Genetic Testing Report

Patient Name:	**DOE, Jane**	**GeneDx Accession No:**	**MockTest056**
Date of Birth:	**Not Provided**	**Date Specimen Obtained:**	**Not Provided**
Specimen Type:	**Blood in EDTA**	**Date Specimen Received:**	**8/6/2013**
Submitters ID No:	**None Provided**	**Date Test(s) Started:**	**1/23/2014**
Ordered By:	**Chris's Practice**	**Date of Report:**	**5/23/2014**

Test(s) requested: Diagnostic Testing / XomeDx / Whole Exome Sequence Analysis

Clinical Indication: Three-year-old female with intellectual disability, coarse facial features, hypertrichosis with sparse scalp hair and seizures.

A sample from this individual's mother (GeneDx#) and father (GeneDx#) were also submitted for variant segregation analysis by whole exome sequencing.

Result Summary:

1. Mutations in genes associated with the reported phenotype:

- **Heterozygous for the de novo R750X mutation in the ARID1B gene**

ACMG Incidental Findings:

- **Heterozygous for the Q563X mutation in the BRCA1 gene**

The results of the mitochondrial genome sequencing and deletion analysis are provided in the attached report.

1. Mutations in Genes Associated with Reported Phenotype:

Gene	Disease	Mode of Inheritance	Variant	cDNA	Zygosity	Inherited From	Classification
ARID1B	Coffin-Siris syndrome	Autosomal Dominant	p.R750X	c.2248 C>T	Het	De Novo	Mutation

ACMG Incidental Finding:

Gene	Disease	Mode of Inheritance	Variant	cDNA	Zygosity	Inherited From	Classification
BRCA1	Hereditary Breast and Ovarian Cancer	Autosomal Dominant	p.Q563X	c.1687 C>T	Het	Mother	Mutation

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Result:

Heterozygous for the De Novo R750X Mutation in the ARID1B Gene

The ARID1B gene encodes an AT-rich DNA interacting domain-containing protein that is a member of the ATP-dependent chromatin remodeling complex SWI/SNF family. Members of this protein family have ATPase and helicase activities and are thought to alter chromatin structure to regulate transcription of certain genes (Reisman et al, 2009). Recently, multiple de novo ARID1B truncating mutations and deletions, as well as other de novo mutations in one of the six SWI/SNF subunit genes, have been identified in patients with Coffin-Siris syndrome (Tsurusaki et al, 2012; Santen et al., 2012). Coffin-Siris syndrome is an autosomal dominant disorder characterized by intellectual disability, growth deficiency, microcephaly, coarse facial features and hypoplastic nail of the fifth finger/toe. Cardiac malformations may also occur. An additional report identified de novo nonsense and frameshift mutations and a partial duplication in the ARID1B gene in 8 unrelated patients with intellectual disability (Hoyer et al, 2012). Another publication identified a de novo frameshift mutation in a patient with clinical presentation of Coffin-Siris syndrome including extreme obesity, macrocephaly, hepatomegaly, hyperinsulinism and polycystic ovarian syndrome (Vals et al., 2014).

ARID1B p.R750X:

p.Arg750Stop (CGA>TGA): c.2248 C>T in exon 5 in the ARID1B gene (NM_020732.3). For the ARID1B gene, 98.8% of the coding region was covered at a minimum of 10x by the XomeDx test.

This individual's parents (GeneDx# XXX and XXX) do not harbor the R750X mutation in the ARID1B gene.

The de novo R750X nonsense mutation in the ARID1B gene is predicted to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay. This mutation has been reported previously as a disease-causing mutation in a child with severe developmental delay (Wieczorek et al., 2013). We interpret R750X as a disease-causing mutation consistent with the reported phenotype in this individual.

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ACMG Incidental Findings:

Heterozygous for the Q563X Mutation in the BRCA1 Gene.

Known and expected pathogenic variants in 56 genes recommended to be reported by the ACMG (Green et al., 2013) are reported for the proband and relatives submitted for variant segregation by whole exome sequencing. ACMG incidental findings are not reported for relatives submitted for segregation analysis only or that opted out of receiving ACMG incidental findings. Only variants that have been previously reported and are a recognized cause of the disorder (known pathogenic; KP) or variants that are previously unreported but are of the type which is expected to cause the disorder (expected pathogenic; EP), as specified in the ACMG recommendations are reported (Green et al., 2013; Richards et al., 2008).

BRCA1 Q563X:

p.Gln563Stop (CAG>TAG): c.1687 C>T in exon 4 in the BRCA1 gene (NM_007294.3). For the BRCA1 gene, 99.6% of the coding region was covered at a minimum of 10x by the XomeDx test.

This individual's mother (GeneDx# XXX) is heterozygous for the Q563X mutation in the BRCA1 gene. This individual's father (GeneDx# XXX) does not harbor the Q563X mutation in the BRCA1 gene.

