

Casein kinase-1($\alpha1/\delta/\gamma1$) & $2\alpha1$ (CSNK) : Time behavioural study of 3rd order combinations in WNT3A stimulated HEK 293 cells

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Abstract

Casein kinase (CSNK) are serine/threonine-selective protein kinase, which selectively modifies other proteins by covalently adding phosphates to them (phosphorylation) as opposed to kinases which modify lipids, carbohydrates, or other molecules. Gujral and MacBeath [1] provides a quantitative, and dynamic study of WNT3A-mediated stimulation of HEK 293 cells, where they record time based expression profiles of several response genes which correlated significantly with proliferation and migration. By monitoring the dynamics of gene expression using self-organizing maps, they identified clusters of genes that exhibit similar expression dynamics and uncovered previously unrecognized positive and negative feedback loops. However, their study depicts/uses singular measurements of individual gene expression at different time snapshots/points to infer the system wide analysis of the pathway. At any particular time point, it is often the case that genes are working synergistically in combinations, even though their expression measurements are singular in nature. Here, I • enumerate and rank all 2415 CSNK (family member) related 3rd order combinations in a forest of ${}^{71}C_3$ combinations using four different sensitivity methods; • show the conserved rankings for CSNK-X-X combinations, which point to existence of biological synergy of some of these combinations across the different sensitivity methods; and • study the behaviour of some of these combinations related to WNT3A response genes that are ranked by the machine learning search engine (Sinha [2]) in time. Patterns of combinations emerge, some of which have been tested in wet lab, while others require further wet lab analysis.

Keywords: Sensitivity analysis, Support vector ranking, Hilbert Schmidt Independence Criterion indices (HSIC) and Sobol indices, WNT3A

[☆]Time behavioural study of 3-odr CSNK comb. in WNT3A stimulated cells

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1. Significance

Sinha [2] recently demonstrated the use of machine learning based search engine to rank/reveal gene combinations at 2nd order for the time series data by Gujral and MacBeath [1] and showed how it is possible to locate combinations of priority that might be working synergistically, using sensitivity methods and powerful support vector ranking algorithm. However, the problem explodes combinatorially with even a small set of 71 recorded genes in the study by Gujral and MacBeath [1], when one steps to explore 3rd order combinations. With the total number of ${}^{71}C_3$ (= 57155) combinations, it becomes nearly impossible for any biologist to study the system wide dynamics of any pathway. Also, the amount of time usually needed to search for and test a combination is far more than the search down by the machine learning based search engine. Here, I extend the research work by Sinha [2] to conduct a behavioral study of 3rd order FOXN1 related combinations using individual gene expressions measured in time, in WNT3A stimulated HEK 293 cells.

2. Introduction

The details of the machine learning based search engine has been recently published in Sinha [2] and deployed to explore the 2nd order combinations of genes in the data set provided by Gujral and MacBeath [1]. Nevertheless, here, I point to the fundamentals of the published work for completeness.

2.1. A combinatorial problem

Sensitivity analysis plays a major role in computing the strength of the influence of involved factors in any phenomena under investigation. When applied to expression profiles of various intra/extracellular factors that form an integral part of a signaling pathway, the variance and density based analysis yields a range of sensitivity indices for individual as well as various combinations of factors. These combinations denote the higher order interactions among the involved factors. Computation of higher order interactions is often time consuming but it gives a chance to explore the various combinations that might be of interest in the working mechanism of the pathway. For example, in a range of fourth order combinations among the various factors of the Wnt pathway, it would be easy to assess the influence of the destruction complex formed by APC, AXIN, CSKI and GSK3 interaction. But the effect of these combinations vary over time as measurements of fold changes and deviations in fold changes vary. So it is imperative to know how an interaction or a combination of the involved factors behave in time and Sinha [2] develops a procedure to track the behaviour by exploiting the influences of these involved factors.

2.2. A possible solution

In this work, after estimating the individual effects of factors for a higher order combination, the individual indices are considered as discriminative features. A combination,

then, is a feature set in higher order (≥ 2 , i.e. multivariate). With an excessively large number of factors involved in the pathway, it is difficult to search for important combinations in a wide search space over different orders. Exploiting the analogy with the issues of prioritizing webpages using ranking algorithms, for a particular order, a full set of combinations of interactions can then be prioritized based on these features using a powerful ranking algorithm via support vectors Joachims [3]. Recording the changing rankings of the combinations over time reveals how higher order interactions behave within the pathway and when an intervention might be necessary to influence the interaction within the pathway.

2.3. The earliest research using Casein

A phosphoprotein is a protein that is post-translationally modified by the attachment of either a single phosphate group, or a complex molecule such as 5'-phospho-DNA, through a phosphate group. In eukaryotes, the target amino acid is mostly serine, threonine, or tyrosine residues, while in prokaryotes, it is aspartic acid or histidine residues. Cozzone [4] summarizes and documents the phosphorylation of proteins, as a major regulatory mechanism in cells.

