

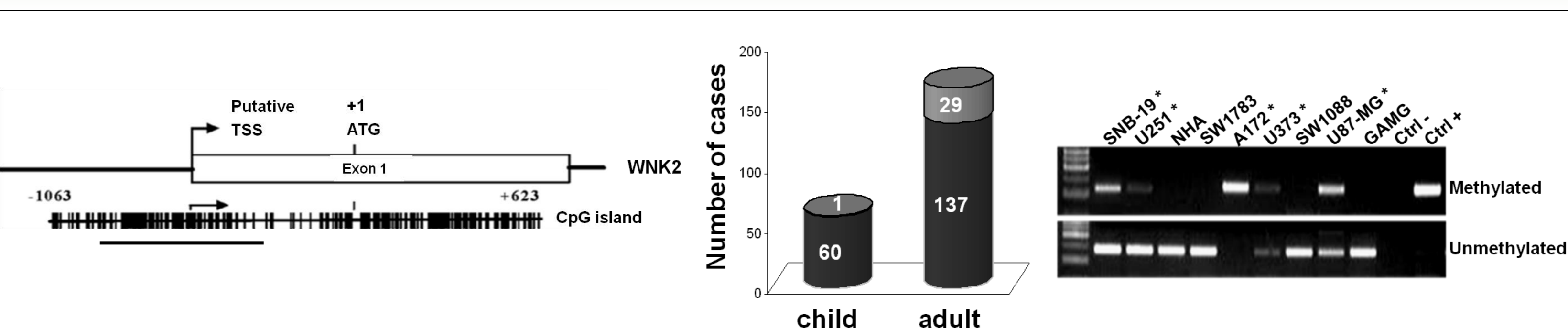
Protein Kinase WNK2 has a Tumour Suppressor Role in Gliomas.

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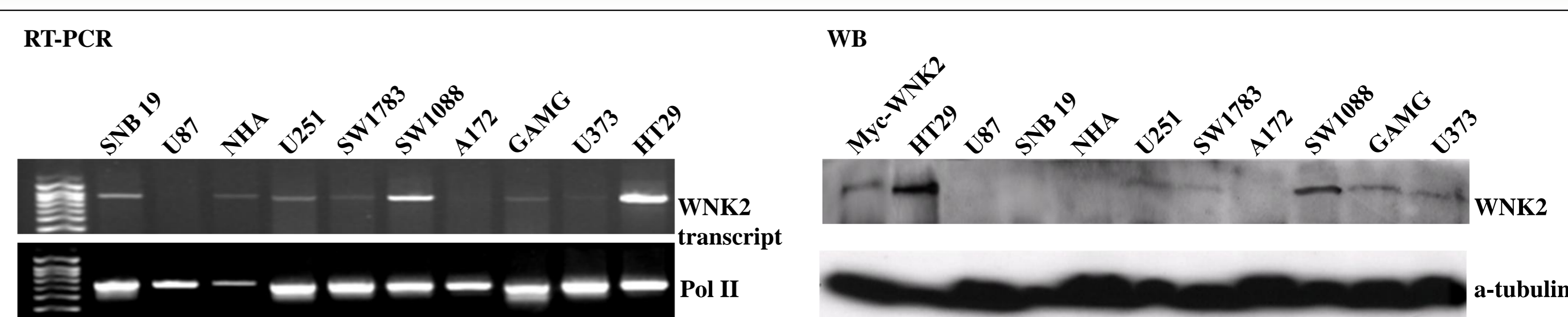
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SUMMARY Malignant glioblastoma is the most common and lethal adult brain tumour type. Recently, the promoter region of the protein kinase WNK2 gene was found to be hypermethylated in 29 of 31 infiltrative gliomas and about 5 of 7 meningiomas. We have previously described that the experimental depletion of WNK2 expression decreases RhoA activity whilst leading to increased Rac1 activity. RhoA/Rac1 activities are important for cell migration and glioblastomas are very invasive tumours so that we tested the effects of WNK2 on wound-healing assays in glioma cell lines SW1088 and A172. SW1088 cells express endogenous WNK2 and we observed that wound closure was increased upon experimental depletion of endogenous WNK2. In contrast, A172 cells display complete promoter region methylation and WNK2 re-expression was found to decrease migration. Consistently, we observed an increase in Rac1 activity in SW1088 cells upon WNK2 down-regulation, but lower levels of active Rac1 in A172 cells stably expressing WNK2 cDNA when compared with an equivalent cell line stably transfected with the same empty vector. Our studies indicate that loss of WNK2 expression promotes Rac1 activation and may contribute to the highly invasive phenotype that glioblastomas present.

