University of Colorado Denver

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Department of Pediatrics
DNA Diagnostic Laboratory

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DNA ANALYSIS REPORT

DATE: 12/08/2010 DATE RECEIVED: 11/16/2010

REPORT TO: David Johnson, MD; Colorado Retina Associates

PATIENT	DATE OF BIRTH	SPECIMEN TYPE
Paul Martz	1/7/1963	Blood
DIAGNOSTIC REQUEST	CASE # / ACCESSION #	HOSPITAL# / SPECIMEN #
ADRP panel	ADRP-090 / #10-3134	59229

INDICATION FOR STUDY: Autosomal Dominant Retinitis Pigmentosa

RESULT: likely positive

INTERPRETATION: Paul Martz possesses a novel variation in the *RP1* gene, namely p.D2066N:c.6196G>A. The variation was predicted to be probably damaging by PolyPhen-2 with a score of 0.995 (the highest score for a damaging variation is 1.0). An additional novel variation was also identified in the *PRPF31* gene, namely p.N413N:c.1239C>T. The variation is likely benign. Finally, a reported variation with an allele frequency of 0.129 was also identified in the *RDH12* gene, namely p.R161Q:c.482G>A. The variation was predicted to be probably damaging with a score of 0.941. The variation was identified in three other RP patients with different mutations. Therefore, this variation may be a modifier of the condition. All of the variations identified in the patient are listed in Table 1 (see page 2). The clinical significance of these identified variations was predicted based on our current knowledge. Whether or not some of these identified variations can modify disease presentation is not clear at this time.

(sequence variations are reported according to nomenclature by *den Dunnen and Antonarakis (Hum Genet 109(1):121-124, 2001)*

TECHNIQUES: Direct testing for mutations in the 21 known adRP genes including *ASCC3L1*, *BEST1*, *CA4*, *CRX*, *FSCN2*, *GUCA1B*, *IMPDH1*, *KLHL7*, *NRL*, *NR2E3*, *PRPF3*, *PRPF8*, *PRPF31*, *RDH12*, *RDS*, *RHO*, *ROM1*, *RP1*, *RP9*, *RP31* and *SEMA4A* is performed by PCR amplification and DNA sequencing in two directions of all coding exons and the exon/intron borders. Codon 1 corresponds to the start ATG and nucleotide 1 to the A.

LIMITATIONS: Only the coding regions of the gene and immediately flanking intron sequences were examined. Changes in the promoter region, farther into the introns, or in other non-coding regions of the gene would not be detected. The sensitivity of DNA sequencing is 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Multiple exon deletions, multiple exon insertions, complete deletion of one allele may not be identified using these methods.

If you have any questions concerning the information in this report, please feel free to contact Dr. Pei-Wen Chiang (pei-wen.chiang@ucdenver.edu; 303-724-3805).

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RECOMMENDATION FOR FURTHER TESTING: Please provide us parental samples to confirm the clinical significance of the identified variations.

Elaine B. Spector, Ph.D., FACMG
Director, UCD Diagnostics Laboratory

Pei-Wen Chiang, Ph.D., FACMG
Assistant Director, UCD Diagnostics Laboratory

Please note that while mutation and/or linkage analysis often gives precise information about genotype, there are several sources of error. These include sample misidentification, erroneous paternity identification, and genotyping errors resulting from contamination of PCR reagents or contamination of fetal samples with maternal cells. Rare genetic variants may also interfere with accurate analysis. Families should understand that rare diagnostic errors might occur for these reasons. *This test was developed and its performance characteristics determined by the UCD DNA Diagnostic Laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary* **REFERENCES:** Eur J Hum Genet 2005, 13:302-308.

Table 1. Heterozygous SNPs and mutations identified in the patient. Non-synonymous variations were predicted by PolyPhen (http://genetics.bwh.harvard.edu/pph/) and by SIFT (http://sift.jcvi.org/). Synonymous variations were analyzed by using RESCUE-ESE program (http://genes.mit.edu/burgelab/rescue-ese/). Intronic variations were analyzed by NetGene2 server (http://www.cbs.dtu.dk/services/NetGene2/).

Gene	Variations/mutations	SNP	pathogenicity
ASCC3L 1	IVS40-20A>G	rs3214063	not likely (allele frequency)
BEST1	IVS4+44C>T	rs195162	not likely (allele frequency)
	IVS5insTCCTCCTCC	rs72141234	not rare
	p.T470T:c.1410G>A	rs149698	not likely (allele frequency)
FSCN2	5'UTR-39C>T	rs2075720	not likely (allele frequency)
GUCA1B	p.Y57Y:c.171T>C	rs3749921	not likely (allele frequency)
PRPF31	IVS5-31T>C(homozygous)	rs2303557	not likely (allele frequency)
	IVS10-9T>C(homozygous)	rs655240	not likely (allele frequency)
	p.N413N:c.1239C>T	no SNP data	polymorphism (mutation taster)

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PRPH2	p.Q304E:c.910C>G(homozygous)	rs390659	not likely (allele frequency)
	p.R310K:c.929G>A(homozygous)	rs425876	not likely (allele frequency)
	p.D338G:c.1013A>G(homozygous)	no SNP data	polymorphism
	3'UTR+13C>T(homozygous)	rs361524	not likely (allele frequency)
RDH12	p.R161Q:c.482G>A	rs17852293	modifier? (allele frequency; 0.129)
ROM1	p.R223R:c.669G>C	rs1801144	not likely (allele frequency)
	IVS1-26het_dupT		likely benign
RP1	p.D2066N:c.6196G>A	no SNP data	probably damaging (PolyPhen-2, 0.995)
RP9	IVS3+44T>A	rs11771864	not likely (allele frequency)
	IVS3-9C>T(homozygous)	rs6462460	not likely (allele frequency)
RP31	5'UTR-28G>C	rs15014	not likely (allelle frequency)
PRPF31	IVS9-34G>A	no SNP data	unknown
SEMA4A	p.P572P:c.1716C>T	rs12401573	not likely (allele frequency)