In rat liver mitochondria, Burnett and Kennedy [5] discovered an enzyme capable of catalyzing the transfer of phosphate from ATP to protein. Of a number of proteins tested, they observed that only casein was phosphorylated at an appreciable rate. α -casein was observed to phosphorylate at about 4 times the rate of β -casein. Further, nearly all of the radioactivity transferred from ATP labeled with P^{32} to casein could be accounted for as radioactive phosphoserine in acid hydrolysates of the casein. Free phosphoserine did not appear to be an intermediate in the reaction.

Casein is a family of related phosphoproteins, known in the form of α -S1 (encoded by CSN1S1), α -S2 (encoded by CSN1S2), β (encoded by CSN2) and κ (encoded by CSN3), casein. Fujiwara et al. [6] isolated and characterized 5 yeast artificial chromosome (YAC) clones containing the human casein gene family, to study the control mechanisms for the expression of these genes. They performed, partial restriction analysis in conjunction with the chromosomal fragmentation method and fluorescence in situ hybridization (FISH) analysis, to construct a detailed physical map of the casein gene family and determined the chromosomal localization of these genes. The isolated YAC clones 748F3, 882G11, 886B3 and 960D2 contained the entire casein gene family, while the κ -casein gene was absent in 750D11. The human α S1-, β - and κ -casein genes were found to be closely linked and arranged in the order α S1- β - κ . The casein gene family was localized to chromosome 4q21.1 by FISH analysis.

2.4. Casein kinase (CSNK)

The Casein kinase family of protein kinases are serine/threonine-selective enzymes, which selectively modifies other proteins by covalently adding phosphates to them (i.e. phosphorylation, Cohen [7]) as opposed to kinases which modify lipids, carbohydrates, or other molecules.

In the Golgi apparatus of lactating rat mammary gland, Bingham and Farrell Jr [8] found a casein kinase that catalyzed the phosphorylation of dephosphorylated α -S1-

casein by ATP. They report that dephosphorylated β - and κ -caseins were also phosphorylated by this enzyme, while other milk proteins (β -lactoglobulin, α -lactalbumin, native α -S1-, β -, and κ -casein, and proteins of the fat globule membrane) were phosphorylated to a limited extent. They observed that the optimum pH for phosphate incorporation into dephosphorylated casein was 7.6; the K_m for dephosphorylated α -S1-casein was 12 μ m (.27 mg per ml), whereas the K_m for ATP was 80 μ m. Further, the casein kinase required a divalent cation for maximum activity (both Ca^{2+} and Mg^{2+} could satisfy this requirement). These findings suggested that the phosphorylation of casein (a food protein), was quite different from the phosphorylation of cellular enzymes, which required cyclic AMP, was inhibited by Ca^{2+} and was involved in control mechanisms.

Hanks and Hunter [9] carried out a monumental task of analyzing and collating the amino acid sequences of all protein kinases and defining the conserved structural features that characterize the portion of these proteins that is responsible for catalytic activity. In their review, they present information about the eukaryotic protein kinases (a large superfamily of homologous proteins), which are related by their kinase domains (also known as catalytic domains), which consist of \approx 250-300 amino acid residues. They observe that the kinase domains that define this group of enzymes contain 12 conserved subdomains that fold into a common catalytic core structure, as revealed by the 3-dimensional structures of several proteinserine kinases. There are two main sub-divisions within the superfamily: the protein-serine/threonine kinases and the protein-tyrosine kinases. Further, they suggest that a classification scheme can be founded on a kinase domain phylogeny, which reveals families of enzymes that have related substrate specificities and modes of regulation.

2.4.1. Casein kinase 1 (CSNK1 / CK1)

CSNK1A1 - Tapia et al. [10] isolated and sequenced, a cDNA clone coding for human protein kinase CK1 (casein kinase 1), thus demonstrating that it corresponded to a homolog of the CK1 α (CSNK1A1) form found in bovine brain. Using this cDNA sequence and PCR amplification, they further isolated YAC genomic clones that contain this human CK1 α sequence. These YACs were used for fluorescent in situ hybridization in order to localize the human CK1 α gene to chromosome 13q13.

Fish et al. [11] reported the cloning and characterization of a novel isoform of CKI from a human placental cDNA library. The cDNA for this isoform, hCKI ϵ (CSNK1E), predicted a basic polypeptide of 416 amino acids and a molecular mass of 47.3 kDa. They observed that it encoded a core kinase domain of 285 amino acids and a carboxyl-terminal tail of 123 amino acids. The kinase domain was 53-98% identical to the kinase domains of other CKI family members and was most closely related to the δ isoform. Localization of the hCKI ϵ gene to chromosome 22q12-13 and the hCKI δ (CSNK1D) gene to chromosome 17q25 confirmed that these were distinct genes in the CKI family. In summary, hCKI ϵ was a novel CKI isoform with properties that overlapped those of previously described CKI isoforms.