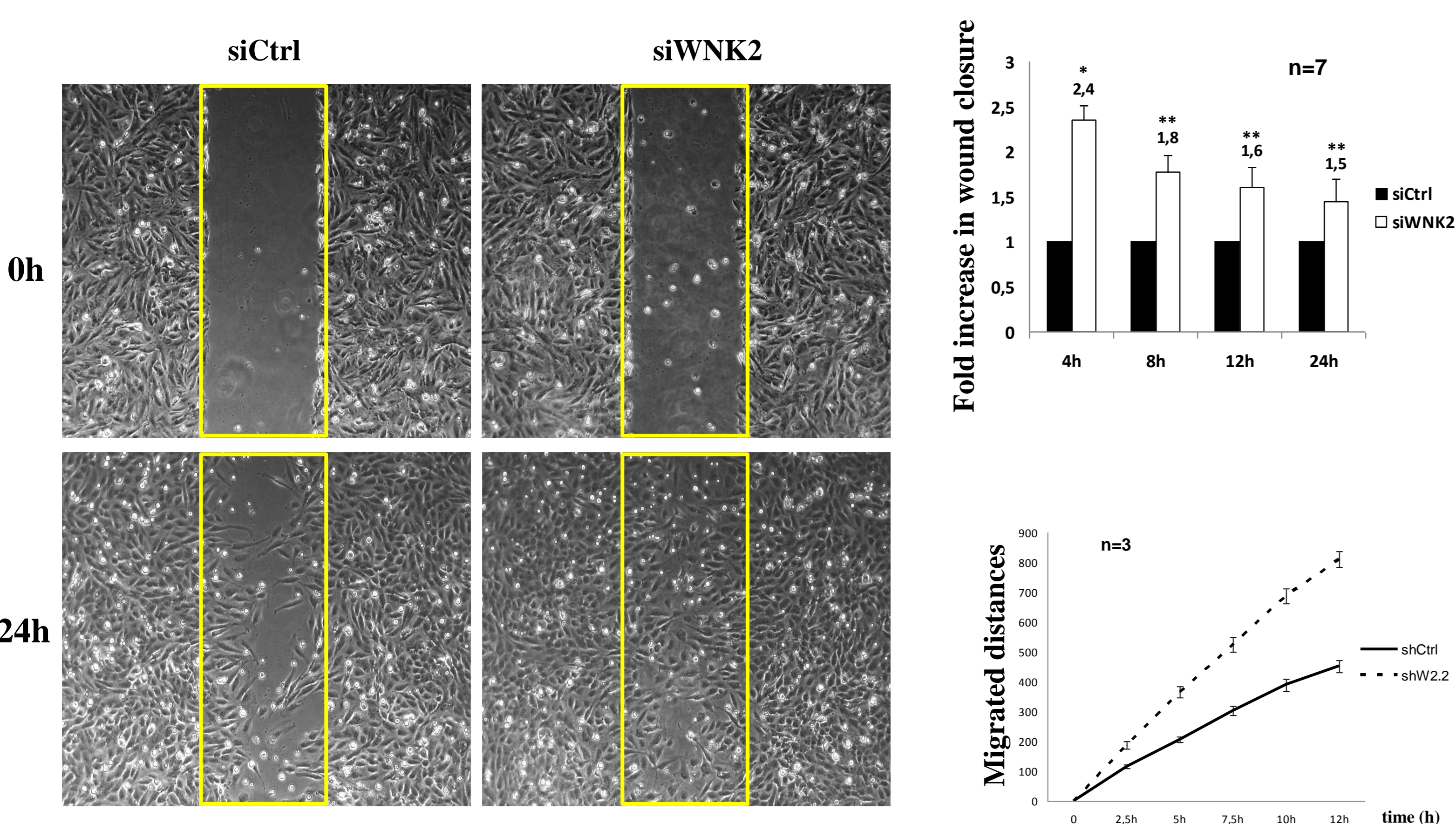
WNK2 promoter methylation



