Atlas of Genetics and Cytogenetics in Oncology and Haematology

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# Gene Section
## Review

# TRIO (triple functional domain (PTPRF interacting))

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## Identity

**Other names:** ARHGEF23, FLJ42780, tgat

**HGNC (Hugo):** TRIO

**Location:** 5p15.2

**Local order:** The human gene maps to chromosome 5p14-p15.1; between markers D5S2894 and RH45695.

**Gene orientation:** forward strand.

**Note:** By remodeling the actin cytoskeleton, Rho-GTPases are involved in many physiological processes such as cell motility, proliferation and differentiation in different cellular systems. Rho-GTPases cycle between an inactive GDP-bound state and an active GTP-bound state. They are activated by Guanine-nucleotide Exchange Factors (GEFs), which often show tissue- and/or developmental-specific distribution and therefore represent key components to temporally and spatially control Rho-GTPase activities.

The RhoGEF TRIO is a good example for the panel of physiological and pathological processes GEFs are implicated in, since it participates both in muscle and neuronal development and in cancer. TRIO is a complex protein harboring two GEF domains (GEF1 and GEF2), activating the GTPases Rac1/RhoG and RhoA, respectively, and thus potentially linking several Rho-GTPase signaling pathways in vivo. In invertebrates, TRIO plays a central role in cell migration and axon guidance, mainly through the activation of Rac1 by the GEF1 domain. In mammalian cells, TRIO is required for RhoG-mediated neurite outgrowth in response to NGF, and is responsible for Rac1 activation elicited by the attractive cue Netrin-1 via its receptor DCC, during axon outgrowth and guidance.

Recently, an oncogenic isoform of TRIO, called Tgat, has been identified from adult T-cell leukemia patient cells, which encodes only the RhoA-specific GEF domain. Tgat induces cell transformation and tumor formation in nude mice, mainly via activation of RhoA.

## DNA/RNA

**Note**

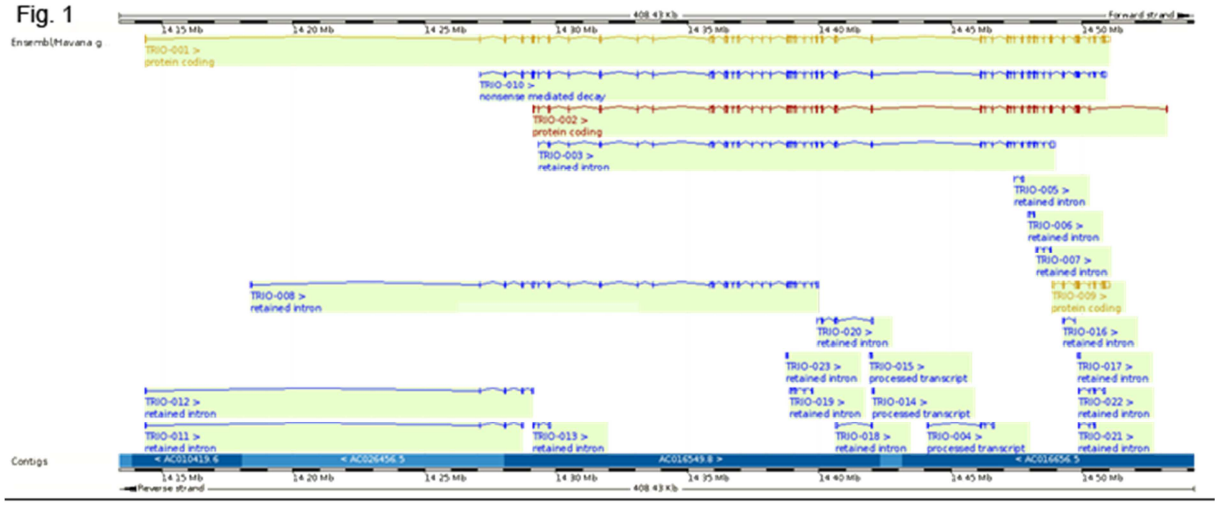
The Ensembl Database shows several TRIO transcripts, only one of which encodes the full length protein and two, which are translated into parts of the protein (Figure 1). In addition, 6 splice variants have been identified and characterized at the protein level (Figure 2) (Portales-Casamar et al., 2006).

