NEXTFRONTIERS TOCURECANCER2022
DE 22 A 25/06 - 100% ONLINE

A.C.Camargo Cancer Center
Especializado em Vida

Detection of germline and somatic alterations in chondrosarcomas and ultra-rare sarcomas in young patients using exome sequencing analysis

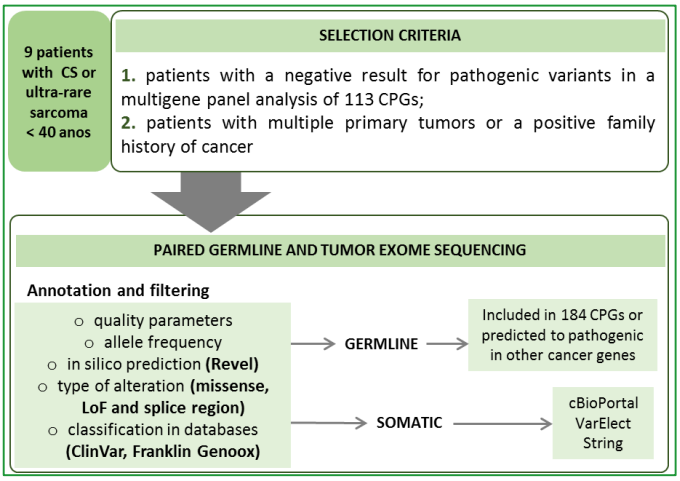
Nathália de Angelis de Carvalho[1], Karina Miranda Santiago[1], Maria Nirvana Da Cruz Formiga[1], Diogo Cordeiro De Queiroz Soares[1], Daniele Paixão Pereira[1], Felipe D'Almeida Costa[1], Barbara Rivera Polo[2], Dirce Maria Carraro[1], Giovana Tardin Torrezan[1]
1 – AC Camargo Cancer Center, São Paulo - BR; 2. IDIBELL, Barcelona - ES

Introduction

Sarcomas are rare tumors with phenotypic and histological heterogeneity, generally demonstrating an aggressive behavior with higher incidence in the younger population. Their biological mechanisms are not yet well-understood, which makes a personalized therapeutic approach more difficult to be considered[1]. With that, the implementation of comprehensive molecular techniques, such as exome sequencing, has allowed the detection of genetic alterations, which may help to understand these rare tumors[2].

Aims: to identify novel cancer predisposing genes (CPGs) and relevant molecular pathways that may be associated with the development of chondrosarcomas and ultra-rare sarcomas in young patients.

Methodology



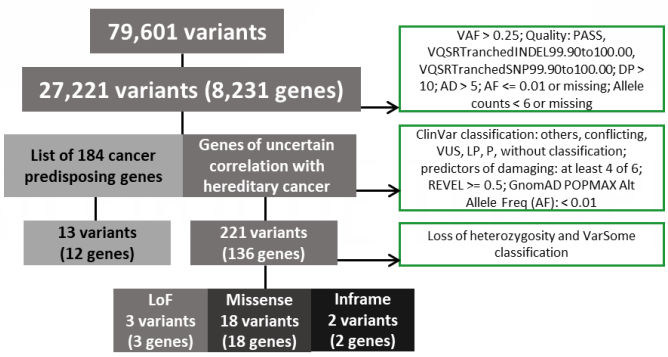
Results

5 chondrosarcomas (CS) **4** ultra-rare sarcomas
- 2 with second primary neoplasm;
- 3 with a family member with cancer

Sample ID	Gender	Age of diagnosis	Histology of sarcoma	Other primary neoplasms	Family history of cancer
GRY_02	F	33	Grade I CS	N/A	Uninformed
GRY_28	M	39	CS	Papillary urothelial neoplasm	Uninformed
GRY_38	M	30	Epithelioid angiosarcoma	N/A	Paternal grandmother: lung cancer (smoker); maternal grandmother: uterine cancer at 30 years
GRY_41	M	31	Grade I CS	N/A	Maternal grandfather: unspecified cancer
GRY_68	M	39	Grade II myxofibrosarcoma	Liposarcoma	Uninformed
GRY_332	M	24	Low grade fibromyxoid sarcoma	N/A	Uninformed
GRY_365	M	8	Fibroblastic sarcoma	N/A	Uninformed
GRY_383	M	35	Grade II CS	N/A	Mother: breast cancer at 50 years
GRY_388	F	18	CS	N/A	Uninformed

EXOME ANALYSIS

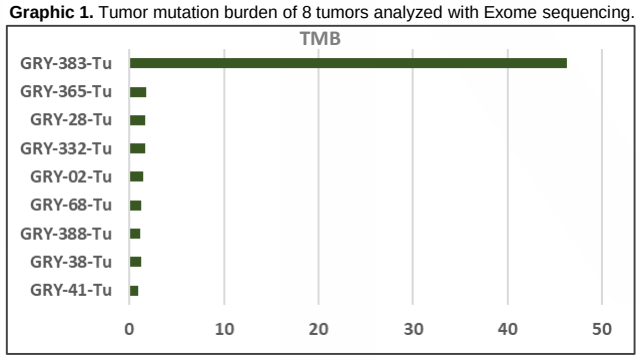
Germline calling



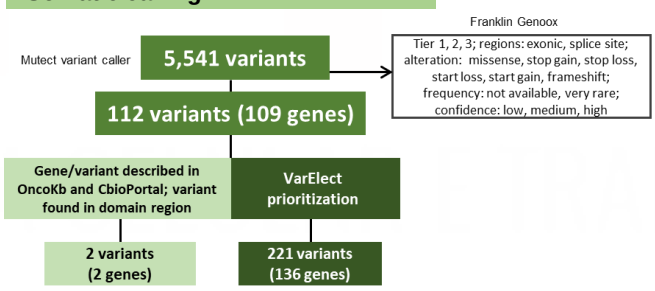
In 8 tumors, known CPGs as *RECQL4*, *BARD1* and *RET* were found and the three LoF were in *RAD50, EFHB* and *ADAM18*. The selected genes are being analyzed using VarElect, where genotype-phenotype is correlated and pathways are shown, helping to prioritize candidate CPGs.

In somatic analysis, 8 tumors had a median of 65 mutations and a median tumor mutation burden (TMB) of 1.4. One chondrosarcoma had a striking high number of somatic mutations and TMB (4,517 and 46, respectively) (Graph 1).

Graphic 1. Tumor mutation burden of 8 tumors analyzed with Exome sequencing.



Somatic calling



We found three genes previously reported as drivers in sarcomas, as *TP53*, *PTCH1*, *CREBBP,* and other genes of unknown function in cancer and sarcomas, such as *FBN3, MOS, MYF6* and *THOC3*. Two variants were observed in domain regions, such as *VPS16*:p.Arg187* and *TP53*:p.Pro151Ser, where the last one was already reported in databases.

Conclusion

With these findings, we expect to contribute with the elucidation of chondrosarcomas and ultra-rare sarcomas behavior, based on molecular evidence that pinpoint the role of novel candidate genes and pathways involved in the process of tumorigenesis for individuals diagnosed with these tumors.

Contats

E-mail: nathalia.carvalho-aluno@accamargo.org.br

REFERENCES:
1. BALLINGER, M. L. et al. Monogenic and polygenic determinants of sarcoma risk: an international genetic study. **Lancet Oncol.**, 2016; 17(9):1261-71;
2. MIRABELLO, L. et al. Frequency of Pathogenic Germline Variants in Cancer-Susceptibility Genes in Patients With Osteosarcoma. **JAMA Oncol**. 2020;e200197.

FINANCIAL SUPPORT:
FAPESP CAPES