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THE RARE DISEASE COMPANY

Tabular List of Additional Pathogenic and Likely Pathogenic Variants

What Is this *Tabular List* about?

At CENTOGENE, we are committed to providing cutting-edge diagnostic services – shortening patients' diagnostic odyssey and accelerating life-saving treatments.

To ensure that we are offering the most comprehensive medical solutions, we have recently added a *'Tabular List'* variant section to medical reports. This section incorporates a list of pathogenic/likely pathogenic genetic variants from a selection of highly penetrant genes which are known to be linked to early onset severe diseases identified in the proband when using Next Generation Sequencing (NGS). The list of genes covered currently includes more than 2,000 genes, which are frequently reviewed and updated.

The *Tabular List* makes potentially relevant, but often unreachable additional information accessible to physicians/genetic counsellors – allowing them to take actionable steps to potentially help prevent morbidity and mortality of the patient and/or their family. This section is available free of charge for CentoXome®, CentoGenome®, CentoDx®, and numerous NGS panels.

Reporting of these genetic variants is based on the pathogenic/likely pathogenic classification in CentoMD®, what we believe to be the world's largest data base repository of rare diseases.

Why Does CENTOGENE Report these Variants in the *Tabular List*?

NGS data reports can only be based – using the individual bioinformatics pipeline – on the quality and quantity of the description of the clinical data being available at the time of the analysis. In other words, pathogenic/likely pathogenic variants (class 1/class 2 according to ACMG criteria) not related to the phenotype are typically NOT reported. The main reason for doing so is to reduce the risk of reporting undesired genetic findings or variants of no benefit for the diagnosis at this stage.

However, in some instances such non-reported variants may be relevant for the tested index patient or families. Under specific circumstances such variants could potentially even be the most relevant cause of the disease – but missed if the clinical phenotype may not be completely described or patient demonstrates an atypical course of the disease or might be in the early, not-full blown phase of the clinical manifestation. Furthermore, sometimes the physician is not reporting normally essential clinical features, because these features seem to be unrelated to the suspected disease or were not present during clinical evaluation. Consequently, the genetic variant is not reported. Only the physician/genetic counselor can decide if those genetic variants are of clinical relevance.

Considering the nature and possible implications of such findings, the responsible physician/genetic counselor therefore is informed about such findings and enabled to decide how/when to properly proceed. Centogene provides most comprehensive information to support the physician.

In our experience, the information in the *Tabular List* is relevant in various ways and is a further source of information in the context of genetic testing. Frequently, the genetic findings in the *Tabular List* can guide the next step in the genetic analysis for the proband and their family - facilitating clinical decisions, genetic interpretation, and proper treatment that can influence the patient's health and medical outcome. Having all available data and information is crucial when providing a clinical interpretation.

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Tabular List vs. Incidental Findings

Incidental findings are unexpected positive findings of medical relevance for the patient that are not directly related to the indication (or disease) investigated but are related to other genetic disorders and are of great value for predictive early diagnosis. Currently, the ACMG has provided recommendations for the management of incidental findings in comprehensive NGS genetic studies, however they limit the reporting to only pathogenic/likely pathogenic variants in 59 specific genes.

For this reason, we are implementing the reporting of such information in the *Tabular List*, which comprises a pretty stringent selection of more than 2,000 genes that address exclusively early onset diseases with severe phenotypes. This means that the information reported is not predictive, but eventually diagnostic.

How Were the Genes in the *Tabular List* Chosen?

The gene selection is based on OMIM® phenotypes and CENTOGENE internal data. These genes have been carefully analyzed by our medical experts using the following criteria:

- Early onset severe disease:
  Onset of the disease in childhood
- Individual gene curation
- Including treatable or not treatable diseases with severe clinical course and highly penetrant phenotype
- Genes classified as Tier 1 (Causative for human disease)
- Mechanism of inheritance involve autosomal recessive, autosomal dominant and X-linked
- Genes causing early onset cancer are included in the list, for instance, retinoblastoma
- **Exclusions: Mitochondrial genes are not included in the *Tabular List*. Furthermore, cancer genes causing late onset diseases, e.g., ATM, BRCA1, BRCA2, are not included in the *Tabular List*. Genes causing late onset diseases such as Alzheimer disease, are also not included.**

Benefits of the *Tabular List*

Access to Otherwise Unreachable Data

Allows the physician/genetic counselor to have a broader and more accurate overview of patients' genetic state by revealing highly relevant, but otherwise unreachable data – facilitating a better understanding and interpretation of the current condition.

Transparency and Empowerment

The *Tabular List* reveals critical information detected and allows the physician/genetic counselor to decide if it is relevant for the patient/family. It also reduces the overall need for additional testing for already identified variants.

Only Relevant Variants Reported

Exclusively pathogenic/likely pathogenic variants in accordance with our CentoMD® database. Includes selected genes with high penetrance exclusively related to early-onset diseases with severe phenotypes, resulting in highly relevant diagnostic information for the patient and their family.

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Unmasking and Identifying Unidentified Issues

As variants reported in the *Tabular List* are not related to the described phenotype but are in nature highly predictive for early onset severe diseases, the identification and reporting of such may alert the health professionals of unexpected issues and allow them to redirect medical efforts accordingly.

Increase in the Diagnostic Yield and Clinical Utility

- Missing clinical information: The list fills a potential gap in the interpretation if the description of the clinical phenotype is incomplete or when the patient's symptoms are evolving over the diagnostic process.
- Enables a potential diagnosis for cases which clinical presentation is not yet well stablished, atypical, characterized by attenuated and/or clinical signs and symptoms not evident at the time of the genetic analysis.
- Dual/complex diagnosis: Facilitates the identification of dual/complex diagnosis, as more than 4% of patients with a genetic condition have more than one gene affected. This can be much higher in endogamy populations or consanguineous families.
- Biased clinical descriptions: Overcomes the risk of biased clinical descriptions where the suspected diagnosis 'fit' into expected findings.

Reproductive Risk Reduction

Allows for the identification of other severe genetic conditions that may also be present in the family and may not manifest in the index case (or not at the time of request). This is especially relevant in endogamy populations or consanguineous families.

How Should a Genetic Counsellor / Physician Analyze This *Tabular List*?

Here is an example of how these variants are reported.

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
NPC1	• Chr2:241817467-241817468 • NM_000271.4:c.1901A>G	p.(Tyr634Cys)	rs202140203	heterozygous	2/4 pathogenic Conservation_nt,aa: high,high 2/2 likely splice effect	gnomAD: 0.0000081 ESP: - 1000 G: 0.0000081 CentoMD®: -	Missense Pathogenic (class 1)

In this case, a heterozygous variant for Niemann-Pick disease, type C1 was detected.

It is recommended to expand clinical inspection and examination regarding suspicious genetic variants. From time to time, the genetic diagnosis can be found there. In other cases, the reported variants can help to determine carrier status, which might be relevant for reproductive decisions for the proband and their family.

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Which are the limitations of the reported variants in *Tabular List*?

In case this additional information is used in the further differential diagnosis process, orthogonal validation of relevant variants is necessary. The classification of these variants may change over time. CENTOGENE is not liable for any missing variant in this list and/or any provided classification of the variants at a certain point of time.

Insofar as the identified variants may indicate (additional) genetic risks or diagnoses in the patient and/or his family and/or inform about reproductive risks, we strongly recommend following applicable local guidelines about informing the patient about such findings.

REFERENCES

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