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BRIEF REPORT

Copy-number variants in the ACMG secondary finding genes: A reporting framework for clinical cytogeneticists

Mahmoud Aarabi[1,2,*], Helia Darabi[2], Aryan Bashar[3], Daniel Bellissimo[2], Aleksandar Rajkovic[4,5], Svetlana A. Yatsenko[1,2,6]

[1]Departments of Pathology, and Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]Medical Genetics and Genomics Laboratories, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; [3]Data Science Graduate Program, University of Colorado Boulder, Boulder, CO; [4]Department of Pathology, and Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco, San Francisco, CA; [5]Institute of Human Genetics, University of California San Francisco, San Francisco, CA; [6]Magee-Womens Research Institute, Pittsburgh, PA

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ABSTRACT

Purpose: To determine the pathogenicity and frequency of copy-number variants (CNV) in the 81 secondary finding (SFv3.2) genes recommended by the American College of Medical Genetics and Genomics (ACMG).

Methods: Review of published evidence on pathogenicity of partial or complete copy-number losses or gains in ACMG SFv3.2 was performed. Frequency of reportable CNVs in the ACMG SFv3.2 genes was investigated among 10,959 patients tested by chromosomal microarray analysis in a single academic testing laboratory at the University of Pittsburgh Medical Center during 2011 to 2023.

Results: We identified 58 ACMG SFv3.2 genes for which sufficient evidence supports reporting of partial or complete copy-number losses as secondary findings. On the contrary, reporting of copy-number gains was not supported by evidence in any of the ACMG SFv3.2 genes. Overall, CNVs in SFv3.2 genes were detected in 32 of 10,959 (0.29% or 1 in 343) patients in our cohort.

Conclusion: This study provides a framework for consistent reporting of CNVs, detected by chromosomal microarray analysis, exome, or genome sequencing, in any of the ACMG SFv3.2 genes. To our knowledge, this is the largest cohort of patients studied for estimation of frequency of reportable CNVs in the ACMG SFv3.2 genes.

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*Correspondence and requests for materials should be addressed to Mahmoud Aarabi, Department of Pathology, University of Pittsburgh School of Medicine, 300 Halket Street, Pittsburgh, PA 15213. *Email address:* aarabim@upmc.edu

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Introduction

The American College of Medical Genetics and Genomics (ACMG) provides guidelines and recommendations for reporting of secondary findings (SF) in clinical exome and genome sequencing.[1-3] SF refer to the discovery of pathogenic or likely pathogenic (P/LP) variants in genes unrelated to the primary reason for testing.[4] The list of SF genes has been continuously updated; the most recent version (v3.2) consists of 81 genes.[5-7] SF list includes genes related to categories of cancer, cardiovascular, inborn errors of metabolism, and miscellaneous conditions.

The focus of ACMG's guidance on SF reporting is on variants detected by clinical exome and genome sequencing that are largely single-nucleotide variants or small indels. Copy-number variants (CNV) may be detected by sequencing or, more commonly, by chromosomal microarray analysis (CMA). CMA has been utilized as the first-tier choice for patients with neurodevelopmental problems and congenital birth defects.[8] Classification standards for CNVs involving SF genes are different from the sequencing variants[9,10] and may not be universally adapted by clinical laboratories.[11-13] Consistent classification of CNVs in SF genes is necessary for cytogenetics and genomics laboratories to ensure reporting such cases is not missed because of unclarities. Here, we reviewed the pathogenicity of CNVs in SFv3.2 genes based on available resources and consensus among clinical laboratory experts. Furthermore, we investigated the frequency of CNVs in the SFv3.2 genes in 10,959 patients tested by CMA in a single academic testing laboratory.

Materials and Methods

Results of CMA data were reviewed from 10,959 patients (pediatrics and adults) tested between January 2011 and June 2023 at the Medical Genetics and Genomics Laboratories of the University of Pittsburgh Medical Center. DNA from peripheral blood specimens were analyzed for CNVs by array comparative genomic hybridization using either a 135K CGH (Roche NimbleGen) or a 180K CGH + SNP oligonucleotide array (ISCA design, Agilent), as previously described.[14] Patients' clinical presentations were obtained from a retrospective medical chart review.