### *Description*

The TRIO gene consists of 58 exons encoding for a 10244 bp transcript.

### *Transcription*

TRIO mRNA shows a ubiquitous expression pattern in adult human tissues (Debant et al., 1996). It is also present in embryonic tissues, as in mice it is detectable starting from around embryonic day 10 (E10) (Portales-Casamar et al., 2006).



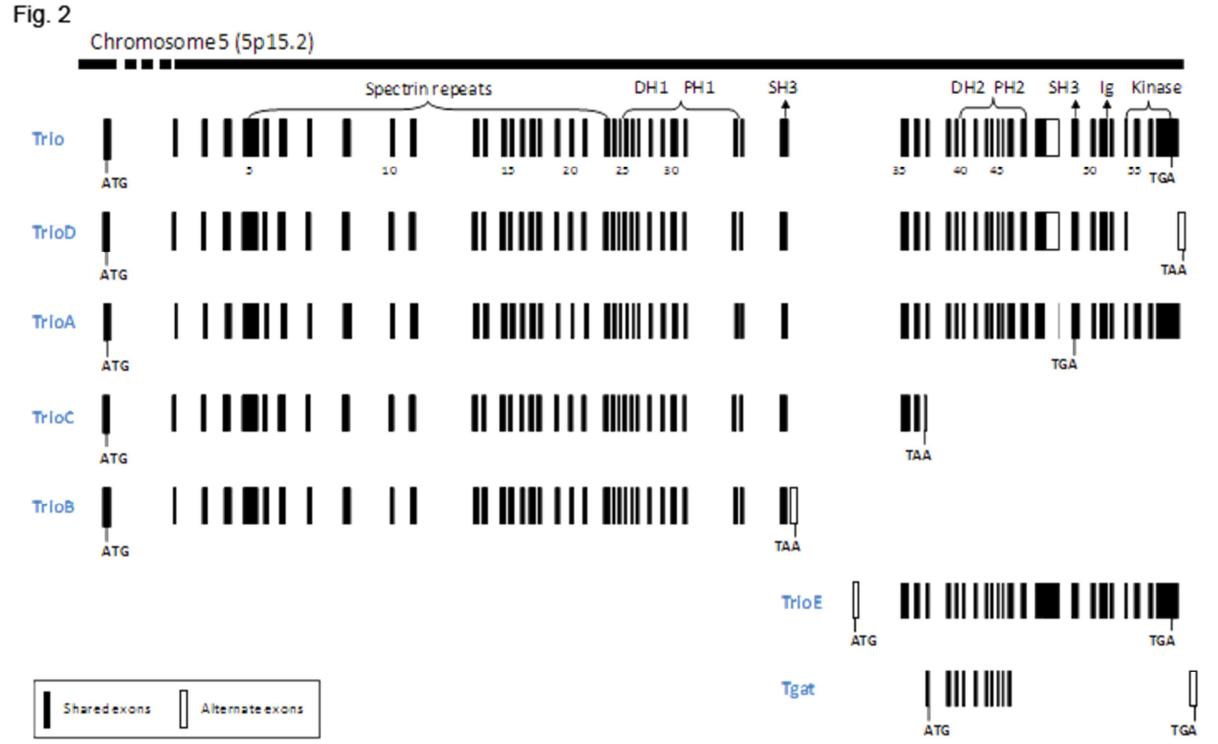




**Figure 1: Localization of the TRIO gene on human chromosome 5 and exon structure. Figure 2: Genomic organization of the splice variants of the TRIO protein.** The common exons between TRIO and the isoforms are represented as black boxes, while the specific exons are in white boxes.

