Somatic PDGFRB Mutation in a Mosaic Aneurysm Patient

Dr. Ferreira Lab

Daphne Toglia

August 9th, 2019
Intracranial aneurysms are relatively common, with a prevalence of approximately 4%.

There are two kinds of aneurysms, the more common saccular (90%-90%) and fusiform (4%-6%).

Abundant evidence supports a genetic component to the etiology of intracranial aneurysms.

The role of somatic genetic alterations or mosaicism in intracranial aneurysms remains unknown.

However, Dr. Ferreira’s lab discovered that there is a somatic mutation involved.
A 22-year-old man presented at UWMC with progressive fusiform aneurysms on his right side. The index individual underwent a series of genetic evaluations, but were unrevealing. Genetic sequencing between blood and fibroblasts derived from the diseased areas detected a single novel variant predicted to cause a change within the platelet-derived growth factor receptor β gene (PDGFRB).

Notably, PDGFRB variant was not found in DNA isolated from blood or the histologically normal, left-sided, radial artery, therefore confirming post-zygotic or somatic
Activation of the PDGFRB receptor leads to the upregulation of downstream signaling pathways, most notably angiogenesis.

PDGFRB is normally expressed in several vascular cell types.

4/6 fusiform aneurysm UWMC patients were also found to have a mutation in the PDGFRB gene.

A PDGFRB mutation was not found in saccular aneurysms.
Methods: DNA Extraction

> Process by which DNA is separated from proteins, membranes, and other cellular material contained in the cell/tissue from which it is recovered.

> There are four commonly used DNA extraction protocols.

> Dr. Ferreira’s lab implements a solid phase extraction method.

> Specifically, Qiagen QIAmp DNA Mini Kit.
Droplet Digital PCR (ddPCR) is a method for performing digital PCR that is based on water-oil emulsion droplet technology.

A sample is fractionated into 20,000 droplets and PCR amplification of the template molecules occurs in each individual droplet.

ddPCR is capable of detecting low-level mutations using low nucleic acid inputs.
Findings

% Alternate Allele Frequency (AAF) of JS Samples

- Affected-Intima
- Affected-Skin-Cell-Culture
- Affected-Skin-FB
- Coronary Aneurysm
- Affected-Radial-Aneurysm
- Affected-Skin
- Affected-Skin-Mixed
- Basilar Aneurysm
- Affected-Skin-explant
- Affected-Skin-Cell-CultureB
- Affected-Skin-Cell-CultureC
- Affected-Skin-Endo
- Coronary Artery
- Aneurysm-Mixed
- Normal-Skin-CultureA
- Aorta
- Normal-Vein
- Normal-Skin-CultureB

JS Samples
Findings

### Alternate Allele Frequency (AAF) by JS Aneurysm Samples

- **Coronary Aneurysm**: 22%
- **Radial Aneurysm**: 21.9%
- **Basilar Aneurysm**: 16.4%
Findings

JS Affected Skin and Skin Culture

Alternate Allele Frequency (AAF)

Skin Culture Sample

Affected-Skin-Fibroblasts
Affected-Skin
Affected-Skin-Mixed
Affected-Skin-Cell-CultureB
Affected-Skin-Cell-CultureC
Affected-Skin-Endo
Normal-Skin-CultureA
Rest In Peace J.S
Samples remain to be run through ddPCR and further analyzed.

A larger cohort of cerebral fusiform aneurysm patients.

Treatments and observing their efficacy remain.

In conclusion, JS affected areas carry varying allele frequencies and cell of origin could be fibroblasts.
Acknowledgements

> Dr. and Mrs. Ellenbogen
> Julie Bould
> Sylvia Zavatchen
> Jim Pridgeon
> Tina Busald
> Dr. Manuel Ferreira
> Muhammad Ansary
> UW Neurological Surgery Department
> Dr. Christine Mac Donald
> Other students in the NSSSP
> Thank You to the Donors