absent from dbSNP and 1000 Genomes data, that we propose to be a cause of BVVL. We also describe the clinical and genetic heterogeneity that is present in BVVL.

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Acknowledgments

We are grateful to the families for their essential support and to the Genetic Alliance. This work was supported in part by the Intramural Research Programs of the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, the National Institute of Environmental Health Sciences, the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; project number Z01 AG000958-07. We would also like to thank the The Medical Research Council (MRC) (fellowship to HH, G0802760).

Web Resources

The URLs for data presented herein are as follows:

1000 Genomes, http://www.1000genomes.org/page.php
Burrows-Wheeler Aligner (BWA), http://bio-bwa.sourceforge.net/
dbSNP, http://www.ncbi.nlm.nih.gov/projects/SNP/
Genetic Alliance, http://www.geneticalliance.org
Genome Analysis Toolkit, https://www.broadinstitute.org/gsa/wiki/index.php/The_Genome_Analysis_Toolkit
Integrative Genomics Viewer (IGV), http://www.broadinstitute.org/igv/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/
Picard, http://picard.sourceforge.net/index.shtml
SAMTools, http://samtools.sourceforge.net/

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DOI 10.1016/j.ajhg.2010.05.021.

Response to Johnson et al.

To the Editor: Johnson et al. report that a second mutation in *C20orf54* (MIM *613350) is seen in their BVVLS family "2008," which appears to be the same individual as our "case 4,"[1] implying that this patient is a compound heterozygote (p.E71K and p.Y213X) rather than homozygous for Y213X. Upon reexamination of the sequence traces, even with the benefit of hindsight, we still see a homozygous change at Y213X, although we do see a heterozygous change at E71K. We concur that this patient is most likely a compound heterozygote on the basis of the results of Johnson et al. This clearly demonstrates the advantage of testing additional family members, including parents whom we did not have access to at the time of paper submission.

We can confirm that we have also identified the homozygous mutation p.P28T in a sample provided to us by H. Houlden, which appears to be the second BVVLS patient reported by Johnson et al. (sample 48111). This result was not published in our report.[1]

We read with interest the exome-sequencing data the authors provide in their Letter. Before we submitted our paper, Dr. Singleton, upon learning that we had identified mutations in our BVVLS patients, provided us with a short list of 364 variants in 223 candidate genes from his study. Neither *c20orf54*, nor the other four genes mentioned in their letter appeared in this short list. The approach of whole-exome sequencing for determining causative mutations in rare monogenic disorders is one of the many exciting developments of next-generation sequencing.[2] It is currently still a very expensive, sledgehammer approach, which will undoubtedly become more cost effective in the near future. Some of the pitfalls demonstrated by Johnson et al. may also be ameliorated by technical improvements. Notably, sequencing several patients, filtering by dbSNP, and shortlisting mutations that occur in all patients may yield confusing results if, as in the

Johnson et al. study, one of the patients does not have a point mutation in the candidate gene.

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Web Resources

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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