# Protein

## *Description*

The human TRIO gene encodes a protein of 3097 amino acids, with a predicted molecular weight of 340.6 kD. The TRIO protein harbors distinct domains (Figure 3). Six shorter isoforms have been described, which are listed in Figure 4 with their respective molecular weights. TRIO is a complex protein containing three catalytic domains (hence the name "TRIO"): two tandem Dbl Homology (DH) - pleckstrin homology (PH) domains, and a Serine/Threonine kinase domain (Debant et al., 1996). The DH-PH module activates the small GTPases of the Rho family by mediating guanine nucleotide exchange. The DH1PH1 domain (also named GEF1) activates the GTPases RhoG and Rac1, while DH2PH2 (GEF2) activates RhoA (Bellanger et al., 1998; Blangy et al., 2000). So far, the kinase domain has not been characterized further. In addition to these domains, TRIO harbors numerous other motifs, including a Sec14 lipid-binding domain (also called CRAL-TRIO domain), eight spectrin repeats, two Src Homology 3 domains (SH3) and an Immunoglobulin domain. The presence of these numerous domains suggests that TRIO functions as an integrator of multiple upstream inputs and as an activator of multiple downstream pathways.

Fig. 3


**Figure 3: Domain structure of the TRIO protein:** Sec14, domain homologous to S. cerevisiae phosphatidylinositol transfer protein (Sec14p); spectrin repeats; DH, Dbl homology domain; PH, pleckstrin homology domain; SH3, Src homology 3 domain; Ig, Immunoglobulin-C2 type domain; S/T Kinase, Serine/Threonine Kinase domain.

Fig. 4

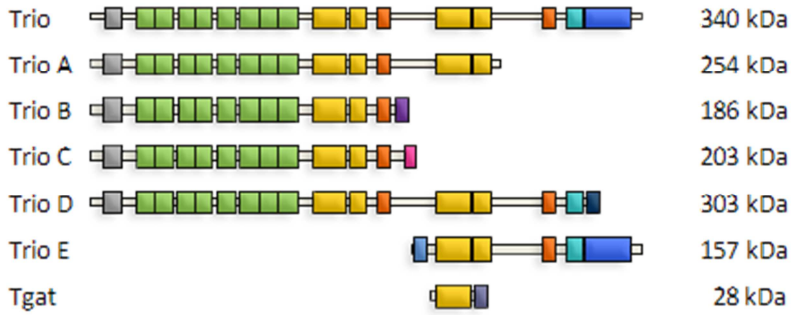



**Figure 4: Isoforms of TRIO** are represented schematically, together with their respective molecular weights (on the right).

## Expression

The full length TRIO protein is ubiquitously expressed, although at a low level, but its shorter isoforms have a more specific expression pattern. Isoforms TRIO A, B and D are strongly and exclusively expressed in various regions of the brain, throughout development (starting at E10) and in the adult, while the expression of the isoform TRIO C is specific to the cerebellum (Portales-Casamar et al., 2006; Sun et al., 2006). To date, Isoform TRIO E has only been detected in human neuroblastoma cell lines (Portales-Casamar et al., 2006). The Tgat isoform has been detected at the mRNA level in cells from patients with adult T-cell leukemia (ATL) (Yoshizuka et al., 2004).

## Localisation

TRIO protein is primarily located in the cytoplasm of cells, but it is also found partly associated with the plasma membrane, as in the case of the TRIO C isoform (Sun et al., 2006), or colocalizing with F-actin at the tip of the growth cone in PC12 cells (Estrach et al., 2002). The link between TRIO and the actin cytoskeleton is further strengthened by its interactions with the actin-binding proteins Filamin A and Tara (Bellanger et al., 2000; Seipel et al., 2001), as well as its association with Focal Adhesion Kinase (FAK) (Medley et al., 2003).

