Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/6/2024
Sex:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication

ARUP test code 2011156

Primary Antibody Deficiency Specimen	Whole Blood
Primary Antibody Deficiency Panel Interp	Positive

RESULT
One pathogenic variant was detected in the TNFRSF13B gene. Two variants representing a complex allele of uncertain significance were detected in the KMT2D gene.

PATHOGENIC VARIANT
Gene: TNFRSF13B (NM_012452.3)
Nucleic Acid Change: c.542C>A; Heterozygous
Amino Acid Alteration: p.Ala181Glu
Inheritance: Autosomal dominant/ Autosomal recessive

COMPLEX VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: KMT2D (NM_003482.4)
Nucleic Acid Change: c.[2497C>G; 2587C>T]; Heterozygous
Amino Acid Alteration: p.[Leu833Val; Arg863Trp]
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.542C>A; p.Ala181Glu, was detected in the TNFRSF13B gene by massively parallel sequencing. Pathogenic germline variants in TNFRSF13B are associated with common variable immunodeficiency 2 (CVID2; MIM: 240500) and immunoglobulin A deficiency 2 (MIM: 609529; OMIM (R)). While initially described as an autosomal recessive syndrome, evidence suggests monoallelic variation may impart disease risk (Pulvirenti 2016, Salzer 2009). CVID patients with TNFRSF13B (TACI) variants typically present with hypogammaglobulinemia (Lucena 2015, Romberg 2015). Therefore, this patient is predicted to be at least a carrier of and may be affected with a TNFRSF13B-related disorder; clinical manifestations show a wide range of onset and severity. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

One complex allele of uncertain clinical significance comprised of two amino acid changes detected in cis (on the same chromosome), c.[2497C>G; 2587C>T]; p.[Leu833Val; Arg863Trp] was detected in the KMT2D gene by massively parallel sequencing. Pathogenic variants in KMT2D are associated with autosomal dominant Kabuki syndrome 1 (MIM: 147920) and branchial arch abnormalities, choanal atresia, athelia, hearing loss, and hypothyroidism syndrome (BCAHH; MIM: 620186, OMIM(R)). However, it is uncertain whether this variant is disease-associated or benign.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and

limitations of this test.

Evidence for variant classification:
The TNFRSF13B c.542C>A; p.Ala181Glu variant (rs72553883, ClinVar Variation ID: 5303) is reported in the literature in multiple individuals diagnosed with common variable immunodeficiency (Castigli 2005, Salzer 2005, Martinez-Gallo 2013). This variant is also observed in clinically asymptomatic relatives and is found in the Finnish European population with an overall allele frequency of 2.4% (603/24990 alleles, including 8 homozygotes) in the Genome Aggregation Database (v2.1.1), suggesting it may act as a susceptibility or disease-associated variant, possibly with other genetic and/or environmental factors (Dong 2010). Still, case-control studies demonstrate the p.Ala181Glu variant is significantly enriched in affected individuals (OR >5, p< 0.05) (Pan-Hammarstrom 2007, Dong 2010, Freiberger 2012). Functional characterization of the p.Ala181Glu protein in mice (A144E) and human B-cells indicate disrupted NF-KB signaling and significantly impaired B-cell function (Lee 2009, Fried 2011). Based on available information, the variant is considered to be pathogenic.

The KMT2D complex variant c.[2497C>G; 2587C>T]; p.[Leu833Val; Arg863Trp] to our knowledge, is not reported in the medical literature but the p.Arg863Trp is reported in ClinVar (Variation ID: 2195889). This variant is also absent from the Genome Aggregation Database(v2.1.1), indicating it is not a common polymorphism. Computational analyses predict that this variant is neutral (REVEL: 0.032-0.069). However, given the lack of clinical and functional data, the significance of this variant is uncertain at this time.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Genetic consultation is recommended. At-risk family members should be offered testing for the identified pathogenic TNFRSF13B variant (Familial Targeted Sequencing, ARUP test code 3005867). Surveillance of the literature for new information concerning the uncertain variants is recommended.

