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Multifactorial susceptibility to Familial Multiple Myeloma: Genomic analysis of a Brazilian family with emphasis on patterns of variants in *CDKN2B-AS1* and *HOGA1*

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INTRODUCTION

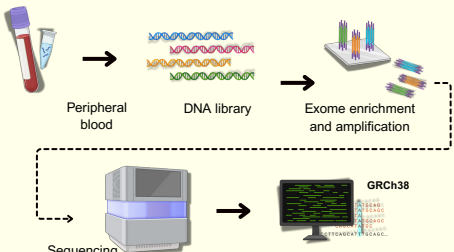
Multiple myeloma (MM) is a rare plasma cell neoplasm that accounts for 1% of cancers and 10% of hematologic malignancies. Although traditionally described as sporadic, evidence of familial aggregation is part of a growing discussion about the disease. The underlying hereditary susceptibility, however, remains largely unexplored, especially in Latin American society. Our study investigates the genomic landscape of familial MM in a Brazilian family, using whole exome sequencing (WES) to identify germline variants that may confer disease risk.

OBJECTIVES

To investigate germline variants in a Brazilian family with recurrent MM or related hematologic conditions, possibly associated with disease susceptibility, in order to compare the genetic basis of risk identified among affected and non-affected individuals.

METHODS

Seven samples (two affected, five unaffected) from one family with recurrent MM were analyzed by WES (Illumina NextSeq 1000). Bioinformatic analysis included read mapping, variant calling (Dragen 4.3.6), and annotation (ANNOVAR) aligned with ACMG. Variants were filtered by quality, allele frequency (Brazilian and global populations), and predicted impact. Candidate variants were cross-referenced with cancer susceptibility gene databases and evaluated for familial segregation and biological relevance.



RESULTS AND DISCUSSION

WES generated **~60,000 variants/sample**. After our filtering pipeline, the two affected individuals (proband and uncle) shared a specific pattern of **five risk variants in *CDKN2B-AS1***, together with **one pathogenic polymorphism in *HOGA1***. Non-affected family members exhibited a variable subset of these SNPs, suggesting **incomplete penetrance and variable expressivity**. No direct physical interaction was found between them, but their co-occurrence points to a **synergistic risk modulation** as they **converge on oncogenic pathways**.

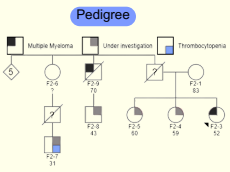


FIGURE 1. Pedigree of the family analyzed.

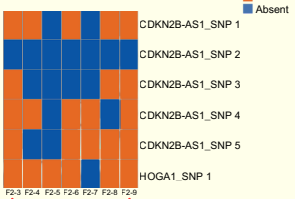


FIGURE 2. Heatmap of variants in *CDKN2B-AS1* and *HOGA1* in individuals.

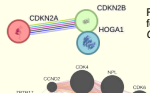


FIGURE 3. STRING Network analysis for *CDKN2A* and *CDKN2B*, regulated by *CDKN2B-AS1*, together with *HOGA1*.

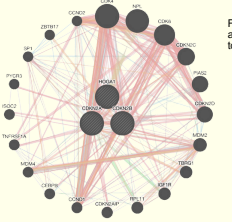


FIGURE 4. GeneMania Network analysis for *CDKN2A* and *CDKN2B* together with *HOGA1*.

This suggests their role as **novel candidate genes for MM susceptibility**, pointing to a **multifactorial inheritance model.**

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CONCLUSIONS

The identified variants may **act synergistically to modulate penetrance and risk**. Integrated investigations are needed to understand the **etiology of MM**. Our results reinforce the need for studies in **admixed populations** and the search for a broader spectrum of variants.

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HIGHLIGHTS

First evidence of a **polygenic and multifactorial inheritance** model for **Familial Multiple Myeloma in a Brazilian family,** highlighting germline variants in ***CDKN2B-AS1*** and ***HOGA1.***