## Function

TRIO has originally been identified in human in 1996, in a two-hybrid screen using the cytoplasmic fragment of the tyrosine phosphatase LAR as bait (Debant et al., 1996). TRIO is a RhoGEF for the GTPases RhoG/Rac1 on one hand (via its GEF1 domain) and RhoA on the other hand (via its GEF2 domain). TRIO is implicated in the regulation of different physiological processes, most notably in neuronal physiology, but also in myogenesis and phagocytosis, processes that all require the rearrangement of the actin cytoskeleton. At the pathological level, evidence accumulates that TRIO is implicated in disease, mainly cancer, most likely by regulating actin cytoskeleton dynamics in migrating or invasive cells.

### The TRIO Rho-GEF and neuronal physiology

The first evidence for a role of TRIO in neuronal physiology came from genetic analyses of TRIO orthologues in Caenorhabditis elegans (unc-73) and in Drosophila (D-TRIO), which established the TRIO family as a key component of the intracellular signaling pathway that regulates axon guidance and cell migration, mainly in the nervous system (Steven et al., 1998; Awasaki et al., 2000; Bateman et al., 2000; Liebl et al., 2000; Newsome et al., 2000).

Gene targeting studies in mouse have then shown that TRIO is required for late embryonic development, probably by playing essential roles in the development of the nervous system and in fetal skeletal muscle formation (O'Brien et al., 2000). Consistently, mammalian TRIO has been shown to be required for RhoG-mediated neurite outgrowth in PC12 cells in response to NGF (Estrach et al., 2002). A direct interaction between TRIO and the integral membrane protein Kidins220/ARMS was further shown in this pathway, which might regulate membrane localization of TRIO in response to NGF (Neubrand et al., 2010). And more recently, a role for TRIO in mediating netrin-1-induced axon guidance has been found (Briançon-Marjollet et al., 2008). During development of the nervous system, Netrin-1 has been shown to promote axonal outgrowth through the binding of its receptor DCC. The binding of netrin-1 to DCC

activates the small GTPase Rac1, through a Rho-GEF which had not been identified. Briançon-Marjollet and colleagues have shown that TRIO is the GEF responsible for this Rac activation signal elicited by Netrin-1/DCC, during axon outgrowth and guidance (Briançon-Marjollet et al., 2008). Further studies have also shown that TRIO regulates the organization of neuronal clusters in the hindbrain in vivo (Backer et al., 2007).

The ultimate evidence for the essential role of TRIO in the development of the nervous system has been brought recently with the generation and characterization of mice with a neural specific knock-out of TRIO (TrioNKO) (Peng et al., 2010). About 90% of TrioNKO mice died within 1 day after birth. Surviving mice showed a reduced body weight and smaller brain, with defective cerebella and severe signs of ataxia, probably due to the absence of granule cells in the internal granule cell layer (Peng et al., 2010).

**TRIO and muscle development**

In addition to neuronal defects, TRIO KO mice show also defects in secondary myogenesis, suggesting a role for TRIO in this late developmental process (O'Brien et al., 2000). More recently, Charrasse and colleagues have clarified this role using C2C12 cells (Charrasse et al., 2007). Myoblast fusion requires M-Cadherin-dependent Rac1 activation. It appears that TRIO is complexed with Rac1 and M-Cadherin prior to myoblast fusion, leading to Rac1 activation. In contrast TRIO knockdown by shRNA inhibits this fusion process.

**TRIO and phagocytosis of apoptotic cells**

TRIO is implicated in phagocytosis of apoptotic cells both in mammals and in worms (deBakker et al., 2004). In mammals, the ELMO/DOCK180/CrkII complex is able to activate Rac and to induce cytoskeletal modifications leading to phagocytosis. TRIO activates RhoG, which in turn interacts with and activates this ELMO/DOCK180/Rac complex. This pathway is conserved in C.elegans.

**TRIO and cancer**

This topic is dealt with in the following section concerning diseases TRIO is implicated in.

