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Appendix

How to use the A-to-I RNA editing pipeline

Below are the main scripts necessary to run the pipeline. Directories where the tools were installed were based on the HPC cluster used in GIS, and therefore need to be changed and specified accordingly. The steps before variant calling (1-8) were done for individual samples. A streamlined version of these scripts will be submitted to the author's GitHub page (https://github.com/fachrulm).

1. Run 2-pass mapping using STAR (*VCmapSTAR.sh*, then *2pass_VCmapSTAR.sh*).
   #NOTE: Check BAM file with Picard's ValidateSamFile (validbam.sh) each time a BAM is generated.
2. Add read group using Picard's AddOrReplaceReadGroups (*addReadGroup.sh*).
3. Identify and remove duplicate reads with Picard's MarkDuplicates (*picardup.sh*).
4. Filter reads with low MAPQ (<20) with samtools (*filtersam.sh*).
5. Index BAM file from the previous step (*index.sh*).
6. Split N Trim BAM file of N CIGAR reads using GATK's SpliNCigarReads (*splitncigar.sh*).
7. Base Score Recalibration with GATK's BaseRecalibrator (*base_recalibrator.sh*).
8. Apply base recalibration with GATK's applyBQSR (*applybqst.sh*), then run variant calling with GATK's HaplotypeCaller (*gvcf_haplotypeCaller.sh*).
9. Merge GVCF files into a single VCF file with GATK's GenotypeGVCFs (*genotypegvcfs.sh*).
   #NOTE: Check VCF file with Picard's ValidateVCF (validvcf.sh).
10. Variant Score Recalibration with GATK's VariantRecalibrator (*variantRecalib.sh*), then applyVQRSR (*applyvqsr.sh*) to generate a variant-recalibrated VCF.
11. Select only variants from VCF (*snponly.sh*), then filter variants against known SNPs [avsnp138] and splicing junctions [dbscsnv11] with ANNOVAR (*inputannovar.sh*, *dbsnp_annovar.sh* and *spl_annovar.sh*).
12. Filter only A-to-I editing sites (*AtoIFilter.sh*).
13. Remove mismatches in the first 6 bp of reads (**mismatch6bp.sh**)
14. Separate variants in Alu and non-Alu regions (*alufilter.sh*).
15. For variants in Alu regions, directly annotate to UCSC's knownGene (**knownGene.sh**). The rest of the steps are solely for variants in non-Alu regions.
16. Remove variants located in simple repeats (**bedfilter.sh**) and homopolymer regions (**homopolymer.sh**).
17. Ensure unique mapping (**BLAT.sh**).
18. Separate variants into those located in repetitive and nonrepetitive non-Alu regions (**repeatorno.sh**), and annotate them to UCSC's knownGene (**knownGene.sh**).

- **VCmapSTAR.sh**
```
#!/usr/bin/bash

STAR=/mnt/AnalysisPool/libraries/tools/STAR/STAR-
STAR_2.4.2a/bin/Linux_x86_64/STAR
qpath=$1

mkdir -p ${qpath%/*}/output

R1="$(ls -dm $qpath/*R1.fastq.gz | tr -d '\n')"
R2="$(ls -dm $qpath/*R2.fastq.gz | tr -d '\n')"

echo ${qpath%/*}/output/${qpath##*/}
```

```
$STAR --runThreadN 8 --genomeDir
/mnt/AnalysisPool/libraries/genomes/hg19/star/ --readFilesIn $R1
$R2 --readFilesCommand zcat --outSAMmapqUnique 60 --outSAMtype
BAM SortedByCoordinate --outFileNamePrefix
${qpath%/*}/output/${qpath##*/}_
```

- **2pass_VCmapSTAR.sh**
  ```
  #!/usr/bin/bash

  STAR=/mnt/AnalysisPool/libraries/tools/STAR/STAR-
  STAR_2.4.2a/bin/Linux_x86_64/STAR
  qpath=$1

  R1="$(ls -dm $qpath/*R1.fastq.gz | tr -d '\n')"
  R2="$(ls -dm $qpath/*R2.fastq.gz | tr -d '\n')"
  R3="$(ls ${qpath%/*}/output/*.tab)"

  #echo $R3
  #echo ${qpath%/*}/output/${qpath##*/}_2pass_

  $STAR --runThreadN 8 --genomeDir
  /mnt/AnalysisPool/libraries/genomes/hg19/star/ --readFilesIn $R1
  $R2 --readFilesCommand zcat --outSAMmapqUnique 60 --outSAMtype
  BAM SortedByCoordinate --outFileNamePrefix
  ${qpath%/*}/output/${qpath##*/}_2pass_ --sjdbFileChrStartEnd $R3
  ```

- **validbam.sh**
  ```
  #!/usr/bin/bash

  #source /usr/bin/java

  i=$1

  #Remove Duplicates
  java -jar /mnt/AnalysisPool/libraries/tools/picard/picard-tools-
  1.137/picard.jar ValidateSamFile I=$i MODE=SUMMARY
  ```

- **addReadGroup.sh**
  ```
  #!/usr/bin/bash

  i=$1
  nodir=${i##*/}
  basename=${nodir%2_pass*}
  sm=$2
  id=$3

  PICARD=/mnt/AnalysisPool/libraries/tools/picard/picard-tools-
  1.137/picard.jar
  #echo ${i%Aligned*}withRG.bam
  java -jar $PICARD AddOrReplaceReadGroups I=$i
  O=${i%Aligned*}withRG.bam RGID=$id RGLB=$basename RGPL=illumina
  RGPU=unit1 RGSM=$sm
  ```

- **picardup.sh**
  ```
  #!/usr/bin/bash
  ```

```
#source /usr/bin/java

i=$1

#Remove Duplicates
java -jar /mnt/AnalysisPool/libraries/tools/picard/picard-tools-
1.137/picard.jar MarkDuplicates I=$i
O=${i%_withRG*}_marked_dup.bam M=${i%_withRG*}_marked_dup.metrics
CREATE_INDEX=true VALIDATION_STRINGENCY=SILENT
```

- **filtersam.sh**
```
#!/usr/bin/bash

samtools=/mnt/AnalysisPool/libraries/tools/samtools/samtools-
1.2/samtools

i=$1

echo $samtools

$samtools view -bq 20 $i > ${i%.*}_filtered.bam
```

- **index.sh**
```
#!/usr/bin/bash

samtools=/mnt/AnalysisPool/libraries/tools/samtools/samtools-
1.2/samtools

i=$1

$samtools index $i
```

- **splitncigar.sh**
```
#!/usr/bin/bash

i=$1

/home/fmuhamad/localtools/gatk-4.0.2.1/gatk SplitNCigarReads -R
/mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa -I $i -O
${i%_mark*}.splitN.bam
```

- **base_recalibrator.sh**
```
#!/usr/bin/bash

i=$1

/home/fmuhamad/localtools/gatk-4.0.2.1/gatk BaseRecalibrator \
    -R /mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa \
    -I $i \
    --known-sites
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/dbsnp_138.hg19.vcf \
    --known-sites
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/Mills_and_1000G_gold_
standard.indels.hg19.sites.vcf \
```

```
    --use-original-qualities \
    -O ${i%.*}_recal_data.table \
```

- **applybqsr.sh**
```
#!/usr/bin/bash

i=$1

#/home/fmuhamad/localtools/gatk-4.0.2.1/gatk SplitNCigarReads -R
/mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa -I $i -O
${i%_mark*}.splitN.bam

/home/fmuhamad/localtools/gatk-4.0.2.1/gatk ApplyBQSR \
    -R /mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa \
    -I $i \
    --bqsr-recal-file ${i%.*}_recal_data.table \
    -O ${i%_2pass*}.final.bam
```

- **gvcf_haplotypeCaller.sh**
```
#!/usr/bin/bash

i=$1

java -jar
/mnt/AnalysisPool/libraries/tools/GATK/GenomeAnalysisTK.jar \
    -T HaplotypeCaller \
    -R /mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa \
    -I $i \
    -o ${i%.final*}_raw_variants.g.vcf \
    -stand_call_conf 0 \
    -mbq 25 \
    -ERC GVCF \
    --output_mode EMIT_VARIANTS_ONLY \
    --dbsnp
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/dbsnp_138.hg19.vcf \
    -variant_index_type LINEAR -variant_index_parameter 128000
```

- **genotypegvcfs.sh**
```
#!/usr/bin/bash

i=$1

echo ${i%/*}/albert_differentiation_raw.vcf

java -jar
/mnt/AnalysisPool/libraries/tools/GATK/GenomeAnalysisTK.jar \
    -T GenotypeGVCFs \
    -R /mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa \
    --variant $i \
    -o ${i%/*}/wilson_ihd_raw.vcf
```

- **validvcf.sh**
```
#!/usr/bin/bash
i=$1
```

```
#/home/fmuhamad/localtools/gatk-4.0.2.1/gatk SplitNCigarReads -R
/mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa -I $i -O
${i%_mark*}.splitN.bam

/home/fmuhamad/localtools/gatk-4.0.2.1/gatk ValidateVariants \
    -R /mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa \
    -V $i \
    --dbsnp
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/dbsnp_138.hg19.vcf
```

- **variantRecalib.sh**
```
#!/usr/bin/bash

i=$1

/home/fmuhamad/localtools/gatk-4.0.2.1/gatk VariantRecalibrator \
    -R /mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa \
    -V $i \
    --resource
hapmap,known=false,training=true,truth=true,prior=15.0:../../ref/
hg19/hapmap_3.3.hg19.sites.vcf \
    --resource
omni,known=false,training=true,truth=false,prior=12.0:../../ref/h
g19/1000G_omni2.5.hg19.sites.vcf \
    --resource
1000G,known=false,training=true,truth=false,prior=10.0:../../ref/
hg19/1000G_phase1.snps.high_confidence.hg19.sites.vcf \
    --resource
dbsnp,known=true,training=false,truth=false,prior=2.0:../../ref/h
g19/dbsnp_138.hg19.vcf \
    -an QD -an ReadPosRankSum -an DP -an FS -an SOR \
    -mode SNP \
    --output ${i%.*}.output.recal \
    --tranches-file ${i%.*}.output.tranches \
    --rscript-file ${i%.*}.output.plots.R
```

