Relevance of secondary findings in cancer susceptibility genes in a Reference Service for Rare Diseases in Bahia

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1 Introduction

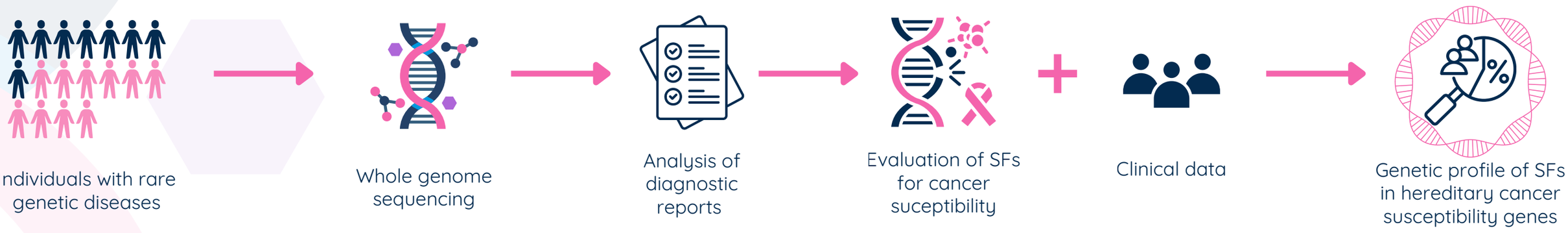
Secondary findings (SFs) are clinically significant genetic variants detected in genes outside the primary scope or purpose of the genetic testing. Advances in genomic sequencing have increased the detection of SFs, including those in genes associated with hereditary cancer susceptibility. The clinical relevance and prevalence of these findings in individuals with rare diseases warrant investigation to perform genetic counselling.

2 Objective

This study evaluates the prevalence and genetic profile of SFs in hereditary cancer susceptibility genes, among patients enrolled in the Brazilian Rare Genomes Project, from a reference center for rare diseases in Salvador, Bahia, Brazil.

3 Methodology

A total of 1.582 individuals were included for whole genome sequencing (WGS), as part of the Brazilian Rare Genomes Project. Approximately 99% of patients provided consent to receive related to secondary findings. Individuals for whom hereditary cancer syndromes were the primary indication for testing were excluded from the analysis. WGS reports from the remaining patients were analyzed for SFs in cancer susceptibility genes according to the American College of Medical Genetics. Clinical data, including primary suspected diagnosis and demographics, were collected and correlated with SFs.



4 Results

At least one secondary finding for hereditary cancer susceptibility was identified in 1.5% (23/1.566) of patients. The clinical and molecular characteristics of individuals with SFs in cancer susceptibility genes are shown below:

Gender distribution of the cohort

Gender	Number of patients (%)
Male	15 (65)
Female	8 (35)

Age group among individuals

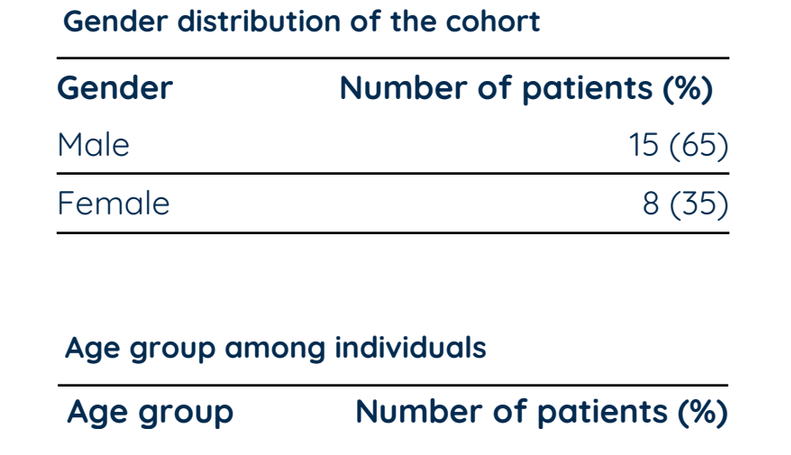
Age group	Number of patients (%)
0-9	9 (39)
10-19	7 (30)
20-29	3 (13%)
30-39	2 (9)
40-49	2 (9)