CSNK1D - Rowles et al. [12] purified casein kinase I (CKI) over 6000-fold from bovine thymus and sequenced seven tryptic peptides that accounted for nearly 25% of the primary sequence of the enzyme. They isolated partial cDNAs encoding CKI and

a related enzyme (CKI δ), by using PCR. Further, they used the CKI PCR product to probe a bovine brain cDNA library from which cDNAs corresponding to CKI (CKI α) and two homologous enzymes (CKI β and CKI γ) were identified. Their finding of the existence of least four CKI-like enzymes suggested that CKI activity in tissues/cell extracts may be composed of multiple related but distinct protein kinases. Based on this, they suggest that this group of enzymes was not similar to any other known protein kinases and may, therefore, represent an additional branch of the protein kinase family.

Graves et al. [13] reported the molecular cloning and characterization of a 49-kDa form of casein kinase I from rat testis. A cDNA clone encoding the enzyme, designated casein kinase I δ (CSNK1D), contained an open reading frame of 1284 nucleotides that predicted a polypeptide of 428 amino acids with a M_r of 49,121. The predicted amino acid sequence shared 76% identity with casein kinase I α , a 37-kDa form that was cloned from bovine brain by Rowles et al. [12]. Further, expression of the casein kinase I δ cDNA in *Escherichia coli* resulted in active enzyme that phosphorylated casein, phosphovitin, and the peptide substrate DDDDVASLPGLRRR. They observed that Casein kinase I δ represented a separate member of the casein kinase I family distinguished by its larger size and unique kinetic behavior with respect to heparin.

Kusuda et al. [14] isolated and sequenced a cDNA clone coding for human casein kinase I (CKI). They found that the entire amino acid sequence of human CKI was 97% homologous to that of rat CKI δ , and their sequences in the kinase domain (284 amino acid residues) were completely identical, thus predicting that the obtained cDNA was for a human homolog of the CKI δ isoform (CSNK1D). The human CKI δ gene was mapped to chromosome 17q25.2q25.3 by fluorescence in situ hybridization and polymerase chain reaction analysis of the human/rodent hybrid cell panels.

CSNK1G1 - Kusuda et al. [15] isolated two types of cDNA for human casein kinase I γ 1 (hCK1 γ 1). They found hCK1 γ 1S to encode a polypeptide consisting of 393 amino acids, which was highly homologous with already reported rat CKI γ 1 (rCK1 γ 1), while the other type of cDNA (hCK1 γ 1L) encoded a polypeptide consisting of 422 amino acids, which was quite identical in the kinase domain, but different in the C-terminal sequence from hCK1 γ 1S. Further, hCK1 γ 1L had a characteristic sequence of 50 amino acids at the C-terminal end and this motif was shown to be shared by the casein kinase γ 2 and γ 3 from rat and human, thus suggesting that it was a signature sequence of the gamma-isoforms. RT-PCR analysis revealed that hCK1 γ 1S mRNA was predominantly present in the testis, whereas the abundance of hCK1 γ 1L mRNA was nearly the same in the twelve tissues examined. Finally, the human hCK1 γ 1 gene (CSNK1G1) was mapped to chromosome 15q22.1–>q22.31 by fluorescence in situ hybridization.

2.4.2. Casein kinase 2 (CSNK2 / CK2)

By immunological screening of λ gt11 expression libraries, Saxena et al. [16] isolated cloned cDNAs encoding both subunits of *Drosophila melanogaster* casein kinase II, and the complete amino acid sequence of both polypeptides was deduced by DNA sequencing. The alpha cDNA contained an open reading frame of 336 amino acid residues and the expected semi-invariant residues present in the catalytic domain of previously sequenced protein kinases, confirming that it was the catalytic subunit of the

enzyme. On the other hand, the beta subunit was derived from an open reading frame of 215 amino acid residues and exhibited no extensive homology to other proteins whose sequences were known at the time of this research.

Using a *Drosophila* casein kinase II cDNA probe, Meisner et al. [17] isolated a human cDNA encoding the alpha subunit of casein kinase II and a partial cDNA encoding the rat homologue. The *Drosophila* enzyme sequence was found to be 90% identical with the human casein kinase II sequence, and there was only a single amino acid difference between the published partial bovine sequence and the human sequence. These results were consistent with the possibility that two genes could encode the alpha subunits.

Casein kinase II holoenzyme appears to be a tetramer, containing two α or α' subunits (or one of each) and two beta subunits. Study by Lozeman et al. [18], show that there are two distinct catalytic subunits for casein kinase II (alpha and alpha') and that the sequence of these subunits was largely conserved between the bovine and the human.

Yang-Feng et al. [19] localized the human CKII- α DNA sequence to two loci: 11p15.5p15.4 and 20p13, using a combination of segregation analysis of rodent-human hybrid cells and chromosomal in situ hybridization. In contrast, they mapped the CKII- α' gene to chromosome 16, by somatic cell hybrid analysis. Taken together with their previous assignment of the CKII regulatory β -subunit gene to 6p12p21, these results indicated that although the products of these genes formed a single biological complex, they were encoded on different human chromosomes.

CSNK2A1 - Finally, Wirkner et al. [20] isolated and characterized a 18.9-kb genomic clone representing a central portion of the human casein kinase II (CKII) subunit α gene (CSNK2A1). Using the whole clone as a probe, the gene was localized on chromosome 20p13. The clone contained eight exons whose sequences comprised bases 102 to 824 of the coding region of the human CKII α and the exon/intron splice junctions conformed to the gt/ag rule. Three of the nine introns were located at positions corresponding to those in the CKII α gene of the nematode *Caenorhabditis elegans*. The introns contained eight complete and eight incomplete Alu repeats. Some of the Alu sequences were arranged in tandems of two or three, which seemed to originate from insertions of younger Alu sequences into the poly(A) region of previously integrated Alu sequences, as indicated by flanking direct repeats.

I present 3rd order combinations of CSNK with other genes, that the machine learning based search engine points to, as possible synergistic combinations that might be working in time.

3. Methods

Please refer to sections of Sinha [2] for methods, design of study and analysis of data for 2nd order combinations. The same method and design of study is used to generate results for 3rd order combinations presented in this study.

4. Time series data

Gujral and MacBeath [1] present a set of 71 WNT-related gene expression values for 6 different times points over a range of 24-hour period using qPCR. The changes represent the fold-change in the expression levels of genes in 200 ng/mL WNT3A-stimulated HEK 293 cells in time relative to their levels in unstimulated, serum-starved cells at 0-hour. Gujral and MacBeath [1] state that qPCR data are the means of three biological replicates. Only genes whose mean transcript levels changed by more than two-fold at one or more time points during the 24-hour time course were considered significant. Positive (negative) numbers represent up (down) -regulation. We have already covered the issues related to these data sets in detail in Sinha [21]. Readers are requested to go through them in the pointed reference. The tools of study which are used here have been published in another foundational work in Sinha [21].

5. Design of experiment

5.1. Pipeline for time series data

For the case of time series data, interactions among the contributing factors are studied by comparing triplets of fold-changes at single time points. The procedure begins with the generation of distribution around measurements at single time points with added noise is done to estimate the indices. A distribution is generated for the fold changes at single time points. Then for every gene, there is a vector of values representing fold changes as well as deviations in fold changes for different time points and durations between time points, respectively. Next a listing of all C_k^n combinations for k number of genes from a total of n genes is generated. k is ≥ 2 and $\leq (n - 1)$. Each of the combination of order k represents a unique set of interaction between the involved genetic factors. After this, the datasets are combined in a specified format which go as input as per the requirement of a particular sensitivity analysis method. Thus for each p^{th} combination in C_k^n combinations, the dataset is prepared in the required format from the distributions for two separate cases which have been discussed above. (See .R code in mainScript-1-1.R). After the data has been transformed, vectorized programming is employed for density based sensitivity analysis and looping is employed for variance based sensitivity analysis to compute the required sensitivity indices for each of the p combinations. This procedure is done for different kinds of sensitivity analysis methods.

After the above sensitivity indices have been stored for each of the p^{th} combination, the next step in the design of experiment is conducted. Since there is only one recording of sensitivity index per combination, each combination forms a training example which is allotted a training index and the sensitivity indices of the individual genetic factors form the training example. Thus there are C_k^n training examples for k^{th} order interaction. Using this training set SVM_{learn}^{Rank} Joachims [3] is used to generate a model on default value C value of 20. In the current experiment on toy model C value has not been tuned. The training set helps in the generation of the model as the different gene combinations are numbered in order which are used as rank indices. The

model is then used to generate score on the observations in the testing set using the $SVM_{classify}^{Rank}$ Joachims [3]. Note that due to availability of only one example per combination, after the model has been built, the same training data is used as test data to generates the scores. This procedure is executed for each and every sensitivity analysis method. This is followed by sorting of these scores along with the rank indices (i.e the training indices) already assigned to the gene combinations. The end result is a sorted order of the gene combinations based on the ranking score learned by the SVM^{Rank} algorithm. Finally, this entire procedure is computed for sensitivity indices generated for each and every fold change at time point and deviations in fold change at different durations. Observing the changing rank of a particular combination at different times and different time periods will reveal how a combination is behaving.

Note that the following is the order in which the files should be executed in R, in order, for obtaining the desired results (Note that the code will not be explained here) - • use source("mainScript-1-1.R") with arguments for Dynamic data • source("SVMRank-Results-D.R"), to rank the interactions (again this needs to be done separately for different kinds of SA methods), • use source("Combine-Time-files.R"), if computing indices separately via previous file, • source("Sort-n-Plot-D.R") to sort the interactions. Note that the sorting is changes the interaction ranking in time. Thus • use source("Interaction-Priority-Intime.R") to find the prioritized ranking of each and every interaction over the different time points and finally • use source("Print-Ranking-AND-Interaction-Rank.R") to print individual ranking of the required input factor with other interaction factors.

6. Results & Discussion

6.1. Time series data by Gujral and MacBeath [1]

NOTE - Ranking was assigned on scores that were sorted in DECREASING values. So, 1 was assigned to highest score and vice versa.

Results for the 3rd order interactions are presented here. The results first discuss the behaviour of interactions across the snapshots of time using the computed sensitivities on fold change measurements per time snapshot. The analysis was done using 4 different sensitivity indices. Out of the 7C_3 combinations, I consider/present only those combinations that show a ranking within first 10,000 out of 57,155. This choice is liberal and biologists/oncologists can have a more stricter choice as per need. Two observations are made, • the ranking of a particular combination is conserved (i.e within the 10,000 range) in a particular time point or in the early phase or late phase of WNT3A stimulation, across the majority of the four sensitivity methods, which is a strict criteria of assessment or • the ranking of a particular combination is conserved across time points/phase (i.e they are within the 10,000 range) and the majority of the four sensitivity methods, which is relaxed criteria of assessment. Applying this filter helps reveal important combinations of interest that might be working synergistically at a higher order level in the cell.

Regarding technical points of implementation, the rankings were generated without scaling/normalizing the time series data provided by Gujral and MacBeath [1].

For estimating the sensitivity indices, a small gaussian distribution using the function **rnorm** that generates a vector of normally distributed random variables given a vector length n (here 9, the 10th one is the mean/recorded gene regulation itself), a population mean μ and population standard deviation σ . The syntax for using **rnorm** is as follows: **rnorm(n, mean, sd)**. Further, I use the **jitter** function to add a little bit of noise to the data. This helps to see if the generated rankings are robust or not.

6.2. Enumeration and ranking of 2415 CSNK1A1-X-X combinations from Gujral and MacBeath [1]

In the supplementary section, I present four files, each containing the rankings of 3rd order combinations, that vary in time (shown for 5 time points). Each file represents the rankings computed using a particular sensitivity method. The changing rankings in time for a particular combination represents the importance of contribution/role that combination plays in the cell stimulated with WNT3A. The sensitivity methods used are Hilbert Schmidt Independence Criterion indices (HSIC) indices (with rbf and linear kernel in Da Veiga [22]) and Sobol indices (with 2002 implementation in Saltelli [23] and martinez implementation in Martinez [24] and Baudin et al. [25]).

6.3. Conserved machine learning rankings for tested CSNK1A1-X-X combinations

A total of 2415, 3rd order combinations involving CSNK1A1 were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 2, 3 and 4 show the rankings for the same combinations as in table 1, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

6.3.1. Examining the behaviour of DVL-CSNK1A1-X combinations

Dishevelled (DVL) protein plays a central role in WNT pathway by transducing the signal from the Wnt receptor complex to the β -catenin destruction complex. DVL also plays a pivotal role in the planar cell polarity pathway that involves the c-JUN N-terminal kinase (JNK). JNKs were originally identified as kinases that bind and phosphorylate c-JUN on Ser-63 and Ser-73 within its transcriptional activation domain. Cong et al. [26] found that casein kinase I (CKI), a positive regulator of WNT signaling, stimulated DVL activity in the WNT pathway, but dramatically inhibited DVL activity in the JNK pathway. Consistent with this, they observed that overexpression of CKI in *Drosophila melanogaster* stimulated WNT signaling and disrupted planar cell polarity. Furthermore, by using RNA interference, they demonstrated that the *Drosophila* CKI homologue double time positively regulated the β -catenin pathway via DVL and negatively regulated the DVL-induced JNK pathway. They thus suggested that CKI

