Molecular Pathology of Thymic Epithelial Tumors

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12.1 Introduction

Integrated genomic analyses of thymic epithelial tumors (TETs) demonstrate significant genetic and molecular heterogeneity among the different histological subtypes [1]. Type A, type AB thymomas, type B thymomas, and thymic carcinomas segregate into distinct genetic/molecular entities on multiplatform omics studies with differences in the loci and frequency of their chromosomal copy number alterations, recurrent gene mutations, miRNA profiles, and, more recently, DNA methylation patterns. Gene fusions and expression of viral/bacterial antigens have not been identified in these tumors [1]. Overall, there is limited understanding of the molecular pathogenesis of thymic epithelial tumors and successful targeted therapies are yet to be discovered. In this chapter, we highlight select molecular genetic features of diagnostic, prognostic, or potential therapeutic significance in TETs.

12.2 Recurrent Gene Mutations in Thymic Epithelial Tumors

Thymic epithelial tumors harbor one of the lowest rates of somatic mutations among adulthood onset cancers with estimated tumor mutation burden of approximately 0.48 mutations per mega base [1]. Whole genome sequencing studies have identified recurrent mutations in a very limited number of genes (Fig. 12.1), the most frequent being the General Transcription Factor 2I (*GTF2I*) gene, point mutations of which occur in ~39% of all TETs [1]. Recurrent mutations of

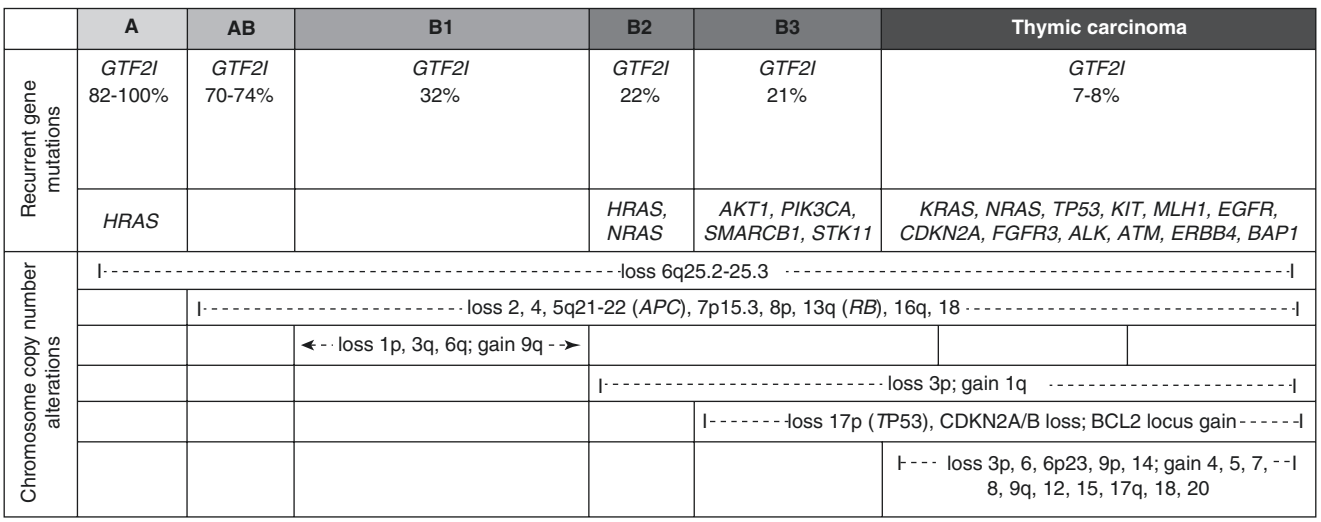

Fig. 12.1 Recurrent gene mutations and chromosomal copy number alterations in the different histological subtypes of thymic epithelial tumors

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genes involved in the EGFR signaling pathway such as *RAS* family, *PIK3CA*, *AKT*, *EGFR*, and *TP53*, also occur, albeit at much lower frequencies [1].

12.2.1 *GTF2I* (General Transcription Factor 2I) Mutations

- *GTF2I* is localized on chromosomal region 7q11.23 and encodes for members of the transcription factor IIi, a group of ubiquitously expressed proteins involved in diverse signaling pathways.
- Mutations are most frequent in type A (82–100%) and type AB (70–74%) thymomas, less common in type B thymomas (20–30%) and thymic carcinoma (7–8%) [1, 2].
- Characterized by a missense mutation in exon 15 at a single codon (L424H) resulting from T>A nucleotide substitution (Fig. 12.2) [3].
- Highly specific for thymic epithelial tumors; rare *GTF2I* mutations described in tumors other than thymomas involve other codons [1].
- *GTF2I* mutant tumors show higher expression of genes involved in cell morphogenesis, receptor tyrosine kinases, retinoic acid receptors, neuronal processes, and WNT and SHH signaling pathways [1].
- *GTF2I* mutation status not associated with myasthenia gravis [1].
- Within individual histological subtypes, *GTF2I* mutant tumors show better outcomes as compared to those wild type [4].

