Coagulation factor V is expressed in tumors and predicts favorable outcome in aggressive breast cancer

Mari Tinholt, Øystein Garred, Elin Borgen, Elsa Beraki, Marit Sletten, Kristine Sahlberg, Per Morten Sandset, Nina Iversen

Oslo University Hospital, Oslo, Norway

Co
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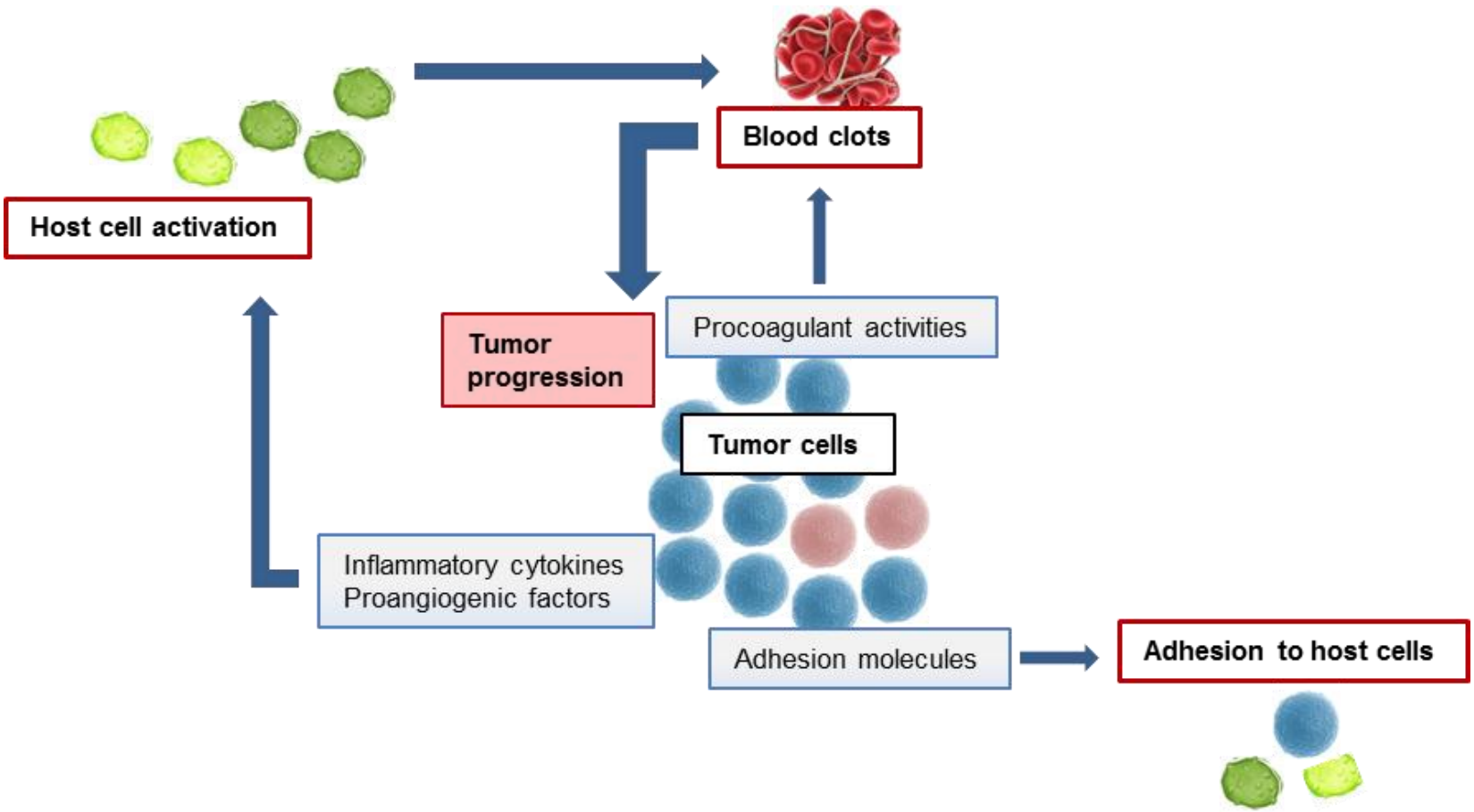
Coagulation-Cancer-FV

Coagulation ⟷ Cancer progression



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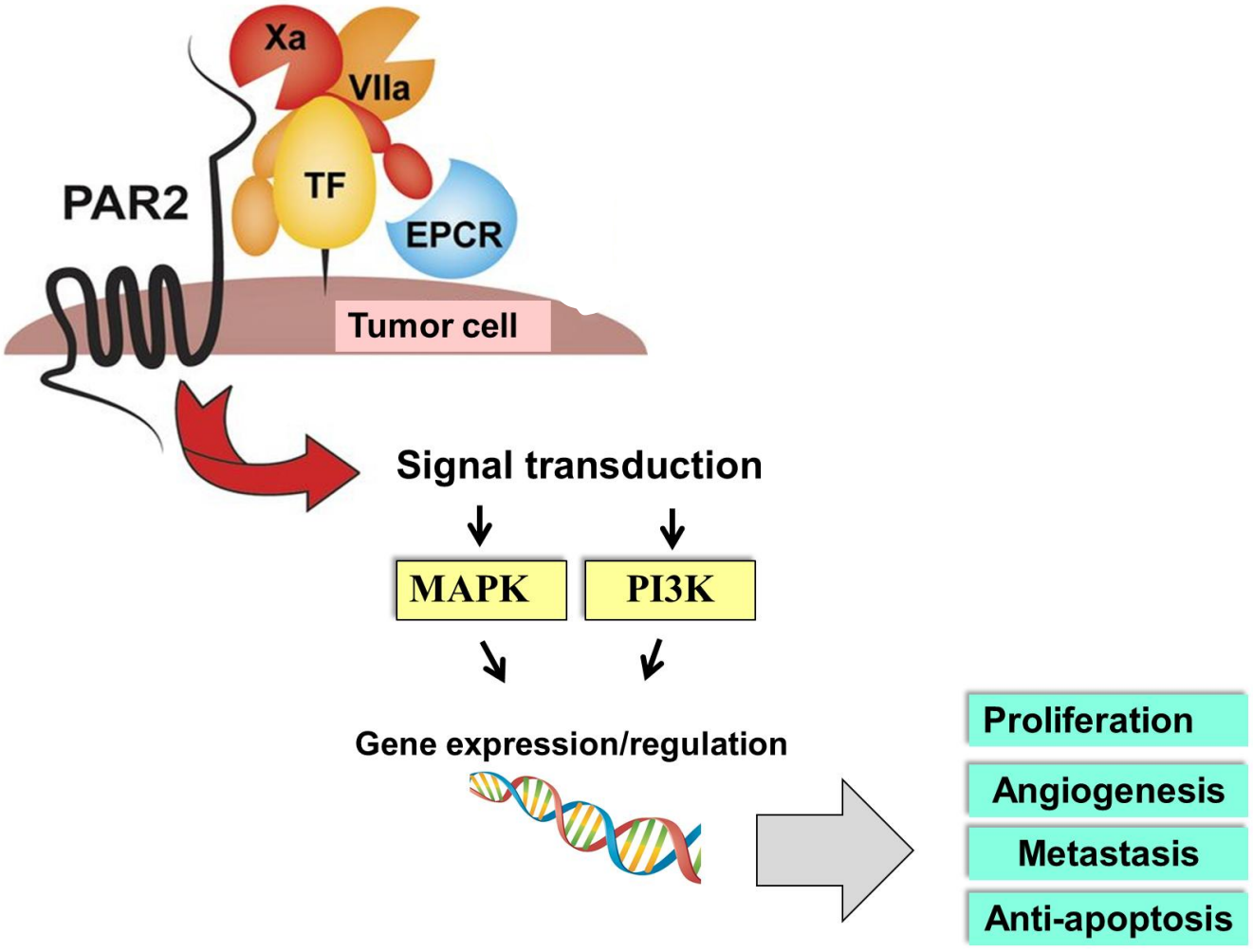
Coagulation ⟷ cancer progression



