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Letter to the Editor

Response to letter to the editor on "Germline NGS targeted analysis in adult patients with sporadic adrenocortical carcinoma"

Dear Editor,

we welcome the letter by Bouys and Colleagues for their thoughtful comment on our article [1] that allows us to better shape the interpretation of our findings.

Based on their large experience with patients affected by Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) and extensive research on ARMC5 gene, Bouys and Colleagues challenge our interpretation that the c.2192C > G variant has a potential pathogenic role for adrenocortical carcinoma (ACC).

Concerning the variant frequency, we underline that the minor allele frequency of the c.2192C > G variant in the Non-Finnish European population is currently estimated at 0.0009475 % [2]. Given that a frequency of 0.2 % was found in our cohort of 150 patients with ACC, this ARMC5 variant was very enriched compared to the general population.

Concerning the lack of a second hit, we underline that this ARMC5 variant was validated via Sanger sequencing, confirming its presence in a heterozygous state at both germline and somatic level. Although this finding lets us to exclude a loss of heterozygosity event, we were not able to detect the presence of a possible different second hit (somatic point mutation or deletion) also because we only analyzed the coding sequence of exon 6.

Concerning the lack of pathogenic potential of the c.2192C > G variant, we underline that the bioinformatic analysis conducted on this variant using the SIFT algorithm (score 0.0) [3] and the Polyphen algorithm (score 0.859) [4], predicts a probably deleterious impact on the ARMC5 protein. The moderately high Grantham score (103) [5] reflects a significant chemical imbalance between the substituted amino acids (proline to arginine), suggesting a likely impact on protein folding or interaction dynamic. At the time when our analysis was done, the variant was classified as conflicting interpretation of pathogenicity (CIP) according to the ClinVar database [6]. The remarkable enrichment of this variant in our patients with ACC and the results of the predictive bioinformatic tools led us to attribute a possible pathogenetic role to this variant. The classification of this variant has evolved over time, reflecting ongoing development in the interpretation of genetic data and better integration of accumulating evidence. Currently, in the ClinVar database the variant is categorized as CIP, with five submissions: three "variants of uncertain significance (VUS)" and two "likely benign (LB)". On the other hand, the Universal Protein Knowledgebase [7] classifies the variant as pathogenic.

Therefore, we believe that the jury is still out, but we certainly share the view of Bouys and Colleagues that patients harboring an ARMC5 pathogenic variant should not be managed as having an ACC favoring condition. We did not made such a conclusion in our paper and we believe that this comment may help to interpret more correctly our findings. Given the pathological evidence of both PBMAH and ACC in a carrier of the variant, we argued that progression from PBMAH to ACC is possible, a statement that has a completely different meaning. We believe that this condition has a striking analogy with the recently reported possibility of progression of an adrenal adenoma to ACC [8,9]. However, given the extreme rarity of this event, we do not consider adrenal adenomas as pre-malignant conditions [10].

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Declaration of interests

None.

CRediT authorship contribution statement

Puglisi Soraya: Visualization, Writing – review & editing. **Berruti Alfredo:** Conceptualization, Supervision, Validation, Writing – review & editing. **Tomaiuolo Pasquale:** Writing – review & editing. **Grisanti Salvatore:** Conceptualization, Writing – original draft, Writing – review & editing. **Scatolini Maria:** Conceptualization, Writing – original draft, Writing – review & editing. **Terzolo Massimo:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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