### *Homology*

TRIO has originally been identified in human in 1996, as an interactor of the tyrosine phosphatase LAR (Debant et al., 1996). Since then, TRIO orthologs have been identified in invertebrates, C. elegans and Drosophila, called Unc-73 and DTRIO respectively (Steven et al., 1998; Lin and Greenberg, 2000). In mammals, there exists a paralog of TRIO, called Kalirin that was originally identified in rat (Alam et al., 1997). Interestingly, the structural organization of TRIO family members is very well conserved through evolution. Human TRIO and human Kalirin share 61.4% identity, and both show a similar identity to DTRIO (43.6% and 43.2% respectively) and to Unc-73 (29.3% and 29.6% respectively). Identity between orthologs is even higher if the domains are considered separately (up to 92% for TRIO and Kalirin GEF1 for example).

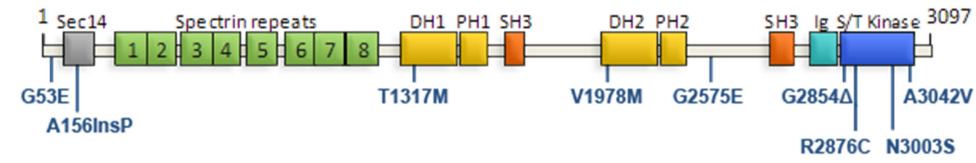
TRIO function is also conserved through evolution, since all orthologs are implicated in neuronal specific functions, ranging from neuronal development to cell migration, axon outgrowth and guidance, and synaptic plasticity.

## Mutations

**Note**

A systematic sequencing of cancer genomes led to the identification of more than 1000 somatic mutations in the coding exons of 518 protein kinase genes. In this study, 9 mutations have been found in the TRIO gene (Greenman et al., 2007).

Fig. 5




| Mutation | Nucleotide substitution | Primary tissue | Histology |
|---|---|---|---|
| G53E | G158A | skin | melanoma |
| A156InsP | C469-470CCC | brain | glioma |
| T1317M | C3950T | skin | melanoma |
| V1978M | G5932A | skin | melanoma |
| G2575E | G7724A | skin | melanoma |
| G2854Δ | 8561delG | large intestin | adenocarcinoma |
| R2876C | C8626T | breast | infiltrating ductal carcinoma |
| N3003S | A9008G | kidney | carcinoma |
| A3042V | C9125T | large intestine | adenocarcinoma |

**Figure 5: Schematic representation of the TRIO protein annotated with the mutations found in various cancers.**

More detailed information of this study can be found on the following website:
http://www.sanger.ac.uk/genetics/CGP/Studies/

### Germinal

None reported.

### Somatic

A systematic sequencing study of cancer genomes obtained from 210 diverse human cancers (primary tumors and immortalized cell lines) has been performed to find possible mutations in the 518 kinases of the human genome (Greenman et al., 2007). The screened cancers included breast, lung, colorectal, gastric, testis, ovarian, renal, melanoma, glioma and acute lymphoblastic leukemia. Over 1000 somatic mutations were detected in 321 kinases, including mostly single substitutions, and a few small insertions, deletions or complex changes. Statistical analysis allowed determining a factor indicating whether these mutations are "driver" or "passenger" mutations. TRIO having a kinase domain in its C-terminus was among the genes sequenced in this study. Nine mutations were identified in the TRIO gene, spanning the whole sequence (Figure 5). Interestingly, 6/9 mutations lied within the catalytic domains of TRIO (both DH-PH domains and the kinase domain). The cancer types these mutations were found in were diverse, with a prevalence of melanoma however. The "driver/passenger" selection pressure factor was 0.78 for TRIO, suggesting that the mutations are passenger mutations.

## Implicated in

### Various cancers

**Note**

In the past 5-6 years, a number of publications have emerged in the literature implicating TRIO as a potential cancer gene. Most notably, in many different cancer types (see list below), copy number gains and high-level amplifications of the short arm of chromosome 5 (band 5p) are frequently observed. This suggests the presence of driver genes on 5p involved in malignant progression. Interestingly, the TRIO gene maps precisely to this region.