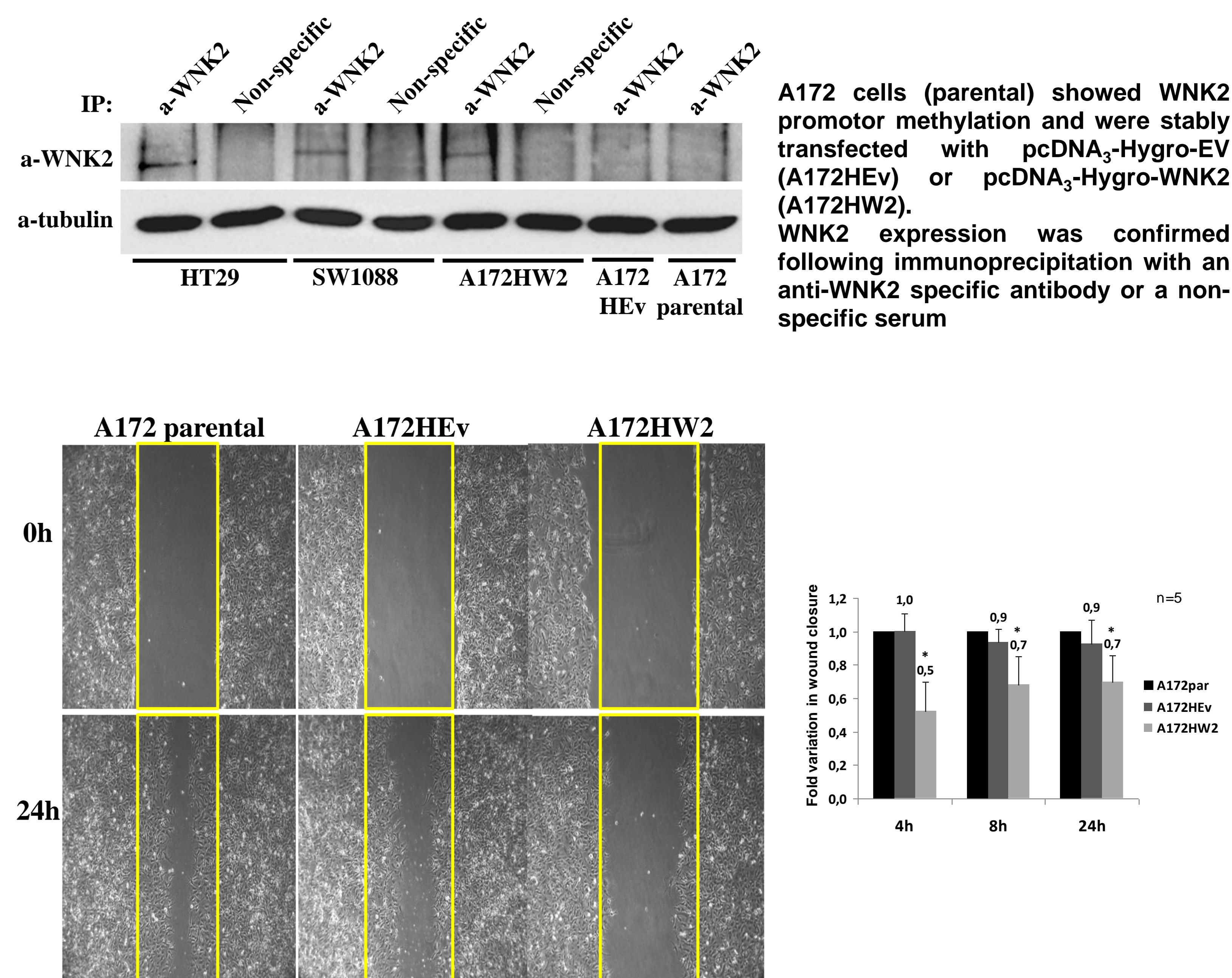
WNK2 expression in glioblastoma cell lines



