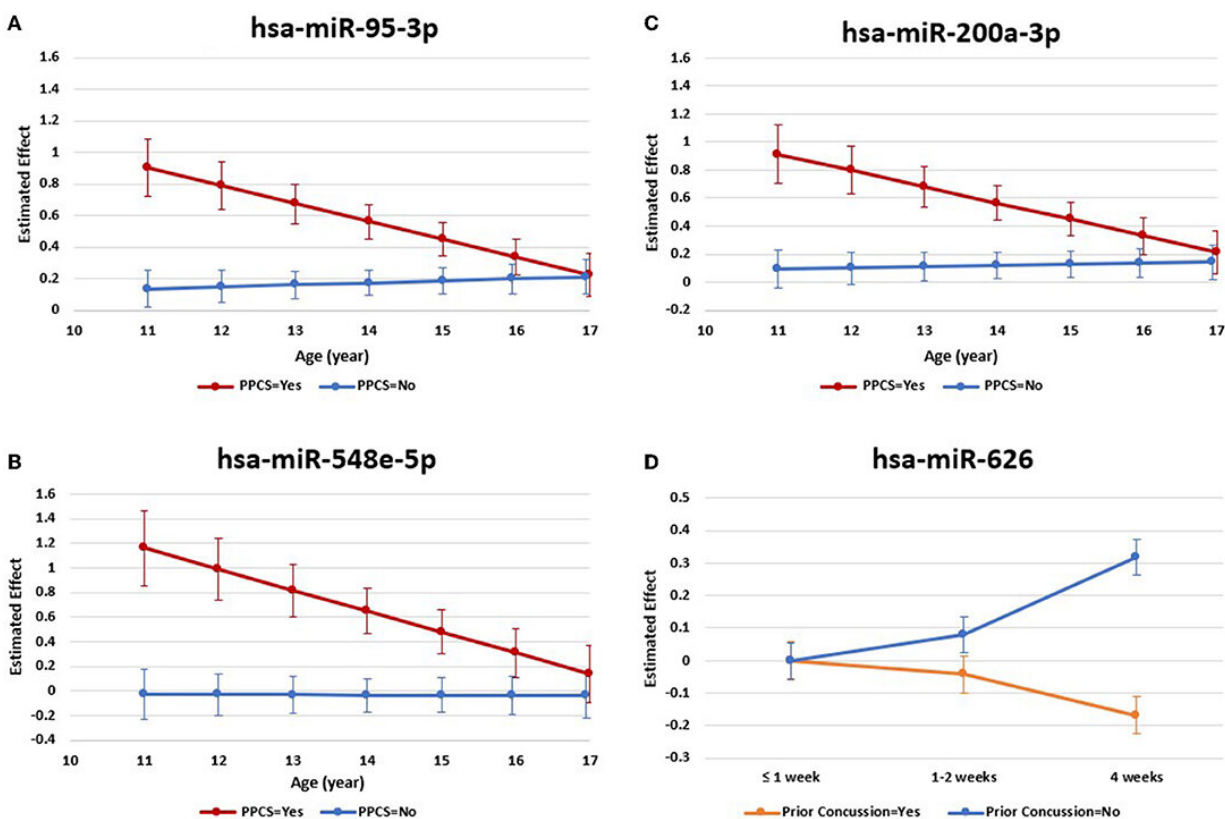# Saliva, genomic analysis used to identify promising biomarkers for persistent post-concussive symptoms in children

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miRNA expression levels with significant interactions post-injury. We found a statistically significant interaction between age and presence of PPCS in the expression levels of three miRNAs [(A) hsa-miR-95-3p; (B) hsa-miR-548e-5p; (C) hsa-miR-200a-3p]. Results also revealed a statistically significant interaction between time and history of prior concussion in the expression levels of one miRNA (D hsa-miR-626). These results were based on adjusted models in longitudinal analyses. Credit: *Frontiers in Public Health* (2022). DOI:

Predicting clinical recovery of children with concussion is challenging. While concussion symptoms typically resolve within one to three weeks, up to one-third of children develop persistent post-concussive symptoms (PPCS), including headache, nausea, dizziness, blurred vision and sensitivity to light and/or sound.

Compared with children without PPCS, children with PPCS are at increased risk of experiencing disruption to their daily routines and functioning, such as missed school days, depressed mood and loss of social activities, leading to lower quality of life.

In a study published in *Frontiers in Public Health*, researchers with the Center for Injury Research and Policy, Division of Sports Medicine, and the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital have demonstrated a method by which increased risk of PPCS in children with concussion can be identified. This could allow families and their care teams to better assess recovery time of children with concussion.

"The diagnosis of concussion is based on self-report, and it can be difficult for children, especially those who are very young, to describe their symptoms following injury," explains senior author Jingzhen Ginger Yang, Ph.D., MPH, a principal investigator at the Center for Injury Research and Policy of the Abigail Wexner Research Institute at Nationwide Children's Hospital.

"Currently, there are no markers to objectively predict who is going to recover sooner or later. If physicians could identify children at risk for prolonged recovery, they may be able to intervene earlier, providing

personalized concussion care, to improve patient recovery."

Previous research suggests that salivary microRNAs—small molecules that can regulate the amount of specific proteins a cell makes—may serve as potential markers to identify children with concussion who are at increased risk of PPCS. However, no studies have focused specifically on children, and it remains unknown whether and how salivary microRNA expression levels differ over time between children with or without PPCS.

In this study, Dr. Yang and colleagues demonstrated that the expression levels of 13 salivary microRNAs differ over time following concussion in children with versus without PPCS. To identify microRNAs and evaluate their predictive value in children with concussion, the researchers recruited 60 children between 11 and 17 years of age who were diagnosed with a concussion by a physician at Nationwide Children's.

They collected saliva at up to three timepoints (within one week of injury, one to two weeks post-injury, and four weeks post-injury) and participants' daily post-concussion symptom ratings throughout their enrollment using the Post-concussion Symptom Scale. PPCS was defined as symptoms that persisted at 28 days post-concussion.

"The approach we used for sample collection is very promising because it is noninvasive and easy, for both the investigator and the patient, to collect the sample. The lack of pain and convenience is appealing to families," explains co-first author James MacDonald, MD, MPH, a physician for Nationwide Children's Division of Sports Medicine and principal investigator of the study.

The researchers measured expression levels of 827 salivary microRNAs in 135 collected saliva samples. Of the 827 microRNAs analyzed, the

team identified 91 that had heightened expression levels, and of those 91 microRNAs, they identified 13 with significantly different expression levels across the three timepoints post-concussion between children with and without PPCS. Among the 13 microRNAs identified by the team, one was also found to have different expression levels between children with and without PPCS in a prior study.

"This research is an excellent example of the team science approach and what can be accomplished with multidisciplinary collaborations," adds co-first author Katherine Miller, Ph.D., a principal investigator in the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's. "The value of our publication is that our findings come from multiple time points. We need more studies like this to continue to track how these microRNAs change over time and hone in on those that are most consistent across patient populations."

"It is critical that we develop objective measures for diagnosis and prognosis of concussion, as there is potential overlap between that diagnosis and so many others," said Dr. MacDonald. "Having this information can help us better assess the needs of each patient and ensure that we are making the most informed recommendations possible to prevent any long-term issues."

More information: Katherine E. Miller et al, Salivary miRNA Expression in Children With Persistent Post-concussive Symptoms, *Frontiers in Public Health* (2022). DOI: 10.3389/fpubh.2022.890420

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