SVAI

Ranking mutations

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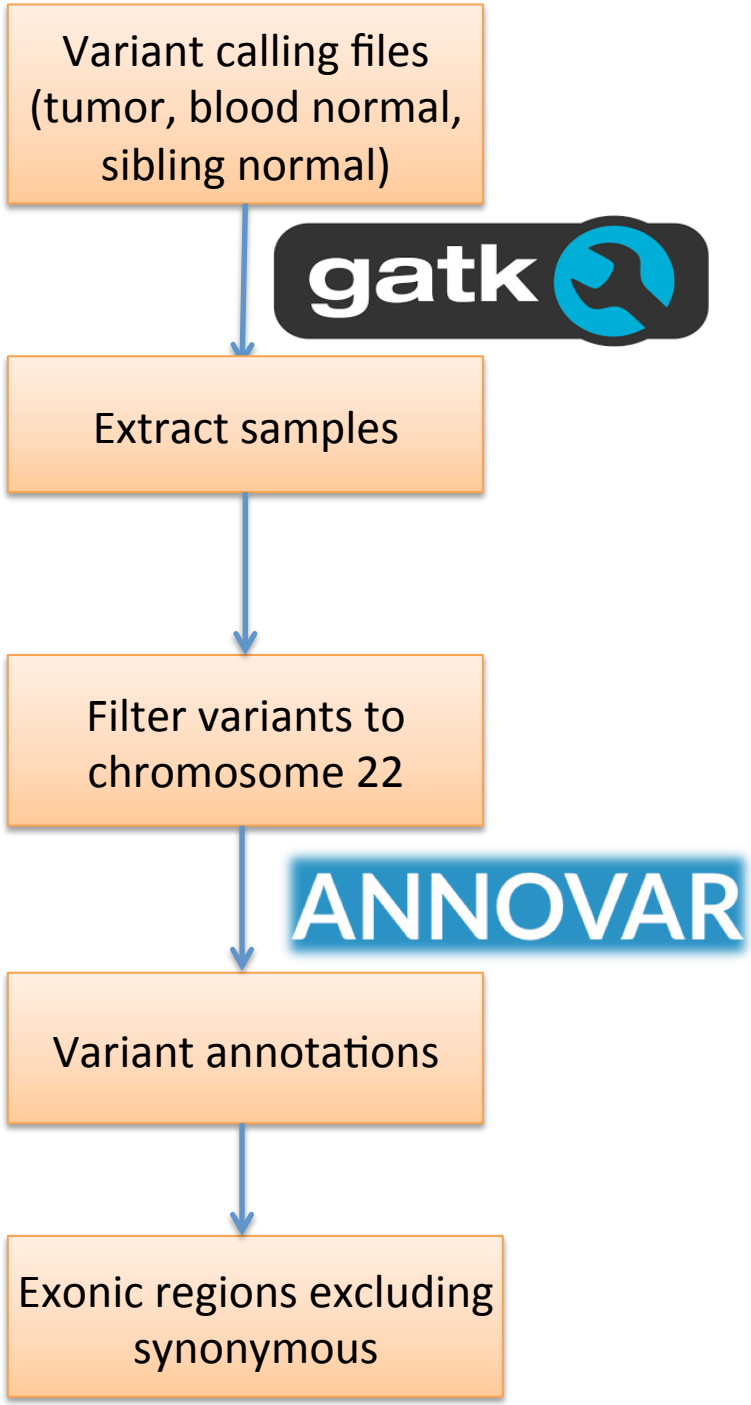
Sequence analysis pipeline



