Abstract for HiTSeq 2016

Title: Individual genome interpretation in newborns with rare disorders

Aashish N. Adhikari[1], Jay P. Patel[2], Alice Y. Chan[3], Divya Punwani[3], Haopeng Wang[3], Antonia Kwan[3], Theresa A. Kadlecek[3], Morton J.Cowan[3], Marianne Mollenauer[3], John Kuriyan[1], Shu Man Fu[4], Yangyun Zou[1], Yaqiong Wang[1], Uma Sunderam[5], Prisni Rath[5], Sadhna Rana[5], Ajithavalli Chellappan[5], Kunal Kundu[5], Dae Lee[6], Flavia Chen[3], Brad Dispensa[3], Mark Kvale[3], Richard Lao[3], Dedeepya Vaka[3], Brandon Zerbe[3], Arend Mulder[7], Frans H J Claas[7], Joseph A Church[8], Arthur Weiss[3], Richard A. Gatti[9], Robert Nussbaum[3], Robert Currier[10], Joseph Sheih[3], Renata Gallagher[3], Sean Mooney[6], Neil Risch[3], Barbara Koenig[3], Pui Kwok[3], Jennifer M. Puck[3], Rajgopal Srinivasan[5] , Steven E. Brenner[1*]

[1]University of California, Berkeley, CA, USA; [2]Children's Hospital of Los Angeles, Los Angeles, CA, USA; [3]University of California, San Francisco, CA, USA; [4]University of Virginia School of Medicine, Charlottesville, VA, USA; [5]Innovation Labs, Tata Consultancy Services Hyderabad, AP, India; [6]University of Washington, Washington, WA; [7]Leiden University Medical Centre, Leiden, The Netherlands; [8]University of Southern California, Los Angeles, CA, USA; [9]University of California Los Angeles, CA, USA; [10]California Department of Public Health, CA, USA;
*Corresponding author email address: brenner@compbio.berkeley.edu

Background

High-throughput sequencing technologies are being increasingly integrated into clinical settings, aiding the detection and diagnosis of disease. However, our ability to reliably interpret genomic data lags behind the ability of the sequencing technologies to generate them. Here, we present an analysis protocol we developed for individual genome interpretation which we applied to exomes from newborns with undiagnosed primary immune disorders. Using multiple callers with multisample calling and an integrated variant annotation, variant filtering, and gene prioritization pipeline, we were able to diagnose several cases of elusive immunodeficiencies.

Results

In two unrelated infant immunodeficient girls with no diagnoses, we discovered compound heterozygous variants in the *ATM* gene for both the infants offering a very early diagnosis of Ataxia Telangiectasia (AT). In addition to avoiding diagnostic odyssey, this allowed for avoidance of undue irradiation and live vaccinations, and for appropriate counseling of the parents regarding their carrier status. In another case, the affected siblings had early onset bullous phempigoid, a chronic autoimmune disorder. Our analysis revealed compound heterozygous mutations in ZAP70, a gene associated with profound primary immunodeficiency, the opposite phenotype. Cellular immunological studies indicated that one variant was hypomorphic and the other was hyperactive. These combined to yield a novel presentation, adding to the existing phenotype repertoire of ZAP70 in humans. We also discovered pathogenic variants in PRKDC occurring after the stop codon encoded in the reference genome; we correctly

identified that the reference genome had a rare pathogenic variant with frameshift leading to a premature stop codon. In a normal reference, the mutations observed in this case led to nonsynonymous changes. Our protocol has been similarly revealing in other SCID and CID cases including Nijmegen Breakage Syndrome, which highlight unique features of the analysis framework that facilitate genetic discovery.

Conclusions

With a diagnostic rate of ~50% in cases involving family trios, these early diagnosis using exome sequencing help provide crucial information to offer prompt appropriate treatment, family genetic counseling, and avoidance of diagnostic odyssey. We have also begun exploring how exome sequencing could potentially augment public health newborn screening of a large number of rare disorders in newborns, currently performed using tandem mass spectrometry (MS/MS) technologies. In collaboration with the California Department of Public Health under an IRB-approved protocol, we aim to evaluate the current ability to predict disease status from exome sequences using de-identified archived dry blood spot samples of all California newborns confirmed to have metabolic disorders for a period of 8.5 years since the introduction of MS/MS screening, as well as samples that were false positives on the MS/MS screening.