



From the ¹TRYUMPH Research Program, ²Department of Anesthesiology, UNC-CH and ³Lineberger Comprehensive Cancer Center, UNC-CH; ⁴Department of Cell Biology and Physiology, UNC-CH; ⁵Department of Emergency Medicine Henry Ford Hospital; ⁶Department of Emergency Medicine Shands Jacksonville Medical Center; ⁷Department of Emergency Medicine Albert Einstein Medical Center; ⁸Department of Emergency Medicine Detroit Receiving; ⁹Department of Emergency Medicine Sinai Grace; ¹⁰Department of Emergency Spectrum Health-Butterworth Campus; ¹¹ Department of Emergency Medicine St. Joseph Mercy Health System; ¹²Department of Emergency Medicine William Beaumont Hospital; ¹³Department of Emergency Medicine, UNC-CH

INTRODUCTION

microRNA (miRNA) are small non-coding RNA molecules that regulate gene expression by binding target mRNA. miRNA are highly stable in blood.

During the past decade, the study of miRNA has transformed understanding of the regulation of major biological pathways and advanced understanding of the molecular pathogenesis of many common diseases. Available data suggest that miRNA may also play a critical role in the pathogenesis of many chronic pain conditions.

Widespread pain (WP) is a disorder associated with substantial suffering and disability. One known trigger of WP is motor vehicle collision (MVC). A recent study found that 179/859 (21%) of European American individuals presenting to the emergency department (ED) after MVC and discharged to home after evaluation developed WP.

Molecular mechanisms mediating the development of WP after MVC remain poorly understood. This lack of understanding is a major barrier to the development of preventive interventions.

OBJECTIVE

The purpose of this preliminary investigation was to evaluate whether miRNA circulating in the immediate aftermath of MVC differ in individuals who do and do not subsequently develop WP 6 weeks after MVC. This investigation was performed in an African American (AA) cohort because AAs are a high risk, understudied group.

METHODS

ED evaluation included assessment of participant sociodemographic characteristics and blood sample collection (PAXgene RNA tube). Number of body regions with pain (NBRP) prior to MVC was assessed in the ED, NBRP 6 weeks after MVC was assessed via telephone/internet-based questionnaire. WP was defined by the presence of >=7 body regions of pain; 2 individuals reported WP prior to MVC and were dropped from analyses.

miRNA expression was evaluated using Next Generation Sequencing (NGS). miRNA expressed at <300 counts across all samples were removed. NGS data were normalized using standard quantile methods. miRNA expressed in those with and without WP at 6 weeks were compared using the Mann-Whitney U test. DIANA miRPath predictions were then used to identify biological pathways targeted by WP-associated miRNA. Target Scan was used to identify pain genes predicted to be targeted by differentially expressed miRNA.

