Motif and Pathway Identification with Designing Novel Ligands for Sandhoff Disease

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Abstract. Sandhoff's disease is a lysosomal disorder. It's an inherited lipid storage disease. Progressively destroys the nerve cells in brain and spinal cord. It's a rare inherited disorder. Which is commonly seen in infants. Here I took the HEXB gene from Sandhoff's disease because we did motif analysis and peak, pathway identification. ChIP sequencing is used for the analysis of protein and DNA interactions. I got the result of high-quality immunoprecipitation ChIP Peak is detected in our results which imply high concentration of DNA binding protein genes. Molecular docking is a technique which is used for the computational drug designing, by using docking one can predict the interactions between the macromolecules and the micro-molecules. A well-known in-silico structure-based technique utilized extensively in drug development is molecular docking.

Keywords: ChiP-seq · HEXB gene · Docking · Ligand · computational drug design

1 Introduction

Standoff's disease is a lysosomal disorder. It's an inherited lipid storage disease. Progressively destroys the nerve cells in brain and spinal cord. It's a rare inherited disorder. Mostly seen in infants. Clinically indeterminable from the tay-sach disease and hard to diagnose at early disease. Slow deuteriation of muscles in child's body from the build-up of gangliosides as the body is unable to create the enzymes which is needed with in the central nervous system. The main causes of this disease are glycosphingolipid with one or more sialic acids connected on the sugar chain makes up a molecule called a ganglioside. Mutations in the α- and β-subunits of hexosaminidases are the cause of GM2 gangliosides. GM2 activator protein mutations that cause These are illustrative neuronopathic lysosomal storage disorders, which are clinically similar and invariably deadly. HEXB is the faulty gene that causes Standoff's illness. The use of next-generation sequencing (NGS) to analyse ChIP data has uncovered new information about the gene regulation processes. Chromatin immunoprecipitation is one frequently utilised method, it enables a genome-wide analysis of the structural and functional features, like transcriptional regulatory elements, encoded in a genomic sequence. That clear the path for the drug discovery and drug development against the standoff's disease.

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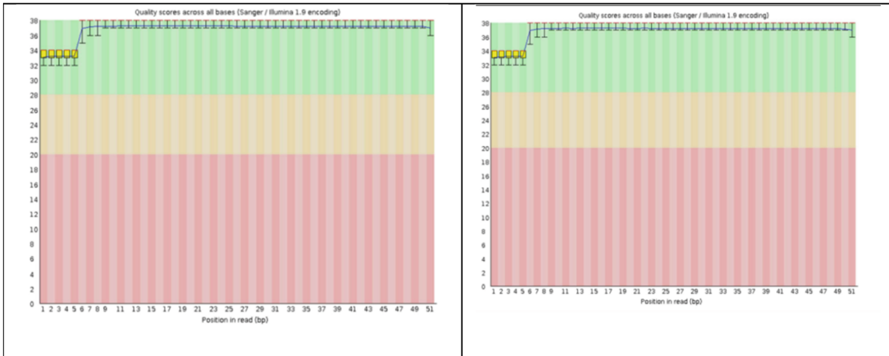

Fig. 1. FASTQC Quality reports of SRR6941411.1 and SRRR6941410.

2 Methodology

Sandhoff's disease SRA sequences SRR6941410 and SRR6941411.1 were retrieved from the SRA database. Then we use FASTQC tool to do some quality control checks on raw sequence data. The sequence FASTQC are mapped using a tool such as Bowtie2 that aligns the sequence with the mammalian genome. There are several mapped outputs of Bowtie2 we get such as BAM and SAM files, this file was summarised and removed all PCR duplicates we used RmDUP.

For further analysis, MACS2 tool are used to identify the significantly enrich loci in the genome also called peak calling. MACS2 tool is the most commonly used tool that provides 100% accuracy peak calling.

Next, we used the filter and sort tool for the quality check in the chip seq. Sample because it was very critical to analyse the quality of the sample for further analysis.

For the visualization of chip seq. Data and detection of the suspicious peak derived from the sample data, we used the UCSC genome browser that integrates the obtained chip sequence data with other annotation data such as evolutionary and gene in various tissue.

For further analysis, we used Bed tools and intersect interval tools to screen between two sets of genomic features. Then with the help of the Galaxy cistron tool, we find motifs enriched in a set of regions.

Further we analysis gene with the help of swiss port for drug discovery and mol-inspiration and structure analysis was done for drug development. After receptore and drug was docked and interaction and docking scored obtained.