Modified from W Ruf, *Blood* 2014

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Genetic association study of the TF pathway in breast cancer

Tinholt *et al. BMC Cancer* 2014, **14**:845
http://www.biomedcentral.com/1471-2407/14/845

BMC Cancer

RESEARCH ARTICLE Open Access

Increased coagulation activity and genetic polymorphisms in the *F5, F10* and *EPCR* genes are associated with breast cancer: a case-control study

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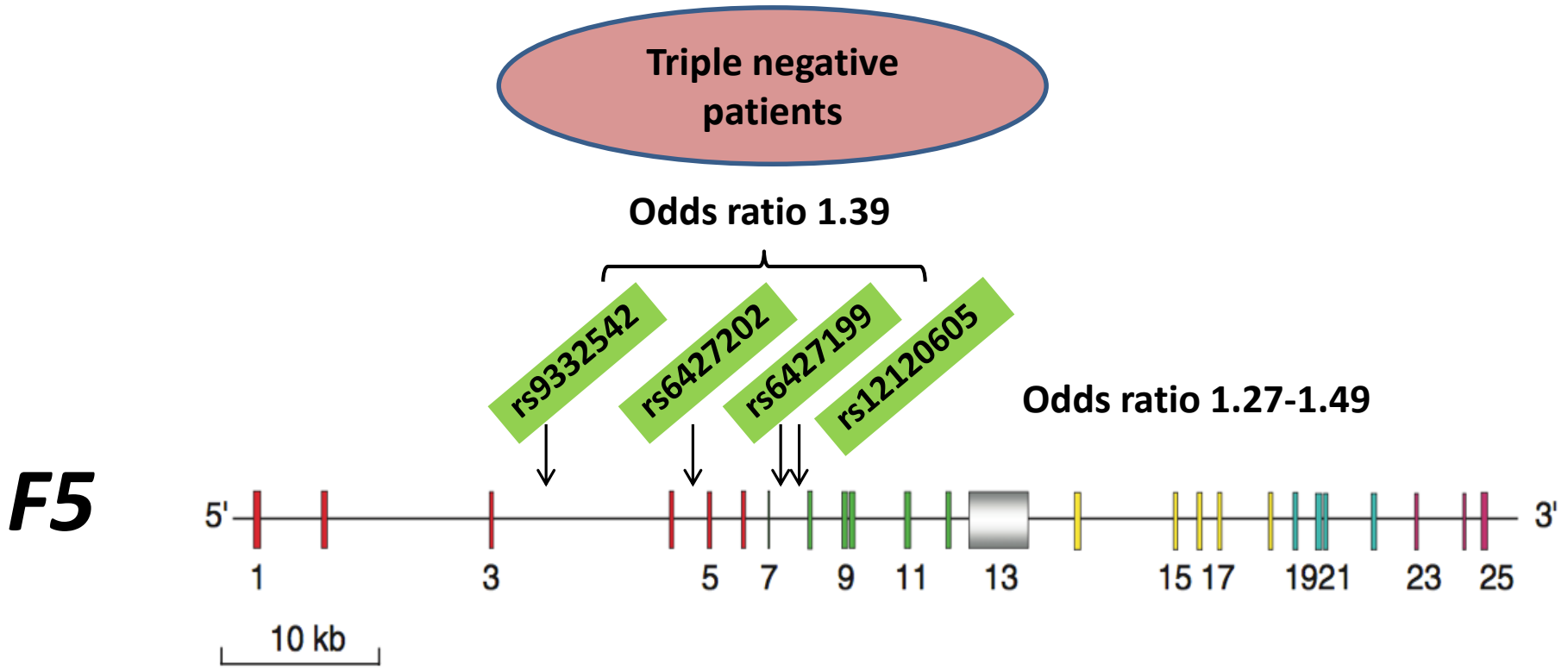
F5 SNPs are associated with breast cancer



Tinholt et. al, *BMC Cancer*, 2014

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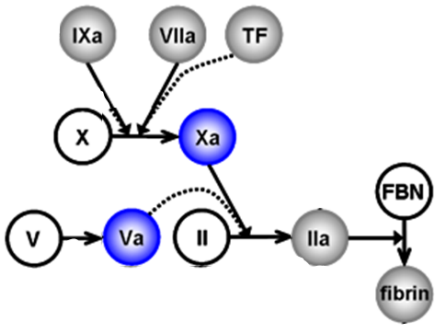
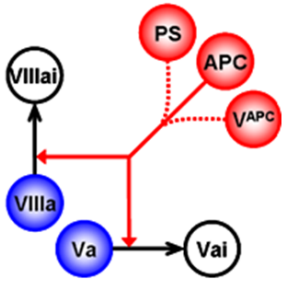
FV protein

- 2224 amino acids
- Synthesized in the liver, stored in platelets
- Activated by thrombin, FXa and APC
- FVa acts as a co-factor with both pro- and anti-coagulant properties