For classification of CNVs in ACMG SFv3.2 genes, we reviewed information on haploinsufficiency, extra gene dosage, or a dominant-negative effect, caused by loss/gain involving the entire gene or intragenic regions. ACMG technical standards for classification of constitutional CNVs were utilized.[9] Data were collected and summarized from ClinGen, ClinVar, the Human Gene Mutation Database, and published literature and were subject to review by a panel of board-certified laboratory geneticists with expertise in CMAs.

Results

Classification of ACMG SF v3.2 Genes

To determine the pathogenicity of copy-number gains or losses involving SFv3.2 genes, we evaluated published evidence for triplosensitivity and haploinsufficiency and curated each gene. At the time of this study, none of the genes in the SFv3.2 list had evidence for triplosensitivity, meaning that a gain of a whole gene is not likely to cause a relevant condition. There are 50 genes in the ACMG SFv3.2 list with evidence for haploinsufficiency based on published literature and ClinGen dosage sensitivity score of 2 or 3 (Table 1, Supplemental Table 1), predicting that their loss-of-function variants would cause disease. Therefore, complete or partial copy-number losses in these genes would be reportable as part of the ACMG secondary findings. On the other hand, 11 ACMG SF genes have no evidence of haploinsufficiency with a ClinGen dosage sensitivity score of 0 or 40, suggesting that loss-of-function variants may not cause disease. Thus, complete or partial copy-number losses in these genes would not be reportable as part of the ACMG SF (Table 1, Supplemental Table 1).

Of the remaining 20 SF genes, 12 have little evidence for haploinsufficiency (*ACTA2*, *ACTC1*, and *TNNI3*) or have not been curated by ClinGen at the time of this study (*CALM1, CALM2, CALM3, DES, MYL2, PALB2, RBM20, TNNC1,* and *TTR)*. We reevaluated the available reports on these genes. Most of the reported *ACTA2* (MIM# 102620) variants, in patients with thoracic aortic aneurysms and dissections, are missense with functional studies supporting dominant-negative effects on the protein and alteration of actin filament structure as a possible mechanism. Individual studies report patients with *ACTA2* variants that are predicted to cause loss of function.[15] Similar to *ACTA2*, most of the reported variants in *ACTC1* (MIM# 102540) include missense and in-frame deletions, associated with autosomal dominant hypertrophic cardiomyopathy. Reported P/LP variants in *TNNI3* (MIM# 191044) are missense with the dominant-negative impact on the protein as the mechanism in hypertrophic cardiomyopathy. Truncating and nonsense *TNNI3* variants have been reported in patients with cardiomyopathy; however, haploinsufficiency does not appear to be an established mechanism in such cases. Aberrations in *CALM1*, *CALM2*, and *CALM3* (MIM# 114180, 114182, 114183, respectively) genes, all encoding the calmodulin protein, are associated with calmodulinopathies that are life-threatening arrhythmia syndromes. ClinGen has confirmed the gene-disease validity for all 3 genes as definitive for Long QT Syndrome; however, reported disease-causing variants are all missense. Similarly, reported P/LP variants mostly consist of single missense or in-frame indels for *DES* (MIM# 125660), *MYL2* (MIM# 160781), *RBM20* (MIM# 613171), *TNNC1* (MIM# 191040), and *TTR* (MIM# 176300) genes. These variants result in a wide range of

Table 1 Recommendations on reporting CNVs encompassing ACMG secondary finding genes