3 Result and Discussion

FASTQC quality reports was given quality control to H. Sapiens chip-sequences with SRA accession number SRRR6941411.1 and SRRR6941410 FASTQC results were given in SRR6941411.1 and SRR6941410 (Fig. 1 and Table 1).

Table 1. (RmDup tool removed the all PCR duplicates from the SRR6941411.1 and SRRR6941410)

SN7001427:381:CC2M6ANXX:2:2302:7860:51988/1	16	chr1	30018355	1	51M	*	0	0	TAATTCTAATAGGCCTGCATTTATATGTTGCTTGACCTTTTTCCCTTACTG	GGGGGGGGGGGGGGGGGGGGGGFGGGGGGGGGGGGGGGGGBGGGGGBBCCC
SN7001427:381:CC2M6ANXX:2:2207:7197:97314/1	0	chr1	30163328	1	51M	*	0	0	GGTTTTATGTGGAGTTCCTTAATCCACTTAGATTTGACCTTAGTACAAGGA	BBBBBGGGGGGGGGGGGGGGGGGGGGGGEGGGGGGGGGGGGGGGGGGGGG
SN7001427:381:CC2M6ANXX:2:1213:20175:86466/1	16	chr1	30396988	1	51M	*	0	0	GACACTACCTCAGAGTGAAAGGCTGGAAAACAATTTTCCAAGCAAATGGTC	GGFGGGGGGGGFGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGCCCCCC
SN7001427:381:CC2M6ANXX:2:2216:5820:68974/1	16	chr1	30436355	1	51M	*	0	0	TGTAGCTGTCTCTTGTGAGACTATGCCGGGGCCTAGCAAACACAGAAGTGG	GGGGGGGGGGGGGGGGGFGGGGFGGGGGGGGGGGGGGGGGGGGGGCCCCC
SN7001427:381:CC2M6ANXX:2:2209:9314:37421/1	0	chr1	30575592	1	51M	*	0	0	CTGTTTTTTCCACAGAATGCTACAAGAGCATGCTAGCTTCCAATGTGACAG	BCCBBFGGGGGGGGGGGGGGGGGGFGGGGGGGGGGGGGGEGGGGGGFGGGG
SN7001427:381:CC2M6ANXX:2:1308:8015:20917/1	16	chr1	30831888	1	51M	*	0	0	TCTCTCTCTTTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCT	EGFFBGEGF1GGGGGGGGGGGGGGGGGGGGGGGGGEGGGFGECFGGGCCCCC
SN7001427:381:CC2M6ANXX:2:2301:6023:38003/1	16	chr1	31070996	1	51M	*	0	0	TGTTGAGGGGCATCTGGGTTCTTTCCAGCTTCTGGCTATTAGAAATAAGGC	GGGGFGGGGGGGGGGGDGGGGGGGGGGGFGGGGGGGGGGGGGGGGGGGCCCCC
SN7001427:381:CC2M6ANXX:2:1106:8182:99280/1	0	chr1	31388880	1	51M	*	0	0	CTGCATGGTACTGGTATAGAGACAGACAAGTAGACCAATGGAATAGAATTG	BAAAAEFGGGGGGGGGGGGGG>DGGGGGGGGGGGGGGGGGGEFGGGGGGGE
SN7001427:381:CC2M6ANXX:2:1314:1722:78464/1	0	chr1	31431994	1	51M	*	0	0	CAGAAAATGGAGTCGCTTATATAGCCCTCAGCCATGGCGTTTCAGCACCTG	@B=0AFGGGFGGGGGGGGGGGGGGGEGGGGGGGGGGGGGGGGGGGGGGGG
SN7001427:381:CC2M6ANXX:2:1306:19040:78921/1	16	chr1	31469908	1	51M	*	0	0	ATATCAATTGAACGGAACTAAAGTCTGTGACAGTGGACATAGCTGCTGGAC	GGGGEGGGGGGCDGEGEGGGGGF:GGGGGGGGEGGGGGGGGGEEGEBBBAB
SN7001427:381:CC2M6ANXX:2:1106:14267:77697/1	16	chr1	31514663	1	51M	*	0	0	TGTGTTGGATAATAAAGATGGTATAAAAAACTTTATCTGCAAAGCCGAGAG	GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGCCCCC
SN7001427:381:CC2M6ANXX:2:2203:7264:23689/1	16	chr1	31523444	1	51M	*	0	0	TCTAGTTATGTTTGTCTTTGTAAATAGATTAGACAAACAGTTTGGTTATAG	GGGGGGGGGGGGGGGCGGGGGGGGGGGGGCGGGGGGGGGGGGGGGGGBBBCB
SN7001427:381:CC2M6ANXX:2:2304:10897:97699/1	16	chr1	31532559	1	51M	*	0	0	GAACAATCAAACCTTAATTTGTATATTAATAGTCAATGCCATATCTCTGAG	EGGGGGGGGGGGEGGGGGGGGGGGGGGGGGCFEGG>GGGGGGGGGBCBCB
SN7001427:381:CC2M6ANXX:2:1211:14854:9802/1	16	chr1	31532889	30	51M	*	0	0	AGTCAATGCCATATCTCTGAGCTCGCAATTGCTTAAATTGTTCATCCCTCG	CGGGB<BFF<<1E1F@BEGC>C99:1@DCGG@GGG;DGGGDDBBGCAAAAA
SN7001427:381:CC2M6ANXX:2:1206:14781:99976/1	16	chr1	31540331	1	51M	*	0	0	TTCTCCTTTCTTCAGTGTGACCAGCCATTCTAACTCAATCTTAGACTGGTC	GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGFGEGGGGGGGGFCCCCC
SN7001427:381:CC2M6ANXX:2:1314:8100:60921/1	16	chr1	31543392	1	51M	*	0	0	ATTCTGACTCTTCTGGTAAGTATCATTCTAAAGACTAAAATTCCTTTTGTG	GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGCCCCC
SN7001427:381:CC2M6ANXX:2:1310:11794:82703/1	0	chr1	31549928	1	51M	*	0	0	CAGCTCCTATTTTAGCCACAAATCGTGGTGTTACTAATGACATAATTCTTG	CCCCCGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
SN7001427:381:CC2M6ANXX:2:1101:16691:96239/1	16	chr1	31559866	1	51M	*	0	0	ATTATTCGGCGGGAATCGGGTCCCCTCCCCCTTCCTTCATAACTAGTGTCG	GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGFGGGCGGGGGGGGGCBCCC

(*continued*)

Table 1. (*continued*)

SN7001427:381:CC2M6ANXX:2:2301:5225:51078/1	16	chr1	3156003	1	51M	*	0	0	GGGTCCCCTCCCCCTTCCTTCATAACTAGTGTCGCAACAATAAAATTTGAG	GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGDCBBBB
SN7001427:381:CC2M6ANXX:2:1208:5509:63170/1	0	chr1	3175613	1	51M	*	0	0	CAACAATCGTTCAGTCGCAGCTGTGAATGGAAGTCCAAGGATCTAGCAGTT	CCCCCGGGGGGGGGGGGGGGGGGGGGGGGGGGGFGGGGGGGGGGGGGGGG
SN7001427:381:CC2M6ANXX:2:2211:17033:81413/1	16	chr1	3175822	1	51M	*	0	0	TCGGAGATTCAATCTTCTGGAATCCATAGCCACTATGGCTCAAGATCTTCA	GGGGGGGGGGGGGGGGGGGGFGGGGGGGGGGFGGGGGGGGGGGGGCCCCC
SN7001427:381:CC2M6ANXX:2:2114:3597:40858/1	0	chr1	3175903	1	51M	*	0	0	TCCAGATAAGGGTCACTGGTGAGCCTTCCAATTCCGGATTGTAGTTCATTC	CCCCCGGGGGGGGGGGGGGGGGEGGGGGGGGGGGGGGDGGGGGGGGGGGG
SN7001427:381:CC2M6ANXX:2:2108:12088:84412/1	16	chr1	3178931	1	51M	*	0	0	GGAACTTCACATAAAACCAGAGACACTGAAACTTATAGAGGAGAAAGTGGG	GGGGGGCFFGGGGGGGGGF>GEGGGGGGGGGGGGGGGGEGGGGGGBBBBA
SN7001427:381:CC2M6ANXX:2:1114:8260:62264/1	16	chr1	3180260	1	51M	*	0	0	TCTGCAACCCTATAGGTGGAACAACATTATGAACTAACCAGTACCCCGGAG	GGF>BBGFGGB@F1DGFCDDEEDD@EGF@>FGGGGF:::1;CGE/E0B?BB
SN7001427:381:CC2M6ANXX:2:2106:14016:18680/1	0	chr1	3191785	1	51M	*	0	0	GCAAGGCCTAGGAATTTAGGGGTCCGTGACACTACATTATTCTTGAGGCCT	CCCCCGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
SN7001427:381:CC2M6ANXX:2:1308:18420:78984/1	0	chr1	3191792	1	51M	*	0	0	CTAGGAATTTAGGGGTCCGTGACACTACATTATTCTTGAGGCCTGCCAAGA	CCCCCGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
SN7001427:381:CC2M6ANXX:2:2114:21136:67301/1	0	chr1	3191792	1	51M	*	0	0	CTAGGAATTTAGGGGTCCGTGACACTACATTATTCTTGAGGCCTGCCAAGA	BBCBCGGGGGGGGFGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
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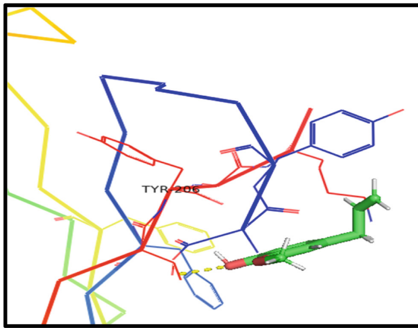
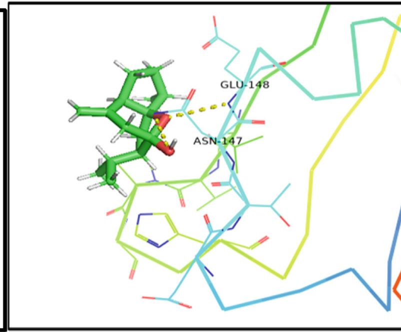
SN7001427:381:CC2M6ANXX:2:1207:6173:30758/1	0	chr1	3191793	1	51M	*	0	0	TAGGAATTTAGGGGTCCGTGACACTACATTATTCTTGAGGCCTGCCAAGAG	CCCCBGGGGGGFGGFGGGGGGGGGGGFGGGFEGEGGGGGGEGGGGGGDBF
SN7001427:381:CC2M6ANXX:2:2115:6847:97012/1	0	chr1	3191793	1	51M	*	0	0	TAGGAATTTAGGGGTCCGTGACACTACATTATTCTTGAGGCCTGCCAAGAG	BBCCBGGGGGGGGGGGGGGEGGCEGEGGGGFGGCGGGGEBGEGGFGEGGGB
SN7001427:381:CC2M6ANXX:2:1212:18753:64091/1	0	chr1	3191794	1	51M	*	0	0	AGGAATTTAGGGGTCCGTGACACTACATTATTCTTGAGGCCTGCCAAGAGT	BCCCCGGGGGGGGGGGGGEGGGGGGGGGGGGGGGGGGGFGGGGGGGGGGG

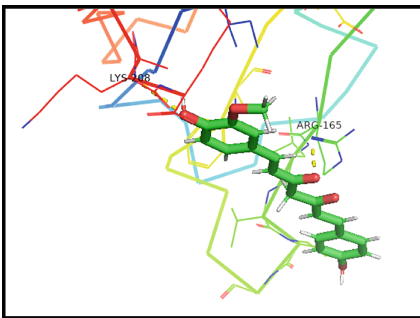
As per the MACS2 peak results, the gene's ENSMUST00000022535.8 corresponding receptor protein is taken for further studies (Figs. 2, 3, 4 and Table 2).

Eugenol **Curcumol**





Demethoxycurcumin



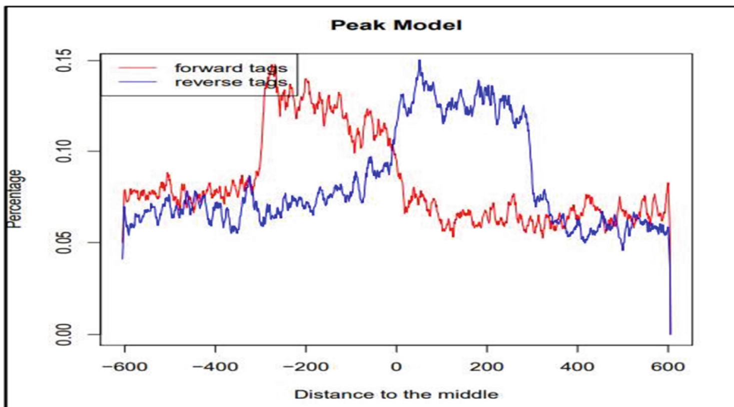


Fig. 2. MACS calculated to identify the centre of your peaks. Peaks: bed and peaks: interval provides information about the peaks MACS found in the data. Identify the significantly enrich loci in the genome.

