CeGaT GmbH | Paul-Ehrlich-Str. 23 | D-72076 Tübingen | Germany

Dr. Jane Doe
Paul-Ehrlich-Str. 23
D-72076 Tübingen

Patient	XXX, XX
ID #	Female (*DD.MM.YYYY)
Sample receipt	xxx
Material	DNA
External ID	#
Report date	xxx
Report-ID	R#

Genetic Report – XXX, XX (*DD.MM.YYYY)

Indication Ventricular septal defect, otherwise well, suspected Noonan syndrome

Order Analysis of the familial variant c.173A>G; p.Asn58Ser in gene *PTPN11*.

Result: Report with Significant Findings

- **Heterozygous identification of the familial variant c.173A>G; p.Asn58Ser in gene *PTPN11*, which is consistent with Noonan syndrome in your patient.**

Gene	Variant	Zygosity	Heredity	MAF (%)	Classification
PTPN11	**c.173A>G; p.Asn58Ser** **chr12:112888157 A>G (hg19)**	**het.**	**AD**	**< 0.01**	**likely pathogenic**

Information for the interpretation of this table can be found in section *Additional Information*.

Recommendation

We recommend further clinical evaluation and management according to the current guidelines for *PTPN11*-associated Noonan syndrome (Roberts, updated 2022, PMID: 20301303, GeneReviews).

It is possible to investigate further affected family members regarding the variant identified in gene *PTPN11*.

Testing of adult asymptomatic family members regarding the variant c.173A>G; p.Asn58Ser identified in gene *PTPN11* may only be performed following genetic counseling.

Genetic Relevance

Your patient is heterozygous for a likely pathogenic variant in gene *PTPN11*. This may be of relevance for at-risk family members.

Individual variants have a 50% probability of being passed on to each respective offspring.

Clinical Information and Variant Interpretation

PTPN11, NM_002834.5

OMIM / Reference	Phenotype	Heredity
151100	LEOPARD syndrome 1 (LPRD1)	AD
156250	Metachondromatosis (METCDS)	AD
163950	**Noonan syndrome 1 (NS1)**	**AD**
607785	Juvenile myelomonocytic leukemia caused by somatic or germline mutations in PTPN11 (JMML)	AD

The ***PTPN11*** gene encodes a protein also known as SHP2, a member of the protein tyrosine phosphatase (PTP) family. PTPs are signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitosis, and oncogenic transformation. Because patients with Noonan syndrome 1 (NS1) or LEOPARD syndrome 1 (LPRD1; also known as Noonan syndrome with multiple lentigines (NSML)) frequently have subtle phenotypic features, and due to ascertainment bias and variable expressivity, penetrance of NS1 and NSML/LPRD1 is difficult to determine. Noonan syndrome manifests with variable symptoms, mainly dysmorphic features, short stature, congenital heart defects, and developmental delay of variable degree. In addition, patients may have a broad or webbed neck, an unusual chest shape, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Sensorineural hearing loss has been observed as an isolated or predominant clinical feature in *PTPN11*-associated Noonan syndrome (Gao et al., 2021, PMID: 32737134). Many affected adults are diagnosed only after the birth of a clearly affected child (Roberts, updated 2022, PMID: 20301303, GeneReviews; Gelb and Tartaglia, updated 2022, PMID: 20301557, GeneReviews). Patients with Noonan syndrome 1 or Noonan syndrome-like disorder due to a *PTPN11* pathogenic germline variant have an increased risk of developing juvenile myelomonocytic leukemia (JMML) (OMIM #607785) and other malignancies (Roberts, updated 2022, PMID: 20301303, GeneReviews; Jongmans et al., 2011, PMID: 21407260).