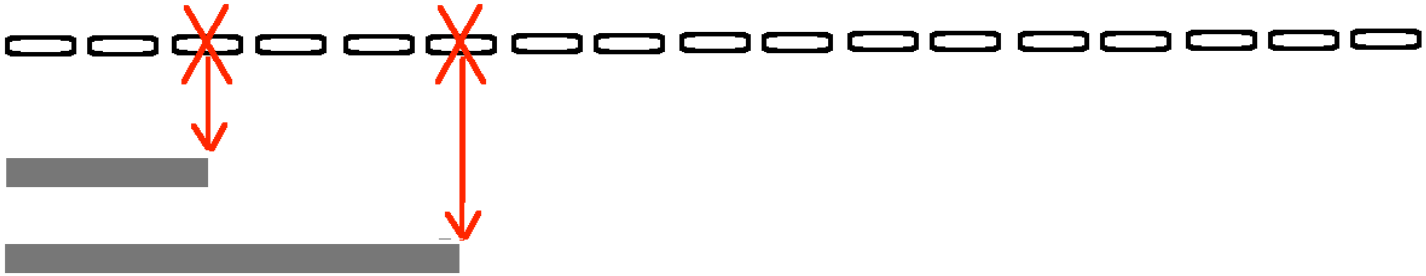
NF2 (neurofibromatosis type 2)

- Question: is this a somatic or germ line mutation?
- There are only intronic variants (SNPs and indels) in normal and sibling normal samples
- Tumor sample:
  - Two stop stopgains

Chrom	Start	End	Ref	Alt	Function	Gene	Function	Clinvar
22	30050657	30050657	C	G	exonic	NF2	stopgain	Novel
22	30057302	30057302	C	T	exonic	NF2	stopgain	Yes

Biological mechanism of NF2 mutations

- Both alleles of NF2 were mutated



- Double-knockout

Chrom	Start	End	Ref	Alt	Function	Gene	Exonic Function	Clinvar	Genotype
22	30050657	30050657	C	G	exonic	NF2	stopgain	Novel	CG
22	30057302	30057302	C	T	exonic	NF2	stopgain	Yes	CT

Summary of variants on chromosome 22

- Excluding intronic, intergenic, non-coding RNA, 5'- and 3'-UTR

	Tumor	**Normal blood**	**Sibling blood**	**Tumor − Normal_blood**	**Tumor − Sibling_blood**	**Normal − Sibling**
Total variants	72852	71772	71385	-	-	-
All exonic variants	549	545	538	11	539	536
Non-synonymous exonic variants (genes)	289 (155)	287 (155)	267 (142)	7 (5)	93 (38)	92 (38)

7 non-synonymous exonic variants present in tumor compared to blood normal

Chr	Position	Ref	Alt	Function	Gene	Exonic Function
22	16287339	C	T	exonic	POTEH	nonsynonymous SNV
22	20456765	G	A	exonic	RIMBP3	nonsynonymous SNV
22	21570373	C	T	exonic	GGT2	nonsynonymous SNV
22	29075651	G	A	exonic	TTC28	stopgain
22	29075660	C	T	exonic	TTC28	nonsynonymous SNV
22	30050657	C	G	exonic	NF2	stopgain
22	30057302	C	T	exonic	NF2	stopgain

38 genes that have variants in tumor, but not in sibling

- MICAL3, MRPL40, TBX1, COMT, DGCR8, TRMT2A, ZDHHC8, TMEM191B, MED15, P2RX6, CCDC116, MAPK1, DRICH1, DERL3, SLC2A11, GSTT2;GSTT2B, GGT1, MN1, TTC28, NF2, LIF, SEC14L3, SMTN, PLA2G3, PIK3IP1, PRR14L, BPIFC, TMPRSS6, GGA1, APOBEC3B, ATF4, MKL1, EP300, FAM109B, A4GALT, CERK, SELENOO, SHANK3

- COMT:
  - Controls estrogen, neurotransmitter, and toxin elimination, anxiety and mood swings are prevalent.
- MAPK1: non-synonymous exonic variant
  - T→C SNP
  - an essential component of the MAP kinase signal transduction pathway
  - the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements.

Insertion in *MN1 (Meningioma 1)*

- 3-base pair insertion
- In Onno's tumor and blood samples, but not in his sibling
- MN1 Proto-Oncogene, Transcriptional Regulator

Conclusions

- NF2 was sporadic mutations occurred during embryonic development
  - Two stopgains (SNP) in *NF2* genes, but no such exonic mutations in blood normal or sibling normal
- Discovered a novel variant in *MN1*