Gene	MIM	Reporting Recommendation	Gene	MIM	Reporting Recommendation
ACTA2	102620	CNV Not Reportable	*MYL2*[b]	160781	CNV Not Reportable
ACTC1	102540	CNV Not Reportable	*MYL3*	160790	CNV Not Reportable
ACVRL1	601284	Evaluate Deletions for Reporting	*NF2*	607379	Evaluate Deletions for Reporting
APC	611731	Evaluate Deletions for Reporting	*OTC*	300461	Evaluate Deletions for Reporting
APOB	107730	Evaluate Deletions for Reporting	*PALB2*[b]	610355	Evaluate Deletions for Reporting[b]
ATP7B	606882	Report Bi-allelic P/LP[a] Deletions	*PCSK9*	607786	CNV Not Reportable
BAG3	603883	Evaluate Deletions for Reporting	*PKP2*	602861	Evaluate Deletions for Reporting
BMPR1A	601299	Evaluate Deletions for Reporting	*PMS2*	600259	Evaluate Deletions for Reporting[c]
BRCA1	113705	Evaluate Deletions for Reporting	*PRKAG2*	602743	CNV Not Reportable
BRCA2	600185	Evaluate Deletions for Reporting	*PTEN*	601728	Evaluate Deletions for Reporting
BTD	609019	Report Bi-allelic P/LP Deletions	*RB1*	614041	Evaluate Deletions for Reporting
CACNA1S	114208	CNV Not Reportable	*RBM20*[b]	613171	CNV Not Reportable[b]
CALM1[b]	114180	CNV Not Reportable[b]	*RET*	164761	Evaluate Deletions for Reporting
CALM2[b]	114182	CNV Not Reportable[b]	*RPE65*	180069	Report Bi-allelic P/LP Deletions
CALM3[b]	114183	CNV Not Reportable[b]	*RYR1*	180901	CNV Not Reportable
CASQ2	114251	CNV Not Reportable	*RYR2*	180902	CNV Not Reportable
COL3A1	120180	Evaluate Deletions for Reporting	*SCN5A*	600163	Evaluate Deletions for Reporting
DES[b]	125660	CNV Not Reportable[b]	*SDHAF2*	613019	Evaluate Deletions for Reporting
DSC2	125645	Evaluate Deletions for Reporting	*SDHB*	185470	Evaluate Deletions for Reporting
DSG2	125671	Evaluate Deletions for Reporting	*SDHC*	602413	Evaluate Deletions for Reporting
DSP	125647	Evaluate Deletions for Reporting	*SDHD*	602690	Evaluate Deletions for Reporting
ENG	131195	Evaluate Deletions for Reporting	*SMAD3*	603109	Evaluate Deletions for Reporting
FBN1	134797	Evaluate Deletions for Reporting	*SMAD4*	600993	Evaluate Deletions for Reporting
FLNC	102565	Evaluate Deletions for Reporting	*STK11*	602216	Evaluate Deletions for Reporting
GAA	606800	Report Bi-allelic P/LP Deletions	*TGFBR1*	190181	Evaluate Deletions for Reporting
GLA	300644	Evaluate Deletions for Reporting	*TGFBR2*	190182	Evaluate Deletions for Reporting
HFE	613609	Report Bi-allelic P/LP Deletions	*TMEM127*	613403	Evaluate Deletions for Reporting
HNF1A	142410	Evaluate Deletions for Reporting	*TMEM43*	612048	CNV Not Reportable
KCNH2	152427	Evaluate Deletions for Reporting	*TNNC1*[b]	191040	CNV Not Reportable[b]
KCNQ1	607542	Evaluate Deletions for Reporting	*TNNI3*	191044	CNV Not Reportable
LDLR	606945	Evaluate Deletions for Reporting	*TNNT2*	191045	CNV Not Reportable
LMNA	150330	Evaluate Deletions for Reporting	*TP53*	191170	Evaluate Deletions for Reporting
MAX	154950	Evaluate Deletions for Reporting	*TPM1*	191010	CNV Not Reportable
MEN1	613733	Evaluate Deletions for Reporting	*TRDN*	603283	Report Bi-allelic P/LP Deletions
MLH1	120436	Evaluate Deletions for Reporting	*TSC1*	605284	Evaluate Deletions for Reporting
MSH2	609309	Evaluate Deletions for Reporting	*TSC2*	191092	Evaluate Deletions for Reporting
MSH6	600678	Evaluate Deletions for Reporting	*TTN*	188840	Evaluate Deletions for Reporting
MUTYH	604933	Report Bi-allelic P/LP Deletions	*TTR*[b]	176300	CNV Not Reportable[b]
MYBPC3	600958	Evaluate Deletions for Reporting	*VHL*	608537	Evaluate Deletions for Reporting
MYH11	160745	CNV Not Reportable	*WT1*	607102	Evaluate Deletions for Reporting
MYH7	160760	CNV Not Reportable			

