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Team breaks new ground in study of malignant pediatric brain tumor

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Scientists are making important progress in the battle against a class of devilishly complex human pediatric brain cancers thanks to a new study from a team of Florida State University students and faculty.

Among young children, there's no brain tumor more common than medulloblastoma. But no specific and effective therapy yet exists for this dangerous disease. Instead, doctors are forced to resort to onerous and invasive treatments like surgery, radiation and chemotherapy, often at the expense of the child's quality of life.

Medulloblastoma, which is divided into four subgroups, is partially caused when a mutation occurs in the "driver genes" that either promote or suppress cancerous tumor growth. These mutations can be inherited, sporadic or environmentally induced, but once they appear, they increase the risk for the unfettered and abnormal cell division that leads to malignant tumors.

A team of FSU researchers, led by Professor of Chemistry and Biochemistry Qing-Xiang "Amy" Sang, was interested in learning more about these mutations. Using data from the Catalogue of Somatic Mutations in Cancer, they identified a series of cancer-causing driver gene mutations and discovered that medulloblastoma is perhaps an even more dynamic and variable tumor than expected.

Their findings were published in the *Journal of Cancer*.

"Most cancer is quite heterogeneous, but medulloblastoma is specifically very heterogeneous," Sang said. "If you look at the driver gene mutation, it's not as if the majority of medulloblastoma cases have the same mutation. In reality, 5 percent may have one mutation, 3 percent may have another mutation and a small percentage may have other mutations. That's why you cannot treat it as one disease."

Using advanced bioinformatics tools, the team was able to pinpoint which driver gene mutations were occurring in which medulloblastoma subgroups. In some cases, they found that mutations once considered specific to one particular subgroup were causing significant disruption in sister subgroups as well. While these findings were surprising, they were exactly the kind of counterintuitive details the team was searching for.

"What we focused on specifically in this paper are the driver genes that we weren't expecting to see," said study co-author Mayassa Bou Dargham, a doctoral candidate at FSU. "We wanted to focus on some infrequent events and stress the heterogeneity of medulloblastoma tumors themselves. That's important whenever we're using targeted therapy for different subgroups."

Medulloblastoma's heterogeneity makes it an exceptionally difficult cancer to characterize and treat. But with a more comprehensive and nuanced understanding of which mutations happen where and when—and which mutations might defy broadly accepted definitions—researchers will be better equipped to identify opportunities for targeted, individualized treatments.

"For medulloblastoma, a more personalized approach will have to happen," said Jack Robbins, who was an undergraduate when he co-authored the study. "The goal we should be striving for is more MATCH-based trials in which we use molecular targets found from these different panels of driver events. These driver events extend past the genomic

code and into epigenetic mechanisms that need to be further studied and assessed in the clinic to identify candidate therapies. We can hopefully give those therapies to patients who aren't responding to the standard of care treatments."

The next step in developing those therapies is to develop credible laboratory models of human medulloblastoma tumor subgroups. These models, researchers say, will be important evaluative tools in the search for potential therapeutics.

The ultimate goal is a regimen of targeted therapies that avoid causing undue burden to vulnerable pediatric patients.

"Children with cancer often receive very toxic, harsh and invasive treatments," Sang said. "If we can avoid those harsh treatments and develop safer and more efficacious therapies, then the patients' outcomes and their quality of life will be much improved."

Cross-disciplinary collaborations may be a key to finding more effective therapies for this intractable disease. But another crucial key, Sang said, will be innovative ideas from a new generation of ambitious researchers.

She said this paper demonstrates the instrumental and field-defining contributions of student scientists. In addition to Robbins, former FSU undergraduates Kevin Sanchez and Matthew Rosen co-authored the paper.

"I'm very fortunate to be at FSU," she said. "The success of our undergraduates demonstrates that FSU is a great university for both top graduate and undergraduate students. I want to emphasize the students' contribution, especially with this paper. It's special."

More information: Charles J. Robbins et al, Decoding Somatic Driver

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Gene Mutations and Affected Signaling Pathways in Human Medulloblastoma Subgroups, *Journal of Cancer* (2018). DOI: 10.7150/jca.27993

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