

## Solid Tumour Section

### Short Communication

# Lung: t(6;12)(q22;q14.1) LRIG3/ROS1 in lung adenocarcinoma

Kana Sakamoto, Yuki Togashi, Kengo Takeuchi

Pathology Project for Molecular Targets, The Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan (KS, YT, KT)

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## Abstract

Short communication on t(6;12)(q22;q14.1) LRIG3/ROS1 in lung adenocarcinoma with data on clinics.

## Clinics and pathology

### Disease

Lung adenocarcinoma

### Epidemiology

ROS1 translocations are found in 0.9 to 1.7% of non small cell lung carcinomas and the majority of the cases are adenocarcinoma (Bergethon et al., 2012; Davies et al., 2012; Takeuchi et al., 2012). Multiple fusion partners have been identified and LRIG3 is one of them. As for LRIG3-ROS1, only one case, a 57-year-old Japanese male patient, has been reported to date (Takeuchi et al., 2012).

### Clinics

The patient had a 5 pack year of smoking history and was diagnosed as having stage 1A lung adenocarcinoma.

### Pathology

This case showed moderately differentiated micropapillary pattern. A mucinous cribriform pattern which is frequently seen in cancers with kinase fusions was not found. This case was negative for EGFR and KRAS mutations as with the most cases harboring ROS1 gene fusions.

### Treatment

The primary tumor was surgically removed and the patient received post-operative chemotherapy with

UFT. Although not administered in this case, Crizotinib and other ALK inhibitors have been reported to be effective in lung cancers with ROS1 translocations (Bergethon et al., 2012; Shaw et al., 2012).

### Prognosis

With 5 years of follow-up, the patient was alive without relapse.

## Genes involved and proteins

### LRIG3

#### Location

12q14.1

#### DNA / RNA

Leucine-Rich Repeats And Immunoglobulin-Like Domains Protein 3.

### ROS1

#### Location

6q22

#### DNA / RNA

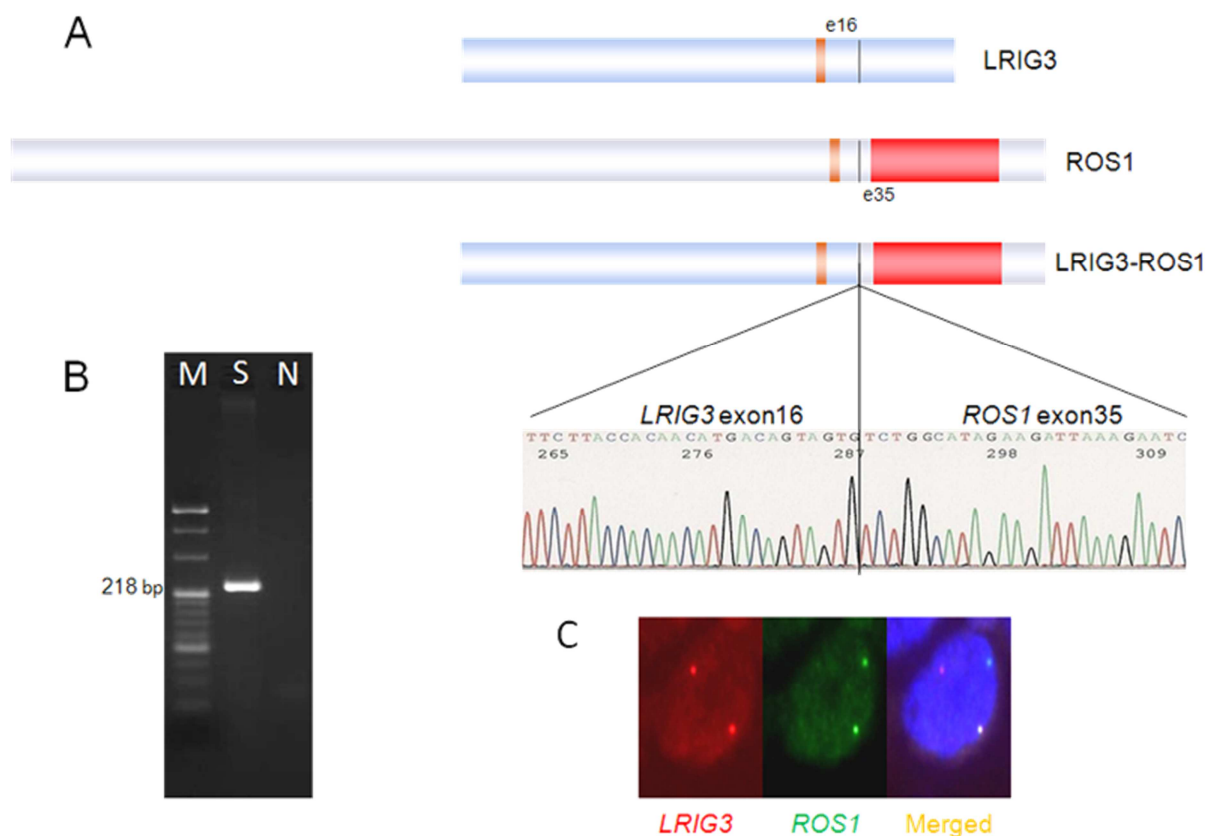
C-Ros Oncogene 1, Receptor Tyrosine Kinase.

## Result of the chromosomal anomaly

### Hybrid Gene

#### Transcript

LRIG3-ROS1 fusion transcript was detected.



**A. The schematic structure of LRIG3, ROS1, and LRIG3-ROS1 proteins and the cDNA sequence around the fusion point:** Exon 16 of LRIG3 fused to exon 35 of ROS1. The break point of ROS1 allows the resulting fusion protein to retain the kinase domain (red). LRIG3 contains a transmembrane domain (orange). **B: RT-PCR confirmation of LRIG3-ROS1 fusion:** Lane M and N represent the size standard (20-bp ladder) and the non-template control, respectively. **C. Fusion FISH analysis:** A fusion signal (yellow) was observed in consequence of the fusion of LRIG3 (red) and ROS1 (green).

### Detection

A 218 bp cDNA fragment harboring the fusion point can be detected with LRIG3 forward primer (5'-ACACAGATGAGACCAACTTGC-3') and ROS1 reverse primer (5'-CACTGTCACCCCTTCCTTG-3').

### Fusion Protein

#### Description

The fusion protein encompasses the constitutive activation of ROS1 tyrosine kinase.

However, the mechanism of it is largely unknown. The role of LRIG3 here has not been clarified. LRIG3 protein does not contain a coiled-coil domain as in the case with most of the other ROS1 fusion partners (Takeuchi et al., 2012).

In respect of the downstream signaling, several growth and survival signaling pathways which are common to other receptor tyrosine kinases have been shown to be involved.

These include PI3K/AKT, JAK/STAT3, RAS/MAPK/ERK, VAV3, and SHP-1 and SHP-2 pathways (Chin et al., 2012; Davies and Doebele, 2013).

### Oncogenesis

The oncogenicity of LRIG3-ROS1 fusion was proven in a focus formation assay and a nude mouse tumorigenicity assay (Takeuchi et al., 2012).

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