

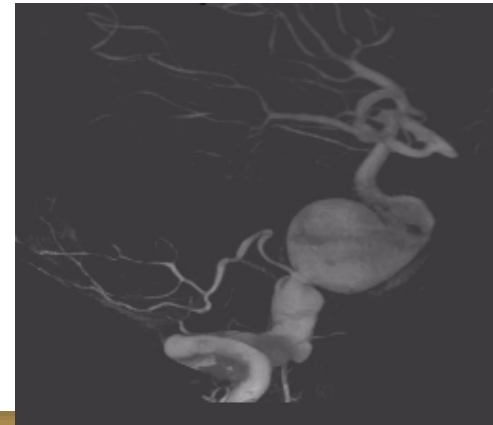
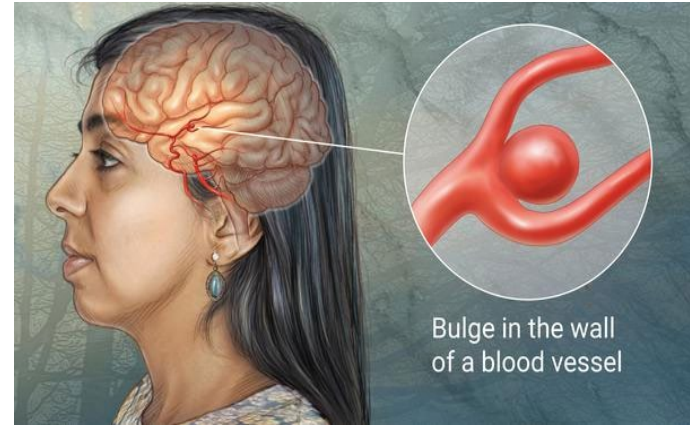
PDGFR β Mutations May Lead to Aneurysm Development

University of Washington Neurological Summer Student Program 2017

What is an Intracranial Aneurysm?

Weakening of a vessel wall in the brain

- May be asymptomatic, but when symptoms are present they include:
 - Headaches, thunderclap headache
 - Light sensitivity
 - Nausea or vomiting
 - Rupture
 - Death
- Treatments:
 - Medications to control blood pressure
 - Surgical intervention
 - Clipping, coils

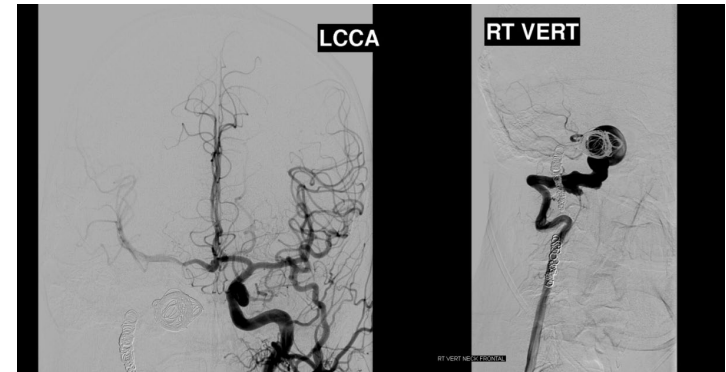
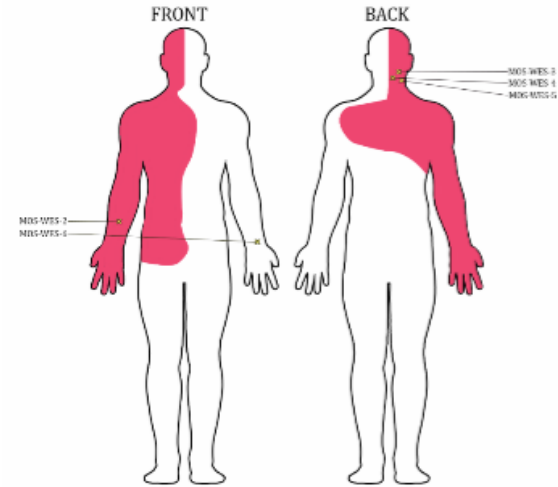


What is a Mosaic?