RANKING @ t_1 USING HSIC - LINEAR												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1A1-CTBP2-FZD7	446	542	23183	19207	56178	CSNK1A1-FBXW4-TLE1	488	2991	1906	41763	1178	
CSNK1A1-FBXW4-WNT4	789	26748	5104	45626	10949	CSNK1A1-CTBP2-KREMEN1	1221	5094	21366	17954	17531	
FZD5-CSNK1A1-FBXW4	1259	19155	9658	41320	14772	CSNK1A1-LRP6-RHOU	1294	10065	15184	54599	10820	
APC-CSNK1A1-DAAM1	1311	30728	35140	1324	45684	CSNK1A1-FGF4-WNT5A	1597	15092	35949	31672	40613	
CSNK1A1-JUN-TCF7L1	1599	2840	51813	45452	5619	CSNK1A1-FGF4-TLE1	1651	4473	39964	19512	17510	
CSNK1A1-CTBP2-SFRP4	1683	356	25182	29226	44294	FZD5-CSNK1A1-FRZB	1755	640	16648	53416	6465	
CSNK1A1-LRP6-PPP2CA	1764	14481	17648	2115	28490	CSNK1A1-CTBP2-SEN2	2061	5536	21907	15112	30719	
CSNK1A1-FGF4-PPP2R1A	2100	34624	20608	35480	22746	CSNK1A1-PORCN-SEN2	2120	49633	16561	8614	20137	
CSNK1A1-FGF4-FOSL1	2196	29619	53247	49107	51945	CSNK1A1-GSK3B-WNT2B	2210	15358	584	7063	10019	
FZD5-CSNK1A1-FBXW11	2246	14811	16635	40200	1914	CSNK1A1-PORCN-TLE1	2312	22675	18816	2981	24170	
CSNK1A1-FBXW4-TCF7L1	2369	4620	4621	46927	2510	CSNK1A1-CTBP2-WNT2B	2408	1933	22108	24942	27389	
CSNK1A1-JUN-TLE2	2445	41824	10945	37149	14097	FZD5-CSNK1A1-GSK3B	2515	19508	3469	33985	5181	
CSNK1A1-DVL2-FZD7	2516	8112	25530	17884	40125	FZD5-CSNK1A1-FZD8	2636	13269	17229	53720	7059	
CSNK1A1-CTBP2-FOSL1	2849	847	23417	33270	57047	CCND3-CSNK1A1-WNT3A	2882	32791	9744	16123	5109	
CSNK1A1-LRP6-SLC9A3R1	3014	37227	8811	14338	41031	CSNK1A1-CTNNB1-T	3099	39820	55326	23807	4207	
CSNK1A1-CTBP2-FRZB	3166	134	23658	36362	51600	CSNK1A1-CTBP2-CXXC4	3187	741	15084	41906	44957	
CSNK1A1-CTBP2-DKK1	3201	279	47279	48129	43482	CSNK1A1-PORCN-WNT4	3257	26979	26665	9094	28864	
CSNK1A1-NLK-TLE1	3280	2505	5178	30696	38811	CSNK1A1-CTBP2-WNT5A	3469	3917	28636	35088	16423	
CSNK1A1-DVL2-WNT2	3544	6290	41631	2705	48649	CSNK1A1-CTBP2-T	3640	4202	2188	18666	8214	
CSNK1A1-CTBP2-GSK3B	3705	1189	19711	11873	27228	CSNK1A1-FGF4-TCF7L1	3882	5238	49459	22324	14558	
CSNK1A1-PORCN-TCF7L1	3915	10340	17278	12348	13374	APC-CSNK1A1-FBXW4	3918	19181	11081	18566	50834	
CSNK1A1-JUN-TLE1	4097	5887	41754	19734	12000	CSNK1A1-PORCN-WNT2B	4109	24272	43637	30113	14274	
CSNK1A1-FGF4-FBXW4	4116	39720	25825	27348	20432	CSNK1A1-FGF4-LRP5	4256	19659	16893	49563	45930	
CSNK1A1-PORCN-TLE2	4303	50645	30117	22021	22867	CSNK1A1-FGF4-SEN2	4319	56449	38778	32596	20602	
CSNK1A1-DVL2-FOSL1	4359	9320	25266	14510	55885	CSNK1A1-PORCN-PPP2R1A	4422	33823	41491	28773	10648	
CSNK1A1-FGF4-RHOU	4425	11288	40651	53938	32204	CSNK1A1-DVL2-PPP2CA	4486	10261	29763	2711	43368	
CSNK1A1-FGF4-FZD7	4502	27827	33012	19654	44184	CSNK1A1-GSK3B-TCF7	4544	30985	20598	9861	25556	
CSNK1A1-FZD8-TLE2	4606	37599	36569	47165	48140	CSNK1A1-CTBP2-TCF7	4623	7101	13671	53019	33372	
FZD5-CSNK1A1-DAAM1	4670	13469	35458	36602	19431	BCL9-CSNK1A1-DVL1	4751	10835	37098	55309	33884	
CSNK1A1-NLK-WIF1	4795	14710	6213	20851	31609	FZD5-CSNK1A1-WNT3A	4851	20216	2057	34374	10916	
CSNK1A1-FGF4-FRZB	4864	38544	45046	49268	34965	FZD5-CSNK1A1-DKK1	4908	20276	35790	42397	25998	
CSNK1A1-DVL2-PPP2R1A	5022	16393	26315	11167	21749	CSNK1A1-FGF4-NLK	5044	42807	34184	50750	42473	
CSNK1A1-CTBP2-FBXW11	5046	5716	43008	56351	10131	FZD5-CSNK1A1-FZD1	5058	1029	34923	56951	24991	
FZD5-CSNK1A1-CSNK2A1	5100	3216	8691	22543	4716	CSNK1A1-JUN-SEN2	5103	50068	52444	22403	16328	
CSNK1A1-FGF4-WNT4	5182	17880	43266	27559	29243	CSNK1A1-PORCN-WNT5A	5243	23800	15741	37419	31250	
CSNK1A1-CTNNB1-WNT5A	5397	18525	21875	41824	20123	CSNK1A1-FGF4-FRAT1	5443	35003	33593	42395	25511	
CSNK1A1-GSK3A-TLE2	5459	50884	31842	40483	25693	CSNK1A1-CTBP2-FRAT1	5487	4451	21319	43529	55767	
APC-CSNK1A1-TCF7L1	5507	18234	27624	29775	13556	APC-CSNK1A1-FZD1	5702	7849	36571	29769	57083	
CSNK1A1-FBXW11-SLC9A3R1	5804	27245	10598	19794	2889	CSNK1A1-FZD8-KREMEN1	5808	27565	28948	42692	2118	
APC-CSNK1A1-WNT2	5896	3204	26912	12707	50298	CSNK1A1-CTBP2-TLE2	5947	3527	38912	46367	43145	
CSNK1A1-CTBP2-DIXDC1	5982	946	22832	39647	5152	CSNK1A1-DVL2-NKD1	6006	6911	49386	18094	11822	
CSNK1A1-CTNNB1-CXXC4	6039	45552	28288	37922	13149	CSNK1A1-FGF4-WNT2B	6087	18229	16667	40000	14677	
CSNK1A1-FGF4-WNT3A	6107	44023	16988	37868	11275	FZD5-CSNK1A1-WNT5A	6117	3531	25494	31085	4978	
FZD5-CSNK1A1-CTNNB1	6181	17864	24940	32407	12133	BCL9-CSNK1A1-SLC9A3R1	6196	5871	38982	49700	55862	
CSNK1A1-FGF4-TCF7	6234	23826	45283	17805	17765	CSNK1A1-CTBP2-FZD6	6303	427	17847	13602	55430	
APC-BCL9-CSNK1A1	6362	6421	39025	30195	57130	APC-CSNK1A1-FZD8	6490	32866	17023	11729	21732	
CSNK1A1-CTBP2-FZD8	6497	3343	16159	12665	40046	CSNK1A1-CTNNB1-FZD7	6524	27559	23464	35198	26190	
APC-CSNK1A1-DKK1	6548	8229	31377	48381	34695	CSNK1A1-FBXW11-LRP6	6607	25137	25384	28481	23089	
CSNK1A1-GSK3A-KREMEN1	6666	39027	8814	55480	2616	CSNK1A1-TCF7-TLE2	6751	29020	41448	31350	1240	
BCL9-CSNK1A1-LRP6	6787	7920	31140	45917	49067	CSNK1A1-DVL2-SEN2	6840	43332	25733	12544	19769	
APC-CSNK1A1-FBXW11	6881	15694	20213	41128	23521	APC-CSNK1A1-GSK3B	6910	25577	3571	6892	35443	
CSNK1A1-WNT3-WNT5A	6941	13287	18743	30373	8529	CSNK1A1-FOXN1-TLE2	7002	3386	8069	5817	10964	
CSNK1A1-LRP6-WNT2B	7049	23299	24935	14963	24570	APC-CSNK1A1-FRZB	7106	3282	24721	18735	45560	
FZD5-CSNK1A1-CTBP2	7154	15543	9364	48713	21016	CCND3-CSNK1A1-FBXW4	7291	47593	10464	26925	40678	
CSNK1A1-PYGO1-TLE1	7320	3097	27930	20790	22458	CSNK1A1-GSK3B-LRP6	7340	4465	32186	3994	22357	
CSNK1A1-CTNNB1-FRAT1	7370	45885	11195	37814	20543	CSNK1A1-CTBP2-SLC9A3R1	7382	583	40075	50715	51438	
APC-CSNK1A1-SEN2	7433	26624	23100	15164	40513	CSNK1A1-FGF4-WNT2	7437	25648	52312	29248	40389	
APC-CSNK1A1-TCF7	7517	16135	52165	53808	18711	CSNK1A1-LRP6-WNT5A	7534	15967	10258	8617	8424	
CSNK1A1-JUN-PITX2	7555	25297	41726	55383	9601	CSNK1A1-GSK3A-SFRP4	7601	47227	13982	21496	16296	
FZD5-CSNK1A1-FOSL1	7612	5474	24493	48455	32808	CSNK1A1-CTNNB1-WIF1	7629	18321	19085	31265	12424	
CSNK1A1-GSK3B-SFRP1	7631	23266	15866	3749	23631	CSNK1A1-SLC9A3R1-WNT5A	7639	15498	47347	33140	11472	
CSNK1A1-FGF4-FZD1	7676	34651	53765	51275	36266	BCL9-CSNK1A1-FZD8	7686	7662	33555	55893	14620	
CSNK1A1-FZD8-MYC	7700	33126	46697	37913	19794	CSNK1A1-TCF7-TCF7L1	7713	4938	16621	29561	538	

