19. A recurrent somatic missense mutation in GNAS gene identified in familial thyroid follicular cell carcinomas in German longhaired pointer dogs

Yun Yu[1*], Freek Manders[2], Markus J. van Roosmalen[2], Guy C M Grinwis[3], Martien A.M. Groenen[1], Richard P.M.A. Crooijmans[1]

[1] Animal Breeding and Genomics, Wageningen University & Research, The Netherlands
[2] Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584CS Utrecht, The Netherlands
[3] Department of Biomolecular Health Sciences, Division of Pathology, Faculty of Veterinary Medicine, Utrecht University, Yalelaan 1, Utrecht, The Netherlands
* Corresponding author. E-mail: yun.yu@wur.nl

We previously reported a familial thyroid follicular cell carcinoma (FCC) in a large number of Dutch German longhaired pointers and identified two deleterious mutations in the TPO gene associated with disease predisposition. The somatic mutation profile of thyroid cancers (TC) in dogs has not been investigated at a genome-wide scale. In this study, we comprehensively investigated the somatic mutations that potentially contribute to the inherited tumor formation and progression using high depth whole-genome sequencing. A GNAS A204D missense mutation was identified in 4 out of 7 FCC tumors by whole-genome sequencing and in 22 out of 32 dogs' tumors by targeted sequencing. In contrast to this, in the human TC, mutations in GNAS gene have lower prevalence. Meanwhile, the homologous somatic mutation in humans has not been reported. These findings suggest a difference in the somatic mutation landscape between canine TC and human TC. Moreover, tumors with the GNAS A204D mutation had a significantly lower somatic mutation burden in these dogs. Somatic structural variant and copy number alterations were also investigated, but no potential driver event was identified. This study provides novel insight in the molecular mechanism of thyroid carcinoma development in dogs. German longhaired pointers carrying GNAS mutations in the tumor may be used as a disease model for the development and testing of novel therapies.

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