PTPN11, c.173A>G; p.Asn58Ser (het.), ClinVar ID: 372483

ACMG/ACGS Criterion	Points	Description
PM1	+2	The variant is located within a critical region of the gene *PTPN11*.
PM5	+2	The variant results in the change of an amino acid residue, for which several different amino acid changes (p.Asn58His, p.Asn58Tyr, p.Asn58Lys, and p.Asn58Asp) have already been described as pathogenic. Limal et al., 2006, PMID: 16263833; Mohan et al., 2022, PMID: 34358384; Musante et al., 2003, PMID: 12634870; Zenker et al., 2004, PMID: 15001945
PP2	+1	Fewer than expected missense variants are present within gene *PTPN11* in the general population, which suggests poor tolerance for missense variation.
PP3	+1	The variant was given a pathogenic prediction by *in silico* tools.
PP4	+1	The associated disease is consistent with specific symptoms in the patient.
ACMG/ACGS Classification: likely pathogenic	+7	B (≤ -7) | LB (-6 - -1) | VUS (Ice Cold) (0) | VUS (Cold) (1) | VUS (Cool) (2) | VUS (Tepid) (3) | VUS (Warm) (4) | VUS (Hot) (5) | **LP (6 - 9)** | P (≥ 10)

Genetic counseling should be offered with all diagnostic genetic testing, especially following the identification of the molecular cause of a genetic disease.

Medical report written by: XXX

Proofread by: XXX

Validated by: XXX

With kind regards,

Friedmar Kreuz

Consultant for Human Genetics

Additional Information

For the correct interpretation of the data, we assume accurate information regarding the familial relationships has been provided.

Information for the interpretation of the tables

Heredity: AD – autosomal dominant, AR – autosomal recessive, XL – X-linked, mito – mitochondrial

MAF: The ***minor allele frequency*** describes the least frequent allele at a specific locus in a given population. For mitochondrial variants, the population frequency (MAF column) is based on the homoplasmic frequency within a reference population (gnomAD).

Classification: Variant classification is based on ACMG, ACGS-2020v4.01, and ClinGen SVI WG guidelines (Richards et al., 2015, PMID: 25741868; Ellard et al., 2020, Association for Clinical Genomic Science; https://clinicalgenome.org/working-groups/sequence-variant-interpretation/). The weighting of criteria and their modification follows the current ACGS guidelines in the strength levels *very strong* (+ 8), *strong* (+/- 4), *moderate* (+/- 2), and *supporting* (+/- 1). According to the respective category (pathogenic or benign) and criterion strength, positive or negative points are assigned as mentioned above (Tavtigian et al., 2020, PMID: 32720330). Variants of uncertain significance (VUS) are subcategorized into *hot*, *warm*, *tepid*, *cool*, *cold*, and *ice cold* VUS according to their likelihood of reaching a pathogenic classification in the future. Posterior probability decreases from 90% to 10% in this order (Ellard et al., 2020, Association for Clinical Genomic Science). If a variant reaches the classification pathogenic, after checking of all benign criteria, not necessarily all other applicable criteria are listed.

The chromosomal positions of variants listed in the report refer to the human reference genome hg19.

Methods

Sequencing: Protein-coding regions, as well as flanking intronic regions and additional disease-relevant non-coding regions, were enriched using in-solution hybridization technology, and were sequenced using the Illumina NovaSeq 6000/NovaSeq X Plus system.

Bioinformatics: Illumina bcl2fastq2 was used to demultiplex sequencing reads. Adapter removal was performed with Skewer. The trimmed reads were mapped to the human reference genome (hg19) using the Burrows Wheeler Aligner. Reads mapping to more than one location with identical mapping score were discarded. Read duplicates that likely result from PCR amplification were removed. The remaining high-quality sequences were used to determine sequence variants (single nucleotide changes and small insertions/deletions). The variants were annotated based on several internal as well as external databases.

Only genes relevant to the assessment of the index patient were evaluated. Variants were classified and reported based on ACMG/ACGS-2020v4.01 guidelines (Richards et al., 2015, PMID: 25741868, https://www.acgs.uk.com/quality/best-practice-guidelines/). The evaluation of variants is dependent on available clinical information at the time of analysis. Potentially causative variants, deletions, and duplications in regions not analysed by our methods, e.g. intronic or intergenic regions, cannot be ruled out.

The sample fulfilled our quality criteria upon arrival and during/after each processing step in the laboratory.

The procedure described above was developed and validated in-house (Laboratory developed test; LDT).

Communication, dissemination and usage of this report for scientific purposes is only permitted in accordance with the German Genetic Diagnostics Legislation.

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