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An integrated framework for detection of copy number variation and insertion/deletions using targeted next generation sequencing data

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Simultaneous detection of small copy number variation (CNVs) (<0.5 kb), insertion/deletions (indels) and single nucleotide variants (SNVs) using targeted next generation sequencing (NGS) data is limited by the lack of robust bioinformatics tools for CNV and indel detection. We describe the development and implementation of two bioinformatics algorithms, Copy Number Variation-Random Forest (CNV-RF) to detect CNVs and ScanIndel to detect indels, using targeted NGS data. Using CNV-RF, we identified 12 of 13 deletions and two cases with duplications in samples with known CNVs. Furthermore, no CNVs were identified among 60 genes in 14 cases with normal copy number. All positive deletions and duplications were confirmed using a qPCR method. CNV-RF was also able to detect heterozygous deletions and duplications with a specificity of 50% across 4,813 genes suggesting that CNV-RF may also be suitable for analysis of CNVs in whole exome analysis. We demonstrated ScanIndel's superior sensitivity and specificity relative to several state-of-the-art indel callers across various coverage levels and indel sizes using simulation data. We also confirmed all indels identified by ScanIndel using Sanger sequencing in clinical samples. Since both CNV-RF and ScanIndel represent orthogonal approaches to identify different but overlapping spectrum of structural gene variation, we utilized these complimentary approaches for highly sensitive detection of structural genetic variation in whole exome sequencing data. The high sensitivity to detect clinically relevant CNVs and indels along with confirmation using a low cost qPCR method provides a framework for providing comprehensive NGS based CNVs/indel detection in a clinical molecular diagnostics laboratory.

Biography

Bharat Thyagarajan has joined the Department of Laboratory Medicine and Pathology at the University of Minnesota in 2007 and is currently an Associate Professor and the Director of the Molecular Diagnostics Laboratory. He has established the Clinical Genomics Core to rapidly develop and implement next generation sequencing (NGS) based clinical tests for a variety of constitutional disorders and malignancies. He also leads the central laboratory for several NIH funded multi-center epidemiological studies on aging, cardiovascular disease and cancer and his work resulted in more than 60 peer- reviewed publications.

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