### Glioblastoma

**Disease**

It has been shown previously that the small GTPases Rac1 and Rac3 play a role in both migration and invasion of malignant gliomas. In order to identify Rac-GEFs that could mediate glioblastoma invasiveness, Salhia and colleagues performed gene expression profiling on a brain tumor expression database and identified the GEFs TRIO, Ect2 and Vav3 as being expressed at higher levels in glioblastoma versus low-grade glioma (Salhia et al., 2008). The expression of these GEFs is also associated with poor patient survival. Real time qPCR and immunohistochemical analyses on an independent set of tumors confirmed this overexpression in glioblastoma compared to either nonneoplastic brain or low-grade gliomas. Moreover, siRNA silencing of TRIO, Ect2 or Vav3 suppressed glioblastoma cell migration and invasion. Depletion of TRIO or Ect2 also significantly reduced the rate of glioblastoma cell proliferation, whereas cell survival was not compromised (Salhia et al., 2008).

**Prognosis**

High expression of TRIO, Ect2 and Vav3 in glioblastoma patients (GBM) is associated with poor patient outcome. According to Kaplan-Meyer survival curves, two distinct patients' clusters could be formed, the first with a long-term median survival, the second with a short-term median survival. Expression of the three RhoGEFs was significantly higher in the second cluster, indicating a relationship between GEF expression and poor patient outcome (Salhia et al., 2008).

### Breast cancer

**Disease**

Lane and co-authors investigated the expression and prognostic value of the RhoGEFs TRIO, Vav1 and Tiam-1 in human breast cancer (Lane et al., 2008). Comparison of breast tumor tissue versus normal background tissue by real time qPCR and immunohistochemistry revealed high expression levels of TRIO, Vav1 and Tiam-1 in breast tumors, reaching a level of significance for TRIO (P=0.013). TRIO levels also increased significantly in patients with poor predictive outcome (Nottingham Prognosis Index), while Tiam-1 levels were significantly higher in tumor tissue from patients who died from breast cancer compared with those who survived (Lane et al., 2008). TRIO could therefore be very useful as a prognostic factor in breast cancer.

Two other related studies looked at the gene expression signatures of breast epithelial cells exposed to estrogens and parathion (an agricultural pesticide) (Calaf and Roy, 2007a; Calaf and Roy, 2007b). There exists indeed an association between breast cancer and exposure to environmental substances. Parathion alone or in combination with 17beta-estradiol (E2) induced malignant transformation of MCF-10F cells, which was confirmed by anchorage independent growth and invasive capabilities. Parathion alone significantly elevated the expression of a number of proteins, including TRIO (1.8-fold), but combination with E2 induced an even stronger increase (2 fold over E2 alone treated cells, in the case of TRIO) (Calaf and Roy, 2007a).

**Prognosis**

TRIO levels increased significantly in patients with poor prognosis index (Lane et al., 2008). This suggests that aberrant regulation of Rho GTPase activities by GEFs may have an important prognostic value in breast cancer.

## Soft tissue sarcoma

**Disease**

Comparative Genomic Hybridization (CGH) array studies have shown that copy number gains and high-level amplifications of the short arm of chromosome 5 (band 5p15) are often observed in soft tissue sarcomas with complex genomic profiles, which aggressive mesenchymal tumors (Adamowicz et al., 2006). Adamowicz et al. analyzed 34 soft tissue sarcomas (10 pleiomorphic liposarcomas (LPs) [PL-LP], 8 dedifferentiated LPs [DD-LP], 6 malignant fibrous histiocytomas [MFH], and 10 peripheral nerve sheath tumors [MPNST]) using cDNA microarray including 418 BAC clones, to precisely identify the genes that are amplified. Amongst other genes, TRIO was consistently found overexpressed in all cases, as confirmed by real-time quantitative PCR. In contrast, NKD2 and IRX2 genes, which are involved in the Wnt developmental pathway, were expressed only in MPNSTs. The mRNA expression level of TRIO, NKD2 and IRX2 strongly correlated with the gene copy number. In conclusion, in soft tissue sarcomas, TRIO was highly amplified and up-regulated in a gene-dosage dependent manner. Thus the TRIO gene represents a candidate target of 5p amplifications in soft tissue sarcomas and might play a crucial role during the progression of the disease (Adamowicz et al., 2006).

