GENETICS IN A DANISH COMMON VARIABLE IMMUNODEFICIENCY COHORT

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BACKGROUND AND AIM

The aetiology of Common Variable Immunodeficiency (CVID) is complex and not fully elucidated. This study presents the clinical and genetic findings of a Danish CVID cohort and investigate whether initial genetic findings can be re-classified upon re-evaluation years later in time.

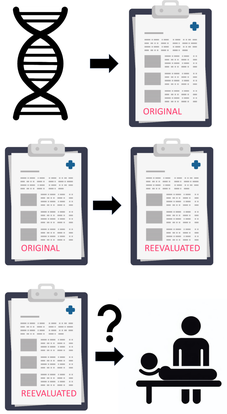
METHODS

From 2016-2021, individuals with CVID or a CVID-like-phenotype were examined using whole exome or whole genome sequencing in combination with comprehensive gene-panels. The results were re-evaluated to ensure up-to-date American College of Medical Genetics and Genomics (ACMG) classification after a median of 3.9 years. Further, a clinical-interpretation-algorithm is proposed.

PHASE I
Genetic analysis of CVID/CVID-like individuals

PHASE II
Re-evaluation of genetic variants

PHASE III
Clinical interpretation
- genotype-phenotype
- inheritance-zygosity
- ACMG-class



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RESULTS

Of 69 enrolled individuals, 57 met the current ESID-CVID-criteria of whom 29 (51 %) had a genetic find. In total 67 ACMG class 3 to 5 variants were detected in 39 different genes. Class 3 variants (variants of uncertain significance (VUS)) accounted for 81 % in the initial analysis. Upon re-evaluation 17 of 54 (31 %) of the originally reported VUS were re-classified to a different ACMG-class or excluded. The developed clinical-interpretation-algorithm demonstrated high interobserver-agreement. A “definite/probable” disease causing (or contributing) genetic variant was found in 19 % of the CVID-cohort and a “possible” in 18 %.

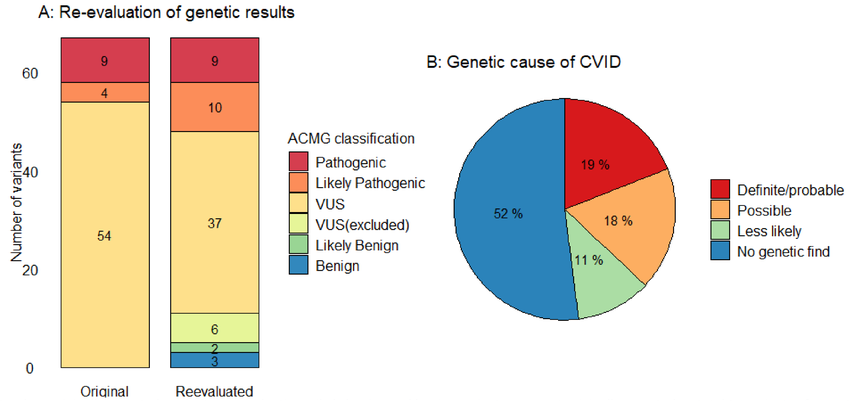

Figure A: ACMG-class-distribution of variants when originally reported, and after re-evaluation. Likely benign and benign variants were not originally reported. In total 17 variants of uncertain significance (VUS) were re-classified upon re-evaluation. These variants were classified as likely pathogenic (n=6), likely benign (n=2) or benign (n=3). Six variants remained of uncertain significance but were excluded according to current reporting algorithm. Figure B: Genetic cause of CVID as defined through the clinical-interpretation algorithm based on genotype-phenotype match, inheritance-zygosity match and ACMG class. ACMG: American College of Medical Genetics and Genomics

CONCLUSION

A genetic cause of CVID could be identified in a minority of CVID-individuals, whereas the majority had no or uncertain genetic findings. Re-evaluation of genetic results over time is recommended, though VUS remain a significant challenge in CVID-genetics. Therefore, continued research in both CVID-genetics and in non-genetic causes of CVID is needed.

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