CNV, copy-number variation.
[a]P/LP: Pathogenic/Likely Pathogenic.
[b]Not curated by ClinGen.
[c]Confirmation needed because of the pseudogenes.

abnormalities, such as altered protein structure, gain of function, or splicing defects. No P/LP variants with partial or complete loss or gain of copy numbers for any of these genes have been reported in ClinVar. Given the insufficient evidence, we do not recommend reporting of complete or partial loss of any of these genes as part of the ACMG SF (Table 1, Supplemental Table 1). Partial losses/gains may be treated cautiously because they may disrupt the normal gene and result in abnormal proteins with dominant-negative effects. Nevertheless, such partial loss and gain CNVs will be classified as variants of uncertain significance and thus not reportable based on the ACMG SF recommendations.

Another SF gene with no ClinGen curation for dosage sensitivity is *PALB2* (MIM# 610355). Heterozygote individuals for loss-of-function variants in *PALB2* are at increased risk of breast cancer, whereas homozygous variants are associated with the autosomal recessive Fanconi anemia complementation group, subtype N.[16] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (National Comprehensive Cancer Network Guidelines) classify *PALB2* as a high-risk gene

with medical recommendations.[17] Several complete or partial losses of *PALB2* have been reported in ClinVar as P/LP. ClinGen considers the gene-disease validity as definitive. We recommend reporting loss of *PALB2* as an ACMG secondary finding.

Finally, 8 of 81 genes in the ACMG SFv3.2 are associated with autosomal recessive (AR) conditions. There is no robust data for P/LP copy number losses in *CASQ2* (MIM# 114251) gene. In the following 7 AR genes, there is sufficient evidence for the existence of homozygous loss of function and deletion variants: *ATP7B* (MIM# 606882), *BTD* (MIM# 609019), *GAA* (MIM# 606800), *HFE* (MIM# 613609), *MUTYH* (MIM# 604933), *RPE65* (MIM# 180069), and *TRDN* (MIM# 603283). Taken together, only partial or complete loss of both copies of these AR genes would be reportable. Gains in the SF genes associated with AR conditions are not reportable as their pathogenicity is not supported by the current literature.

Frequency of reportable CNVs in the ACMG SF v3.2 list

We previously detected 23 patients with reportable CNVs in any of the 59 ACMG SFv2.0 genes in our cohort of patients tested during 2011 to 2018.[18] Here, we expanded the cohort to patients analyzed during 2011 to 2023 and included the 22 new genes from the SFv3.2. Of 10,959 patients analyzed, 26 patients were identified with either losses or gains comprising the entire gene or intragenic alterations in the 22 genes studied (Supplemental Table 2). Median age of patients was 1.5 years (newborn-12 years). The most common reasons for testing were developmental delay/hypotonia, congenital anomalies, and dysmorphic features (Figure 1A). In total, CNVs in 19 of 22 newly added SF genes were identified in our cohort, ranging in size from 0.174 to 37.623 Mb. Genes classified under "cardiovascular" category were the most common to be affected with CNVs (16/26, 61.6%, Figure 1B). Gains were detected in 16 of 26 (61.6%) patients, and losses in 10 of 26 (38.4%) patients (Figure 1C). Three patients had large CNVs that included more than 1 ACMG SF gene (Supplemental Table 1, Supplemental Figure 1). Heterozygous CNVs involving the *TRDN* gene were the most common finding (6/26 patients, 23%), followed by CNVs in the *TTN* gene (3/26, 11.5%, Figure 1D and E). Based on the reporting framework described above, 5 of 26 patients carried losses comprising 1 of the 22 newly added genes (*BMPR1A*, *DSC2*, *DSG2*, *TTN*, and *TTR*) that would be reportable as SF CNVs (Supplemental Figure 2, Supplemental Table 2). Additional 4 patients, tested during 2019 to 2023 and not published previously, were found to have reportable CNVs in the rest of the ACMG SF genes (Supplemental Figure 2). In total, we identified 32 out of 10,959 patients (0.29%) in our cohort with reportable P/LP CNVs in any of the ACMG SFv3.2 genes.