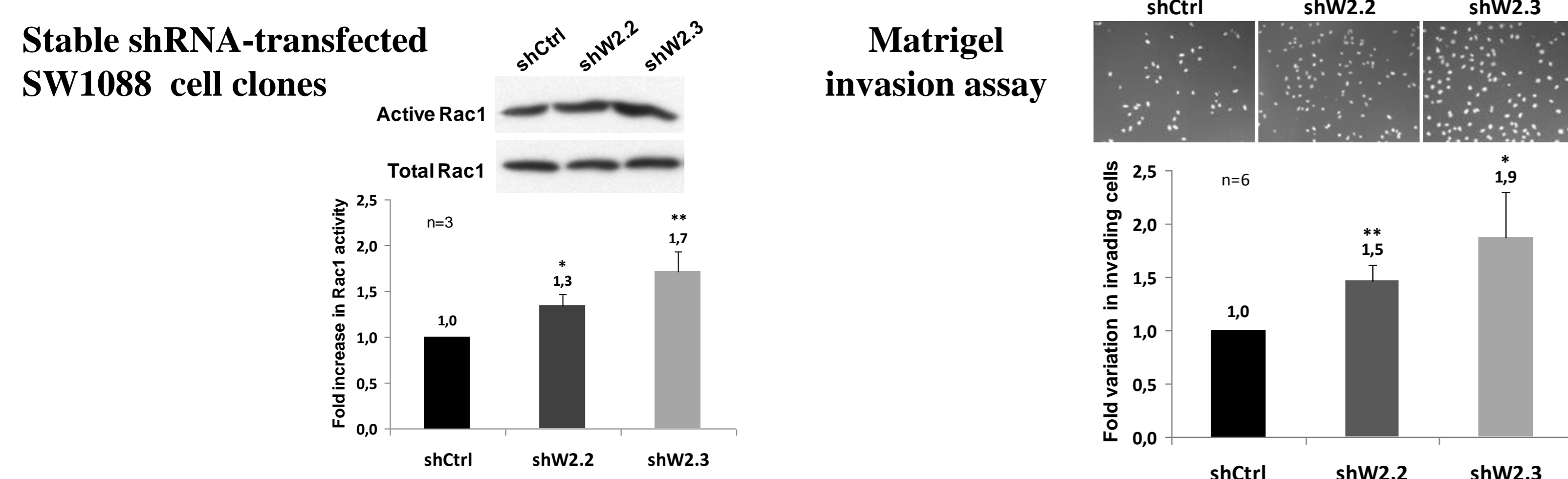
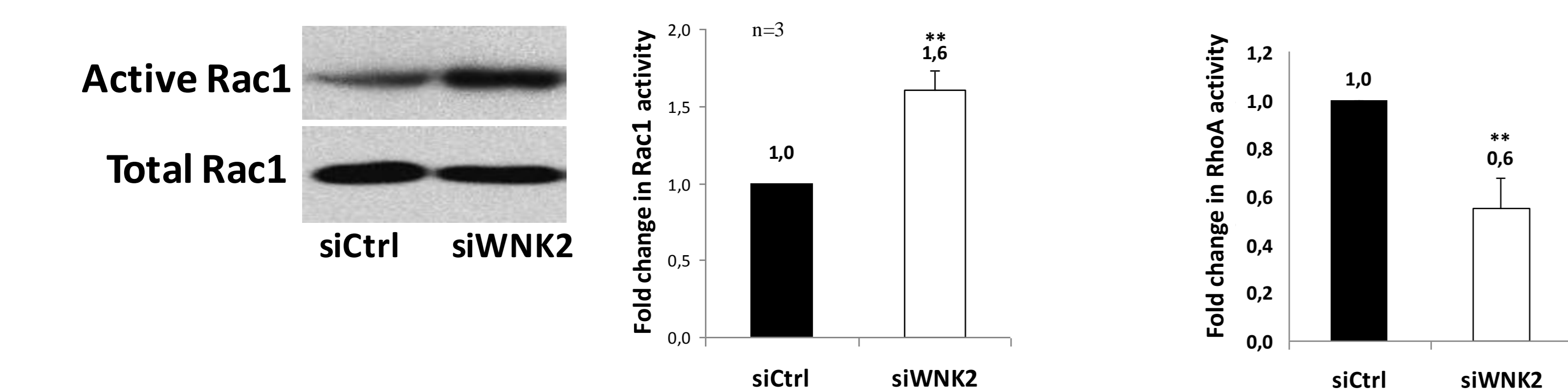
1) Depletion of endogenous WNK2 in SW1088 cells: ... leads to increased wound closure in scratch assays,



