuals 6F & 6S (T/G heterozygotes) have enzyme activity (14-16% of normal) that is comparable (~11-14% of normal) with those of compound heterozygotes 2P & 4P (T/G + C/T).

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests