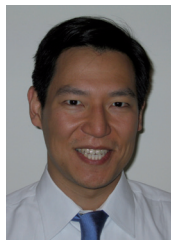


# Molecular fingerprints of medulloblastoma and their application to clinical practice



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“Medulloblastomas are the most common malignant brain tumors in children.”

Medulloblastomas are the most common malignant brain tumors in children. Over the past 25 years, considerable progress has been made in the treatment of this disease. Through improvements of conventional treatments with surgery, external beam radiation and chemotherapy, what was once universally fatal is now cured in more than two-thirds of patients. However, improvements in survival rates have stalled over the past decade, and long-term neurological and neurocognitive sequelae, owing to the aggressive nature of current therapies, have limited our ability to push these treatments forward. This has prioritized our need for the development of newer, more targeted therapies for patients diagnosed with medulloblastoma. Over the past decade, several genomic studies have pushed us closer to this goal [1–6]. The most recent studies by Northcott *et al.* and our group (Cho *et al.*) represent the largest genomic analyses of primary medulloblastomas to date [1,4]. Collectively, these analyses offer us an unprecedented view of the genetic landscape of medulloblastoma and the signaling pathways involved in its pathogenesis. They also offer us the challenge of translating our genomic findings into clinical practice through improved diagnostic, prognostic and therapeutic applications.

Histological heterogeneity (inter- and intratumoral) has been well documented in medulloblastoma, but standard histological subtyping has proven to be inaccurate and highly subjective. This has provided the rationale for the development of a more robust classification system based on molecular features. Genomic analyses have characterized several molecular subgroups of medulloblastoma that each have distinct gene expression and copy-number profiles. These

studies provide the backbone for a more robust and consistent molecular classification system. Northcott *et al.* reported four molecular subgroups (designated sonic hedgehog [SHH], WNT, Group C and Group D) [4]. Our analysis identified the SHH and WNT subtypes but further divided Groups C and D so that medulloblastomas were found to consist of six subgroups (designated c1 through c6) [1]. In comparing our results with those of Northcott *et al.*, the non-SHH/non-WNT subgroups we identified are nested within the subgroups Northcott *et al.* described [KOOB AND TAYLOR, PERS. COMM.], revealing important substructures within broader subgroups of this disease and, importantly, a high degree of concordance between our independent genomics efforts.

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However, the identification of distinct molecular subtypes in medulloblastoma and the further refinement of the substructure within these subtypes is more than just an academic exercise. Each subgroup carries a certain prognostic value. One subgroup identified in our study, designated c1 and characterized by enrichment of MYC expression signatures (usually as a result of a *c-MYC* copy-number increase), has a significantly worse outcome relative to other molecular subgroups [1]. In the analysis by Northcott *et al.*, ‘Group C’ tumors were associated with a particularly low rate of survival [4]. As previously

## Keywords

- genomics
- medulloblastoma
- molecular risk-stratification

mentioned, our subgroups c1 and c5 were nested within the Northcott *et al.* Group C subgroup. Moreover, our data reveal that the c1 tumors predict poor clinical outcome, while patients with c5 tumors have far better survival rates [1]. Going forward, it will be imperative to restrict intensification of therapy to the c1 component of Group C in future clinical trials. On the other hand, both of our analyses independently confirmed previous reports associating WNT/monosomy six subgroup tumors with universally positive outcome [7–9]; the question remains as to whether dose reduction of radiotherapy for this subgroup could reduce treatment-related toxicity without compromising survival.

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In a separate but more proactive approach, rather than associate clinical outcome with medulloblastoma subgroups, we have developed algorithms that utilize molecular features to predict outcome for individual patients diagnosed with this disease. At present, medulloblastoma patients are stratified into one of two primary risk groups – ‘standard risk’ and ‘high risk’ – based solely on clinical criteria (age, metastatic disease at presentation and extent of surgical resection). This stratification schema adjusts the level of therapy that after surgery involves radiotherapy to the entire brain and spine after surgery, and chemotherapy. However, this clinical-based approach has proven to be inaccurate as many standard-risk patients succumb to disease progression [10]. In 2002, we reported that gene expression signatures could outperform the standard clinical risk-stratification for medulloblastoma patients [5]. This outcome signature was further refined to an ‘eight-gene predictor’ that sustained its improved performance over clinical criteria [11]; however, our most recent analysis has revealed that global expression-based models are also limited in their ability to accurately predict outcome [12]. It turns out that the molecular heterogeneity of medulloblastomas limits the ability of any single gene marker or set of markers to globally predict outcome for all individuals diagnosed with this disease. In other words, a good marker in one molecular subtype was often a poor marker in another disease subtype. Therefore, we developed an algorithm that incorporated markers of outcome within each subtype. Indeed, identifying the molecular subtype

and then the factors within that subtype that determine outcome was found to provide more accurate prognostication of medulloblastoma patients at the time of diagnosis.

Although the stratification of patients to varied intensities of chemotherapy and radiation based on molecular markers is currently being considered by the Children’s Oncology Group at the time of writing, the ultimate goal will be to implement and/or develop less toxic and more effective therapies for these patients. However, most genomic analyses only inform us of the relative expression of genes (or the lack thereof); and just because a gene is expressed does not mean the desired biological effect will be achieved when it is targeted. Therefore, functional genomic approaches that can interrogate the effects of targeting a gene or gene product on a genome-wide scale will be useful in identifying the key drivers of this disease from the passengers [10]. Such approaches have revealed potential therapeutic targets in Ras-driven cancers and should greatly facilitate the discovery of putative targets for medulloblastoma as well [13,14].

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Finally, for targeted therapies that are already available and where there is a clear indication for use in medulloblastoma, in light of these recent genomic studies, it should be required that the design of their respective clinical trials includes an assessment of the molecular profile of the individual’s tumor. Therefore, tumor collection for the express purpose of molecular profiling will need to be mandated at the time of diagnosis and/or relapse, and become standard practice in pathology laboratories. Of current relevance are Smoothed inhibitors that target the SHH signaling pathway, which are currently undergoing clinical trials [15]. Since the SHH subtype of medulloblastomas represents only 25–30% of all medulloblastomas, a trial design that does not verify activation of the SHH pathway in individuals enrolled in such a study would destine it for failure [1,5]. Assays that determine molecular subtype and, in particular, the SHH-subtype are in development by our

group and others, and will be incorporated into the inclusion criteria for enrollment into upcoming Phase II clinical trials using Smoothed inhibitors for relapsed medulloblastoma.

To conclude, although progress in improving the survival of patients diagnosed with medulloblastoma has stalled over the past decade, our molecular understanding of the disease has increased exponentially over this same time period. The major challenges we face are in the rational and practical implementation of our genomic knowledge to clinical practice. The clear areas of impact will be in:

- Optimizing risk-stratification protocols for currently used chemotherapy and radiotherapy;
- Developing and designing the most rational and informed clinical trials for the therapies that are already available;
- Identifying and developing novel therapies for this disease through the functional annotation of the medulloblastoma genome.

A significant portion of this effort will go towards developing the platforms necessary to practically implement molecular profiling assays in standard pathology laboratories (with fast turnaround times and low costs) or towards establishing and certifying (Clinical Laboratory Improvement Act/Amendment) central core facilities that can carry out such work. Nonetheless, the medulloblastoma community, clinicians and researchers alike are motivated to take such challenges head on.

#### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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