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Different pediatric brain tumors are associated with different gene expression profiling

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ABSTRACT

Malignant brain tumors are the most common pediatric solid tumors and are the leading cause of death from childhood cancers. These tumors include several histologic subtypes. Due to the particular properties of brain tumors, such as growth and division, examination of brain tumors and the analysis of results are not simple. Up to date there is a dearth of useful biomarkers that have been validated and clinically implemented for pediatric brain tumors. In order to identify the new genetic alterations we recognized, using microarray dataset, chitinases as new potential biomarkers of CNS tumors. The modulation of chitinases was confirmed also in the different histologic subtypes. Our study revealed that distinct patterns of chitinases expression characterize the diverse histological subtypes. In addition evaluating other lisosomal enzymes such as glycosidases and proteases we found that NEU4, CTBS and GBA2 belonging to glycosidases family and CTSC, CTSK and CTSF belonging to proteases family were differently modulated. Future investigations are needed to be performed before some of these enzymes could finally be used as biomarkers of specific types of CNS neoplasms.

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Introduction

Childhood brain tumors are the second leading cause of death from childhood cancers. A broad increase in new cases of CNS tumors has been observed throughout the world (Woehrer et al., 2015). Brain tumors comprise of heterogeneous group of neoplasms, including approximately 120 entities as well as different types of primary brain tumors and a variety of secondary neoplasms (Louis et al., 2007). Generally, the diagnosis of CNS neoplasms is confirmed with histopathology examination and must start with careful neurologic examination followed by suitable brain imaging. Imaging techniques consent to define tumor location, its biologic activity and to estimate the

Abbreviations: PA, pilocytic astrocytoma; EPM, ependimoma; GBM, glioblastoma; MED, medulloblastoma; NB, normal brain; CHIT1, chitotriosidase; CHI3L1, chitinase 3 like 1; CHI3L2, chitinase 3 like 2; CHID1, chitinase domain containing 1; CHIA, chitinase acid; CDK1, CDK2, cyclin-dependent kinases; TP53, tumor protein p53; GABRA, gamma-aminobutyric acid; HS3ST2, heparan sulfate glucosamine genes; KCNAB2, potassium voltage-gated channel; NEU4, sialidase-4; CTBS, chitobiase; CTSC, cathepsin C; CTSK, cysteine protease K; CTSF, cathepsin F.

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http://dx.doi.org/10.1016/j.acthis.2015.02.010 0065-1281/© 2015 Elsevier GmbH. All rights reserved. effects of patients' treatment, to differentiate tumor recurrence and determine tumor progression (Chandana et al., 2008). Blood and tissue biomarkers of central nervous system (CNS) tumors, neuroimaging techniques, especially MRI, are the standard methods in evaluation of disease status of patients with CNS tumors. At the moment, neuroimaging methods are characterized by the lack of specificity for differentiation of brain tumors, thus the tumor typing and grading are still definite by histopathological assessment of tissue sample that require surgical intervention. In addition, the frequency of pseudoprogression as well as pseudoresponse after treatment is a well-known limitation of these techniques. So far, few genes have been considered suitable as clinical biomarkers that may support neuroradiological differential diagnosis of central nervous system (CNS) tumors. The best solution in the process of CNS tumors diagnosis could be easily available biomarkers that should be useful in the monitoring of the disease course, differentiation diagnosis, and improve treatment options (Ilhan-Mutlu et al., 2013). Current treatments for these pediatric brain tumors include surgical resection, radiation, and chemotherapy. However, in young children, these treatments are associated with secondary damage to the developing brain, and result in long-term neuropsychological and neuroendocrine dysfunction. Given this clinical imperative and the limited success in

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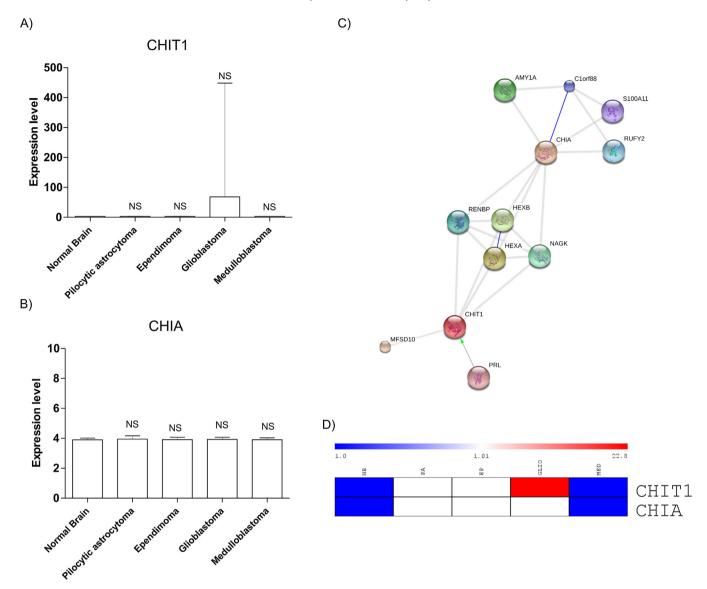


Fig. 1. Chitinases genes expression in pediatric brain tumors. (A, B) No significant change was observed in CHIT1 and CHIA expression. (C) STRING network of Chitinase. (D) Heatmap of chitinases expressed in pediatric brain tumors. Gene expression values are color coded from bright red (most upregulated) to dark blue (most downregulated). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

identifying therapeutic targets by conventional genomic analyses it is imperative to identify the key genetic and growth control pathways de-regulated in the in pilocytc astrocytoma (PA), ependimoma (EPN), medulloblastoma (MED) and glioblastoma multiforme (GBM) which are the most common pediatric brain tumor types sample that require surgical intervention. The spectrum of brain tumors arising in children differs significantly from what is observed in adults, with PA and medulloblastoma (MB) accounting for the largest portion of pediatric low grade and malignant brain tumors, respectively. These tumors rarely occur in adults, who have a higher incidence of meningioma and malignant gliomas, especially GBM (Ostrom et al., 2013). Additionally, the structural alterations and sequence-based changes that characterize pediatric and (Rickman et al., 2001) adult brain tumors are often different and reflect differences in the underlying mechanisms of tumor formation (Fangusaro, 2012; Kilday et al., 2009; Ramkissoon et al., 2013). New genomic technologies such as DNA microarrays may elucidate the molecular mechanisms underlying major human brain pathology including tumors (Anagnostopoulos and Tsangaris, 2014; Glade Bender et al., 2015; Madabhushi et al., 2014; Paratore et al., 2006; Suva and Louis, 2013). Some studies have used microarrays to compare the expression pattern of highgrade tumor with low-grade tumor or non-tumoral brain tissue (Gutmann et al., 2002; Khatua et al., 2003; Mischel et al., 2004; Rickman et al., 2001; Sallinen et al., 2000). They identified cell cycle and growth regulators, invasion and growth factors and cytokines that probably play a role in brain tumors progression. In this study, employing a network-based analytical approach we chose to compare PA EPN, MED and GBM and PA in order to find a new list of genes involved in tumor brain invasion. We were able to identify a number of novel potential candidate genes for the evaluation of the malignancy and prognosis of pediatric brain tumor.

Materials and methods

Selection of a microarray expression dataset

The microarray dataset for the transcriptional profile of pediatric brain tumors was obtained from the NCBI Gene Expression

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