PEDIATRIC ONCOLOGY

11q negative neuroblastoma subgroups predict outcomes and may guide treatment
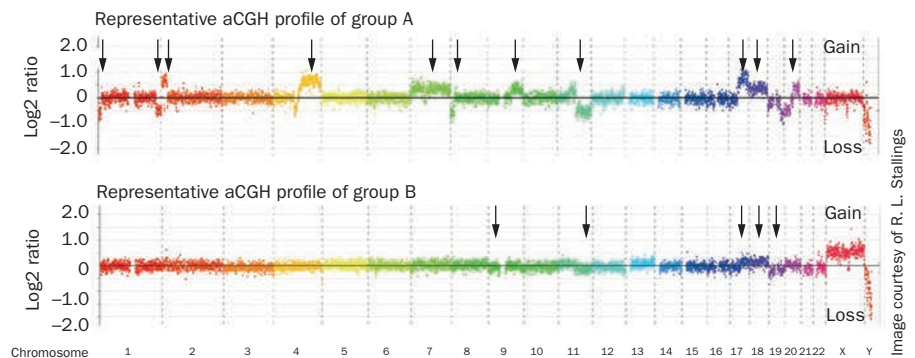
Neuroblastoma, which arises from precursor cells of the sympathetic nervous system, is one of the most common solid pediatric tumors, accounting for approximately 15% of all childhood cancer deaths. The prognosis of patients with these tumors is widely variable, ranging from spontaneous regression to aggressive disease.

The detection of chromosomal abnormalities in these tumors is an established method for the stratification of this disease. Infants with neuroblastoma with whole chromosomal gains and losses and limited structural chromosomal abnormalities have the best prognosis, while disease in older children with chromosomal amplifications, gains and losses is often metastatic at diagnosis and does not respond well to treatment.

The type of chromosomal abnormalities categorize neuroblastoma into different clinical subtypes. For example, tumors with only one copy of a large segment of the 11q chromosome represent an often metastatic subtype with poor clinical outcomes; however, some patients with 11q negative tumors have a better outcome than others.

Researchers, led by Raymond Stallings at the Royal College of Surgeons and the National Children's Research Centre in Ireland, wanted to establish the causes of the varied clinical outcomes. Stallings commented, "at the beginning of our project it was not possible to predict how patients with 11q negative tumors would respond to therapy... being able to predict how a tumor will respond to therapy is important because this information can be used to optimize treatment."

Stallings' group had previously used micro (mi)RNA expression profiling to classify subtypes of neuroblastoma and developed a 15-miRNA expression signature to predict patient survival. The present study built on this work to analyze the signature in an independent group

Representative aCGH profile of group A

Representative aCGH profile of group B

Image courtesy of R. L. Stallings

of 37 11q negative tumors. In addition, 160 primary neuroblastoma samples were assessed by array-based comparative genomic hybridization (aCGH) and the expression of 430 miRNAs profiled.

Stallings explained the use of this approach: "the profiling of 11q negative tumors for miRNA, in addition to allowing patient stratification for more refined treatment regimens, would also allow us to identify miRNAs that are involved in disease pathogenesis, which could be used as potential therapeutic targets."

As expected, all previously reported chromosomal changes were detected in this miRNA analysis with additional novel significant positive correlations being discovered between loss of chromosome 11q with either loss of 4p or gain of 7q.

The 15-miRNA signature was used to divide the 11q negative tumors into two subgroups—A and B—with significantly different prognostic characteristics. In group A, the 15 miRNAs were upregulated and the probability of event-free survival after 4 years was 14.5%, this probability was significantly greater for those in group B (54.7%; $P = 0.04$). This difference could also be observed for overall survival at 4 years with the rate for group A only 25.5% and that for group B increasing to 65.0%.

Stallings commented, "we were also able to demonstrate using aCGH that the unfavorable tumors had a

significantly greater number of [genomic] imbalances than the favorable subtype." No single imbalance was statistically over-represented, so it seems it is the overall increase in imbalances that is responsible for the poor group A survival.

Combining the 15-miRNA signature and the aCGH profile analysis for overall survival prediction in patients with 11q negative tumors resulted in a sensitivity of 82.4% and specificity of 55.7%.

Interestingly, it was possible to demonstrate that the 15 miRNAs used in this study may be regulating the expression of the mRNAs that are also predictive of patient survival.

Although these screens could now be used to stratify patients with 11q negative neuroblastoma and, therefore, guide their therapy, the group have plans for other uses of these data. Stallings elaborates, "we are carrying out functional studies on all the miRNAs that are associated with poor patient survival to elucidate the genetic pathways that have been perturbed and to evaluate the potential of miRNA-mediated therapeutics for neuroblastoma."

Rebecca Kirk