## Urinary bladder cancer

**Disease**

Like in soft tissue sarcomas, lung cancer or cervical cancer, 5p amplification seems to be related to tumor progression in urinary bladder cancer (Zheng et al., 2004; Mhawech-Fauceglia et al., 2006). Zheng and colleagues analyzed 7 genes located to 5p15.31-5p15.1 by FISH (Fluorescent in situ hybridization) using a tissue microarray, containing samples from tumors and cell lines with known 5p amplifications. Amplification frequency was highest for TRIO, which maps to 5p15.2. Analysis of over 2000 bladder tumors showed that TRIO amplification was strongly associated with invasive tumor phenotype, high tumor grade and rapid tumor cell proliferation. However, TRIO amplification was not associated with poor prognosis. Using RNA in situ hybridization (RISH) the authors confirmed that mRNA expression level of TRIO strongly correlated with the gene copy number. This study suggests TRIO as an oncogene candidate within this amplicon and a potential role for TRIO in bladder cancer progression (Zheng et al., 2004).

## Cervical cancer

**Disease**

Two independent studies performed on cervical cancer samples identified the TRIO gene as significantly upregulated in this cancer type (Kloth et al., 2007; Ng et al., 2007). The first study aimed at identifying genes showing high-frequency copy number-driven changes in expression in cervical squamous cell carcinoma (SCC) that would thus contribute to the biology of the disease (Ng et al., 2007). To identify such potential oncogenes, CGH array and qPCR were performed on 36 primary samples and 10 cell lines. The most commonly occurring regions of copy number gain that showed amplification were 5p15.2-14.3 and 5p13.3-13.1. Gene copy numbers were significantly associated with expression levels for three candidate oncogenes: OSMR, TRIO and PDZK3 (Ng et al., 2007). FISH analysis on a tissue microarray of 110 primary cervical SCC samples revealed copy number gain frequencies of 54.5% for TRIO. Survival analysis (Kaplan-Meier) correlation revealed only a correlation for OSMR and PDZK3 in adversely influencing patient survival. TRIO gain did not influence clinical outcome.

In the second study, 10 cervical cancer cell lines were analyzed by CGH array and SNP array (single nucleotide polymorphism) (Kloth et al., 2007). This showed an overall concordance in detection of the same areas with copy number alterations (CNA). Regions frequently targeted by CNA were found with amplification of 5p and 20q and loss of 8p, as confirmed by FISH. At chromosome 5, there was a significant correlation between copy number and gene expression. Genes were significantly upregulated in cell lines with amplifications as compared to cell lines without amplifications. For 3 genes, among which TRIO, expression differences were confirmed by real-time quantitative PCR (Kloth et al., 2007).

## Oral cancer

**Disease**

Array CGH technology was applied to 20 clinical samples of oral squamous cell carcinoma (OSCC) (Baldwin et al., 2005), which is the most common head and neck neoplasm. This allowed the identification of genomic modifications ranging from whole chromosome arm, segmental or gene-size alterations. Amongst others, Baldwin and colleagues found the presence of several novel frequent submegabase alterations, such as a 0.58Mb gain at 5p15.2, containing the TRIO gene (in 9/20 cases). TRIO transcript levels were compared in 4 OSCCs samples and 7 normal specimens by RT-PCR, and this showed that TRIO expression was significantly higher in the cancer samples.

This is the first report of the microamplification of the TRIO locus in oral cancer, as evidenced by tile-path array CGH (Baldwin et al., 2005). Deregulation of TRIO at the transcriptional level shows the biological significance of this locus.

