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“Detecting dysregulated genes in neuroblastoma using allele-specific expression”

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SCIENTIFIC ABSTRACT

Neuroblastoma is the most common extracranial solid tumor in children and affects approximately 500 children per year in the United States. Neuroblastoma patients are stratified into low, intermediate and high-risk groups based on age at diagnosis, pattern of metastases, DNA ploidy, and amplification of the *MYCN* gene. While the intensity of neuroblastoma therapy is dictated by risk group, therapies are not specialized to individual patients due to our limited understanding of the genetics of neuroblastoma. Known genetic drivers of neuroblastoma include *MYCN* amplification and mutations in *ALK*, however many tumors have no identifiable oncogenic mutations. Furthermore, classification of tumors into risk groups is inadequate as many ‘low-risk’ patients experience an aggressive disease that results in relapse and death. Both risk stratification and therapeutic approaches could be improved if we had a more complete picture of the oncogenic mutations in neuroblastoma tumors. We hypothesize that some oncogenic drivers of neuroblastoma have gone undetected because they affect gene regulation rather than directly impacting protein-coding sequences. To test this hypothesis we will identify genes that are dysregulated in neuroblastoma tumors by analyzing allele-specific expression (ASE) and comparing ASE in tumors to a panel of normal tissues. In addition, we hypothesize that some neuroblastoma driver mutations occur in the parental germline or early in embryonic development and are missed by approaches that compare a patient’s tumor and matched normal tissue genomes. To test this hypothesis we will sequence the genomes of neuroblastoma patients’ parents alongside their normal and tumor genomes.

LAY ABSTRACT

Neuroblastoma is a devastating cancer of the sympathetic nervous system that most commonly affects very young children—90% of patients are diagnosed by 5 years of age and the highest rate of diagnosis in the first month of life. Neuroblastoma patients are currently stratified into low-, intermediate- and high-risk groups based on their age at diagnosis, pattern of metastases, and the genetic mutations in their tumor. Unfortunately the accuracy of risk stratification is hampered by our limited genetic understanding of the mutations that drive disease progression and relapse. Improved knowledge of the genetic mutations that are important for neuroblastoma could lead to advances both in neuroblastoma risk

stratification and to new therapeutic approaches. In this study, we propose to identify genes that are inappropriately expressed (i.e. turned off or on) in neuroblastoma tumors using an analysis method known as allele-specific expression. With this approach we will learn how mutations affect genes indirectly by changing their expression instead of the genes themselves. In addition, we will identify mutations in neuroblastoma tumors that occurred in the parents or early in embryonic development. These types of mutations may be more important in neuroblastoma than other cancers because of its extremely early age of onset.