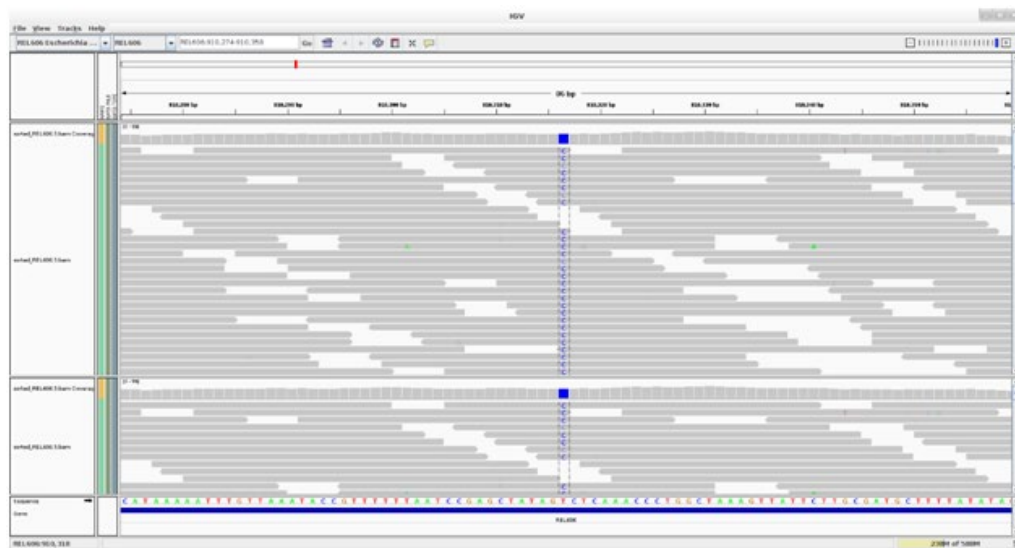
An individual that has two or more populations of cells with different genetic make up

Index patient

- Develops aneurysms only on affected side of his head (right)
 - No other brain abnormalities noted
 - Family history negative
 - Compared blood to affected tissue



Next Generation Sequencing



1 index patient received whole exome sequencing comparing blood and diseased tissue

Cohort of 50 aneurysms had targeted sequencing only on PDGFR β and provided the following variants

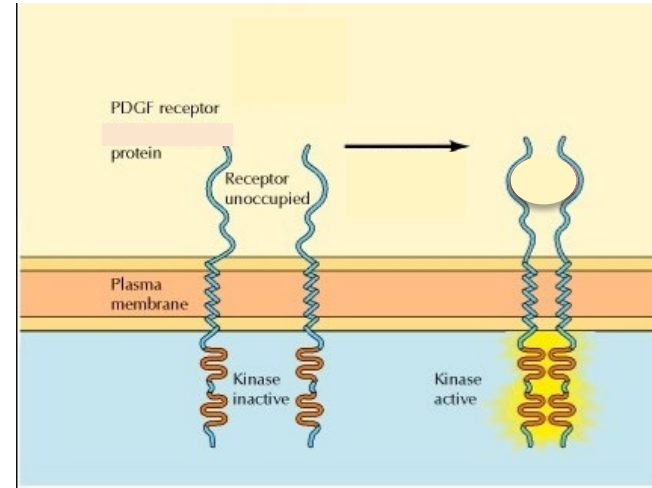
Sequencing millions of reads in parallel with a frameshift in only 1 nucleotide

Allows detection of >1% allele frequency and greater accuracy in variants

Mutants/variants	Primer pairs for SDM
p.Tyr562Cys	5' GAAGAAGCCACGTTGCGAGATCCGATGG 3' 5' CCATCGGATCTCGCAACGTGGCTTCTTC 3'
p.Tyr562_Arg565del	5'- GAAGAAGCCACGTTGGAAGGTGATTGAG -3' 5'- CTCAATCACCTTCGTCGGATCTCGTAAC 3'
p.W566R	5' GTTACGAGATCCGACGGAAGGTGATTGAG 3' 5' CTCAATCACCTTCGTCGGATCTCGTAAC 3'
p.D844G	5' GTCAAGATCTGTGGCTTTGGCCTGGC 3' 5' GCCAGGCCAAAGCCACAGATCTTGAC 3'
p.Arg849_Lys860delinsHAGLELHLQ	5'- GAC TTT GGC CTG GCT CAT GCG GGA CTC GAA TTA C -3' 5'- GTAATTCGATGCCGATGAGCCAGGCCAAAGTC -3'
	and
	5'- CTC GAA TTA CAT CTC CAA GGC AGC ACC T -3' 5'- AGG TGC TGC CTT GGA GAT GTA ATT CGA G -3'
p.Asp850Tyr	5' CTTTGGCCTGGCTCGATACATCATCGGGGACTC 3' 5' GAGTCCCAGATGATGATCGACCCAGGCCAAAG 3'