## Esophageal squamous cell carcinoma

**Disease**

A very recent study was performed on patients with esophageal squamous cell carcinoma (ESCC) exposed to tobacco and betel quid in India (to evaluate environmental risk factor contributions)

(Chattopadhyay et al., 2010). 10K single nucleotide polymorphism (SNP) array on 20 tissue samples allowed the identification of 22 amplified regions and 16 deleted regions. Among the relevant candidate genes located on amplified regions was TRIO (5p15.2) (Chattopadhyay et al., 2010).

## Lung cancer

**Disease**

**A. Small cell lung carcinoma (SCLC):** Like in other cancer types, genomic amplification of regions on chromosome arm 5p has been observed frequently in small cell lung carcinoma (SCLC) (Coe et al., 2005). To identify candidate genes on this chromosome arm, Coe and colleagues developed a high-resolution BAC CGH array for chromosome 5p and examined a panel of 15 SCLC cell lines. This allowed fine mapping of regional copy number aberrations, and allowed the identification of previously undetected microdeletions and the identification of TRIO and ANKH as novel putative oncogenes. FISH confirmed these amplifications (in 6/15 cell lines). However, the biological relevance of TRIO and Ankh to SCLC remains to be explored.

**B. Non-small cell lung cancer (NSCLC):** Using genomic profiling of pre-invasive alterations, Garnis and co-authors identified multiple early genetic events on chromosome 5p in lung cancer progression (Garnis et al., 2005). Using a high-resolution 5p-specific genomic array, they discovered 9 novel minimal regions of loss and gain in bronchial carcinoma in situ (CIS) samples, which are pre-invasive. Within these regions they identified 2 candidate genes novel to lung cancer, TRIO, which was differentially expressed in tumors, and GDNF, which is normally expressed during lung development. Real-time quantitative PCR performed on 8 paired normal and squamous cell carcinoma (SqCC) samples showed an overexpression of the TRIO transcript in 6/8 pairs. This expression pattern was confirmed by additional semi-quantitative RT-PCR on 13 more samples, showing significant overexpression of TRIO. This concordance of copy number increase and overexpression in tumor samples strongly suggests a role for TRIO in SqCC, while its frequent amplification in pre-invasive lesions (CIS) suggests its early involvement in tumorigenesis.

## Acute adult T-cell leukemia (ATL)

**Disease**

An alternative splice variant of TRIO with transforming properties has been identified from patients with adult T-cell leukemia (ATL) (Yoshizuka et al., 2004). Using a cDNA library built from ATL patients' cells, Yoshizuka and colleagues isolated one gene with transforming properties in NIH 3T3 fibroblasts. This gene turned out to be an alternative splice variant of TRIO, harboring only the catalytic DH domain activating RhoA and a unique 15 amino acid C-terminal sequence (Yoshizuka et al., 2004). Overexpression of Tgat induced cell transformation in NIH 3T3 fibroblasts (foci formation, growth in soft agar) and tumor formation in nude mice. This required the presence of both protein domains. Tgat has been proposed to enhance tumor invasion by stimulating Matrix MetalloProteinases (MMPs) via the RECK protein (Mori et al., 2007) and by activating the transcription factor NF-kappaB, which plays a crucial role in tumorigenesis, including ATL (Yamada et al., 2007).

Interestingly, a recent peptide inhibitor screening strategy has identified one peptide, $TRIP^{E32G}$, which specifically inhibits Tgat GEF activity in vitro and significantly reduces Tgat-induced RhoA activation and foci formation. Furthermore, subcutaneous injection of cells expressing Tgat and $TRIP^{E32G}$ into nude mice reduces the formation of Tgat-induced tumors. This demonstrates that this peptide is a potent inhibitor that can be used to interfere with Tgat functions in vivo (Bouquier et al., 2009).

**Oncogenesis**

Overexpression of Tgat in NIH 3T3 fibroblasts induced foci formation, growth in soft agar, and, upon injection into nude mice, tumor formation.

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