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Clinical Pathogenicity Prediction Of Histone 3 Family Component With An *In-silico* Screening Of H3.3A Gene In Human

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Background

Histone variant H3.3 is a member of human histone H3 family, it is expressed in whole cell cycle phases. H3.3 histone is encoded by two genes named H3.3A (H3F3A) and H3.3B (H3F3B) located on **chromosome 1** and **chromosome 17** respectively **[1-3]**

Several studies have shown the possible role of histones methylation and acetylation with cancer **[4]**, but none have investigated the potential role and consequences of those genetic variations

The goal of the present study is to explored different SNP variations in H3.3A gene and pathogenetic variations.

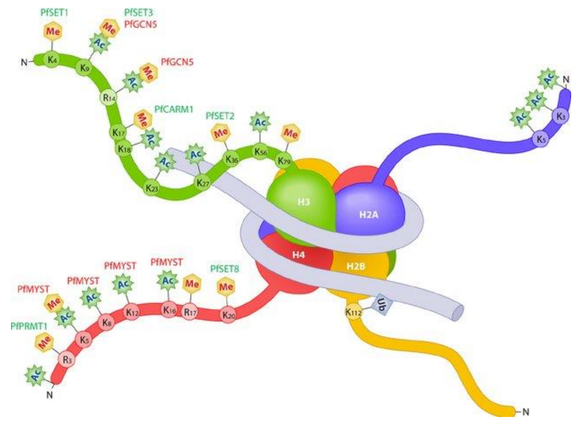

Figure1
Schematic drawing of a nucleosome with the four canonical histones (H3, H4, H2A, and H2B)

Methods

- ❑ Ensembl, dbSNP NCBI**[5],** and Uniprot databases were used to collect gene information.
- ❑ To evaluate the pathological nature of those variations, we selected 19 SNVs from 10 transcripts of the gene.
- ❑ We compared scores and prediction with 4 different software; SIFT**,**Polyphen-2**,** REVEL**,** and MUTATION- Assesor **.**

Results

After checking all the transcripts and exons, we compared 19 SNP **(table1)**

- The SIFT score SIFT score consider a mutation from 0.0 as (deleterious) and to 1.0 as (tolerated). This method shows that 18 SNVs are considered to be deleterious.
- The levels of probably damaging and possibly damaging were classified as functionally significant (≤0.5) and the benign level being classified as tolerated (≥0.51) with PolyPhen-2, and in this study, it does only considered 13 SNPs as Probably damaging and 1 as Possibly damaging
- REVEL Scores above 0.5, as 'likely disease causing' and display scores below 0.5 as 'likely benign, and this tool considered 7 SNPs as likely diseases causing.
- For Mutation-ASSESOR, the score is one of 'neutral', 'low', 'medium' and 'high', and the rank score, which is between 0 and 1 where variants with higher scores are more likely to be deleterious, and our results show only 2 SNPs as deletirous.

Table 1: Summary of damaging mutations comminating different software

SNP ID	A.A replacement	SIFT		Polyphen-2		Revel		MUTATION-ASSESOR	
		Prediction	Score	Prediction	Score	Prediction	Score	Prediction	Score
rs532531600	L/R	Damaging	0	Probably damaging	0.999	likely disease causing	0.874	Medium	0.91
rs1464306889	K/E	Damaging	0	Probably damaging	0.981	likely disease causing	0.685	High	0.977
rs767113562	Q/H	Damaging	0.01	Probably damaging	0.996	likely disease causing	0.874	Medium	0.91

Combining results of all methods, only 3 mutations appear to be *clinically damaging* , with a change from hydrophobic to hydrophile amino acid in only one mutation.

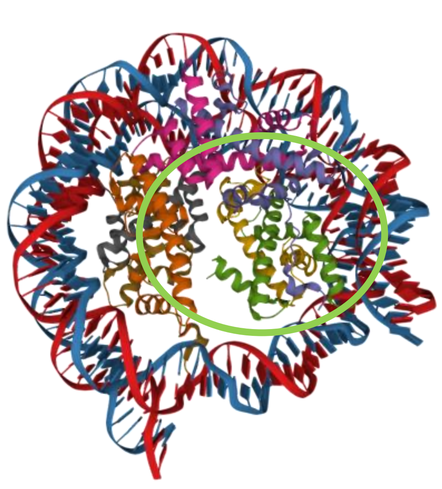

Figure 2:
The crystal structure of the nucleosome containing histone H3.3 (in green)

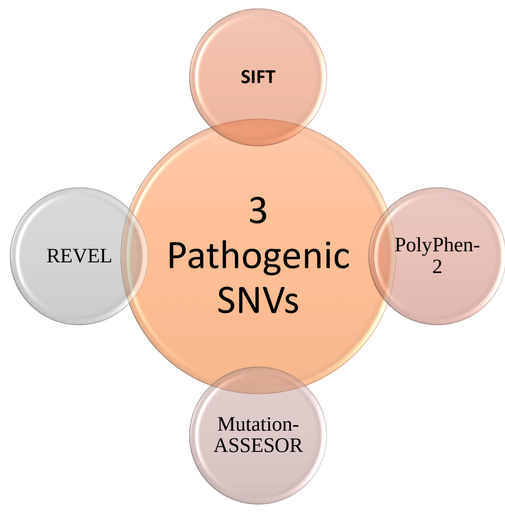

Figure 3 : 3 clinically damaging mutations identified by 4 tools

Conclusion

The present study shows combination of different softwares by an *in-silico* approach, to define most diseases-associated mutations, in the H3-3A gene. Protein prediction methods are recommended to a better understanding of structures and function.

References

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