Procoagulant co-factor



Anticoagulant co-factor



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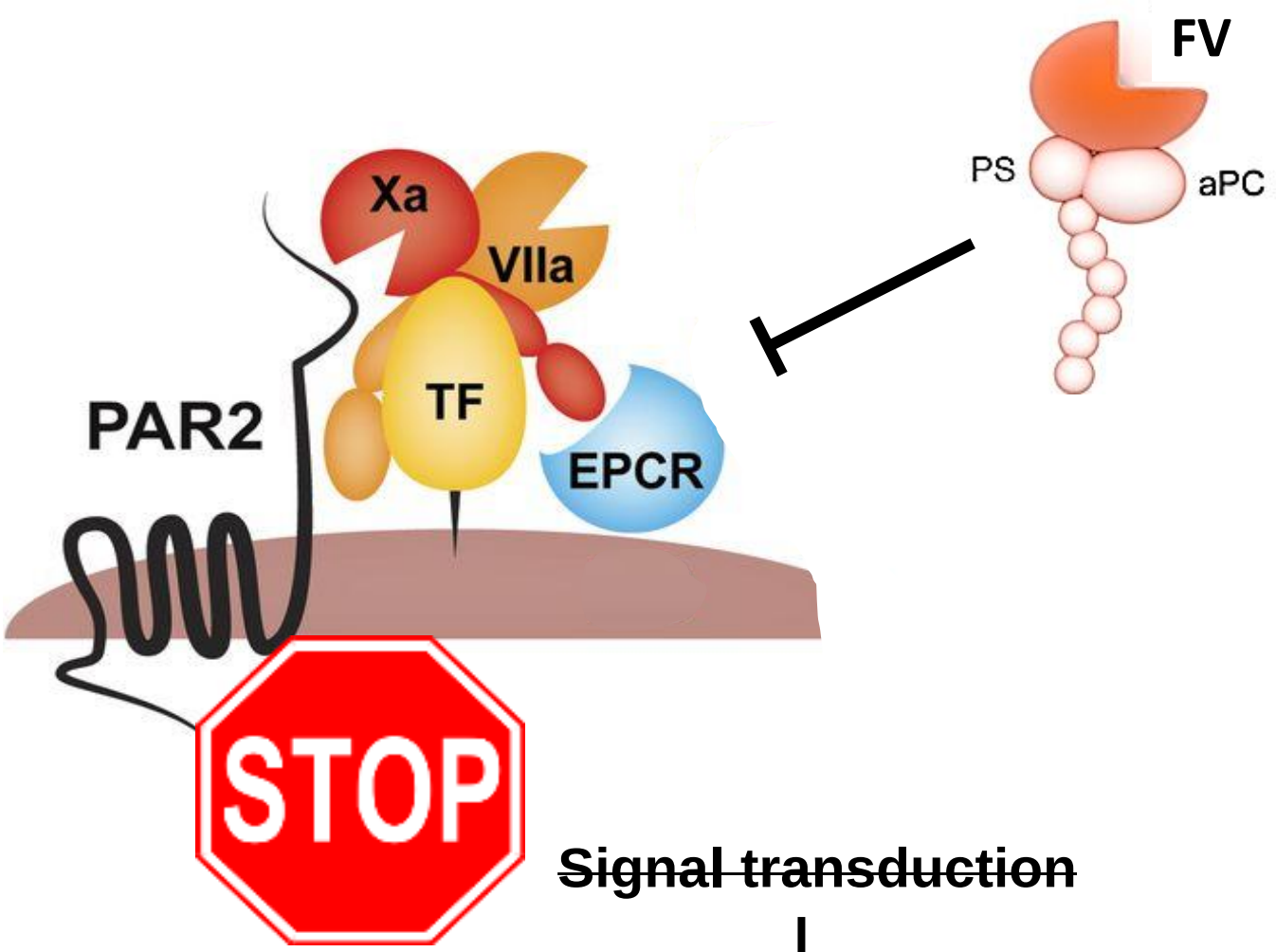
FV: anti-inflammatory co-factor



~~Signal transduction~~

↓

~~Inflammatory response~~

Modified from
W Ruf, *Blood* 2014 and Sun H, *Blood*, 2015

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Co
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Coagulation-Cancer-FV

Aim of the study

- Clinical significance of FV expression and the regulatory role of *F5 SNPs* in breast cancer

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Breast Cancer Cohorts

- OsloII cohort of Scandinavian women, n=503
- Gene Expression-Based Outcome for Breast Cancer Online (GOBO), n=1881
- The Cancer Genome Atlas (TCGA), n=1100

Clinical significance of *F5* expression

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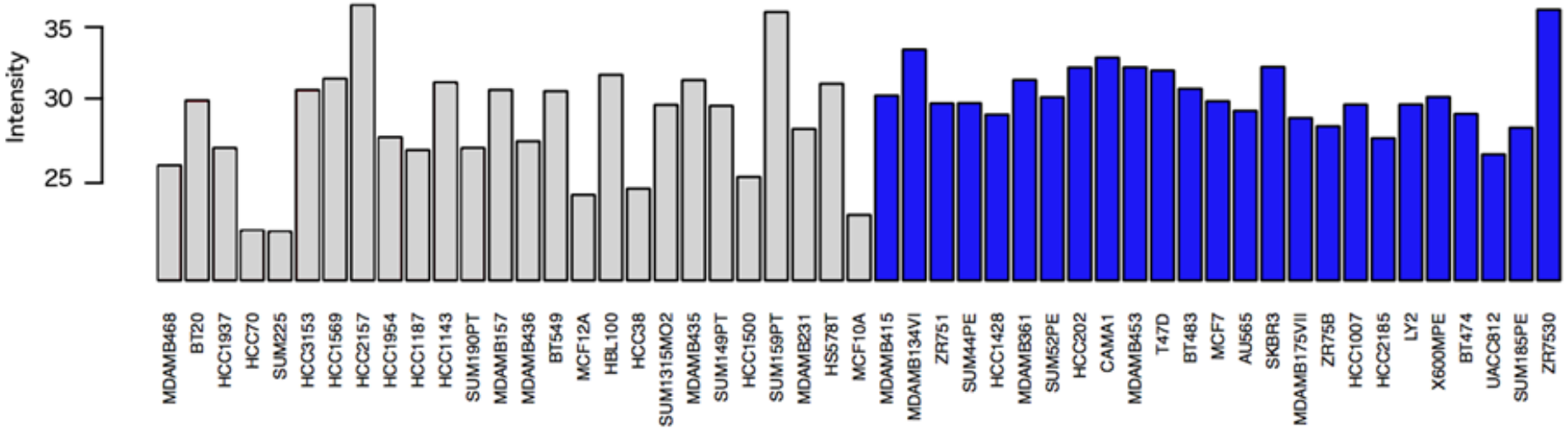
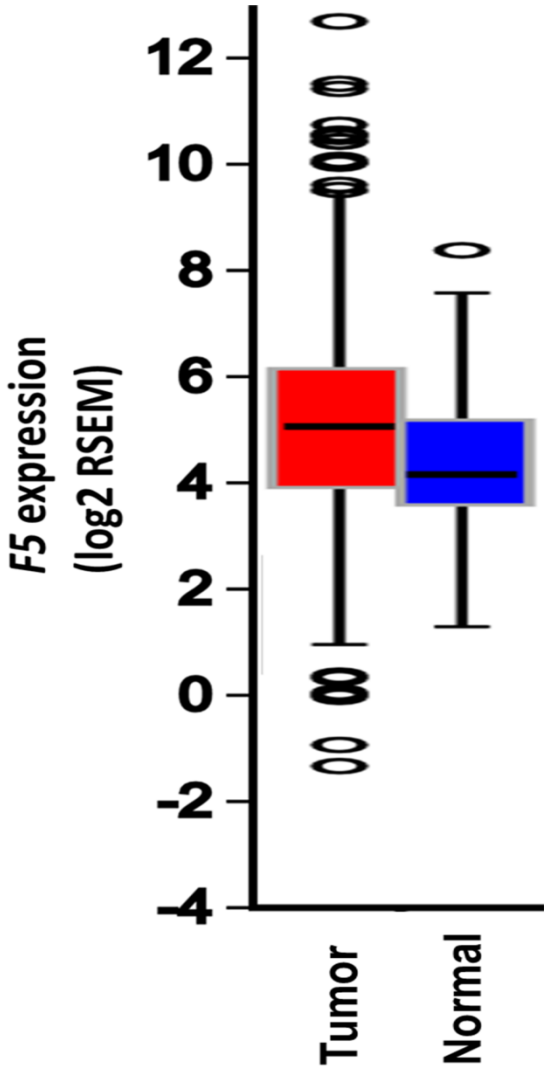
F5 mRNA expression in breast cancer cell lines