The Q563X mutation in the BRCA1 gene has been published previously as a disease-causing mutation associated with breast and ovarian cancer (Shattuck-Eidens et al, 1995; Zuradelli et al, 2010; Ghiorzo et al., 2012; Schrader et al., 2012). Based on the ACMG recommendations, Q563X is interpreted as a known pathogenic sequence change.

Limitations Regarding Incidental Findings:
Known or expected pathogenic variants in the 56 genes recommended by the ACMG are reported for the proband (see Appendix 1 for this list of genes (Green et al., 2013)). The presence or absence of the proband's identified incidental findings is available only for relatives who underwent whole exome sequencing as part of the proband's test. Variants that may be present in a relative, but are not present in the proband, would not be detected and therefore are not reported. Known or expected pathogenic variants may be present in a portion of the gene not covered by this test and therefore would not be detected. The absence of reportable incidental findings for any particular gene does not mean there are no known or expected pathogenic variants in that gene, or other variants that may confer susceptibility to the disorders listed.

Additional Analysis Comments:

Analysis of XomeDx for the proband includes evaluation of variants that are identified to be de novo (when both parents submitted), compound heterozygous (when both parents submitted), homozygous, heterozygous and X-linked recessive in addition to relevant analysis based on the family structure and reported phenotype. In view of the phenotype information provided, analysis in this case specifically included review of variants in genes associated with developmental delay, short stature, microcephaly, coarse facial features, hypertrichosis, sparse scalp hair, seizures and abnormal MRI.

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Recommendation:

Clinical correlation is recommended to determine whether any of these findings are consistent with the patient's phenotype. Although neither parent was found to carry the R750X mutation in the ARID1B gene, the possibility of germline mosaicism cannot be excluded and offspring of either parent may be at risk for carrying this mutation.

Clinical evaluation is recommended to address the identified mutation in the BRCA1 gene. The presence of the Q563X mutation permits targeted mutation testing for at-risk family members.

Genetic counseling is recommended to discuss the implications of this report.

Methods:

Using genomic DNA from the submitted specimen(s), the Agilent SureSelect XT2 All Exon V4 kit was used to target the exon regions of the genome(s). These targeted regions were sequenced using the Illumina HiSeq 2000 sequencing system with 100bp paired-end reads. The DNA sequence was mapped to and analyzed in comparison with the published human genome build UCSC hg19 reference sequence. The targeted coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage and data quality threshold values*. The XomeAnalyzer was used to evaluate sequence changes in this individual compared to other sequenced family members. All reported sequence variants in the proband and relative samples (if submitted for variant segregation analysis by whole exome sequencing) were confirmed by conventional di-deoxy DNA sequence analysis or other appropriate method.

**Quality Metrics*

Mean Depth of Coverage[1]	135x
Quality threshold[2]	99.1%

The above values represent metrics from this XomeDx evaluation. [1]Mean depth of coverage refers to the sequence mean read depth across the XomeDx targeted region, defined as coding exons and splice junctions of Agilent SureSelect XT2 All Exon V4 kit targeted protein coding RefSeq genes. [2]The quality threshold refers to the percentage of the XomeDx defined target region where read depth was at least 10x coverage to permit high quality exome variant base calling, annotation and evaluation. Average quality thresholds may range from >90-95% of the XomeDx targeted region, indicating a small portion of the target region may not be covered with sufficient depth or quality to confidently call variant positions.

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Limitations:

Some types of genetic abnormalities may not be detectable with the technologies performed with the XomeDx test. It is possible that the genomic region where a disease causing mutation exists in the proband was not captured using the current technologies and therefore was not detected. Additionally, it is possible that a particular genetic abnormality may not be recognized as the underlying cause of the genetic disorder due to incomplete scientific knowledge about the function of all genes in the human genome. Only variations in genes associated with the medical condition, or thought to potentially be clinically relevant to the proband's medical condition are reported here. The clinical implications of some variations may not be known at the time of this report.

A medical provider can request reanalysis of the exome data generated with the XomeDx test. The current data can be reassessed for the presence of any variants that may be newly linked to this individual's phenotype since the date of this report.

Report electronically signed by:
Not Signed

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Not Signed

References: Reisman, D. et al. (2009) Oncogene, 28:1653-1668; Tsurusaki, Y. et al. (2012) Nat Genet, 44(4):376-378; Santen, G. et al. (2012) Nat Genet, 44 (4):379-380; Hoyer, J. et al. (2012) Am J Hum Genet, 90:565-572; Vals et al., (2014) Eur J Hum Genet Epub; Wieczorek et al. (2013) Hum Mol Genet 22:5121; Green et al. (2013) Genet Med 15:565-574; Richards et al. (2008) Genet in Med 10(4):294-300; Shattuck-Eidens et al. (1995) JAMA 273:535; Zuradelli et al. (2010) Breast Cancer Res Treat 124:251; Chiorzo et al. (2012) Fam Cancer 11:41; Schrader et al. (2012) Obstet Gynecol.

