EGL Genetics | Eurofins Clinical Diagnostics

Lora J. H. Bean, PhD, FACMG, Director
2460 Mountain Industrial Boulevard
Tucker, GA 30084
Toll Free: (855) 831-7447
International: (470) 378-2200
FAX: (470) 378-2250
CLIA#: 11D0683478
CAP#: 7181693

Molecular Genetics Laboratory

PATIENT INFORMATION — FINAL REPORT

PATIENT NAME: **Egl Genetics**
DATE OF BIRTH: **2/13/2017**
PATIENT SEX: **Female**
CROSS REFERENCE #: **123-456**
PATIENT ID: **T0302434**

LABORATORY #: **18NGS10681**
TYPE OF SPECIMEN: **Whole blood (EDTA)**
DATE COLLECTED: **6/19/2018**
DATE RECEIVED: **6/20/2018**
DATE INITIATED: **6/20/2018**
FINAL REPORT: **6/27/2018**

REFERRING DIAGNOSIS: **R62.52 - Short stature (child)**
Q22.1 - Congenital pulmonary valve stenosis
REFERRING CLINICIAN/INSTITUTION: Irma Doctor 555-555-5555 (Fax)

NGS Panel

SUMMARY

Variant(s) detected:

PTPN11 (NM_002834.3): c.205G>C (p.E69Q), Heterozygous**, Pathogenic**

RESULTS AND INTERPRETATION

Sequence analysis of the coding regions of genes on this panel (see methodology) detected the following:

Gene	MIM#	Disease (Inheritance)	Nucleotide change	Amino acid change	Zygosity	Type
PTPN11	176876	Noonan syndrome 1 (AD); LEOPARD syndrome 1 (AD); Metachondromatosis (AD)	c.205G>C	p.E69Q	Heterozygous	Pathogenic

The detection of a *PTPN11* pathogenic variant is consistent with a diagnosis of Noonan syndrome in this individual; however, these results must be interpreted in the context of the individual's clinical and biochemical profile.

***PTPN11* (NM_002834.3): c.205G>C (p.E69Q) -**
The c.205G>C (p.E69Q) variant has been reported in several individuals with Noonan syndrome [1-4], and is classified as a pathogenic variant.

Ref:

1. Musante et al., Eur J Hum Genet. 2003 Feb;11(2):201-6.
2. Croonen et al., Eur J Hum Genet. 2013 Sep;21(9):936-42.
3. Bertelloni et al., Hormones (Athens). 2013 Jan-Mar;12(1):86-92.
4. Atik et al., Indian J Pediatr. 2016 Jun;83(6):517-21.

RECOMMENDATIONS

- These results must be interpreted in the context of this individual's clinical profile and family history.
- Genetic counseling is recommended.
- EGL Genetics offers targeted analysis for family members at risk for carrying the pathogenic variant identified in this individual.

- If clinically indicated, familial testing is recommended for the following variants:
  1. The c.205G>C (p.E69Q) variant to determine if it is inherited or occurred *de novo.*

Please note, our policy for free familial testing has changed. EGL Genetics only offers complimentary testing for two variants of unknown significance (VOUSs) in up to two appropriate family members.

For more information, please visit eglgenetics.com or call (470) 378-2200 to contact a laboratory genetic counselor or to consult with a laboratory director.

COMMENTS

This analysis will not detect large deletions or duplications involving the targeted genes, or pathogenic variants in the promoter or other regulatory regions of these genes. Some intronic pathogenic variants will not be detected by this assay.

NGS PANEL ASSAY INFORMATION

GENERAL INFORMATION: A sample from this individual was referred to our laboratory for molecular testing for Noonan syndrome and related disorders, also known as rasopathies. The rasopathies include Noonan syndrome, LEOPARD syndrome, cardiofaciocutaneous (CFC) syndrome, Costello syndrome, and Noonan-like syndrome with loose anagen hair. The rasopathies, while distinct syndromes, share some overlapping features such as craniofacial dysmorphology, varying degrees of neurocognitive impairments, cutaneous, ocular, and musculoskeletal abnormalities, and cardiac malformations. Some syndromes have an increased risk of cancer.

GENES REPRESENTED ON THE NGS PANEL PANEL: Nucleotide numbering is based on GenBank accession numbers (nucleotide 1 corresponds to the A of the start codon ATG):

BRAF (NM_004333.4)	*CBL* (NM_005188.3)	*HRAS* (NM_005343.2)	*KRAS* (NM_004985.3)	*MAP2K1* (NM_002755.3)
MAP2K2 (NM_030662.3)	*NRAS* (NM_002524.4)	*PTPN11* (NM_002834.3)	*RAF1* (NM_002880.3)	*RIT1* (NM_006912.5)
SHOC2 (NM_007373.3)	*SOS1* (NM_005633.3)	*SPRED1* (NM_152594.2)		

NOTES: Variants are evaluated by their reported frequency. Variants that have a population frequency greater than expected given the prevalence of the disease in the general population are considered to be benign or likely benign. A list of benign and likely benign variants identified in this individual is available upon request. Silent and intronic (4 or more bases from splice sites) VOUSs are not reported unless considered relevant. The interpretation of variants is based on our current understanding of the genes on this panel. These interpretations may change over time as more information about the gene(s) becomes available. Visit EmVClass (eglgenetics.com) for current classification of variants. Possible diagnostic errors include sample mix-ups, genetic variants that interfere with analysis, and other sources.

METHODOLOGY: In solution hybridization of the targeted coding exons within the genes tested (see list below) was performed on this individual's genomic DNA. The genes on this panel were chosen through evidence-based analysis. Direct sequencing of the amplified captured regions was performed using next generation short base pair read sequencing. Exons with inadequate coverage or quality by next generation sequencing were assessed with Sanger sequencing. Reportable variants that did not pass the quality filters were also confirmed using Sanger sequencing. Intronic variants within 10 nucleotides from the exon/intron boundaries are analyzed, unless prohibited by the complexity of the sequence.

Abbreviations: AR - autosomal recessive; AD - autosomal dominant; XL - X-linked; VOUS - Variant of unknown significance

POPULATION DATABASES
- www.ncbi.nlm.nih.gov/projects/SNP
- evs.gs.washington.edu/EVS

- phase3browser.1000genomes.org
- exac.broadinstitute.org
- gnomad.broadinstitute.org

Pursuant to the requirements of CLIA '88, this test was developed and its performance validated by EGL Genetic Diagnostics LLC. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.

Electronically signed by Lora J.H. Bean, Ph.D., FACMG on 6/27/2018 at 03:09 PM	Michael Gambello, M.D., Ph.D., FACMG Medical Consultant