F5 expression in breast tumors



TCGA data

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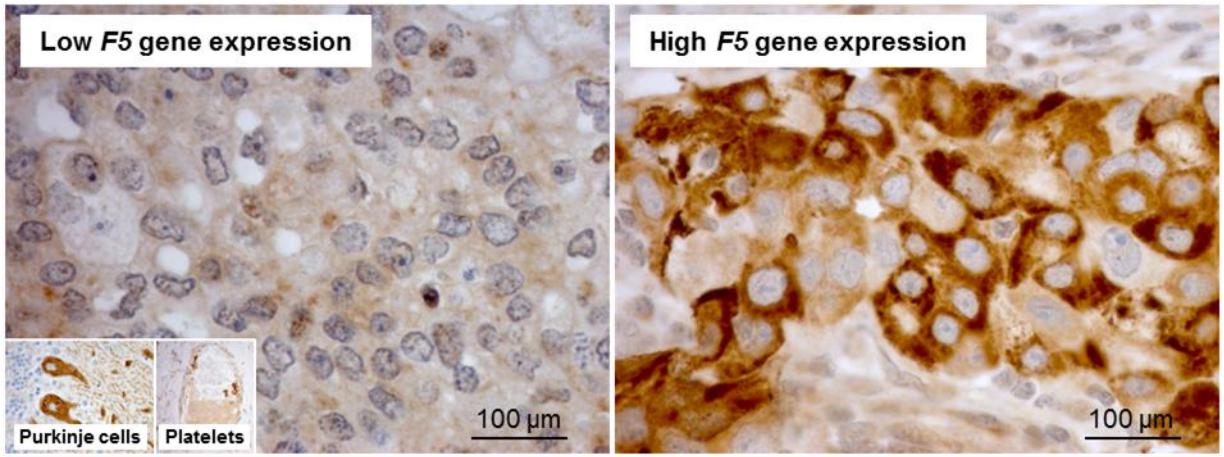
FV protein expression in breast tumors



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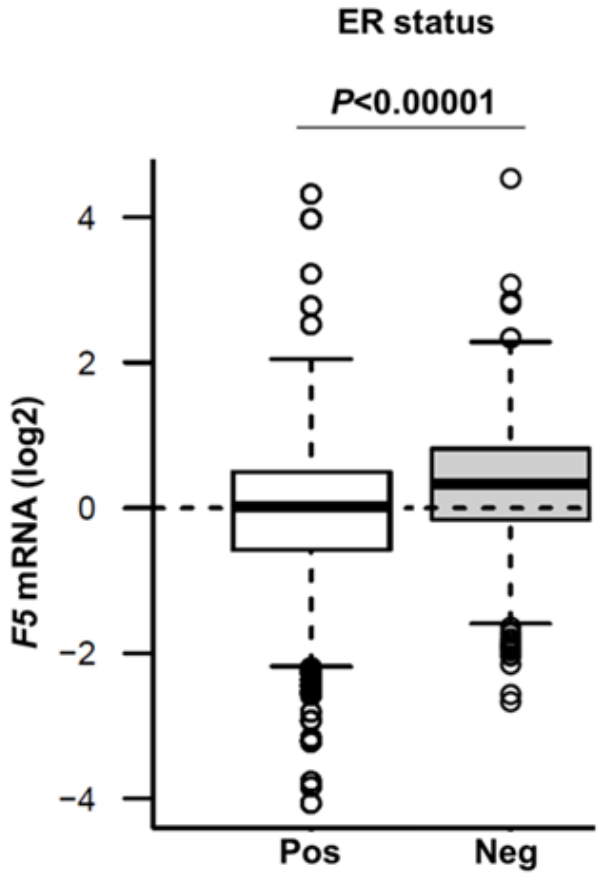
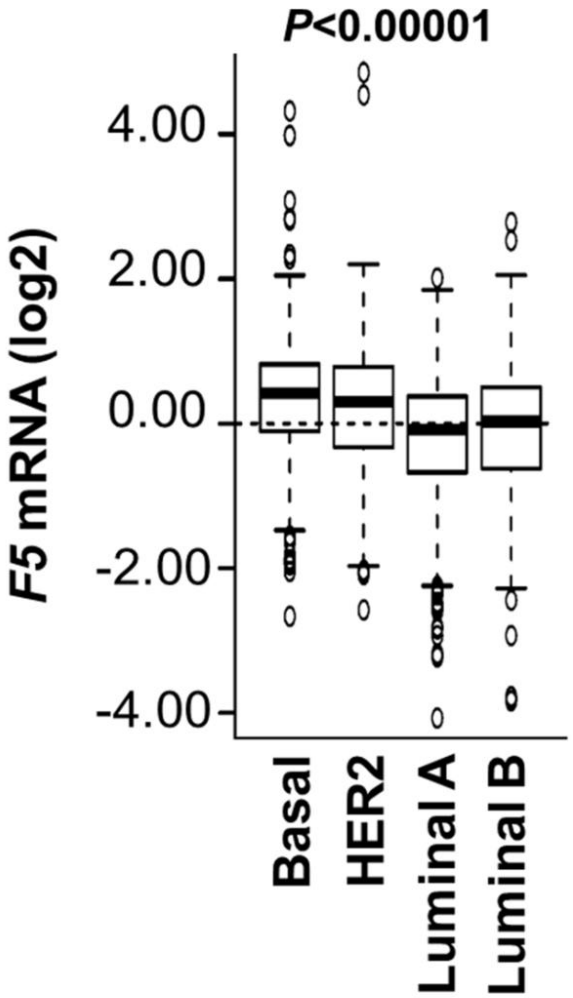
F5 expression in tumor subgroups