Clinical cohorts of patients with SF for cancer predisposition

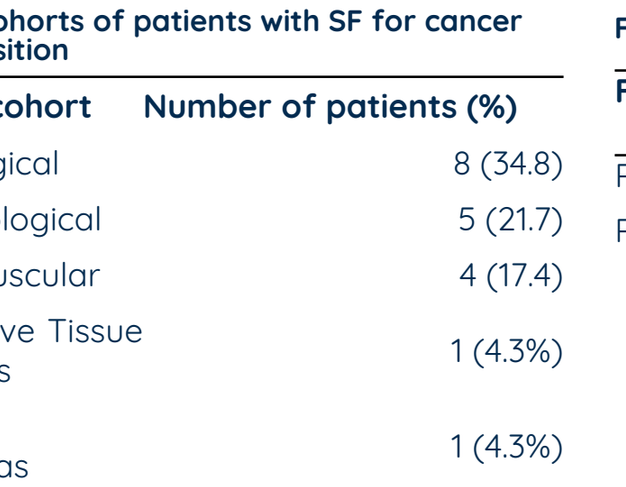
Clinical cohort	Number of patients (%)
Neurological	8 (34.8)
Dermatological	5 (21.7)
Neuromuscular	4 (17.4)
Connective Tissue Disorders	1 (4.3%)
Skeletal Dysplasias	1 (4.3%)
Inborn Errors of Metabolism	1 (4.3%)
Neurocutaneous	1 (4.3%)
Ophthalmological	1 (4.3%)
Established Genetic Syndromes	1 (4.3%)

Family history of cancer among participants

Family history of cancer	Number of individuals (% [when applicable])
Probands with unknown family history	15 (65.2)
Probands with positive family history	8 (34.8)
Overall cancer occurrences	16
Colorrectal	4 (25)
Familial Adenomatous Polyposis (PAF)	3 (18.8)
Prostate	2 (12.5)
Lung	2 (12.5)
Breast	1 (6.3)
Lymphoma	1 (6.3)
Throat	1 (6.3)
Skin	1 (6.3)
Nasopharyngeal	1 (6.3)



Results for primary findings among participants



Frequency of individuals harboring P/LP variants within each gene, highlighting the prevalence of significant genetic alterations

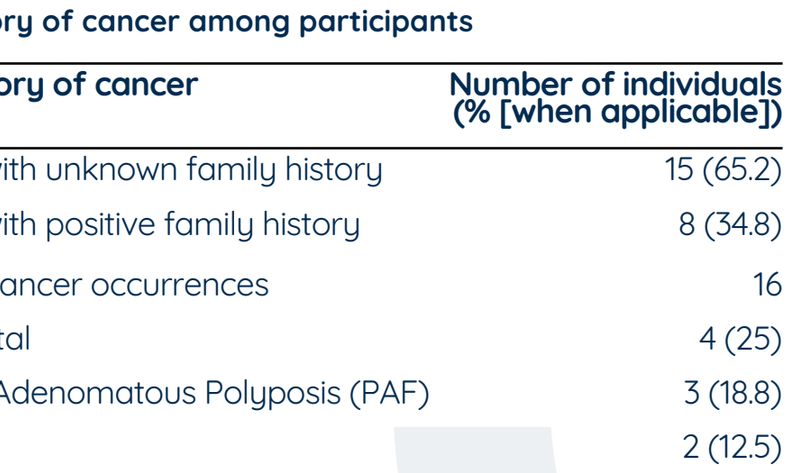
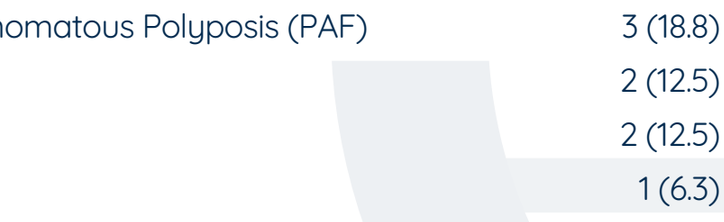


Fig. 3 Recurrent variants among individuals



Novel variants identified

5 Conclusion

Our study reveals a significant prevalence of SFs in cancer susceptibility genes within a rare disease cohort in Bahia. The identification of novel and recurrent variants in unsuspected patients reinforce the importance of systematic screening and genetic counseling for these findings, highlighting their clinical relevance for identifying individuals at high-risk who may benefit from early intervention.

Acknowledgements

This research was made possible through access to the data and findings generated by the Rare Genomes Project; http://www.genomasraros.com.