Appendix 1. 56 Genes Reviewed for Incidental Findings (Green et al., 2013):

Gene	Disease	Mode of Inheritance	MIM-Gene
ACTA1	Marfan Syndrome; Loeys-Dietz Syndromes; TAAD	Autosomal Dominant	102620
ACTC1	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	102540
APC	Familial adenomatous polyposis	Autosomal Dominant	611731
APOB	Familial hypercholesterolemia	Autosomal Dominant	107730
BRCA1	Hereditary Breast and Ovarian Cancer	Autosomal Dominant	113705
BRCA2	Hereditary Breast and Ovarian Cancer	Autosomal Dominant	600185
CACNA1S	Malignant hyperthermia susceptibility	Autosomal Dominant	114208
COL3A1	Ehlers-Danlos syndrome – vascular type	Autosomal Dominant	120180
DSC2	Arrhythmogenic right ventricular cardiomyopathy	Autosomal Dominant	125645
DSG2	Arrhythmogenic right ventricular cardiomyopathy	Autosomal Dominant	125671
DSP	Arrhythmogenic right ventricular cardiomyopathy	Autosomal Dominant	125647
FBN1	Marfan Syndrome; Loeys-Dietz Syndromes; TAAD	Autosomal Dominant	134797
GLA	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	X-linked	300644
KCNH2	Long QT syndrome; Brugada syndrome	Autosomal Dominant	152427
KCNQ1	Long QT syndrome; Brugada syndrome	Autosomal Dominant	607542
LDLR	Familial hypercholesterolemia	Autosomal Dominant	606945
LMNA	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	150330
MEN1	Multiple Endocrine Neoplasia Type 1	Autosomal Dominant	613733
MLH1	Lynch Syndrome	Autosomal Dominant	120436
MSH2	Lynch Syndrome	Autosomal Dominant	609309
MSH6	Lynch Syndrome	Autosomal Dominant	600678
MUTYH	MYH-Associated Polyposis	Autosomal Recessive	604933
MYBPC3	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	600958
MYL2	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	160781
MYL3	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	160790
MYLK	Marfan Syndrome; Loeys-Dietz Syndromes; TAAD	Autosomal Dominant	600922
MYH7	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	160760
MYH11	Marfan Syndrome; Loeys-Dietz Syndromes; TAAD	Autosomal Dominant	160745
NF2	Neurofibromatosis type 2	Autosomal Dominant	607379
PCSK9	Familial hypercholesterolemia	Autosomal Dominant	607786
PKP2	Arrhythmogenic right ventricular cardiomyopathy	Autosomal Dominant	602861
PMS2	Lynch Syndrome	Autosomal Dominant	600259
PRKAG2	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	602743
PTEN	PTEN Hamartoma Tumor Syndrome	Autosomal Dominant	601728
RB1	Retinoblastoma	Autosomal Dominant	614041
RET	Multiple Endocrine Neoplasia type 2; Familial Medullary Thyroid Cancer	Autosomal Dominant	164761
RYR1	Malignant hyperthermia susceptibility	Autosomal Dominant	180901
RYR2	Catecholaminergic polymorphic ventricular tachycardia	Autosomal Dominant	180902
SCN5A	Long QT syndrome; Brugada syndrome	Autosomal Dominant	600163
SDHAF2	Hereditary Paraganglioma-Pheochromocytoma Syndrome	Autosomal Dominant	613019
SDHB	Hereditary Paraganglioma-Pheochromocytoma Sydnrome	Autosomal Dominant	185470
SDHC	Hereditary Paraganglioma-Pheochromocytoma Sydnrome	Autosomal Dominant	602413
SDHD	Hereditary Paraganglioma-Pheochromocytoma Sydnrome	Autosomal Dominant	602690
SMAD3	Marfan Syndrome; Loeys-Dietz Syndromes; TAAD	Autosomal Dominant	603109
STK11	Peutz-Jeghers syndrome	Autosomal Dominant	602216
TGFBR1	Marfan Syndrome; Loeys-Dietz Syndromes; TAAD	Autosomal Dominant	190181
TGFBR2	Marfan Syndrome; Loeys-Dietz Syndromes; TAAD	Autosomal Dominant	190182
TMEM43	Arrhythmogenic right ventricular cardiomyopathy	Autosomal Dominant	612048
TNNI3	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	191044
TNNT2	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	191045
TP53	Li-Fraumeni Syndrome	Autosomal Dominant	191170
TPM1	Hypertrophic cardiomyopathy; Dilated cardiomyopathy	Autosomal Dominant	191010
TSC1	Tuberous Sclerosis Complex	Autosomal Dominant	605284
TSC2	Tuberous Sclerosis Complex	Autosomal Dominant	191092
VHL	Von Hippel Lindau syndrome	Autosomal Dominant	608537
WT1	WT1-related Wilms tumor	Autosomal Dominant	607102