Table 2. Gene motif and their function

Gene motif	Functions:
ENSMUST00000022535.8	Enables enzyme activator activity Enables hydrolase activity Enables identical protein binding Enables kinesin binding Enables mRNA binding Enables transcription factor binding
ENSMUST00000013759.5	Enables protein binding
ENSMUST00000238890.1	Enables protein binding
ENSMUST00000205276.1	Enables protein binding Enables identical protein binding
ENSMUST00000205911.1	Enables protein binding Enables identical protein binding
ENSMUST00000038359.5	Enables protein binding Enables identical protein binding
ENSMUST00000052550.12	Enables calcium ion binding Enables low density lipoprotein particle receptor activity Enables protein binding
ENSMUST00000002678.9	Enables antigen binding Enables cytokine activity Enables enzyme binding Enables growth factor activity Enables identical protein binding

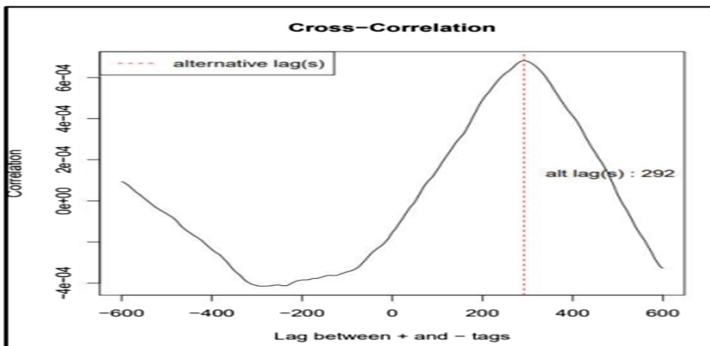


Fig. 3. After aligning de-duplicated reads to the genome, peak caller can be used to find regions of the genome with an enrichment of reads, or peaks.

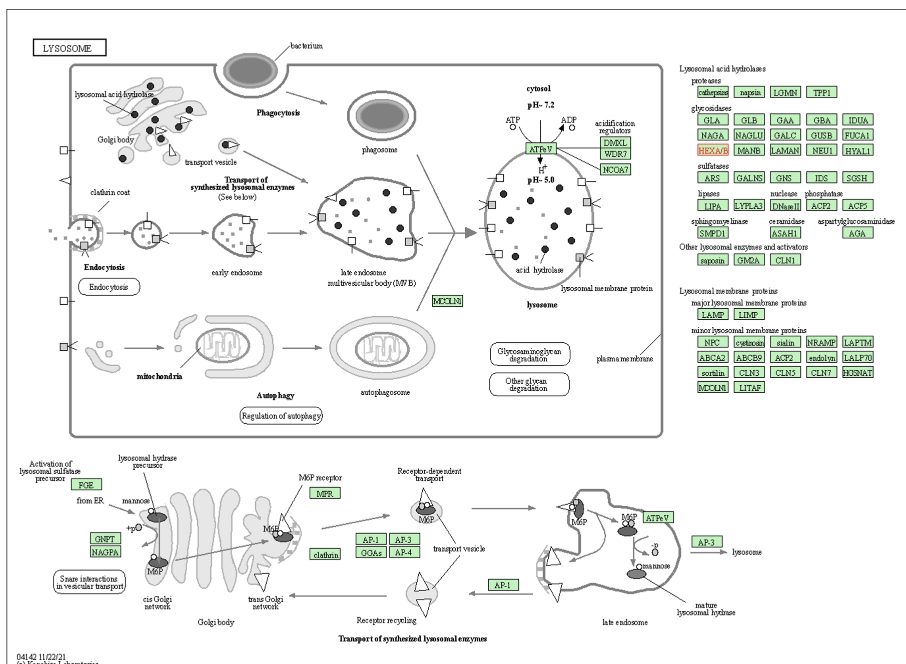


Fig. 4. Lysosomal degradation pathway

4 Conclusion

After mapping out of two SRR accession, I used the tool Collect Alignment Summary Metrics tool take the summary of mapping done above. Both tables contain the alignment summary SRR6941411.1 and SRR6941410. Next, I used MAC2 call peak tool to identify areas in the genome that are enriched with the aligned reads. Model-based Analysis of Chip-Seq (MACS) is a commonly used tool for identifying transcription factor binding sites. Then I identified the motifs present in our Mus musculus genome.

As per the chip-seq peak the genes identified are: ENSMUST00000022535.8, ENSMUST00000013759.5, ENSMUST00000238890.1, ENSMUST00000205276.1, ENSMUST00000205911.1, ENSMUST00000038359.5, ENSMUST00000052550.12 and ENSMUST00000002678.9. The receptor corresponding to ENSMUST00000022535.8 docks best with demethoxycurcumin. Hence, this phytocompound can be selected as ligand for the receptor.

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