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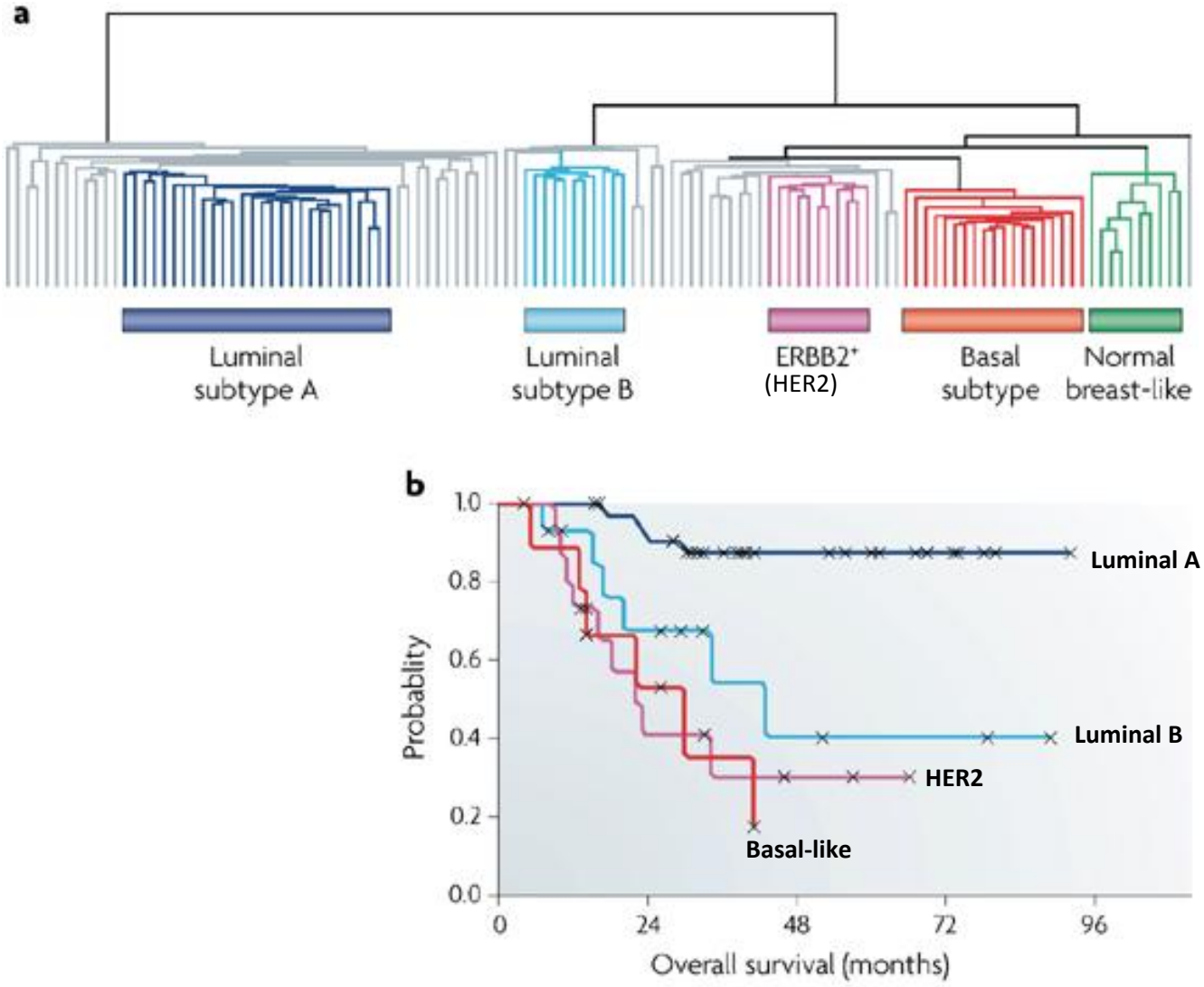
Breast cancer subgroups and survival



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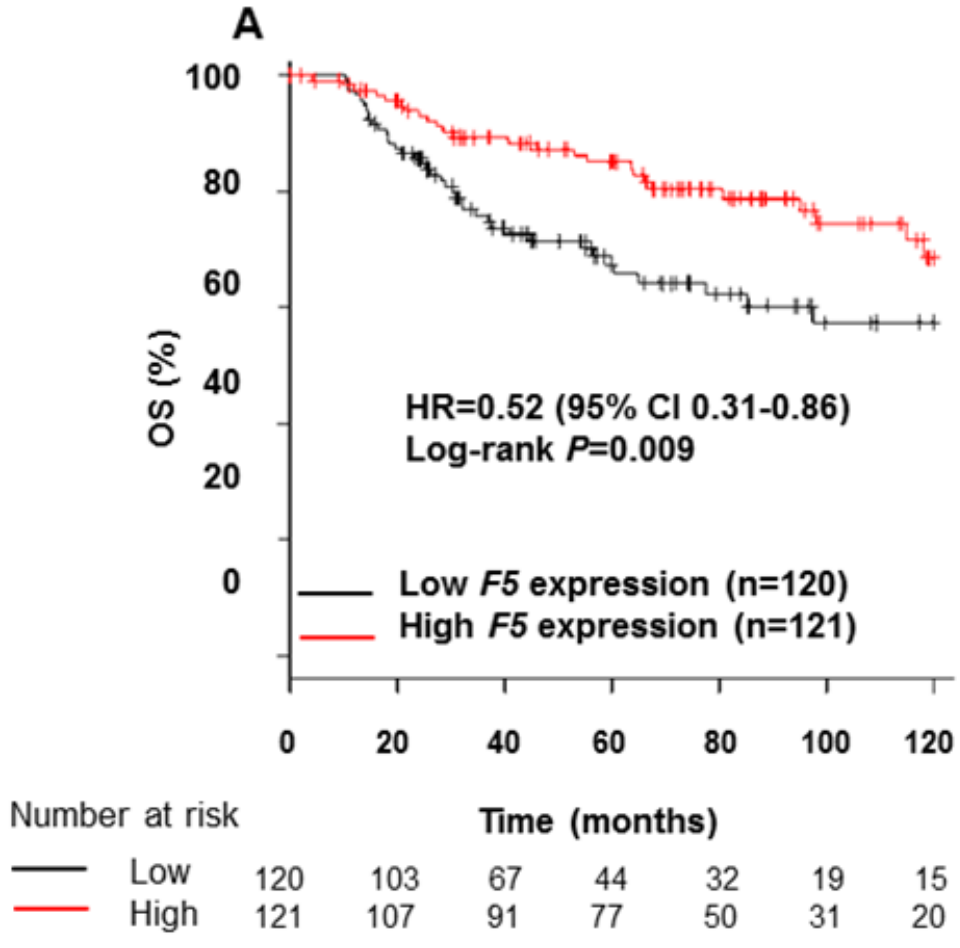
F5 expression in tumors and effect on survival

Basal-like tumors



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Regulatory role of *F5* SNPs

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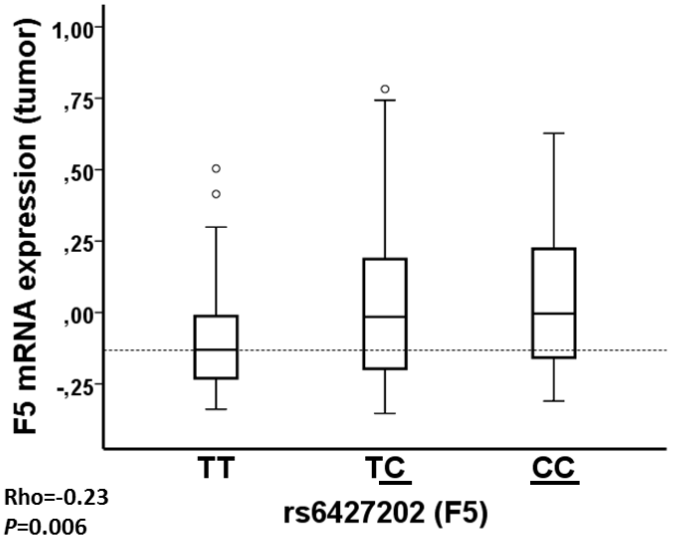
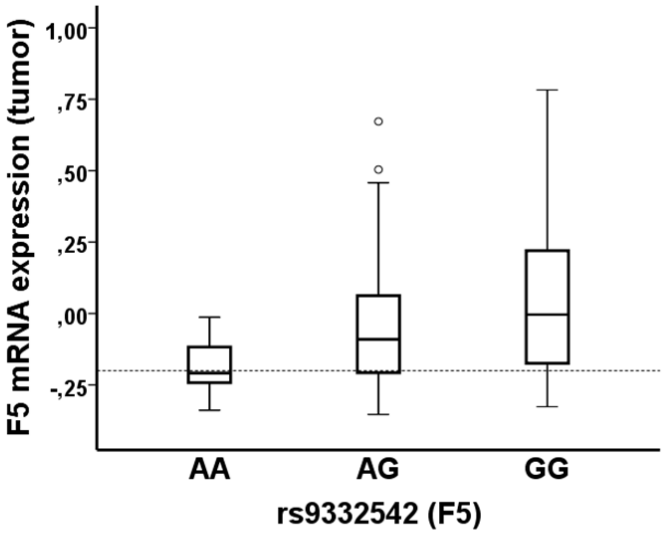
F5 SNPs and FV expression

