BLOODCENTER of WISCONSIN™
PART OF VERSITI
Diagnostic Laboratories

BloodCenter of Wisconsin, Inc
638 N 18 St • Milwaukee, WI 53233-2121
414.937.6250 • 800.245.3117 • Fax 414.937.6206
www.bcw.edu • labinfo@bcw.edu

Patient: **MockThromb,**

Birth Date: Gender:Male
Alt ID:

MRN/Req: 3000560147 - 99990000020778
Physician: Not Provided
Additional Copies:

Client # : 9999
ZZ Test Organization
SAMPLE REPORT
638 North 18 Street
Milwaukee, WI 53233-2121

Hematology Genetics

Sequencing Result(s)

TEST REQUESTED: Inherited Thrombocytopenia Panel
COLLECTION DATE: xxxxx
SPECIMEN TYPE: EDTA WB

GENES TESTED: *ACTN1, ANKRD26, CYCS, ETV6, FLI1, GATA1, GP1BA, GP1BB, GP9, HOXA11, ITGA2B, ITGB3, MASTL, MPL, MYH9, NBEAL2, PRKACG, RBM8A, RUNX1, STXBP2, TUBB1 and WAS*

Clinical History

History is abstracted from information provided by the referring facility. The patient is a 10 year old male with a history of thrombocytopenia since birth with platelet counts that have been less than 100,000/uL. Mild bleeding symptoms are reported. The family history is significant for thrombocytopenia in the patient's father and several paternal family members.

Results

A clinically significant variant was identified

Gene Transcript	Exon	DNA Change	AA Change	Zygosity	Pathogenicity	Genomic Coordinates
ANKRD26 NM_014915.2	exon 1	c.-134G>A	NA	heterozygous	Pathogenic	g.27389389C>T

Summary

In this patient with thrombocytopenia and positive family history of thrombocytopenia in multiple paternal relatives, the presence of a pathogenic variant in *ANKRD26* confirms a diagnosis of *ANKRD26*- related thrombocytopenia (thrombocytopenia-2), an autosomal dominant disorder. This disorder has been associated with mild bleeding tendency, thrombocytopenia and an increased predisposition to hematologic myeloid malignancies.

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Recommendations

1. Correlation with this patient's clinical history, family history and laboratory findings is recommended.
2. Based on autosomal dominant inheritance, this patient inherited this pathogenic variant from one of his parents or it occurred de novo. The reported family history indicates that the patient's father and other paternal other family members have thrombocytopenia and thus likely have this same pathogenic *ANKRD26* variant. Targeted variant analysis is recommended for this patient's family members for accurate recurrence risk information and for clinical diagnosis and management. Children of this patient have a 50% chance to inherit this pathogenic variant.
3. Genetic counseling is recommended.

Individual Variant Interpretations

***ANKRD26* c.-134G>A**

The variant *ANKRD26* c.-134G>A, in the 5' UTR changes the nucleotide guanine to adenine. This sequence variant has been previously reported in patients with thrombocytopenia (Pippucci, 2011). Functional studies of the variant in K562 and Dami cells demonstrated an increased expression in ANKRD26 (Pippucci, 2011). To date, this variant has not been reported in the general population (Exome Aggregation Consortium, Exome Variant Server). In summary, the collective evidence supports *ANKRD26* c.-134G>A, as a pathogenic variant. Pathogenic variants in *ANKRD26* are associated with mild bleeding tendency, thrombocytopenia and an increased predisposition to hematologic myeloid malignancies (Noris, 2011 and Noris, 2013).

For Questions

Please call Client Services at 800-245-3117 option 1 to be directed to the appropriate member of our laboratory team.

Background

Inherited thrombocytopenia is a heterogeneous group of disorders that are characterized by low platelet counts that are typically less than 150,000/uL, but can vary with age, gender and ethnic background. Symptoms of thrombocytopenia may include purpura, petechiae, prolonged bleeding from cuts, epistaxis, gum bleeding, excessive bleeding after surgery, hemoptysis, hematuria and menorrhagia in women. Severe inherited thrombocytopenias can present in the newborn period, while mild thrombocytopenia may remain undiagnosed until incidental detection on routine blood testing in adulthood. Some inherited types of thrombocytopenia have only hematologic manifestations, which may include differences in platelet size or distinctive granulocyte inclusions, while other syndromic types present with additional non-hematologic manifestations. Certain types of inherited thrombocytopenia cause predisposition to acute myelogenous leukemia or myelodysplastic syndromes. Variants in several different genes known to cause syndromic or non-syndromic thrombocytopenia may be inherited in an autosomal recessive, autosomal dominant or X-linked recessive manner.

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More common and many rare types of inherited thrombocytopenia will be identified with this panel, including *MYH9*-related disorders, Bernard-Soulier syndrome, congenital amegakaryocytic thrombocytopenia, familial platelet disorder with predisposition to acute myelogenous leukemia, *ANKRD26*-related thrombocytopenia, *WAS*-related thrombocytopenia, gray platelet syndrome and others. Additional genes in this panel are associated with syndromes that have thrombocytopenia as a common finding among other non-hematologic features.

Assay Principle
This next-generation sequencing assay analyzes 22 genes, spanning the full coding regions plus a minimum 30bp of non-coding DNA including intron-exon junctions, in addition to approximately 200bp upstream of *ANKRD26* coding region covering all currently known intervening variants of *ANKRD26*. These targeted regions are captured by hybridization, amplified and sequenced by massively parallel sequencing. Regions will have a minimum coverage of 50x and those regions with less than 50 sequencing reads or low quality are supplemented with Sanger sequencing. All regions are covered by bi-directional analysis. Variants are identified by a customized bioinformatics pipeline, analyzed and comprehensively interpreted by our team of directors, scientists, and genetic counselors. All reported variants, including pathogenic, likely pathogenic, and variants of uncertain significance, are confirmed by Sanger sequencing.

For prenatal testing, analysis of variable number of tandem repeats (VNTR) is used to confirm results are not affected by maternal cell contamination.

Assay Sensitivity and Limitations
The analytical sensitivity of this test is >99% for single nucleotide changes and insertions and deletions of less than 20 bp. This assay does not detect large deletions or duplications (>20 bp) or deletions, duplications or variants that are outside the regions sequenced. To order the analysis of copy number variants at the exon or gene level, please refer to the aCGH Deletion/Duplication Analysis test, if available, or contact Client Services before placing your order.

This test was developed and its performance characteristics determined by BloodCenter of Wisconsin. It has not been cleared or approved by the FDA. However, the FDA has determined that such clearance is not necessary. The test has been validated in house and is used for clinical purposes. It should not be regarded as investigational or for research. Our Laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.

Reporting
While this assay is designed to detect germline genetic variants associated with thrombocytopenia, variants unrelated to the indication for testing, but with other clinical and/or reproductive implications, may also be detected. A comprehensive database of gene-phenotype relationships listed by gene name can be found at http://www.omim.org.

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Results are classified and reported in accordance with ACMG next-generation sequencing standards. Variants predicted to be pathogenic, likely pathogenic, and of uncertain significance will be reported; variants classified as likely benign or benign are typically not reported but such data are available upon request. Sequence variants are described using standard Human Genome Variation Society (HGVS) nomenclature (http://www.hgvs.org).

References

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Electronically Signed By:
Matthew W. Anderson, MD, PhD
Medical Director, Diagnostic Laboratories
Report Date: 10/23/17