Author’s response to reviews

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

Authors:

José G. Romero-Quintana (geovannirom@yahoo.com.mx)
Luis O. Frias-Castro (lofc57@gmail.com)
Eliakym Arámbula-Meraz (eliakymarambula@hotmail.com)
Maribel Aguilar-Medina (maribela2@excite.com)
Jesús Dueñas-Arias (jedanet@yahoo.com)
Jesús D. Melchor-Soto (jedanet@yahoo.com)
José G. Romero-Navarro (gromero@uas.uasnet.mx)
Rosalio Ramos-Payan (ramospayan@yahoo.com.mx)

Version: 3 Date: 31 October 2012

Author’s response to reviews: see over
BMC Medical Genetics
Editorial Board

Dear Editor,
We received your letter, and carefully modified the manuscript to address the reviewers’ comments. Below you will find the point-by-point answers to the referees.

The complete description of PLS patients are now more focused (clinical, c.203T>G mutation and c.458C>T polymorphism, enzymatic activity and gene expression level of CTSC). This results, together with the association of HLA-DRB1*11 with the disease, improved the clarity and relevance of the manuscript.

After this revision, we hope you will find the paper suitable for publication in your journal.

Bests regards,

Rosalío Ramos-Payán, PhD
Laboratory of Immunology, Faculty of Biological and Chemical Sciences, Autonomous University of Sinaloa. Email: ramospayan@yahoo.com.mx

ANSWERS TO REFEREES
We thank again the reviewers for their constructive comments. All corrections are now included in the manuscript.

Thank you very much.

REFEREE 1:
Minor essential revisions
-In “discussion” section detail about the polyphen-2/score and residue conservation etc should be in “results” section as a separate sub-section. This would shorten discussion and more meaningful.
Protein homology analysis and prediction of functional effects of mutations were included in Material and methods and Results sections, and only mentioned in discussion.

-Still I feel that reference section is not uniformly set e.g few journal titles are written in full.
References were checked and corrected.

Needs some language corrections before being published
Manuscript was revised and corrected.
REFEREE 2:
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.

Points 1 and 2 were modified in Discussion section to improve clarity and relevance.

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).

Thanks for the observation; we did not perform a correlation analysis (Pearson's r) between c.203T>G heterozygotes and compound heterozygotes (for c.203T>G and c.458C>T), this paragraph was modified.

Enzymatic activity comparison between c.458C>T heterozygotes and compound heterozygotes (c.203T>G and c.458C>T) are now more clear.