		Tumor FV expression				Plasma FV antigen		
SNP	Region	r	P	FDR		r	P	FDR
rs6427202	Intronic	0.23	0.005	0.059		0.18	0.0009	0.004
rs9332542	Intronic	0.23	0.006	0.059		0.16	0.003	0.011





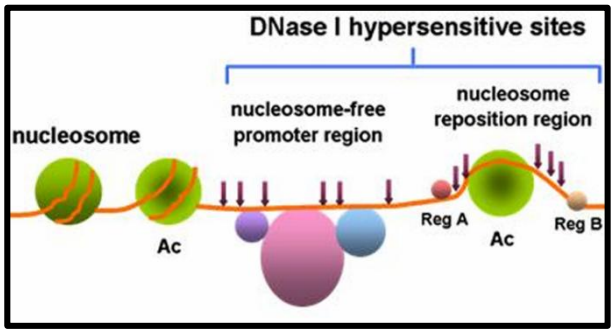
Spearmans rank correlation
Risk alleles are underlined

Functional annotation of *F5* SNPs

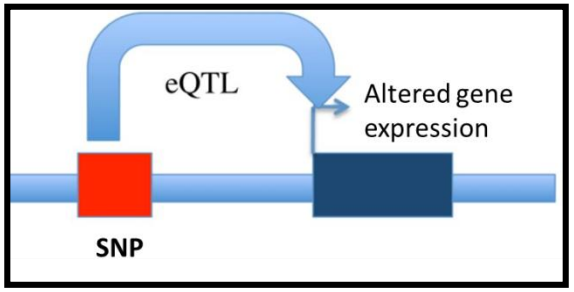
F5 rs9332542
F5 rs6427202

→ SNPs in LD= 86

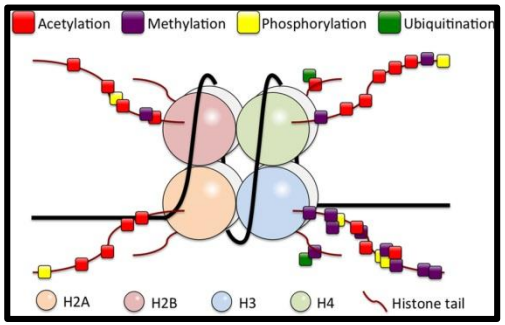
DNAse hypersensitive regions