FIGURE 1. Study sites and methods

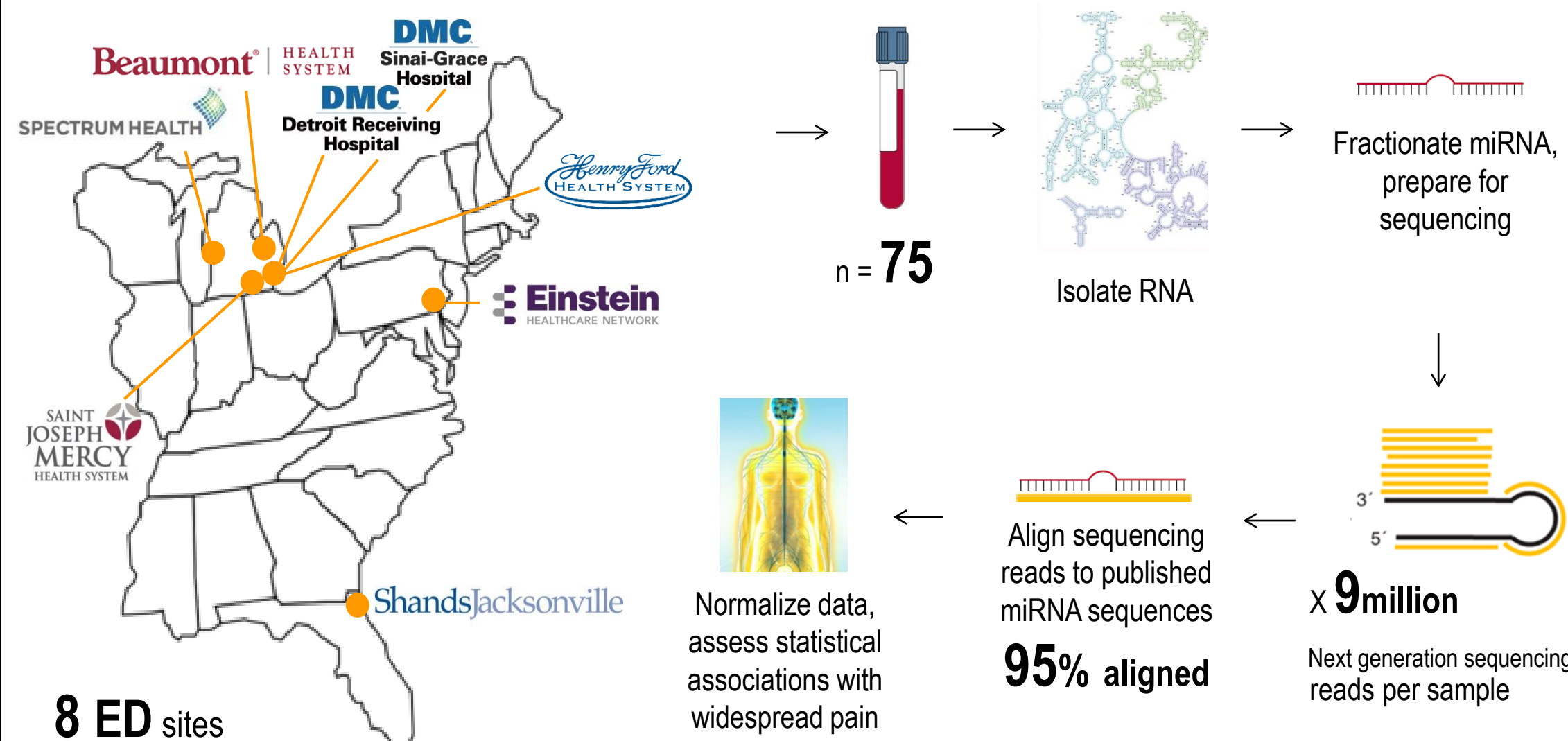


TABLE 1. Study characteristics

Table with 2 columns: Characteristic and Value. Rows include Participants (n=75), Age (mean 36), Females (n=44), Education (n=6-2), and Time to ED (mean 1h46).

RESULTS

Participant characteristics are shown in Table 1. NGS resulted in an average of 9 million sequencing reads per individual, 95% of which aligned to miRNA (Figure 1).

Even in this small sample, 11 miRNA were expressed at significantly different levels in AA who subsequently did and did not develop WP 6 weeks after MVC (Table 2).

Pathway analyses (DIANA miRPath) mapped WP-associated miRNA to a number of neurological/neurotransmitter pathways (Table 3).

Long term potentiation, the biologic pathway most enriched in targeting by differentially expressed miRNA, has been shown to play a role in pain pathogenesis and is predicted to be targeted by differentially expressed miRNA at multiple pathway locations (Figure 2).

miR-92a-3p, which has been shown to exhibit increased expression after acute stress in pre-clinical models, was predicted to target the most genes involved in pain processing, followed by miR-641 and miR-326/miR-330-5p (Table 4).

CONCLUSIONS

These data suggest that miRNA studies may yield novel insights into the pathogenesis of WP after traumatic events such as MVC. Further studies will expand the sample size of the study, examine additional pain outcomes, and will examine differences in miRNA isoforms, modified miRNAs, and trimmed or tailed miRNAs.

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TABLE 2. miRNA whose ED expression levels differed in AAs who did (n = 24) and did not (n = 49) subsequently develop WP 6 weeks after MVC

Table with 3 columns: miRNA, Fold change, P value. Rows include miR-641, miR-361-5p, miR-326/miR-330-5p, miR-92a-2-3p, miR-484, Let7b-3p, miR-550a-3p, miR-140-3p, miR-296-5p, miR-10a-5p.