Discussion

Disease-causing CNVs are commonly detected in 5% to 9% of genetic conditions by CMA, exome, or genome sequencing.[19] Recent investigations of SF genes estimated the frequency of P/LP variants between 1.7% and 4.3% of all tested individuals in various populations (Supplemental Table 3). Earlier versions of the ACMG SF genes were generally evaluated in these studies, with a few recent publications examining the v3.1 list with 78 genes. Importantly, most of these studies evaluated single-nucleotide variants, with no analysis and reporting of CNVs in the SF genes. Our group previously showed a frequency of 0.26% for reportable CNVs in 1 of the 59 SFv2.0 genes.[18] Here, we expanded our cohort and examined the presence of CNVs in the latest release of SF genes (v3.2). In total, our study showed a frequency of 0.29%, approximately 1 in 343 patients for the detection of reportable CNVs in SFv3.2 genes. As expected, addition of new genes slightly increased the likelihood of detection of patients with reportable CNVs in any of the ACMG SF genes. To our knowledge, this is the largest cohort of patients examined for CNVs in the ACMG SF genes.

In addition to the estimation of CNV frequencies, this study provides a comprehensive review for pathogenicity of CNVs involving the entire or part of the SF genes, along with a set of recommendations for reporting such CNVs. Evaluation of CNVs by CMA is different from single variants and is governed by a different set of technical standards provided by ACMG.[9] These standards, along with the information from resources such as ClinGen Dosage Sensitivity Curation are commonly used by the cytogenetics laboratories to determine CNV pathogenicity. As per ACMG guidelines, only P/LP variants need to be reported in SF genes. We hope that the current study provides a framework for consistent classification of CNVs particularly when the ClinGen dosage sensitivity data are not readily available. It should be noted that the proposed CNV classifications may need to change as new functional studies on variants become available. A complete loss of a single copy may not cause a phenotype, although partial gene and intragenic deletions and duplications may have a similar effect as pathogenic single variants or indels. In addition, availability of new population databases may provide information that could be used for variant classification.[20] Therefore, we recommend that clinical laboratories performing CMA analyze the SF genes for any CNVs, classify them in accordance to the ACMG standards, and report the P/LP variants.[7,9] A caveat in reporting CNVs in SF genes is that pretest counseling and consent for receiving secondary findings may not be routine for CMA testing, whereas it is considered standard for exome and genome sequencing. Clinical laboratories performing CMA may struggle with the decision whether to actively search for pathogenic CNVs in SF genes or how to handle their reporting when discovered in routine result review. On the other hand, it would be unfair to patients if the clinical laboratories report P/LP