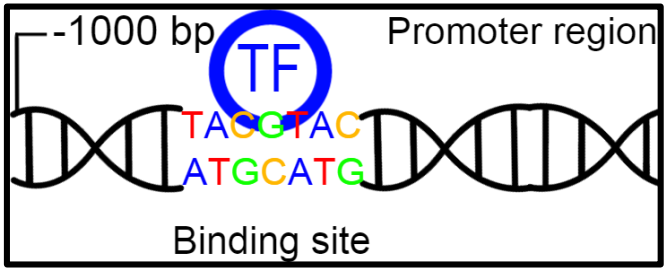
eQTLs



Histone modifications



Altered transcription factor binding

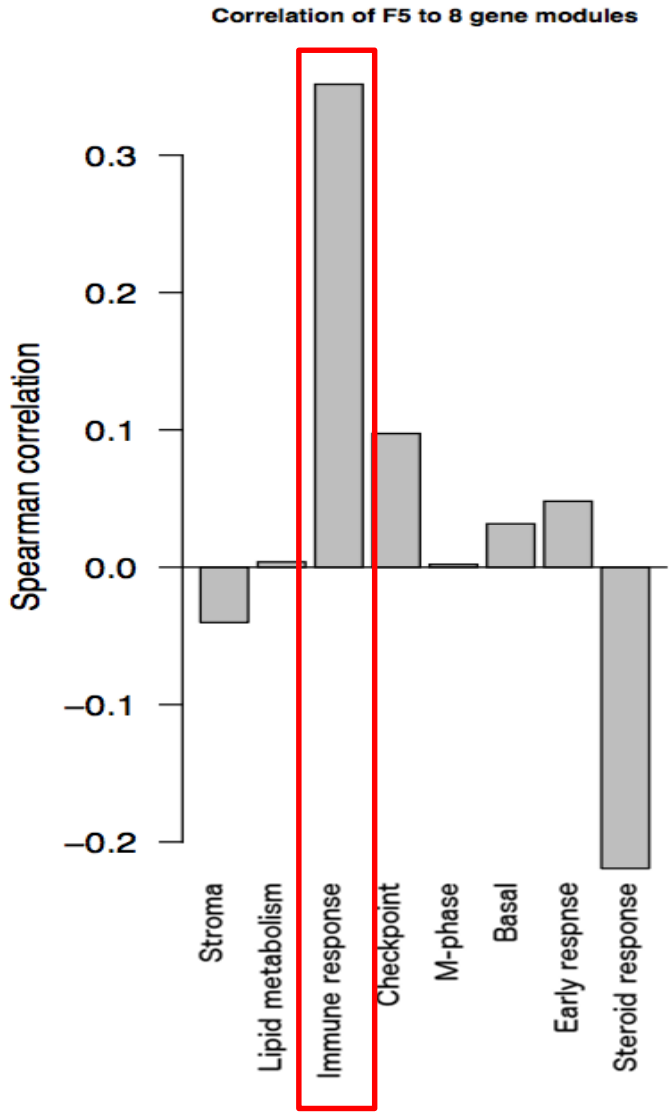


Nica et al. *Philos Trans R Soc Lond B Biol Sci.* 2013

Kato et al. *BoneKEy Reports*. 2015

Biological role of *F5* expression

F5 correlates to immune response genes



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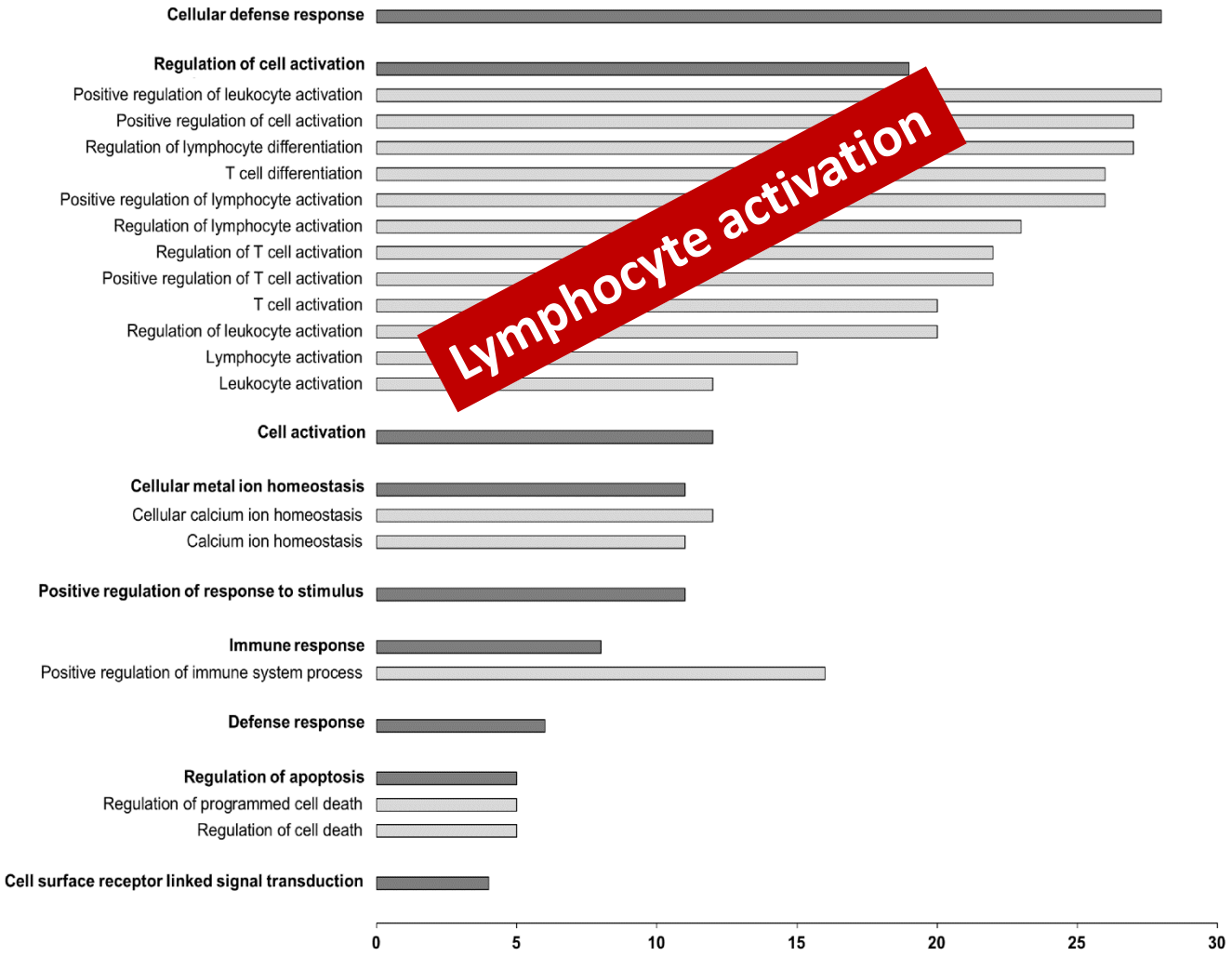
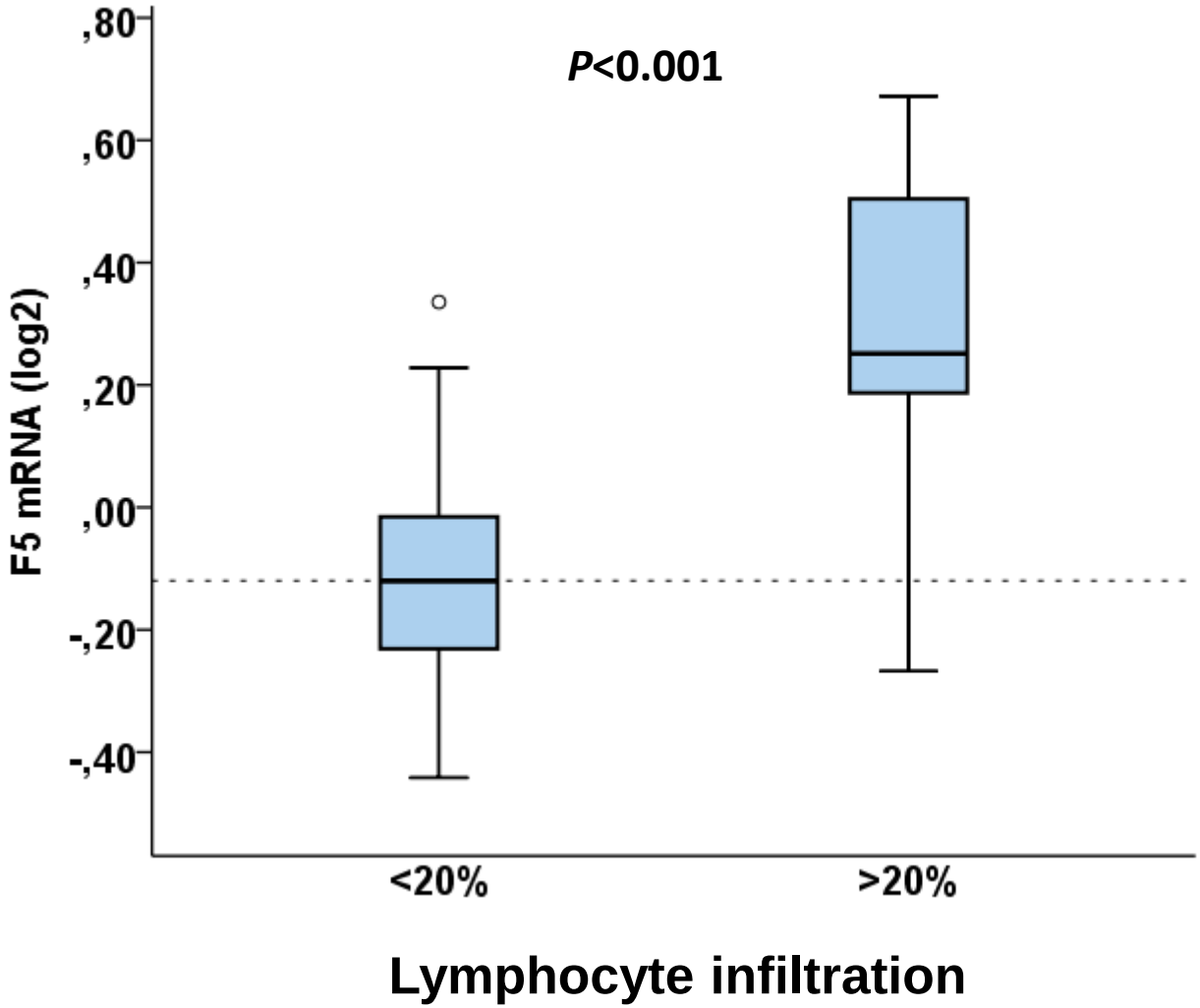
Functional annotation of *F5* correlated genes