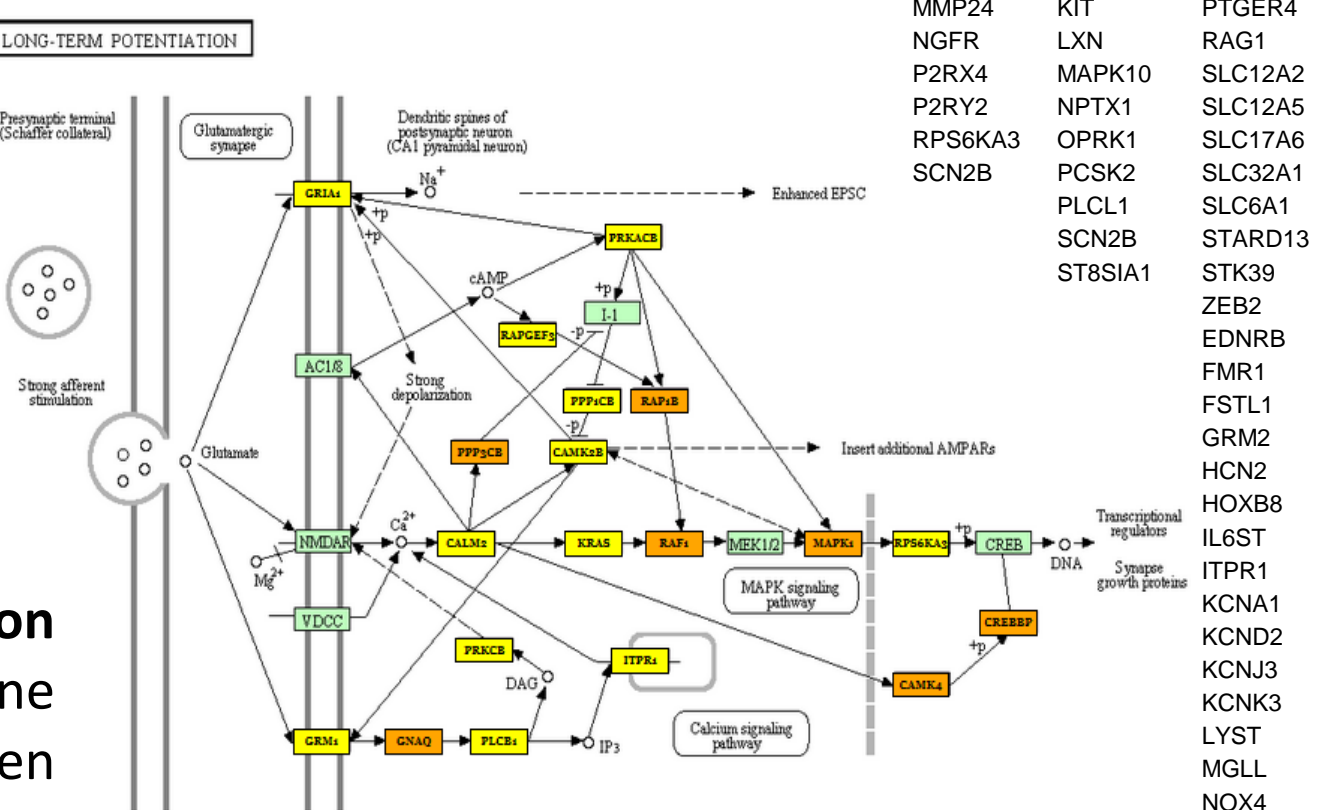
TABLE 3. Ten biologic pathways most significantly enriched in targeting by miRNA differentially expressed between AA who did and did not subsequently develop WP 6 weeks after MVC

Table with 2 columns: KEGG pathway, P value. Rows include Long Term Potentiation, Neurotrophin signaling, ErbB signaling, Pancreatic cancer, PI3K-Akt signaling, Pathways in cancer, Glioma, Non-small cell lung cancer, Renal cell carcinoma, Focal adhesion.

TABLE 4. miRNA associated with WP development following MVC are predicted to target a substantial number of genes involved in pain processing

Table with 10 columns: miRNA (296-5p, 361-5p, 10a-5p, 550a-3p, 484, 140-3p, 326/330-5p, 641, 92a-3p) and corresponding gene names (ADRBK1, ANO1, BDNF, etc.).

FIGURE 2. Map of miRNA targets within the Long Term Potentiation pathway. Orange boxes designate genes targeted by more than one miRNA, yellow boxes designate genes targeted by one miRNA, and green boxes designate genes targeted by no miRNA.



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