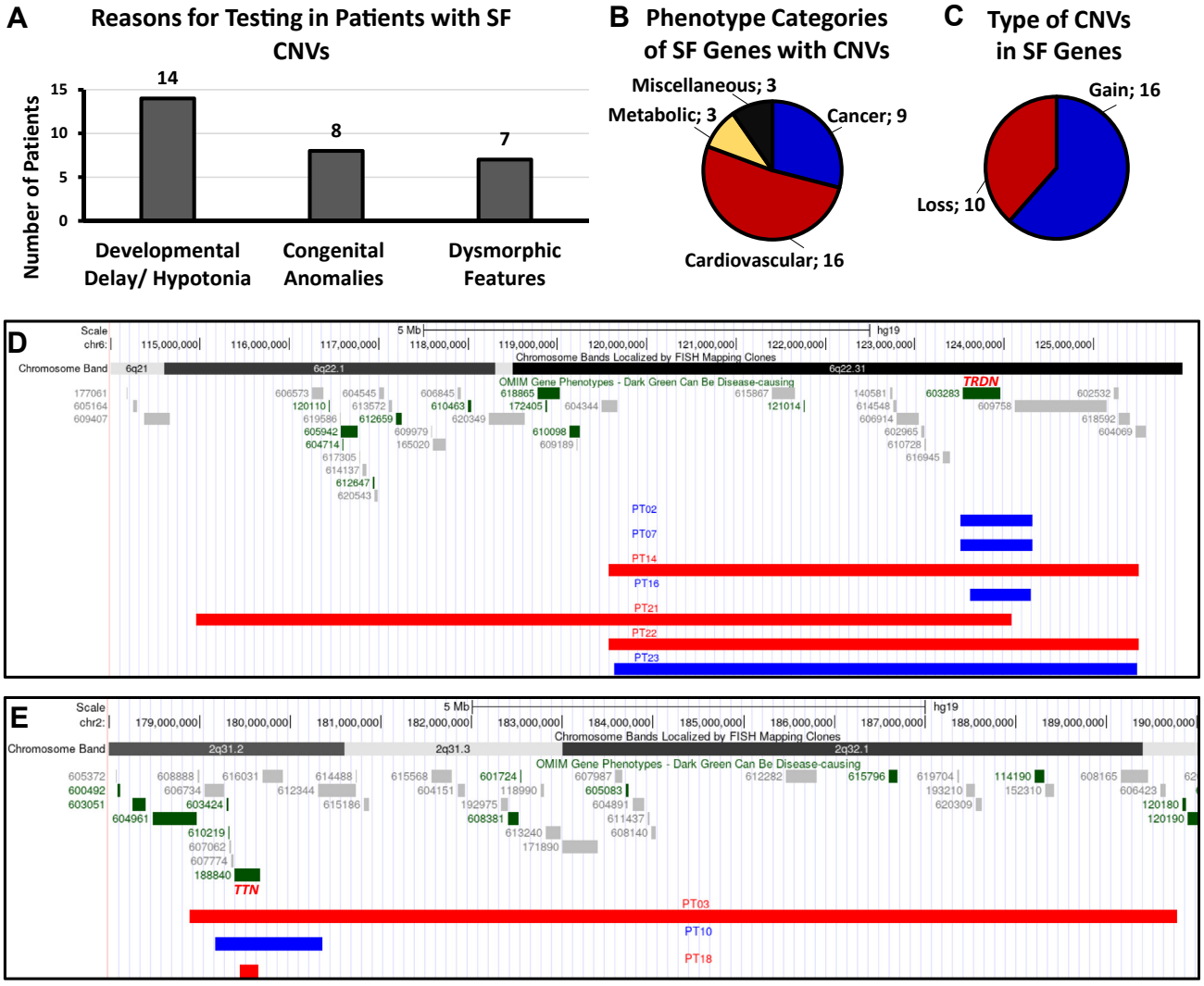

Figure 1 Copy-number variants (CNVs) detected by chromosomal microarray analysis (CMA) in 22 genes added to the ACMG secondary finding genes v3. A. Reasons for referral in patients with CNVs in SFv3.2 genes; some patients had more than 1 category listed as reason for referral. B. Categories of phenotypes associated with SFv3.2 genes with CNVs in our cohort; some patients had several SF genes affected and were included in more than 1 phenotype category. C. Type of CNVs detected in SF genes. D and E. Schematic figures demonstrating the most common CNVs found in *TRDN* (D) and *TTN* (E) genes. Red and blue bars represent copy-number losses and gains, respectively.

variants in SF genes during exome/genome sequencing but not in CMA. Education of providers to include the topic of SF in pretest counseling, along with clear communication of laboratory SF policies, may help to mitigate the risks related to reporting such variants.