Function of PDGFR β

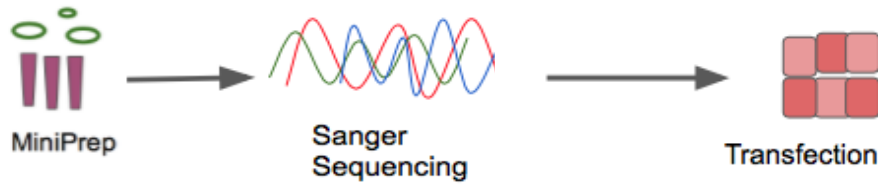
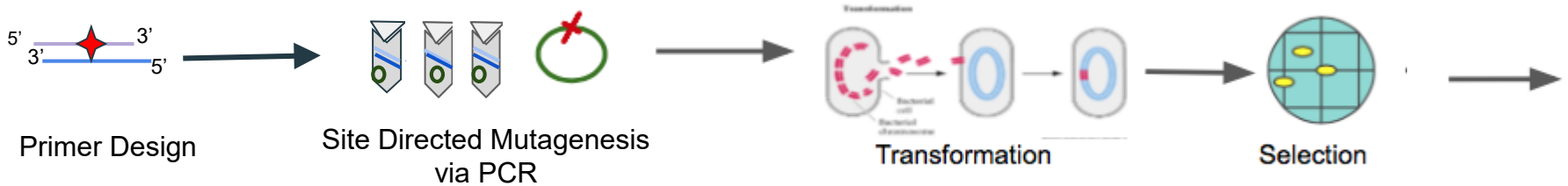
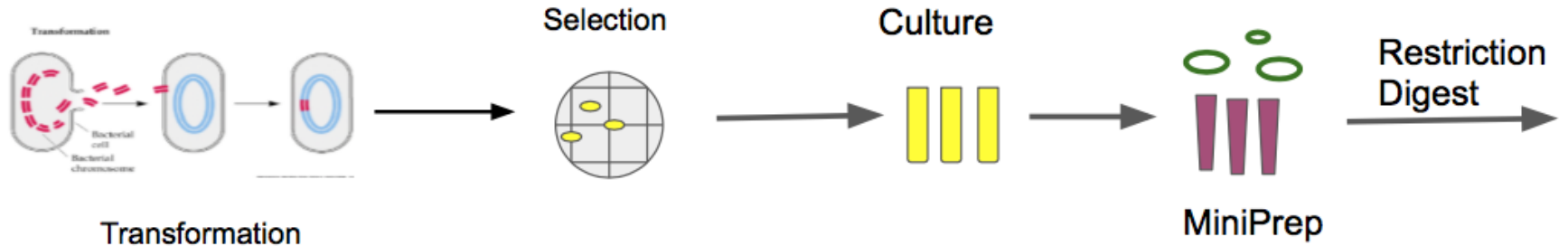
- Platelet- derived growth factor receptor
 - Binds PDGF
- PDGFRB classified as a receptor tyrosine kinase (RTK)
 - Cell surface receptors \rightarrow Cell signaling
 - Pathways lead to angiogenesis, apoptosis evasion, and cell proliferation



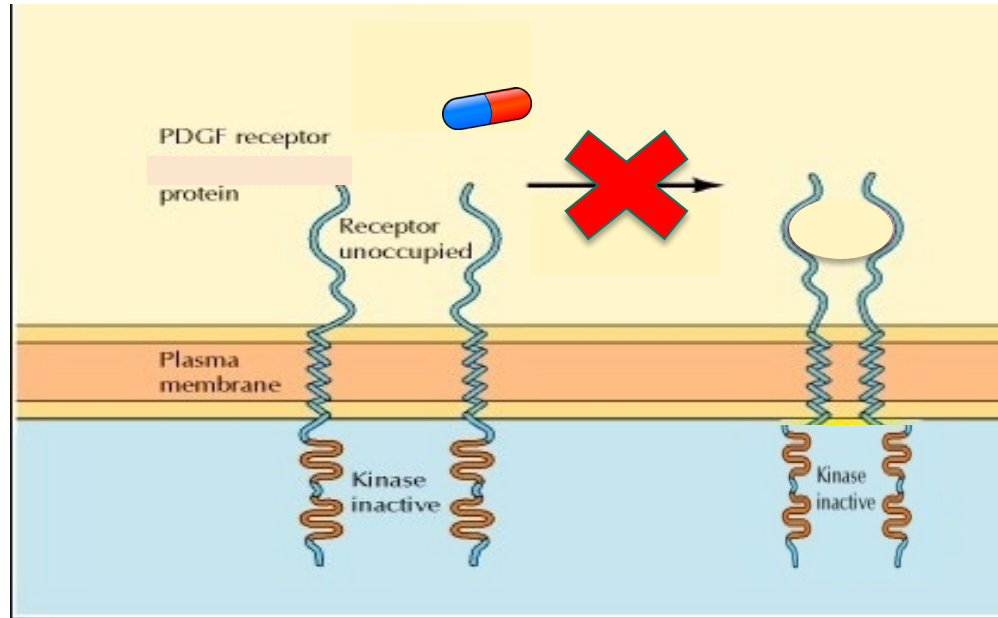
Mutations to this receptor can cause overactivation of pathways

- Y562C gain of function mutation
- Mutations in PDGFR β present in 60% of fusiform aneurysms

Visualizing PDGFR β mutant phenotypes through Site-Directed Mutagenesis



Why is it Important?



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