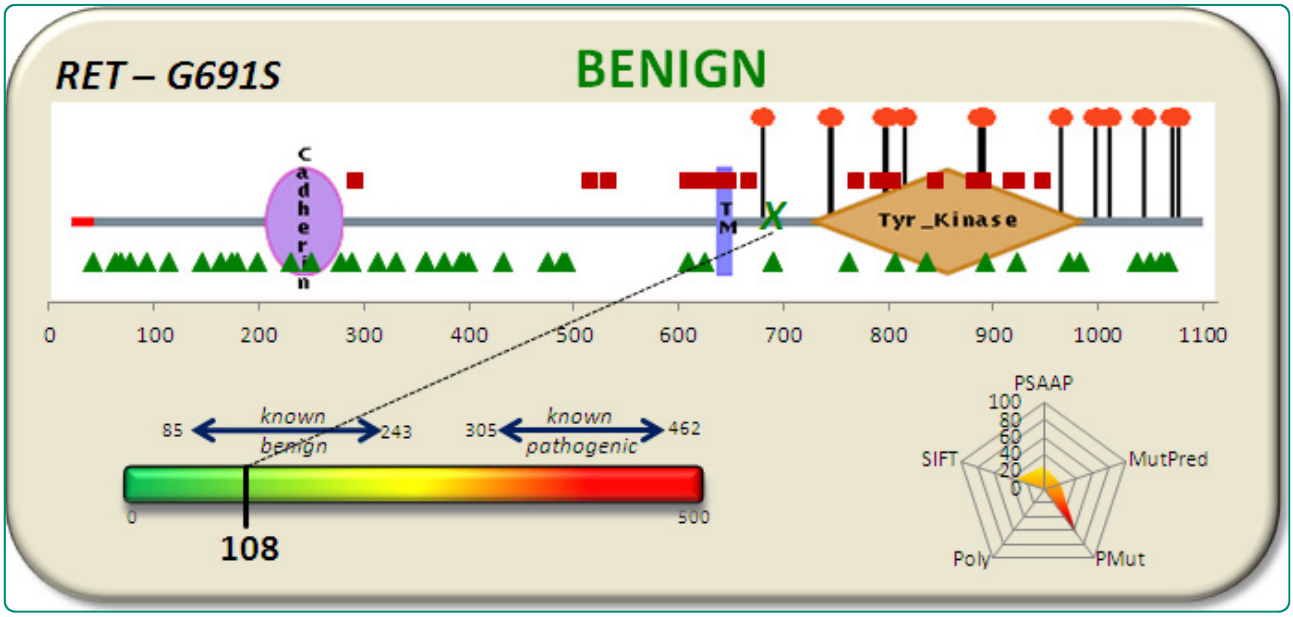
Genome Medicine



Consensus: a framework for evaluation of uncertain gene variants in laboratory test reporting

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Consensus: a framework for evaluation of uncertain gene variants in laboratory test reporting

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Abstract

Accurate interpretation of gene testing is a key component in customizing patient therapy. Where confirming evidence for a gene variant is lacking, computational prediction may be employed. A standardized framework, however, does not yet exist for quantitative evaluation of disease association for uncertain or novel gene variants in an objective manner. Here, complementary predictors for missense gene variants were incorporated into a weighted Consensus framework that includes calculated reference intervals from known disease outcomes. Data visualization for clinical reporting is also discussed.

Background

For appropriate and effective patient treatment, relevant clinical information should be available to the clinician on demand. Accurate interpretation of gene test results, including phenotype association of gene variants, is an important component in customizing patient therapy. Recent endeavors such as the NCBI Genetic Testing Registry, MutaDATABASE, 1000 Genomes and the Human Variome Project draw attention to this growing interest in gene variant annotation and clinical interpretation in human disease [1-4]. Ongoing efforts to catalog human genome variation for many years have led to authoritative repositories of gene variants, with clear association to disease phenotype finally beginning to emerge [5-8].

Rapidly evolving technologies such as SNP chip genome-wide association studies and next-generation sequencing have lowered the cost and increased the speed of genomic analysis, yielding much larger data sets [9]. Currently, gene variants are being discovered at an unprecedented pace. One recent report found an average of 3 million variants per personal genome [10]. Unfortunately, an ever-widening gap exists between this fast growing collection of genetic variation and practical clinical interpretation due to a lack of understanding of the phenotypic consequences (if any) of any given variant. Although the number of genetic testing laboratories has remained around 600 over the past several years, recent data show that clinical testing is currently available for well over 2,200 different genes or genetic conditions [11]. As medical records increasingly incorporate genetic test information, improved decision support approaches are needed to provide clinicians with the preferred course of treatment [12,13]. Furthermore, for decision support rules to be of value, the clinical relevance of laboratory information must be well understood [14,15].

Updated recommendations have been proposed from the American College of Medical Geneticists (ACMG) on reporting and classification of sequence variants, including approaches to help determine the clinical significance of variants of uncertain significance [16]. These guidelines delineate six interpretative categories of gene sequence variation, with defined classifications outlined and the hope of a unified standard terminology in gene test reporting. For improving interpretation of unclassified genetic variants, definitions and terminology have also been recommended by the International Agency for Research on Cancer (IARC), part of the World Health Organization [17].

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