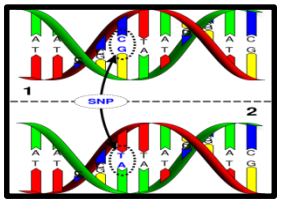


F5 and lymphocyte infiltration in tumors

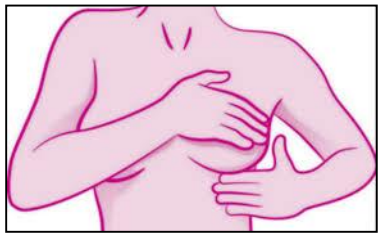


Summary

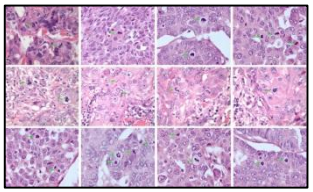
F5 SNPs



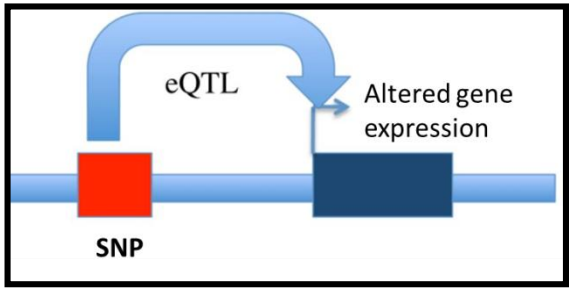
Breast cancer



Clinical subgroups



F5 expression



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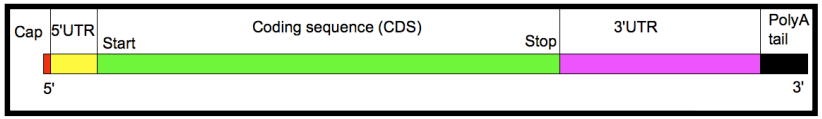
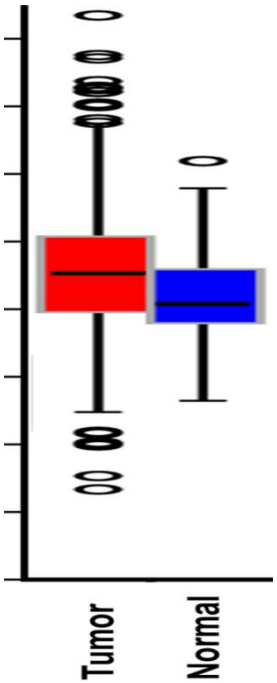
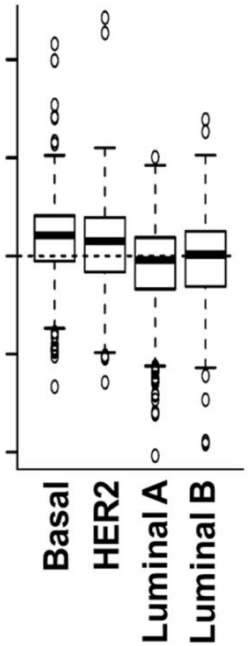
Summary

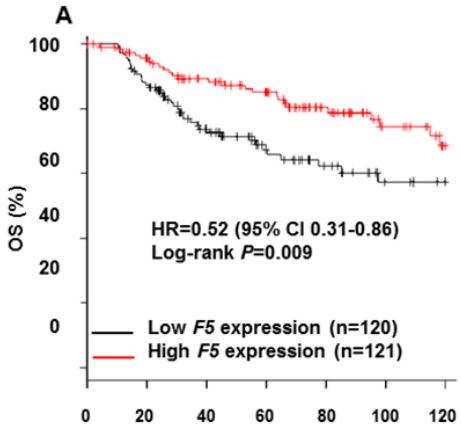
_F5_ mRNA

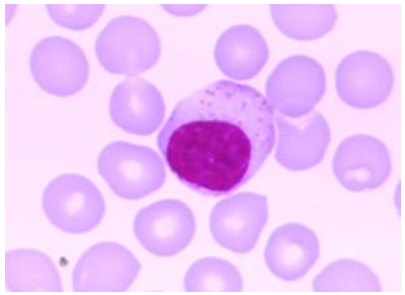


Breast tumors ***Aggressive tumors*** ***Survival*** ***Lymphocyte infiltration***









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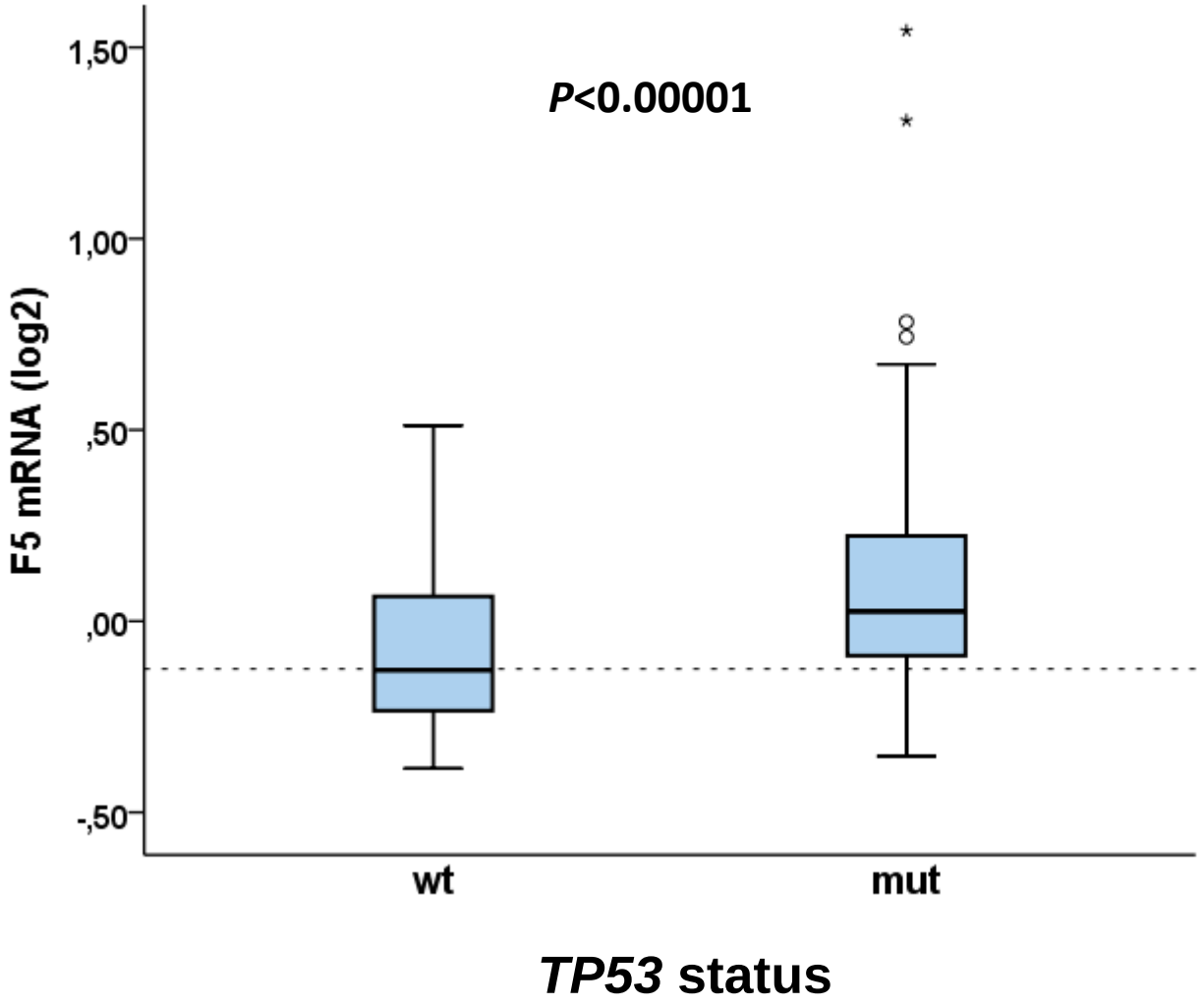
F5 expression and *TP53* status



Conclusion

- These results indicate that F5 is involved in cancer progression

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Thank you for the attention!

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Oslo Breast Cancer Research Consortium, Study II

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