

ATENA: A decision support system for classifying genetic variants and clinical diagnosis.

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Recent advances in computing and the reductions of costs for next generations sequencing procedures resulted in the generation of a massive amount of data consisting of variants that need to be annotated and interpreted by a specialist. Given the importance of these kind of tests in diagnosing genetic diseases, the American College of Medical Genetics and Genomics (ACMG) published a guideline for interpreting and classifying these variants in order to reduce the variability in the classification and mistakes that could possibly occur. Since the rules in the guideline are complex, they might still lead to inconsistent results when they are assessed manually. In the interest of automating this task, we developed a new tool, ATENA, which evaluates multiple parameters and integrates data from scientific literature in order to satisfy these rules and classify and prioritize variants according to its findings. In order to accomplish this automation, the file originated from the ANNOVAR annotation software is used as an input. The resulting variant is classified as one of 5 possible options: Benign, Likely Benign, Pathogenic, Likely Pathogenic and of Uncertain Significance. When performing the analysis, the specialist can change any of the automatic answers to the evaluated rules in accordance to his personal interpretation, which might lead to a reclassification of the variant automatically performed by the Atena. To evaluate our software, we selected BRCA1 and BRCA2 variants previously classified in the ClinVar database and that had no classification conflicts. Altogether, 325 pathogenic variants and 190 benign ones were chosen. Out of the pathogenic group, 89,5% of the variant were correctly classified while 43,1% of the benign variants fell into the correct class. As a result of the automated classification it was possible to increase productivity and provide grounding for decision making in regards to variant pathogenicity classification.