Reviewer's report

Title: Genetic determinants of amidating enzyme activity and its relationship with metal cofactors in human serum

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Reviewer: Ganesh Kumar

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Comments to the authors:

In this study, Gaier et al have performed detailed investigations toward understanding the relationship between amidating enzyme activity and metal cofactor levels in human serum with the goal to establish a genetic underpin for variations in enzyme activity seen among elderly men. Previous elegant studies by the senior author and her group firmly established a pivotal role for PAM in C-terminal amidation of a significant number of bioactive peptides. Given the solo role of PAM in controlling various bioactive peptide-mediated physiological processes, this work represents a major step forward in understanding the functional and clinical significance of PAM related partial activities (PHM and PAL) in human serum. Experimental design involving analyses of serum from 144 elderly men for PHM and PAL activities along with analyses of metal levels (Cu and Zn) and non-coding SNPs seems to be appropriate for the goal of this study. Standard statistical approaches were applied for data analysis. Based on the correlative analysis of SNPs, the authors were able to identify alleles that may confer lower PHM or PAL activities. Overall, the results from this study seem to establish genetic basis of for variations in serum PAM activity seen in aged men. These findings are significant and will propel the field to discover functionality specific biomarkers. The following minor concerns are raised for the authors to consider.

1. The rationale for the gender bias (only aged men with exclusion of women) of this study should be included.
2. A brief explanation for the disparity in correlation between PAL activity and Cu levels would be informative.
3. Are the results applicable to young men?
4. Is the size of the population adequate?