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In Silico Analysis: A New Demand for Molecular Genetic Interpretation

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Dear Editor,

Based on the paper entitled "Novel LDB3 mutation in a patient with autosomal dominant myofibrillar myopathy" that expressed a novel mutation detection method by direct sequencing of DNA in a patient with symptoms of slowly progressive walking difficulties; a single homozygote alternation for *ldb3* was detected. The *ldb3* gene translation results in PDZ domain-containing proteins. Modular protein-protein interaction domains, consist of 80 to 120 amino acids, residues build PDZ motifs. Proteins with PDZ domain interact with cytoskeletal assembly and also other proteins involved in targeting and clustering of the membrane proteins. The ldb3 protein interacts with alpha-actinin-2 through N-terminal PDZ domain and with protein kinase C via C-terminal LIM domains. LIM also interacts with all 3 members of the myozenin family. Mutations detected in this gene are identified to associate with dilated cardiomyopathy and myofibrillar myopathy. Different transcript variants that encode different isoforms; N-terminal PDZ domains are observed in all identified isoforms; while, only longer isoforms such as 1, 2, and 5 include C-terminal LIM domains (1). In silico analysis for new mutation performed in the abovementioned paper, only by Polyphen 2 and sift, clearly indicated protein structure/function and evolutionary conservation. Although in silico assessment helps to interpret the alternation effect, it is not enough. Protein aggregation, amyloid propensity, and chaperone binding tendency are other factors that affect protein function asses (2-4). Without complete assessment of protein alternation, it is not possible to decide about the effect of alternation in the protein structure. Otherwise, domains and motifs are important functional parts of proteins. Any mutation occurs in certain parts of protein can change functional regions, and accordingly provides the conditions to predict the effect of new mutation in protein level. Four distinguish domains are detected for ldb3 according to uniprot.org; each domain is responsible for a unique role and interaction. Majority of the amino acid changes, which cause that pathogenicity, are referred to 400 terminal amino acids both in practice and in silico prediction. Domain study has also a key role for network analysis. Proteins interact through compact networks and the main role for interactions is played by domains. On the other hand, De novo and allelic, functional, segregation and population data analyses are required for certain decisions about the final effect of a variation (2). In silico analysis is only a part of massive investigation to decide about the pathogenicity of a variation, and false negative outcome of in silico assessment is a ddisadvantage of this tool. For clinical interpretation of novel mutations, direct cooperation of bio-statistical experts, computational biology experts, molecular medicine experts, and clinicians is needed.

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