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Patient Name:	Jack Nguyen	Sample Collected Date:	11/20/2015
Patient ID:	V100029	Sample Received Date:	12/02/2015
Age:	40	Report Date:	1/12/2016
DOB:	5/21/1976	Sample Type:	DNA
Sex:	Male	Indication for Testing:	Family history of diabetes
Patient Sample ID:	A4F0G7H5J3	Physician Info:	Dr. Yun Choi
Accession #:	0987654321B		



eMERGE III CAREseq Version 2 Sequencing Report

This test interrogates the protein-coding and exon-splicing regions of 109 genes as well as 1551 single-nucleotide polymorphisms that may impact human health and disease.

Pathogenic Variants

- HETEROZYGOUS COPY NUMBER LOSS IN THE HNF1B GENE DETECTED:** A heterozygous copy number loss was identified in HNF1B was detected in this individual. Deletion of this region causes chromosome 17q12 deletion syndrome [MIM: 614527], which is associated with developmental kidney abnormalities, pancreatic atrophy, young-onset diabetes, and liver abnormalities (PMID 19844256). Mildly abnormal liver enzymes have been found among patients with 17q12 deletion. Clinical correlation is recommended. See Table 1. This result was obtained from coverage analysis of a capture-sequencing test which has limit quality control for CNVs. If clinically correlated, a Molecular or Cytogenetic test such as Chromosomal Microarray Analysis (CMA) is recommended to confirm this finding in this individual.

Table 1: Pathogenic Variant Details:

Disease	Inheritance Pattern	Gene	Position (NCBI 37)	Variant	Zygoty	Notes	Minor Allele Frequency
Diabetes mellitus, noninsulin-dependent [MIM:125853]							
Renal cysts and diabetes syndrome [MIM:137920]	AD	HNF1B	chr17:36047376-36104876	Copy Number Loss Exon 1 to 8	Heterozygous	Z-score: -5.4	N/R
17q12 deletion syndrome [MIM: 614527]							

Likely Pathogenic Variants

1. None Detected

Table 2: Likely Pathogenic Variants Details:

None Detected

Comments & Recommendations:

It is recommended that correlation of these findings with the clinical phenotype be performed. Clinical correlation and genetic counseling for the patient and at-risk family members is recommended for the medically actionable pathogenic variant. A Molecular or Cytogenetic test such as Chromosomal Microarray Analysis (CMA) is recommended to confirm this finding in this individual.

Gene Coverage:

All genes have 100% of targeted bases sequenced to redundant coverage of 20x or greater with the following exceptions: CACNA1B (96.94%), APOB (99.39%), COL5A1 (98.03%), RYR1 (98.74%), KCNQ1 (97.7%), TGFB1 (93.56%).

Further information is available in the ExCID report.

Methodology:

1. CAREseq Version 2 NGS Panel*: for the paired-end pre-capture library procedure, genome DNA is fragmented by sonicating genome DNA and ligating to the Illumina multiplexing PE adapters (reference 1). The adapter-ligated DNA is then PCR amplified using primers with sequencing barcodes (indexes). For target enrichment capture procedure, the pre-capture library is enriched by hybridizing to biotin labeled in-solution probes (reference 2) at 56°C for 16 - 19 hours. For massively parallel sequencing, the post-capture library DNA is subjected to sequence analysis on Illumina HiSeq platform for 100 bp paired-end reads. The following quality control metrics of the sequencing data are generally achieved: >70% of reads aligned to target, >99% target base covered at >20X, >98% target base covered at >40X, average coverage of target bases >200X. SNP concordance to SNPTrace genotype array: >99%. This test may not provide detection of certain genes or portions of certain genes due to local sequence characteristics or the presence of closely related pseudogenes. Gross deletions or duplications, changes from repetitive sequences may not be accurately identified by this methodology.

2. As a quality control measure**, the individual's DNA is also analyzed by a SNP-array (Fluidigm SNPTrace panel (reference 3)). The SNP data are compared with the NGS panel data to ensure correct sample identification and to assess sequencing quality.

3. Data analysis and interpretation by Mercury 3.4 (reference 3): The output data from Illumina HiSeq are converted from bcl file to FastQ file by Illumina bcl2fastq 1.8.3 software, and mapped by the BWA program (reference 4). The variant calls are performed using Atlas-SNP and Atlas-indel developed in-house by BCM HGSC. Variant annotations are performed using the Cassandra tool, developed in-house. Synonymous variants, intronic variants not affecting splicing site, and common benign variants are excluded from interpretation unless they were previously reported as pathogenic variants. The variants were interpreted according to ACMG guidelines (reference 5) and patient phenotypes. Variants related to patient phenotypes are usually confirmed by Sanger sequencing for patients and if available, parents. Sanger confirmation is noted

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in the “Notes” section of the tables if performed. It should be noted that the interpretation of the data is based on our current understanding of genes and variants at the time of reporting.

References:

1. Illumina, Inc. (2011) Multiplexing Sample Preparation Guide (Part # 1005361 Rev. D). 2011.
2. Roche NimbleGen, Inc. (2010) NimbleGen SeqCap EZ Exome Library SR User’s Guide (Version 2.2).
3. Liang-Chu MM, Yu M, Haverty PM, Koeman J, Ziegler J, Lee M, Bourgon R, Neve RM. Human biosample authentication using the high-throughput, cost-effective SNPtrace(TM) system. PLoS One. 2015 Feb 25;10(2):e0116218.
4. Li H. and Durbin R. (2009) Fast and accurate short read alignment with Burrows-Wheeler Transform. Bioinformatics, 25:1754-60. PMID:19451168.
5. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine (2015) 17, 405-423. PMID: 25741868.

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May 4, 2016

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This test was developed and its performance determined by this laboratory. It has not been cleared or approved by U.S. Food and Drug Administration. Since FDA is not required for clinical use of this test, this laboratory has established and validated the test's accuracy and precision, pursuant to the requirement of CLIA '88. This laboratory is licensed and/or accredited under CLIA and CAP (CAP# 8004250 / CLIA# 45D2027450).