Sporadic granular cell tumours lack recurrent mutations in PTP11, PTEN and other cancer-related genes

Granular cell tumour (GCT) is a benign nerve sheath neoplasm of unknown molecular pathogenesis. Although a skeletal muscle cell origin was initially proposed for GCT, its neural origin, derived from Schwann cells, is supported by S-100 immunopositivity. There are few molecular studies on oral GCT. GCTs have been previously described in patients with LEOPARD and Noonan syndrome with PTP11 gene mutations, as well as in a patient with PTEN hamartoma tumour syndrome with PTEN mutation. Therefore, we hypothesised that mutations in these genes could be drivers of sporadic GCT pathogenesis.

A convenience sample of six formalin-fixed, paraffin-embedded (FFPE) sporadic oral GCT was selected from the archives of the author’s institution. All samples were located at the tongue and occurred in female subjects ranging from 18 to 42 years old (median age 34 years old). The H&E stained slides were analysed by two pathologists (CCG and RSG) to confirm the diagnosis (figure 1A). Tumour-enriched areas were ensured by microdissection and DNA was isolated using Qiagen DNA FFPE Tissue Kit (Qiagen, USA) before next-generation sequencing (NGS) library preparation. NGS was performed on Ion 316Chip Kit v2 (Life Technologies) on the Ion Personal Genome Machine System (Life Technologies). Integrative Genomics Viewer (IGV 2.3) was used to exclude false-positive variants. Variants read with a minimum coverage of X100, with a frequency greater than 5%, were reported.

PTPN11 and PTEN mutations were not detected in any of the samples. However, sample no. 1 showed KDR p.Asp257Asn, GNAQ p.Val240Met and GNAQ p.Asp257Asn, which have been previously described in patients with LEOPARD and Noonan syndrome with PTP11 gene mutations, as well as in a patient with PTEN hamartoma tumour syndrome with PTEN mutation. Therefore, we hypothesised that mutations in these genes could be drivers of sporadic GCT pathogenesis.

Figure 1 Granular cell tumour (GCT) histopathology and immunohistochemical results. (A) Sheets and small nests of polygonal cells with indistinct border exhibiting granular eosinophilic cytoplasm are observed (H&E, original magnification X10). Decreased immunohistochemical expression of: (B) anti-phospho-Chk2-Thr68 (clone C13C1) and (C) anti-phospho-histone H2A.X-Ser139 (clone 20E3) was observed in sample no. 1, which exhibited the presence of an ATM missense mutation (original magnification X40).

Figure 2 ATM-mediated DNA damage response. DNA damage might be caused by endogenous and/or exogenous agents and promotes cellular responses that can arrest cell cycle progression, DNA repair and apoptosis. ATM is a damage sensor protein that initiates signal transduction cascades and phosphorylates Chk2. The histone H2A.X is also an ATM substrate and its phosphorylation occurs in response to DNA double-strand breaks. ATM mutation leads to failures in the DNA damage detection and repair, which in turn result in mutation accumulation.

[Diagram showing DNA damage response]
and phospho-histone H2A.X). Sample no. 1, which harboured the ATM missense mutation, showed lower immunorexpression of both proteins when compared with the median of the expressions of the other cases (figure 1B,C). As phospho-Chk2 and phospho-histone H2A.X are normally activated by ATM (figure 2), the fact that the mutant sample showed low immunostaining of these DNA damage signalling markers supports the deleterious effect prediction of the ATM mutation. As the ATM mutation occurred in only one sample, the role of such mutation in oral GCT pathogenesis, if any, remains to be further clarified.

Sample no. 2 showed the presence of SMO rs148484943. The other four samples exhibited KDR rs1870377 and TP53 rs1042522, which are single nucleotide polymorphisms (SNP) (minor allele frequency >0.01). Whether these SNPs can modify the risk for oral GCT development remains to be tested in a large panel of patients with GCT.

In conclusion, only two of six samples showed mutations in the oncogenes and tumour suppressor genes screened, but none occurred in PTPN11 and PTEN genes. Mutations at KDR, GNAQ and ATM are reported for the first time, but no recurrent mutation in the gene panel evaluated was found.

Josiane Alves França,1 Silvia Ferreira de Sousa,2 Rennan Garcia Moreira,3 Vanessa Fátima Bernardes,4 Leticia Martins Guimarães,4 Jean Nunes Santos,2 Marina Gonçalves Diniz,4 Ricardo Santiago Gomez,4 Carolina Cavalli Gomes1

1Department of Pathology, Biological Sciences Institute, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil
2Department of Dentistry, Health and Biological Sciences Institute, Universidade Federal de Sergipe (UFS), Aracaju, Brazil
3Genomics Laboratory, Biological Sciences Institute, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil
4Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil
5Department of Oral Pathology, School of Dentistry, Universidade Federal da Bahia (UFBA), Salvador, Brazil

Correspondence to Dr Carolina Cavalli Gomes, Department of Pathology, Biological Sciences Institute, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG 31270 901, Brazil; carolinagomes@ufmg.br

Handling editor Runjan Chetty.

Acknowledgements We thank Centro de Laboratórios Multiusuários, ICB/Universidade Federal de Minas Gerais for providing support on the next-generation sequencing.

Contributors All authors have made significant contribution to the manuscript, and have seen and approved the final manuscript. Study concept: SFS, MGD, RSG, CCG, JAF. Data acquisition: JNS, LMG, RGM. Data analysis and interpretation: VFB, JAF, MGD, RSG, CCG. Manuscript preparation: JAF, SFS, MGD, RSG, CCG. Manuscript review: JAF, SFS, RGM, VFB, LMG, JNS, MGD, RSG, CCG.

Funding This study was funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)/Brazil, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)/Brazil, and Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG)/Brazil.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Universidade Federal de Minas Gerais Ethics Committee.

Provenance and peer review Not commissioned; internally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.


Received 16 October 2017
Accepted 17 October 2017
Published Online First 2 November 2017


REFERENCES