12.2.2 *RAS* Mutations

- Activating mutations in *HRAS* (codon 12, 13, 117), *NRAS* (codon 61), or *KRAS* are the second most prevalent gene mutations in TETs [1].
- *HRAS* mutations reported predominantly in type A thymomas [1, 5, 6].
- *KRAS* and *NRAS* mutations described in type B2 thymomas and thymic carcinomas [2].

12.2.3 *TP53* Mutations

- Rare, mainly reported in thymic carcinomas and some type B thymomas [1, 2, 5].
- All mutations are pathogenic loss of function mutations.

12.2.4 *KIT* Mutations

- Very rare, detected exclusively in thymic carcinomas (~7% incidence).
- Reported *KIT* mutations include V560 deletion in exon 11, H697Y mutation in exon 14, L576P mutation in exon 11, and D820E mutation in exon 17, of which all except the last predict sensitivity to tyrosine kinase inhibition [7].
- *KIT* mutations do not correlate with KIT protein overexpression which is seen in more than 75% of thymic carcinomas [8].

12.2.5 Others

- *EGFR* mutations are consistently absent in thymomas and very rarely described in thymic carcinomas [5] despite frequent EGFR protein overexpression and *EGFR* gene amplification [8]; thymic epithelial tumors generally do not respond to EGFR tyrosine kinase inhibitors [8].
- Mutations in other genes involved in EGFR signaling, namely, *AKT1* and *PIK3CA*, have been reported in type B3 thymomas and thymic carcinomas [5].
- Rare example of a thymic carcinoma with microsatellite instability due to *MLH1* somatic mutation and high tumor mutation burden has been reported [1].

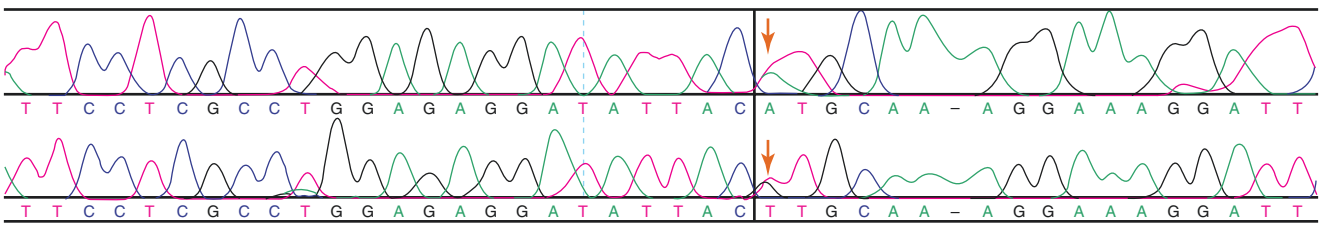

Fig. 12.2 Sanger sequencing chromatogram showing L424H point mutation (T > A nucleotide substitution) in exon 15 of *GTF2I* gene

12.3 Chromosome Copy Number Alterations

Copy number gains and losses of multiple chromosomal regions are well described in thymic epithelial tumors with the frequency and complexity of the alterations increasing with the aggressiveness of the histological type (Fig. 12.1). The biological significance of a majority of these alterations is, however, yet to be determined.

12.3.1 6q25.2-25.3 Loss of Heterozygosity

- Observed in most types of thymomas including thymic carcinomas.
- *FOXC1*, a gene encoding for a transcription factor involved in normal thymus development, is located at this locus and is implicated as a tumor suppressor in the development of thymic epithelial tumors.
- Tumors with reduced m-RNA and protein expression levels of FOXC1 associate with poor prognosis [9].

12.3.2 *CDKN2A/B* Alterations

- Homozygous 9p21.3 (*CDKN2A/B* locus) copy number losses seen only in type B3 thymoma and thymic carcinoma [9].
- Loss of CDKN2A/p16 protein correlates with *CDKN2A* deletions and associates with poor prognosis in thymic carcinomas [10].

12.4 Epigenomic Alterations

- Many miRNAs have been found to be differentially expressed in various histological subtypes of thymic epithelial tumors [11].
- A large microRNA cluster on chr19q13.42 activating the PI3K pathway has been identified as the transcriptional hallmark of type A and AB thymomas and is a potential actionable target [12].
- Altered expression levels of specific miRNAs have been correlated with tumor pathogenesis and prognosis in TETs [8, 13, 14].
- Recent studies have identified significant differences in the DNA methylation patterns among normal thymus, type A thymoma, type B thymoma, and thymic carcinoma with diagnostic and prognostic connotations [15, 16].

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