Gene of the month: *GTF2I*

Shrinidhi Nathany,[1] Rupal Tripathi,[2] Anurag Mehta [3]

[1]Molecular Diagnostics, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India
[2]Department of Research, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India
[3]Department of Laboratory Services, Molecular Diagnostics and Transfusion Medicine, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

Correspondence to
Dr Anurag Mehta, Department of Laboratory Services, Molecular Diagnostics and Transfusion Medicine, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi 110085, Delhi, India; anumehta11@gmail.com

SN and RT contributed equally.

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ABSTRACT

The *GTF2I* is a general transcription factor and its mutations have been reported to be recurrent in thymic epithelial tumours and are rare in other malignancies. Apart from thymic epithelial tumours, these mutations have also been reported in a subgroup of T cell lymphomas, angioimmunoblastic T cell lymphomas. Soft tissue angiofibroma has been reported to harbour *GTF2I-NCOA2* fusion, whereas *GTF2I* partners with Retinoic acid receptor alpha *(RARA)* in acute promyelocytic leukaemia as *GTF2I-RARA*. *GTF2I* has also been implicated in immune disorders and two neuropsychiatric genetic disorders, namely autism and Williams-Beuren syndrome. The various structural, biochemical and functional properties of *GTF2I* suggest towards the oncogenic nature of this gene. Studies involving patients are presently few and the availability of biospecimens amenable to molecular diagnostic studies is limited. Future studies involving biospecimens and transformed cell lines shall provide a clear understanding of the *GTF2I* mechanistic to eventually lead to targeted treatment.

INTRODUCTION

The *GTF2I* (OMIM entry * 601679) alias general transcription factor II-I belongs to the family of general transcription factors, which are a class of protein transcription factors that bind to specific sites on DNA to activate transcription. It is ubiquitously expressed in the human cells, and localises to the cytoplasm of the cell, and translocates to the nucleus at the time of transcription.[1]

HISTORY

The *GTF2I* was discovered 25 years ago and was denoted as a transcription factor.[2] The other names and signals for this gene include WBS, DIWS, SPIN, IB291, BAP135, BTKAP1, WBSCR6 and FLJ38776. Roy *et al*[3] first purified *GTF2I* using nuclear extracts from HeLa cells and cloned it from a Namalwa (Burkitt lymphoma) cDNA library. Spliced variants of *GTF2I* were observed by Cheriyath and Roy[4] who also identified a nuclear localisation signal between the amino acid repeats along with the GTF2I-alpha, GTF2I-beta and GTF2I-gamma variants. Only the beta and delta isoforms of GTF2I expressed in mouse fibroblasts were observed by Hakre *et al*.[5] A unique family of multiprotein corepressor complexes (including a common core of two subunits, HDAC1/HDAC2 and the FAD-binding protein BHC110) modifying the chromatin structure has been studied.[2] An unexpected role of TFII-I as a negative regulator of agonist-induced calcium entry has also been described.[2] An endogenous mouse GTF2I-beta expressed in the nucleus was shown by Hakre *et al*[5] in contrast to the GTF2I-delta which was largely cytoplasmic in the resting cells. Mammoto *et al*[6] observed that a Rho inhibitor modulated the balance of two antagonistic factors, TFII-I and GATA2, and thereby controlled the capillary network formation and retinal angiogenesis.

STRUCTURE

The *GTF2I* gene maps to the long arm of chromosome 7 at position 11.23 (7q11.23). The peptide sequence comprising 998 amino acids is encoded by 35 exons. The domain structure is depicted in figure 1. This protein binds to the initiator element (Inr) and sequence-specific DNA element: E-box element in promoters and it functions as a regulator of transcription (figure 2). It encodes for BAP-135 and TF-II. BAP-135 is also implicated in the normal immune system function.[1–3] Pseudogenes, *GTF2IP1* and *GTF2IP4*, are known to occur and may alter sequencing results, thereby affecting treatment algorithms.

The *GTF2I* has at least four alternatively spliced isoforms in humans which are alpha, beta, gamma and delta, although the expression patterns and transcription functions of beta, gamma and delta forms are largely unknown.[2–4 7]

FUNCTIONS

GTF2I functions as a signal-induced transcription factor. In response to varied extracellular signalling pathways, including B and T cell receptor triggering, the tyrosine residue gets phosphorylated. It also regulates the endoplasmic reticulum stress response pathway, and can specifically interact with cyclic guanosine monophosphate (cGMP) analogues. It can also bind CCCTC-Binding Factor (CTCF), which is a regulator of epigenetic state, in order to drive transcription.[2 8]

It interacts with Serum Response Factor (SRF) and PHOX1 and binds Inr and E-box for upstream stimulators factor 1. This associates with pleckstrin-homology (PH) domain of the Bruton tyrosine kinase[8] and has been implicated in heavy chain immunoglobulin transcription in the immune cells. Additionally, it has also been reported to play an important role in T cell receptor signalling. When the cell surface receptor tyrosine kinases are engaged by their related ligand, there is a calcium influx into the cell which results in generation of inositol 1,4,5-trisphosphate and diacylglycerol through the activation of phospholipase C.[6 9]

GTF2I IN CANCER

GTF2I also undergoes other post-translational modifications like ubiquitination and sumoylation. In response to DNA damaging ionising radiation,

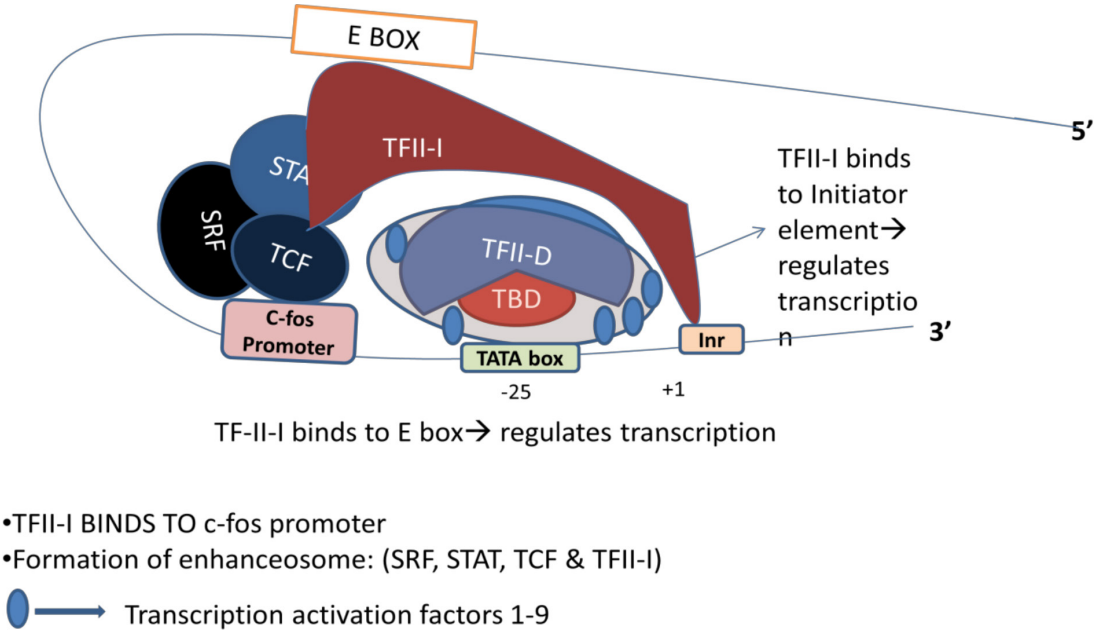

Figure 1 Schematic depiction of TFII-I binding to c-fos promoter and formation of enhanceosome. Inr, Initiator; SRF, Serum Response Factor; STAT, Signal Transducer and Activator of Transcription; TBD, TATA binding domain; TCF, T Cell Factor; TF, Transription Factor.

ubiquitination occurs which causes degradation via proteasomal pathways. This has been well depicted in the murine cells. However, the exact mechanism of degradation is not known and has been reported to involve destruction boxes/degrons, an example of which is the RXXLXX[LIVM] destruction box. Analogous to this, a RILLAKE amino acid sequence destruction box is present in the *GTF2I* gene, which is a non-canonical destruction box. *GTF2I* mutations have been reported to be recurrent in thymic epithelial tumours and are rare in other malignancies.[3 10–12]

In thymic cancers, the mutations have been reported to lie in repeat 2 within the RILLAKE amino acid sequence. Many studies have been carried out in order to detect the *GTF2I* mutation in the thymic epithelial tumours. In a series of 28 cases, a missense mutation was detected involving the g.74146970T>A locus with the p.Leu424His amino acid change[10–14] which was present in a high frequency in type A thymomas. The Cancer Genome Atlas Thymoma study involved sequencing of 117 cases of thymoma of all histological subtypes which revealed recurrent mutations in *HRAS*, *NRAS*, *TP53* and *GTF2I* genes. *GTF2I* alterations were present in 39% cases of the The Cancer Genome Atlas (TCGA) cohort. These mutations are generally detected in type A and B thymomas which are relatively less aggressive, and hence plausibly associated with a better survival. This p.L424H change augments the *GTF2I* expression post-transcriptionally by preventing its degradation. This eventually culminates in cell proliferation which is activated by binding of *GTF2I* to the FOS promoter. This mutation has been described to correlate well with mRNA expression patterns. It has also been reported that the subgroup of type A and AB tumours with mutant *GTF2I* is associated with a decreased prevalence of myasthenia gravis which is a known paraneoplastic autoimmune condition associated with thymoma.[15] Testing for this may help in differentiating type A/AB thymoma from unusual cases of lymphoblastic lymphoma, mediastinal sarcoma and atypical medullary thymoma.

Apart from thymic epithelial tumours, these mutations have also been reported in a subgroup of T cell lymphomas, angioimmunoblastic T cell lymphomas.[16 17] In a study involving 85

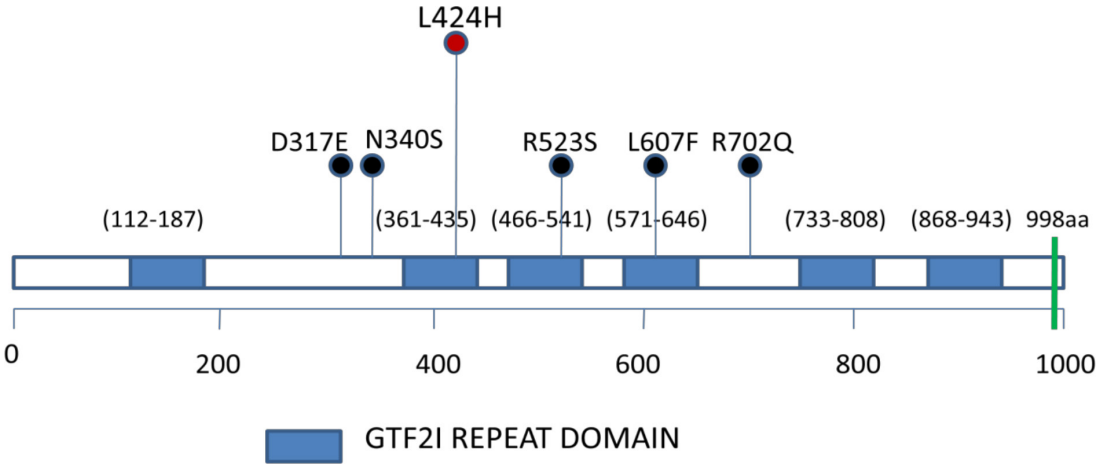

Figure 2 *GTF2I* domain structure showing six repeat domains and the canonical mutations.

such patients, 6% of cases were found to harbour the *GTF2I* mutation, suggesting that deregulated T cell receptor signalling may play a role in the disease pathogenesis, thus paving the way for the development of novel therapeutic targets. Also, apart from RHOA mutations in around 60% cases, half of the patients harboured other mutually exclusive alterations in other T-cell receptor (TCR)-related genes. The mutations detected in lymphomas are however distinct from those in thymic epithelial tumours. These include D317E, N340S, R523S, L607F and R702Q amino acid changes, apart from the already known L424H. The Catalogue of Somatic Mutations in Cancer database has described 120 missense mutations in this gene.[13 16 17]

In addition to gain of function mutations, *GTF2I* has also been reported for fusion products in malignancies. Soft tissue angiofibroma has been reported to harbour *GTF2I-NCOA2* fusion,[18] whereas *GTF2I* has also been seen to partner with Retinoic acid receptor alpha (*RARA*) in acute promyelocytic leukaemia as *GTF2I-RARA*.[19] *GTF2I/BRAF* fusion has been reported in a patient with pilocytic astrocytoma.[20]

GTF2I FUNCTION IN IMMUNE DISORDERS

Data from recent genome-wide association studies have described at least three autoimmune diseases in which *GTF2I* is implicated. These include primary Sjögren syndrome, systemic lupus erythematosus and rheumatoid arthritis.[2 21] The specific association with myasthenia gravis arising in the setting of thymic epithelial tumours still remains elusive.

GTF2I IN GENETIC DISORDERS

GTF2I is implicated in two neuropsychiatric genetic disorders, namely autism and Williams-Beuren syndrome (WBS).[22] WBS is a multisystem disorder characterised by supravalvular aortic stenosis, hypercalcaemia of infancy, cognitive defects and mental retardation. This occurs as a result of hemizygous deletion of 25–30 genes on chromosomes 7q11.23 involving all *GTF2I* family genes. It is inherited in an autosomal dominant fashion.[2]

Microdeletions sparing the *GTF2I* region may still result in cognitive defects of milder intensity, implicating the role of *GTF2I* in driving mental and cognitive development. Many single nucleotide polymorphisms are known to occur in WBS as well.[1 22]

TESTING METHODS

Mutations in *GTF2I* can be detected both in tumour tissue blocks as well as in blood of patients with immune system disorders and WBS. On tissue blocks, it can be detected using allele-specific oligonucleotide PCR, real-time PCR using mutation-specific primer probe sets and direct sequencing. Direct sequencing can be performed using pyrosequencing, Sanger sequencing as well as deep sequencing using next-generation sequencing technology, incorporating *GTF2I* in gene panels. RNA sequencing can be done to detect fusion rearrangements as well as ChIP-seq for detection of target genes and protein changes.

IMPORTANCE

The various structural, biochemical and functional properties of *GTF2I* hint towards the oncogenic nature of this gene, possibly a driver mutation. Two possible explanations which can be given are, first, that this mutation is present in indolent tumours with favourable prognosis, hence is a part of the founder clone which is progressively lost as the tumour evolves to a more aggressive phenotype. Second, it is also involved in multistep processes, both genetic and epigenetic, and may become dominant even in the presence of coexisting pathogenic variants. Studies involving patients are presently few and the availability of biospecimens amenable to molecular diagnostic studies is also limited, hence future studies involving these as well as transformed cell lines may emerge which may provide a clear understanding of the *GTF2I* mechanistic, thus making it amenable to targeted treatment.

CONCLUSION

The frequency of recurrent *GTF2I* mutations appears to be very high specially in the case of indolent tumours. As it represents a marker of favourable prognosis, these may be of help in classifying the thymic epithelial tumours and will be of considerable importance in developing newer targeted therapies with lesser toxicities for these patients.

Take Home Messages

- The *GTF2I* is a general transcription factor and the frequency of somatic mutation (p.L424H) is high in the thymic epithelial tumours especially Type A and Type AB. Identification of this mutation can be used to correctly diagnose and subtype thymomas.
- *GTF2I* mutations have been implicated in two neuropsychiatric genetic disorders, namely autism and Williams-Beuren syndrome. Since these two inherited disorders have overlapping phenotypes with many other neuropsychiatric inherited syndromes, inclusion of *GTF2I* in germline panel shall be useful.
- Future studies involving biospecimens and transformed cell lines shall provide a clear understanding of the *GTF2I* mechanistic to eventually lead to targeted treatment.

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ORCID iD

Anurag Mehta http://orcid.org/0000-0001-6517-3664

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