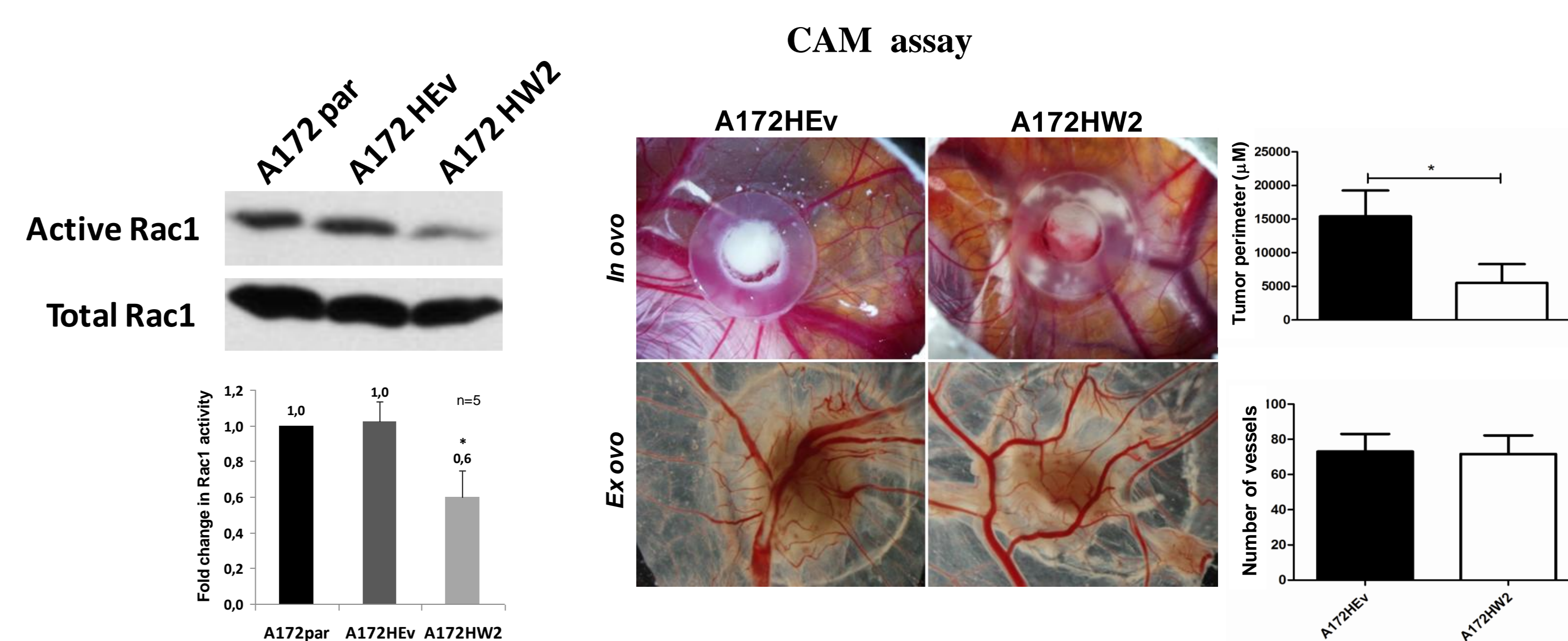
2) Stable re-expression of WNK2 in A172 cells: ...retards wound closure in scratch assays,



...results in increased Rac1 activity and cell invasion.



...results in decreased Rac1 activity and cell growth.



Conclusions:

- The WNK2 gene promoter is methylated in adult gliomas leading to reduced WNK2 expression.
- Experimental manipulation of WNK2 expression levels in glioblastoma cell lines leads to changes in Rac1 activity and invasiveness.
- WNK2 has a tumour suppressing role in brain tumours