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Diagnostic Database Rare Diseases at the D&R Institute of Human Genetics Graz a single center registry

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Background/Aims Increasing use of whole exome sequencing has dramatically improved the diagnostic rate in the field of rare diseases. However, most of detected variants and their functional consequences have not yet been described and investigated and are therefore classified as variant of unknown significance (VUS). Gene-associated phenotypes are often not documented in literature in their entire range. Due to these challenges, recognizable causative variants can still be overlooked during the analysis process. A "Diagnostic Database Rare Diseases" was created to achieve an overview of diagnostic cases and the diagnostic rates depending on evaluation strategies and the patients phenotypes.

Methods/Results The database was created using the RDA platform based on a detailed questionnaire for patient referrals. Between 2020 and 2022 phenotypic information according to the questionnaire, terms of the Human Phenotype Ontology (HPO) used for genetic analysis, testing strategies and detected genetic variants were documented. For the present study, 314 cases were analyzed of which 45 (14%) were prenatal. 65/314 (20.7%) cases were solved, 30/314 (9.3%) were probably/partially solved. 602 different HPO terms were used for description of the phenotypes. The most common terms were global developmental delay (n=72), seizures (n=45), muscular hypotonia (n=30), microcephaly (n=29) and delayed speech and language development (n=28). Solved cases were characterized by assignment of significantly more HPO terms than unsolved cases (median [interquartile range] 5 [3-7] versus 3 [2-6], P=0.019). Two cases included in the database were published as reports of novel gene-phenotype descriptions for the genes ARSK and ATP9A.

Conclusion Number of HPO terms was associated with a better diagnostic rate. Detailed phenotyping in rare disease cases is essential to exploit the diagnostic potential of exome analysis.