t(8;21)(q24;q22) in prostate cancer

Dorothee Pflueger

University Hospital Zurich, Institute of Surgical Pathology, Schmelzbergstrasse 12, 8091 Zurich, Switzerland (DP)

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Identity

Note
NDRG1 (N-myc downstream regulated 1) was identified as a 5’ fusion partner to ERG (v-ets erythroblastosis virus E26 oncogene homolog (avian)) by use of next-generation RNA sequencing (Pflueger et al., 2009).

Clinics and pathology

Disease
Prostate cancer

Note
Prostate cancer is a hormonally sensitive cancer at early stages and eventually becomes hormonally independent as it progresses to castration-resistant prostate cancer (CRPCa). All 5’ fusion partners to ERG described in prostate cancer to date (TMPRSS2, SLC45A3, NDRG1, HERPUD1, FKBP5) are known androgen-regulated genes. By utilizing androgen-responsive “promoters” as 5’ partners, the fusion event drives the upregulation of the oncogene ERG. Estrogen signaling on TMPRSS2 (Setlur et al., 2008), SLC45A3 and NDRG1 (Pflueger et al., 2009) has been observed as an additional level of hormonal regulation. This aspect of ERG fusions in prostate cancer becomes more important in sight of the androgen hormone ablation treatment, leading to CRPCa.

Epidemiology

To date, two studies describe NDRG1-ERG fusion in a total of 3 prostate cancer cases with clinically localized disease (Pflueger et al., 2009; Esgueva et al., 2010). Pflueger et al. and Esgueva et al. estimate NDRG1 to be the 5’ fusion partner in up to 5% of ERG-rearranged prostate cancer. In direct comparison, TMPRSS2 is the 5’ fusion partner in a majority (~78-82%) of ERG-rearranged prostate cancer cases. SLC45A3 is the 5’ partner to ERG in ~6-7% of rearrangement positive prostate cancer. Singular reports exist of a nonrecurring ERG fusion with HERPUD1 (Maher et al., 2009) and FKBP5 (Pflueger et al., 2011), respectively. None of the well known prostate cancer cell lines (LNCaP, VCaP, 22Rv1, PC-3, NCI-H660 and DU145) harbor an NDRG1-ERG fusion (Pflueger et al., 2009).

Genes involved and proteins

NDRG1

Location
8q24.22

Note
NDRG1 (N-myc downstream regulated 1) is a multifunctional protein that is ubiquitously expressed in several tissues. It likely exerts its function cell type and tissue specific. It’s described to act in stress response pathways, golgi transport, cell cycle regulation and mitosis. It is hypothesized that it has a tumor-suppressive function in epithelial cells since lower expression levels have been observed in adenocarcinoma compared to normal tissue. Defects in this gene are found in a subtype of the Charcot-Marie-Tooth disease type 4D (CMT4D), a peripheral neuropathy.
**ERG**

**Location**
21q22.2

**Note**
ERG (v-ets erythroblastosis virus E26 oncogene like (avian)) is a member of the ETS family of transcription factors. It is implicated in lymphoid cell development and endothelial cell differentiation, among other less well described functions in mitogenic signal transduction pathways, platelet activation, DNA methylation, angiogenesis etc. Elevated ERG levels are observed in several disease conditions (i.e. several cancers, Alzheimer's disease, Down syndrome etc.). Its role in oncogenesis is well established since fusions between several genes and ERG are characteristic for Ewing sarcoma, acute myeloid leukemia and prostate cancer.

**Result of the chromosomal anomaly**

**Hybrid Gene**

**Transcript**
The fusion breakpoint(s) on DNA level are unknown.

However, there are at least 2 distinct transcript isoforms described (Pflueger et al., 2009) (see figure above):

- FJ627786: NDRG1 (NM_006096) exon 3 joined with ERG (NM_004449) exon 6.
- FJ627787: NDRG1 (NM_006096) exon 2 joined with ERG (NM_004449) exon 6.

The exon junctions of NDRG1-ERG isoforms are utilizing the same splice sites as the respective wild-type mRNAs possibly indicating the involvement of alternative splicing processes to produce distinct transcript isoforms.

**Fusion Protein**

**Description**
Unlike TMPRSS2-ERG and SLC45A3-ERG, the NDRG1-ERG gene fusion transcripts are in frame, meaning that NDRG1 contributes 33 (FJ627786) and 21 (FJ627787) amino acids, respectively, to an NDRG1-ERG fusion protein (Pflueger et al., 2009). An antibody specific to NDRG1-ERG fusion protein does not exist yet. Hence, the expression of a fusion protein was indirectly verified by monitoring elevated ERG protein expression in cell lines that were transiently transfected with NDRG1-ERG expression vectors. In invasion assays, it was observed that NDRG1-ERG
confers increased invasiveness (unpublished results). Additional functions of the NDRG1-ERG fusion proteins have not been eluded further and it is unclear if they exert similar or differing functions compared to the N-terminally truncated ERG protein encoded by the TMPRSS2-ERG and SLC45A3-ERG fusions (Tomlins et al., 2008; Klezovitch et al., 2008).

References


This article should be referenced as such: