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A distinct gene-expression profile in paediatric Ganglioglioma

on behalf of the Neuro-oncology group

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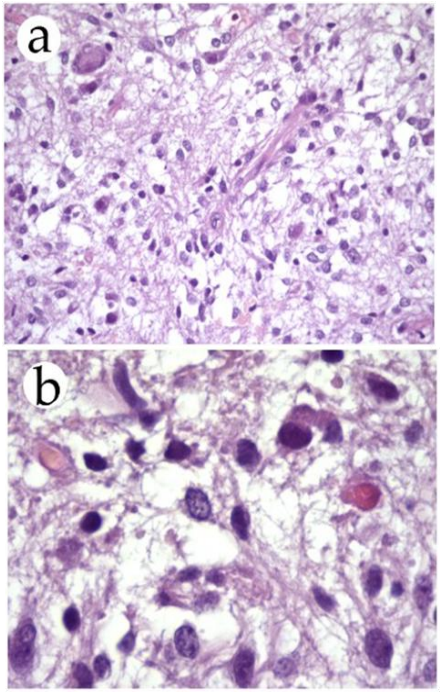
Gangliogliomas



Neuronal and mixed neuronal-glial tumours are well differentiated, slowly growing neuroepithelial tumours, composed of neoplastic, mature ganglion cells, alone (gangliocytoma) or in combination with neoplastic glial cells (ganglioglioma).

They correspond to WHO grade I.

Some gangliogliomas with anaplastic features in their glial component are considered WHO grade III (anaplastic gangliogliomas).

Clinical Context

Rare tumours (4% of all paediatric CNS tumours), >70% occur in temporal lobe locations. Among LGGs: un-favourable *outcome* can be observed with subtotal resection.

Biology

Because of its rare occurrence, little is currently known about the molecular pathology of this neoplasm and there are very few cytogenetic and molecular studies available.

➢Carry out a molecular sub-classification of supratentorial Gangliogliomas (GGs).

We performed gene expression analysis on 12 GGs *versus* 10 Pilocytic Astrocytomas (PAs) by Microarray technology (GeneChip® H.G. U133 Plus 2.0 Array Affymetrix)**

qPCR analysis was then used in order to confirm and validate the results on 21 independent cases.

**Selected from the Neuro-Oncology Bio-Bank of the G. Gaslini Research Institute

Patients enrolled in the study

Inclusion criteria

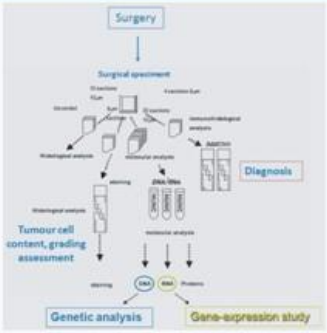
- Diagnosis at IGG in the periods 1990-2005 and 2006 - 2008
- Age at diagnosis < 16 years
- Complete imaging study at diagnosis (MRI and/or CT scan)
- Continuous follow-up during and after treatment concerning:

Survival, QoL and information on functional outcome

- Fresh frozen tumour tissues for expression studies

All tumours were reviewed by the local neuropathologist (P.N.).

Specific procedures were used to extract all nucleic acids



Exclusion criteria

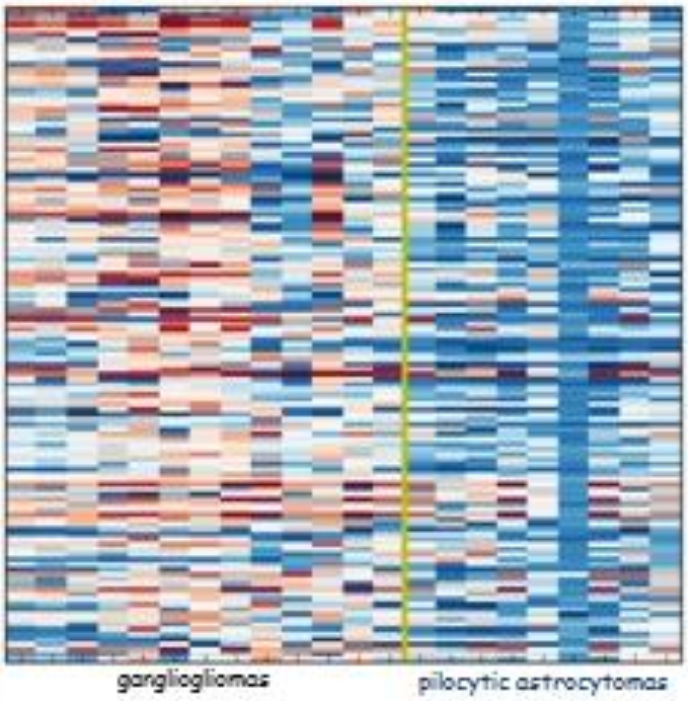
- Patients operated in other centres or
- Lack of histological diagnosis

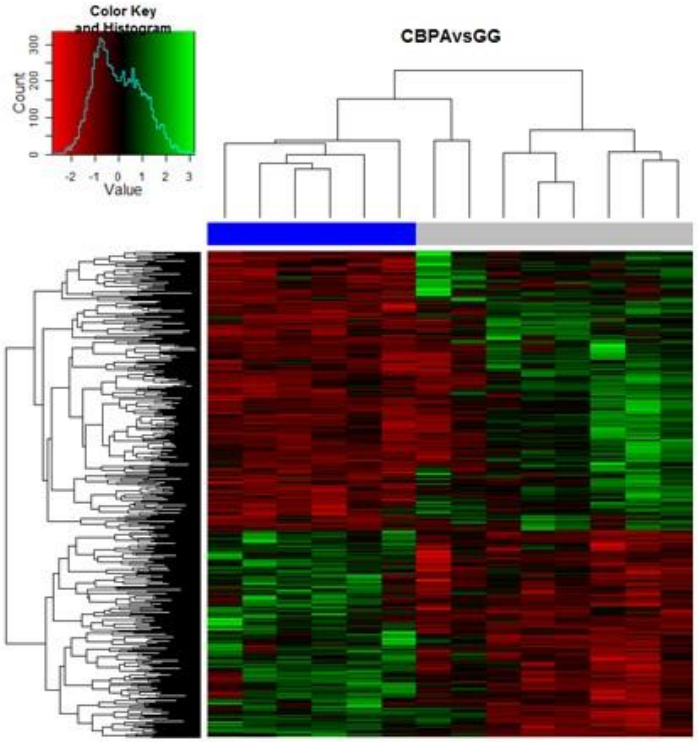
Histology	Brain site of lesion			BRAF status	
	Cerebellum	Cerebrum	Brainstem	Kex16-Bex9	Mutation V600E
Pilocytic astrocytomas (n 25)	12	11	2	37.5% 6/17	6.25% 1/17 (8 ND)
Gangliogliomas (n 20)		18		0.0% 0/19	21.0% 4/19 (1 ND)

Results

The identification of candidate probe-sets was performed by means of l1l2, a machine learning method based on regularization.

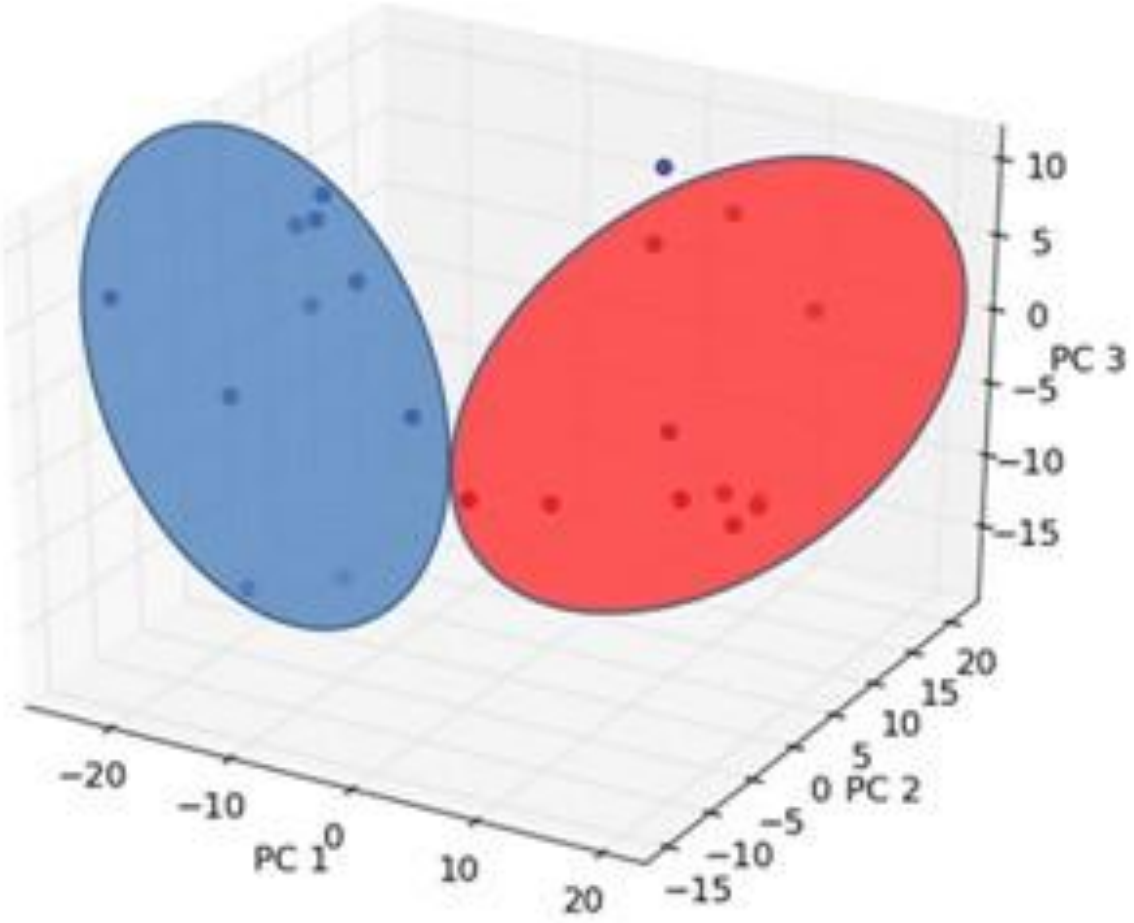
Gene candidate expression heatmap for GGs





The signature consists of 103 probe-sets corresponding to 70 genes

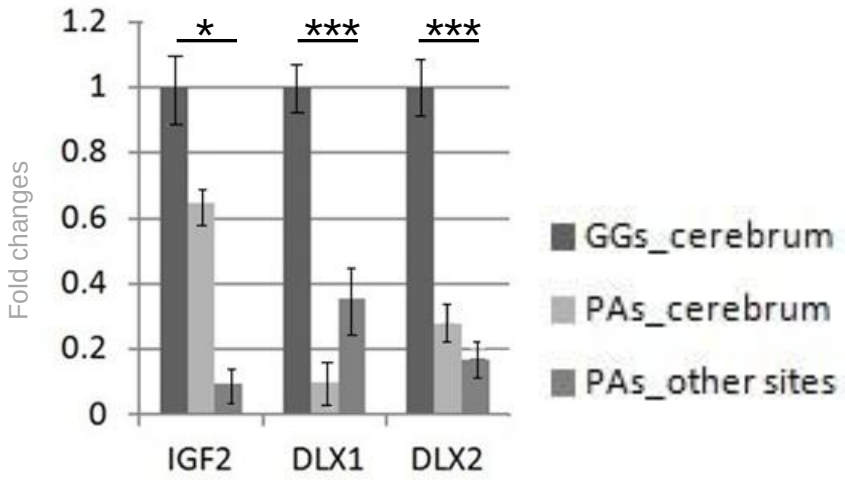
Multidimentional plot



Among the supratentorial tumours, there is a gene signature distinguishing ganglion cell types (GGs) from the classic "pure" pilocytic tumours (PAs).

Genes				Function	
DLX1	*DLX2*	*FLT3*		neurogenesis	
IGF2	*LTBP2*			cell growth	
HBA1/2	*CXCL12*	*CCL5*		immune response	
ASS1	*WBSCR17*	*GALNTL1*	*UGT8*	metabolism	
COL1/3A1/2	*L1CAM*			extracellular matrix and cell mobility	

Validation by qPCR



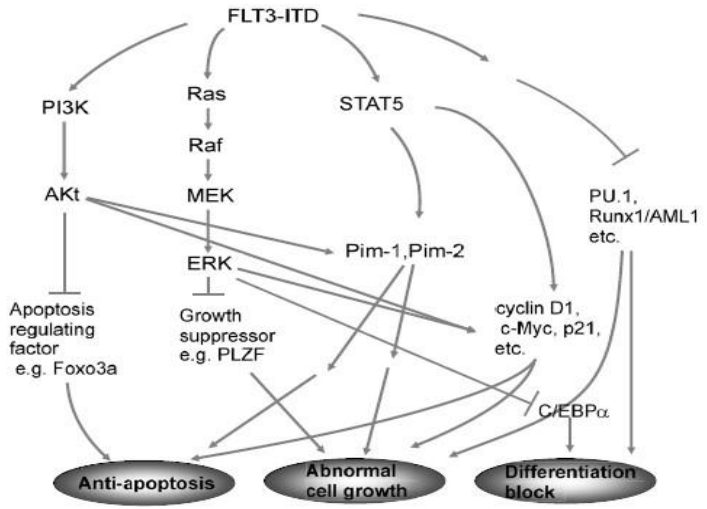
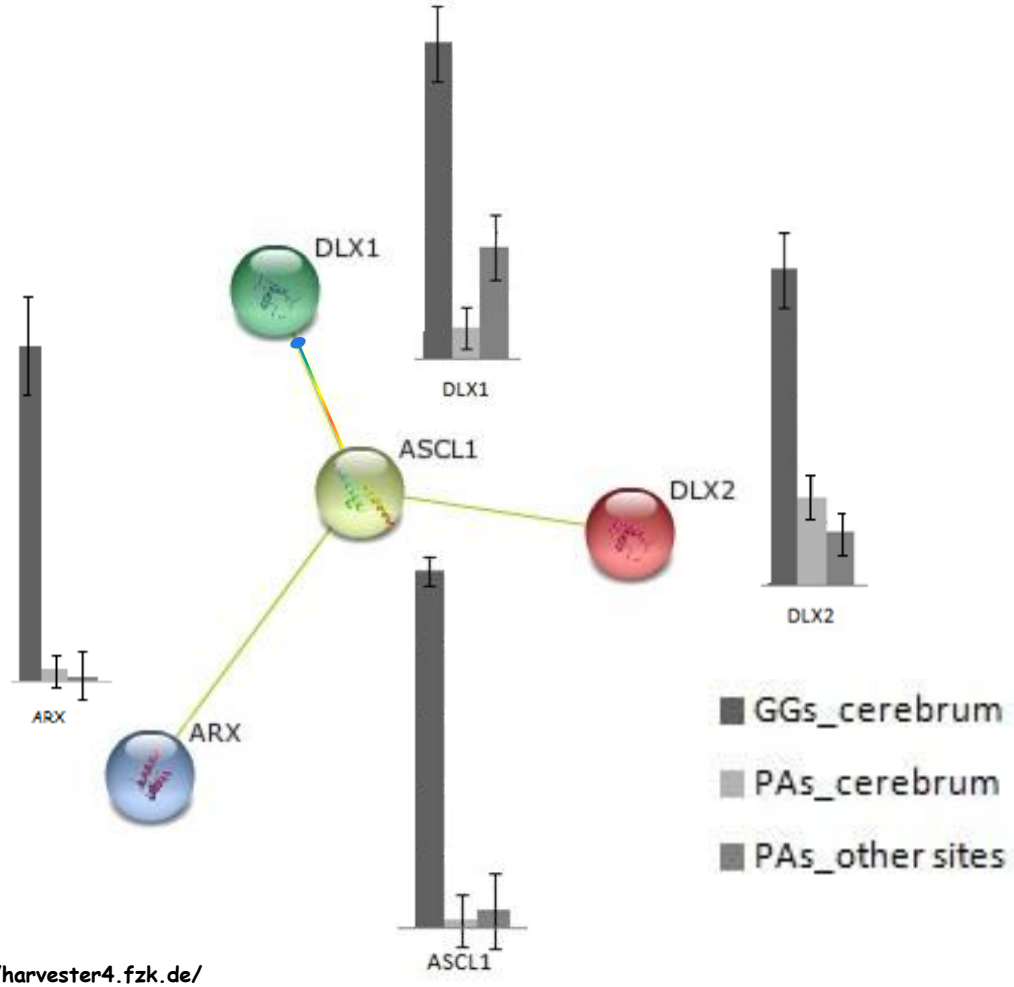


Figure 2 Mechanisms of FLT3-ITD induced leukemogenesis. Depicted is an outline of known pathways downstream of FLT3-ITD.

Takahashi *Journal of Hematology & Oncology* 2011, **4**:13



http://harvester4.fzk.de/

DLX gene family expression is associated with tumours progression and aggressive tumour behaviour .

Conclusions and future goals

- Molecular differences characterizing Ganglioglioma *versus* Pilocytic Astrocytoma may exist.

- Our analyses point to some interesting candidate genes such as *DLX* family member signaling worth investigating further.

- Since commercial Abs are not yet available, RNA *in situ* hybridization analysis is ongoing.

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