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
DCLRE1C(NM_001033855.2) intron 11

REFERENCES
Castigli E et al. TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet. 2005 Aug;37(8):829-34. PMID: 16007086.
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Martinez-Gallo M et al. TACI mutations and impaired B-cell function in subjects with CVID and healthy heterozygotes. J Allergy Clin Immunol. 2013 Feb;131(2):468-76. PMID: 23237420.
OMIM(R) Copyright (C) 1996 - Present year, Johns Hopkins University All rights reserved.
Pan-Hammarstrom Q et al. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet. 2007 Apr;39(4):429-30. PMID: 17392797.
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This result has been reviewed and approved by Hunter Best, Ph.D.

BACKGROUND INFORMATION: Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Primary antibody deficiencies are a group of genetic disorders affecting antibody production. Three categories of primary antibody deficiencies include common variable immunodeficiency disorders (CVID), agammaglobulinemia, and hyper-IgM syndrome.

EPIDEMIOLOGY: Incidence is estimated at 1 in 10,000.

INHERITANCE: X-linked, autosomal dominant, or autosomal recessive; dependent on the causative gene

CLINICAL SENSITIVITY: Approximately 20 percent for CVID; 75-80 percent for hyper-IgM syndrome; 90 percent for agammaglobulinemia; unknown for other syndromes

GENES TESTED: ADA; ADA2; AICDA; ATM; ATP6AP1; BLNK; BTK; CARD11; CD19; CD27; CD40; CD40LG; CD70; CD79A; CD79B; CDCA7; CR2; CTLA4; CXCR4*; DCLRE1C*; DNMT3B; GATA2; HELLS; ICOS; IGHM; IGLL1; IKZF1; IL21R; KDM6A; KMT2D; LRBA; MOGS; MS4A1; NBN; NFKB1; NFKB2; NFKBIA**; PIK3CD; PIK3R1; PLCG2; PRKCD*; RAC2; RAG1; RAG2; RNF168; SH2D1A; STAT3; TCF3**; TNFRSF13B; TRNT1; TTC37; UNG; XIAP*; ZBTB24
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
**Deletion/duplication analysis is not available for this gene.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs)

and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a primary antibody deficiency. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
CXCR4 (NM_001348056, NM_001348059) exon(s) 2
DCLRE1C (NM_001350965) exon(s) 15
DCLRE1C (NM_001350966) exon(s) 13
DCLRE1C (NM_001350967) exon(s) 16
PRKCD (NM_001354676, NM_001354678) exon(s) 1
XIAP (NM_001167, NM_001204401, NM_001378590, NM_001378591, NM_001378592) exon(s) 4

Single exon deletions/duplications will not be called for the following exons:
ADA (NM_000022, NM_001322051) 1; CXCR4 (NM_001348056) 2; CXCR4 (NM_001348059) 2; DCLRE1C (NM_001033855) 4-9; DCLRE1C (NM_001033857, NM_001289077) 6-10; DCLRE1C (NM_001033858, NM_001289079) 7-11; DCLRE1C (NM_001289076, NM_001289078) 3-7; DCLRE1C (NM_001350965) 4-9,15; DCLRE1C (NM_001350966) 3-7,13; DCLRE1C (NM_001350967) 6-10,16; DCLRE1C (NM_022487) 4-8; HELLS (NM_018063, NM_001289067, NM_001289068, NM_001289069, NM_001289070, NM_001289072) 7; HELLS (NM_001289071) 8; HELLS (NM_001289073) 6; IGLL (NM_152855) 2; IKZF1 (NM_001291846, NM_001291847) 4; MOGS (NM_001146158) 2; PRKCD (NM_001354676, NM_001354678) 1; XIAP (NM_001167, NM_001204401, NM_001378590, NM_001378592) 4; XIAP (NM_001378591) 5

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

H=High, L=Low, *=Abnormal, C=Critical

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Primary Antibody Deficiency Specimen	26-148-112651	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Primary Antibody Deficiency Panel Interp	26-148-112651	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical