

Concise Review**GENETIC ANTICIPATION AND TELOMERE-TELOMERASE COMPLEX DYSFUNCTION IN FAMILIAL NON MEDULLARY THYROID CANCER (FNMTC).**

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The clinical and genetic features of patients with familial non-medullary thyroid cancer (FNMTC) are heterogeneous and far from being defined. Familial predisposition in differentiated thyroid carcinoma is reported in 3-10% of the cases (1,2), in absence of recognized predisposing syndromes (Cowden syndrome, Werner syndrome, Carney complex, Familial adenomatous polyposis) and the risk of developing the same tumor in first-degree relatives of subjects with differentiated thyroid cancer (DTC) is significantly higher than in the general population (3,4). Until now, no specific genetic alterations have been demonstrated in the blood of FNMTC patients, apart from susceptibility loci found in a few pedigrees with FNMTC (5-7). Recent studies (8) reported that patients with FNMTC display the features of “*anticipation phenomenon*”, that is the tendency for children to develop clinical disease at an earlier age than the affected parents. In fact, after ruling out the bias of screening effect, patients in the second generation presented an earlier age at disease presentation at diagnosis and at disease onset compared to the first generation and their tumours were more frequently multifocal and bilateral, had higher rate of lymph node metastases at surgery and worse outcome compared to the first generation. The presence of genetic anticipation has been reported in several non-thyroidal diseases (Table1). In thyroid diseases the

occurrence of disease anticipation has been reported in a large multigenerational family with medullary thyroid cancer (9), but in this case the occurrence of anticipation is uncertain because it was biased by the introduction of genetic analysis as a screening procedure. Preliminary evidence of genetic anticipation has been also reported in familial cases of Graves' disease (10).

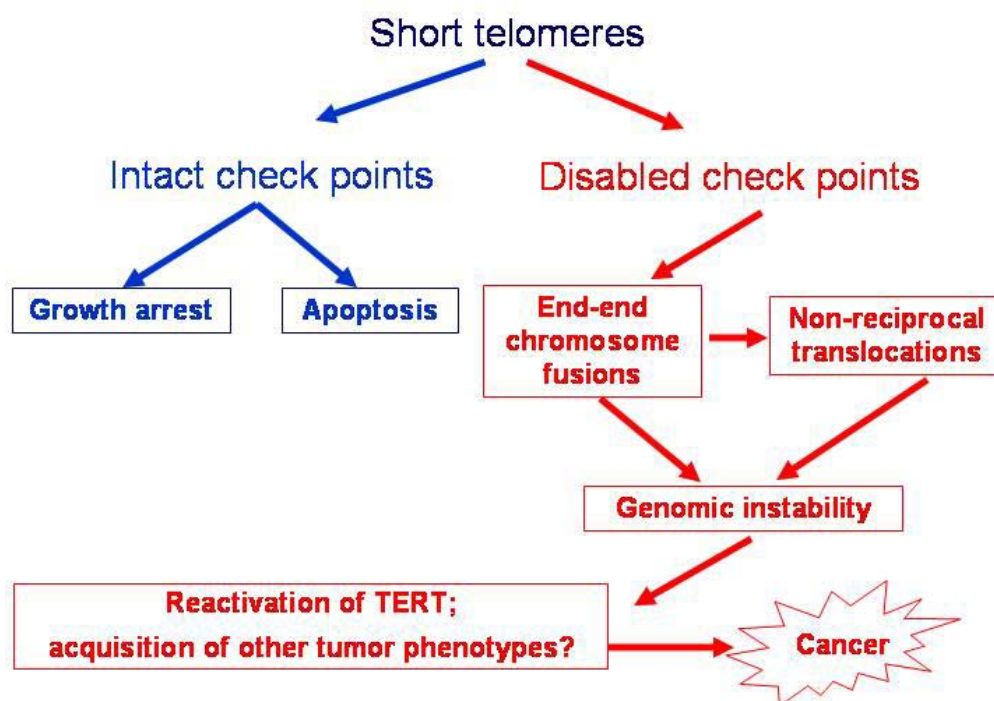
Table 1. Human diseases with demonstrated or suggested anticipation phenomenon.

Fragile X syndrome	Kronquist KE <i>et al.</i> Genet Med. 10:845-7, 2008
Myotonic dystrophy	Mahadevan M <i>et al.</i> Science 255:1253-5, 1992
Spinocerebellar ataxia	Moseley ML <i>et al.</i> Neurology 51:1666-71, 1998
Huntington disease	Ridley RM <i>et al.</i> J Med Genet 25:589-95, 1988
Familial leukemia	Horwitz M <i>et al.</i> Am J Hum Genet 59:990-8, 1996
Familial pancreatic cancer	McFaul CD. Gut 55:252-8, 2006
Bipolar disorders	McInnis MG <i>et al.</i> Am J Hum Genet 53:385-90, 1993
Diabetes type 2	Yaturu S <i>et al.</i> Med Sci Monit 11: 262-5, 2005
Graves disease	Brix TH <i>et al.</i> Thyroid 13:447-51, 2003
Crohn disease	Grandbastien B <i>et al.</i> Gut 42:170-4, 1998
Polycystic kidney disease	Peral B <i>et al.</i> Hum Mol Genet 5:539-42, 1996
Familial adenomatous polyposis	Presciuttini S <i>et al.</i> Ann Hum Genet 58:331-42, 1994
Familial medullary thyroid cancer	Fugazzola L <i>et al.</i> Clin Endocrinol 56: 53–63, 2002
Parkinson disease	Bonifati V <i>et al.</i> Can J Neurol Sci 22: 272-279, 1995
Dyscheratosis congenita	Vuillamy T <i>et al.</i> Nat Genet 36:447-449, 2004

Several molecular mechanism(s) possibly underlying genetic anticipation have been studied in familiar disorders, mainly benign, with particular attention to the telomere-telomerase complex. Telomeres are special structures consisting of a tandem repeats of the sequence TTAGGG at the ends of chromosomes that are maintained by telomerase, a specialized ribonucleoprotein complex that includes an RNA template (*TERC*) and a reverse transcriptase catalytic subunit (*TERT*). Telomerase expression is low or absent in most of human somatic tissues, while it is expressed in germ and stem cell compartments. Telomeric DNA is dynamic, being progressively lost with each cell division due to incomplete replication of the ends of linear DNA. When telomeres become critically short, the cells undergo senescence or apoptosis but if the integrity of checkpoints

mechanisms are altered genomic instability is triggered and leads to cycles of chromosome breakage and fusion, in a period called “crisis” that permit the acquisition of further genetic alterations. Although most cells die by apoptosis during the “crisis”, rare cells survive and maintain stable short telomere lengths through the reactivation of telomerase that facilitates cell immortalization (11). The strong association of telomerase re-activation with cancer provides evidence that this mechanism plays an important role in cancer development (Figure 1). RTL segregates in families (12,13) and a decrease in telomere length may play a role in age-related genetic instability (14). Interestingly, patients who have inherited or acquired genetic defects in telomere maintenance seem to have an increased risk of developing familial benign disease such as dyscheratosis congenital syndrome (15) and malignant diseases such as head, neck, lung, breast, and renal cancers (16).

Figure 1. In cells with intact signalling pathways, short telomeres trigger either senescence or apoptosis. In cells with disabled checkpoints, short dysfunctional telomeres trigger chromosome instability, perpetuated through recurrent breakage-fusion-bridge cycles. Few cells, through reactivation of a telomere maintenance mechanism, usually telomerase, stabilize telomere length and chromosome ends, resulting in cell immortalization. Upon additional somatic events, the latter may eventually acquire malignant phenotype (figure adapted from Londono-Vallejo. Biochimie 91:73-82, 2008).



In sporadic thyroid cancer telomerase re-activation is reported in nearly 50% of thyroid cancer tissues and in the past same authors proposed that the detection of telomerase activity may be helpful to distinguish between malignant and benign thyroid tumours (16-18), but the large majority of these studies were conducted on tumor tissues, while blood was not investigated. Recently, first evidence has been provided that patients with FNMTc have dysfunctional telomeres compared to patients with sporadic differentiated thyroid cancer, patients with benign thyroid diseases, healthy subjects and unaffected siblings of FNMTc patients (19). FNMTc patients had significantly shorter relative telomere length (RTL) in their peripheral blood cells, compared to sporadic cases and normal controls. hTERT gene was significantly amplified in FNMTc patients respect to control groups and it was significantly more represented in 2nd generation with respects to 1st generation. In addition, hTERT mRNA levels and the protein activity were significantly increased in FNMTc patients compared to control groups.

In conclusion, evidences have been provided for the presence in FNMTc of genetic anticipation at the clinical level and of short telomere lengths, hTERT gene amplification and increased telomerase expression in peripheral white blood cells at the molecular level. It is possible that patients born with short telomeres might reach earlier in life the threshold telomere length sufficient to trigger cancer development and this observation is consistent with the presence of genetic anticipation observed in FNMTc patients. If further confirmed in larger series, these results might propose measurement of RTL, as a marker of predisposition to FNMTc.

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