

PYRIN PROTEIN: THE STRUCTURAL EFFECT OF E148Q MUTATION

To the Editor:

In their interesting paper on structural effect(s) of E148Q mutation of pyrin protein, the protein involved in familial Mediterranean fever, Naimushin et al. [1] report a slight energy gain by the pyrin-mutated molecule, thus pointing to a biological role of E148Q in the range of mild mutations. This, according to the authors, seems to support the concept of a disease-causing role for this mutation, and not that of a benign polymorphism.

Such “computational chemistry” data on “mutation nosology” must be interpreted with caution. The controversy regarding the influence of E148Q on phenotype remains unresolved; most groups do not seem to agree on its clinical role, even in their own cases which are clinically stratified according to the same criteria and tested with the same tools. In interpreting such reports, the gene geography data seem to be of importance as well [2].

A few other comments on their paper [1]: First, when considering true E148Q homozygotes one has to overcome the danger of falsely interpreting E148V/E148Q compound heterozygosity as E148Q homozygosity. This can happen with the modern strip assays used today [3]. Mutation E148V may be rare but we are not aware of any clinical comparison between E148Q homozygotes and E148V/E148Q compound heterozygotes. Theoretically, the latter group is not expected to suffer clinically. Second, in structural studies we have to seriously consider the role of medium conditions that may affect both the structure and function of biological molecules in intracellular and intranuclear environments. Although the biomolecules (mutated and unmutated) are all subjected to the same environmental conditions, the interphase (trace elements, pH, temperature,

etc.) effects may not uniformly affect all isoforms. The different solubility of hemoglobin A and hemoglobin S despite their similar behavior in their oxygenated forms is an example of that. As the authors seem to imply, there is a need for models in which the surrounding medium is taken into account. Third, the energy gain of E148Q mutation is shown to be less than of R202Q mutation; interestingly, mutations E148Q (disease-causing) and R202Q (non-disease causing polymorphism) seem equal in terms of energy gain of the full-length protein [1]. These last two observations together suggest that energy effects of the mutation are not the only determinants of pathology.

Molecular modeling is an established tool in the research of biological interactions between several molecules; it is useful in studying drug-molecule interactions and the role of structural alterations of several molecules in cell function and metabolism. Clearly, further structural studies are needed to further explicate the clinical or subclinical role of each of the 180 pyrin mutations reported to date.

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References

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To the Editor:

The first comment by Drs. Konstantopoulos and Kalotychnou, with which we agree, is a word of caution regarding

the possibility of a methodological mistake that might occur while looking for the presence of E148Q pyrin mutation. This point, however, is associated with the general issue of the role of the E148Q pyrin change in familial Mediterranean fever, and not directly related to the results or discussion of our work. His second point is simply a repetition of our own notion in the limitation paragraph of our paper [1], where we indicate that the fluid phase and the neighborhood molecules are not accounted for by the quantum chemistry model we used to evaluate E148Q effect on the structure of the pyrin molecule. Dr. Konstantopoulos's last remark is also referred to in the paper. Originally, the only reason we added data to the deviation indices of the R202Q and M694Q mutations was to put into perspective our finding on E148Q, comparing it to clinically silent SNP on the one hand and to a severe mutation on the other. Finally, a reservation on our side regarding the role of R202Q mutation, which was not mentioned in our paper (to avoid confusion), is that some researchers do consider the R202Q change to be of mild clinical effect [2]. This view is consistent with our finding of a mild structural effect of the R202Q mutation on the pyrin molecule [1].

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“Simplicity is the ultimate sophistication”

Leonardo da Vinci (1452-1519), Italian painter, engineer, musician, and scientist