Based on our findings, we also suggest that ACMG SF Workgroup recognizes the importance of integrating information on CNVs as part of the SF guidelines. To avoid any ambiguity among the clinical laboratories, it is highly recommended that all new loci added to the ACMG SF lists be pre-curated for pathogenicity and dosage sensitivity, and such information becomes readily available to the community as part of the ACMG SF guidelines.

In conclusion, this study provides a framework for consistent reporting of CNVs in SF genes in clinical laboratories. Furthermore, when CNVs are reported in SF genes, genetics providers can use the data presented here for interpretation of results and for determination of follow-up steps in their patients.

Data Availability

The data that support the findings of this study are available by request.

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Author Information

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Ethics Declaration

This study was approved by the University of Pittsburgh Institutional Review Board (IRB-STUDY20010147). Informed consent was not required (not applicable for a retrospective study), and individual data were deidentified.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gimo.2024.101839) contains supplementary material, which is available to authorized users.

References

1. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2017;19(2):249-255. http://doi.org/10.1038/gim.2016.190
2. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1391-1398. http://doi.org/10.1038/s41436-021-01171-4
3. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565-574. http://doi.org/10.1038/gim.2013.73
4. ACMG Board of Directors. The use of ACMG secondary findings recommendations for general population screening: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2019;21(7):1467-1468. http://doi.org/10.1038/s41436-019-0502-5
5. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1381-1390. http://doi.org/10.1038/s41436-021-01172-3
6. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.1 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2022;24(7):1407-1414. http://doi.org/10.1016/j.gim.2022.04.006
7. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2023;25(8):100866. http://doi.org/10.1016/j.gim.2023.100866
8. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86(5):749-764. http://doi.org/10.1016/j.ajhg.2010.04.006
9. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med*. 2020;22(2):245-257. http://doi.org/10.1038/s41436-019-0686-8
10. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. http://doi.org/10.1038/gim.2015.30
11. Brandt T, Sack LM, Arjona D, et al. Adapting ACMG/AMP sequence variant classification guidelines for single-gene copy number variants. *Genet Med*. 2020;22(2):336-344. http://doi.org/10.1038/s41436-019-0655-2
12. Zhang K, Lin G, Han D, Han Y, Peng R, Li J. Adaptation of ACMG-ClinGen technical standards for copy number variant interpretation concordance. *Front Genet*. 2022;13:829728. http://doi.org/10.3389/fgene.2022.829728
13. Masson E, Zou WB, Génin E, et al. Expanding ACMG variant classification guidelines into a general framework. *Hum Genomics*. 2022;16(1):31. http://doi.org/10.1186/s40246-022-00407-x
14. Yatsenko SA, Davis S, Hendrix NW, et al. Application of chromosomal microarray in the evaluation of abnormal prenatal findings. *Clin Genet*. 2013;84(1):47-54. http://doi.org/10.1111/cge.12027
15. Li J, Yang L, Diao Y, et al. Genetic testing and clinical relevance of patients with thoracic aortic aneurysm and dissection in northwestern China. *Mol Genet Genomic Med*. 2021;9(10):e1800. http://doi.org/10.1002/mgg3.1800
16. Xia B, Dorsman JC, Ameziane N, et al. Fanconi anemia is associated with a defect in the BRCA2 partner PALB2. *Nat Genet*. 2007;39(2):159-161. http://doi.org/10.1038/ng1942
17. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2024. National Comprehensive Cancer Network. Accessed December 5, 2023. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
18. Yatsenko SA, Aarabi M, Hu J, et al. Copy number alterations involving 59 ACMG-recommended secondary findings genes. *Clin Genet*. 2020;98(6):577-588. http://doi.org/10.1111/cge.13852
19. Shaikh TH. Copy number variation disorders. *Curr Genet Med Rep*. 2017;5(4):183-190. http://doi.org/10.1007/s40142-017-0129-2
20. Schmitz MJ, Aarabi M, Bashar A, Rajkovic A, Gregg AR, Yatsenko SA. Carrier frequency of autosomal recessive genetic conditions in diverse populations: lessons learned from the genome aggregation database. *Clin Genet*. 2022;102(2):87-97. http://doi.org/10.1111/cge.14148