- **applyvqsr.sh**
```
#!/usr/bin/bash

i=$1

path=${i%/*}
nodir=${i##*/}
basename=${nodir%.*}


/home/fmuhamad/localtools/gatk-4.0.2.1/gatk ApplyVQSR \
    -R /mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa \
    -V $i \
    -ts-filter-level 99.0 \
    --output ${i%_*}.ready.vcf \
    --tranches-file $path/$basename.output.tranches \
    --recal-file $path/$basename.output.recal \
    -mode SNP
```

- **snponly.sh**
```bash
#!/usr/bin/bash

i=$1

path=${i%/*}
nodir=${i##*/}
basename=${nodir%.*}


/home/fmuhamad/localtools/gatk-4.0.2.1/gatk SelectVariants \
    -R /mnt/AnalysisPool/libraries/genomes/hg19/hg19.fa \
    -V $i \
    --output ${i%.*}.SNP.vcf \
    -select-type SNP
```

- **inputannovar.sh**
```bash
#!/usr/bin/bash

i=$1

convert2annovar.pl -format vcf4 $i -outfile ${i%_1_*}.avinput -
allsample –includeinfo
```

- **dbsnp_annovar.sh**
```bash
#!/usr/bin/bash

i=$1

annotate_variation.pl $i
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/humandb/ -filter -
build hg19 -dbtype avsnp138
```

- **spl_annovar.sh**
```bash
#!/usr/bin/bash

i=$1

annotate_variation.pl $i
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/humandb/ -filter -
build hg19 -dbtype dbscsnv11
```

- **AtoIFilter.sh**
```bash
#!/usr/bin/bash

i=$1

echo  ${i%.avinput*}.AtoI.filtered
awk -F "\t" '{ if(($4 == "A" && $5 == "G") || ($4 == "T" && $5 ==
"C")) { print } }' $i > ${i%.avinput*}.filtered.AtoI
```

- **alufilter.sh**
```bash
#!/usr/bin/env bash

i=$1
```

```
bedtools intersect -a $i -b
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/Alu.bed >
${i%.filtered*}_AtoI_in_alu.filtered
bedtools intersect -a $i -b
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/Alu.bed -v >
${i%.filtered*}_AtoI_non_alu.filtered
```

- **mismatch6bp.sh**
  ```
  #!/usr/bin/bash

  i=$1
  bam=$2

  perl
  /mnt/projects/fmuhamad/RNA_Editing/analysis/2_ihd/mismatch6bp.pl
  $i $bam ${i%.filtered*}.candidates
  ```

- **knownGene.sh**
  ```
  #!/usr/bin/bash

  i=$1
  init=${i%.*}
  basename=${init##*avinput.}
  DIR=${i%/*}

  annotate_variation.pl -out $DIR/$basename.final -build hg19 $i
  /mnt/projects/fmuhamad/RNA_Editing/ref/hg19/humandb/ -dbtype
  knownGene
  ```

- **bedfilter.sh**
  ```
  #!/usr/bin/env bash

  i=$1

  bedtools subtract -a $i -b
  /mnt/projects/fmuhamad/RNA_Editing/ref/hg19/simpleRepeat.bed >
  ${i%.*}_simplerepeats.filtered
  ```

- **homopolymer.sh**
  ```
  #!/usr/bin/bash

  i=$1
  init=${i%.*}
  basename=${init##*avinput.}
  DIR=${i%/*}

  perl ~/resources/RNAediting_RNAonly/RemoveHomoNucleotides.pl $i
  $DIR/$basename.nohpl
  ```

- **BLAT.sh**
  ```
  #!/usr/bin/bash

  i=$1
  BAM=$2
  ```

```
perl ~/resources/RNAediting_RNAonly/BLAT_candidates.pl $i $BAM
$i.uniq
```

- **repeatorno.sh**
```
#!/usr/bin/env bash

i=$1

awk 'BEGIN{FS=OFS="\t"} {$2 = $2 OFS $2} 1' $i | cut -f4 --
complement | bedtools intersect -a - -b
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/NonAlu.bed >
${i%_simplerepeats*}_repetitive.txt
awk 'BEGIN{FS=OFS="\t"} {$2 = $2 OFS $2} 1' $i | cut -f4 --
complement | bedtools intersect -a - -b
/mnt/projects/fmuhamad/RNA_Editing/ref/hg19/NonAlu.bed -v >
${i%_simplerepeats*}_nonrepetitive.txt
```