AB006. Molecular profiling of genetic alterations in thymic epithelial tumors by targeted next generation sequencing: a pilot study

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Background: The biology of thymic epithelial tumors (TETs), in particular, the extent of dysregulation in their molecular landscape is poorly understood. Development of newer therapies based on genomic alterations could potentially revolutionize treatment of TETs and result in improved clinical outcomes. The frequency and specificity of candidate biomarkers should be evaluated according to distinct TET types and stages. The aim of our pilot study was to evaluate thymic carcinomas and thymomas by next-generation sequencing (NGS) for single nucleotide variants (SNVs) in 15 genes that are commonly mutated in solid tumors.

Methods: Formalin-fixed paraffin-embedded tumor tissue specimens were collected from 40 cases of TETs (33 thymic carcinomas, 7 thymomas) and analyzed for SNVs in 15 genes using targeted NGS. DNA libraries were constructed using the TruSight Tumor 15 assay (Illumina) and sequenced on the MiSeq instrument (Illumina). Results were analyzed using the BaseSpace Variant Interpreter software (Illumina) and the reference genome version hg19/GRCh37.

Results: SNVs were identified in genes TP53, ERBB2, KIT and KRAS. In thymic carcinomas, the most frequent SNVs were: TP53 p.(Pro72Arg) (32/33, 97%), ERBB2 p.(Ile655Val) (16/33, 48%) and KIT p.(Met541Leu) (3/33, 9%), mostly in squamous cell subtype. In thymomas, TP53 p.(Pro72Arg) (6/7, 86%), ERBB2 p.(Ile655Val) (3/7, 43%) and KIT p.(Met541Leu) (2/7, 29%) showed also the highest frequency. Rare pathogenic missense variants in TP53 [p.(Gly154Val), p.(Arg158Pro), p.(Arg273Cys), p.(Leu194His)], ERBB2 [p.(Val773Met)], KIT [p.(Leu576Pro), p.(Ile690Val)] and KRAS [p.(Gln61Leu)], and pathogenic stop-gained variants in TP53 [p.(Arg306Ter, p.(Gln317Ter)) were found across the samples. The median read frequency of altered variants reached 58% (range, 5–100%) in carcinomas and 54% (range, 51–100%) in thymomas.

Conclusions: The NGS analysis of TET specimens revealed a vast number of SNVs in genes playing important role in p53, AKT, MAPK and K-Ras signaling pathways, which are deregulated in many solid tumor types. The uncertain biological and clinical importance of TP53 p.(Pro72Arg) and ERBB2 p.(Ile655Val) variants in TET development awaits further investigation. Detecting druggable KIT alterations in TETs showed promise for possible therapeutical targeting. The high-quality data gained in this pilot study provided a strong rationale for carrying out more comprehensive genomic profiling of TETs. The study is ongoing.

Keywords: Carcinoma; thymoma; next-generation sequencing (NGS); single nucleotide variant (SNV); KIT gene

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article

doi: 10.21037/med.2021.ab006

Cite this abstract as: Szpechcinski A, Szolkowska M, Winiarski S, Lechowicz U, Wisniewski P, Knetki-Wroblewska M. Molecular profiling of genetic alterations in thymic epithelial tumors by targeted next generation sequencing: a pilot study. Mediastinum 2021;5:AB006.