Table 1: Rankings of CSNK1A1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear

functioned as a molecular switch to direct DVL from the JNK pathway to the β -catenin pathway, possibly by altering the conformation of the C terminus of DVL.

Looking at the tables above, one finds the following combinations for members of DVL family along with CSNK1A1, to be prominent at 3rd order level - CSNK1A1-DVL2-FZD7, CSNK1A1-DVL2-WNT2, CSNK1A1-DVL2-FOSL1, CSNK1A1-DVL2-

RANKING @ t_i USING HSIC - RBF												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1A1-CTBP2-FZD7	16317	1661	21086	34288	43163	CSNK1A1-FBXW4-TLE1	49092	4166	56036	38886	23429	
CSNK1A1-FBXW4-WNT4	40830	22049	52381	8977	9106	CSNK1A1-CTBP2-KREMEN1	10123	4733	30223	55392	43989	
FZD5-CSNK1A1-FBXW4	34906	20157	22887	40008	37683	CSNK1A1-LRP6-RHOU	38981	447	43109	54028	16718	
APC-CSNK1A1-DAAM1	12651	49361	15998	47265	46614	CSNK1A1-FGF4-WNT5A	8952	17873	1108	36340	28004	
CSNK1A1-JUN-TCF7L1	22985	1629	17522	50991	17011	CSNK1A1-FGF4-TLE1	5929	698	14003	4424	52530	
CSNK1A1-CTBP2-SFRP4	23263	372	36592	37924	25352	FZD5-CSNK1A1-FRZB	7949	2308	38721	47952	28703	
CSNK1A1-LRP6-PPP2CA	16978	31404	24202	26610	21103	CSNK1A1-CTBP2-SEN2	10180	748	17421	23226	20154	
CSNK1A1-FGF4-PPP2R1A	4863	12539	3164	12998	34074	CSNK1A1-PORCN-SEN2	17613	53191	22246	23117	47820	
CSNK1A1-FGF4-FOSL1	16622	30625	6828	2304	55529	CSNK1A1-GSK3B-WNT2B	45401	7842	20915	12032	30244	
FZD5-CSNK1A1-FBXW11	21544	13116	21853	34874	52683	CSNK1A1-PORCN-TLE1	19117	12891	16501	828	46802	
CSNK1A1-FBXW4-TCF7L1	48117	2346	53009	52827	51924	CSNK1A1-CTBP2-WNT2B	35362	599	27812	55812	11216	
CSNK1A1-JUN-TLE2	9969	39782	34294	35377	45681	FZD5-CSNK1A1-GSK3B	24659	34626	40940	53965	6278	
CSNK1A1-DVL2-FZD7	54315	43923	45290	36847	55206	FZD5-CSNK1A1-FZD8	30859	9203	14750	32125	25534	
CSNK1A1-CTBP2-FOSL1	34000	288	23729	11736	43862	CCND3-CSNK1A1-WNT3A	17118	24899	2478	56125	79	
CSNK1A1-LRP6-SLC9A3R1	53177	39860	38405	32345	53617	CSNK1A1-CTNNB1-T	37593	26808	5906	40154	10358	
CSNK1A1-CTBP2-FRZB	17546	627	23800	44636	36066	CSNK1A1-CTBP2-CXXC4	6148	356	31122	45700	47540	
CSNK1A1-CTBP2-DKK1	19169	5090	29233	47297	16573	CSNK1A1-PORCN-WNT4	22396	7881	36610	47685	56275	
CSNK1A1-NLK-TLE1	16274	1109	56566	37347	24936	CSNK1A1-CTBP2-WNT5A	17747	9071	3307	44304	37334	
CSNK1A1-DVL2-WNT2	9554	14803	52557	24557	22238	CSNK1A1-CTBP2-T	18329	1981	2473	46154	25672	
CSNK1A1-CTBP2-GSK3B	8633	749	40115	56524	23325	CSNK1A1-FGF4-TCF7L1	7278	398	11123	53191	50489	
CSNK1A1-PORCN-TCF7L1	23258	3050	20521	49747	55799	APC-CSNK1A1-FBXW4	30069	35774	8994	41297	29918	
CSNK1A1-JUN-TLE1	39566	2527	36899	22974	3068	CSNK1A1-PORCN-WNT2B	29063	5140	20656	25842	56335	
CSNK1A1-FGF4-FBXW4	3944	43071	7924	16423	35504	CSNK1A1-FGF4-LRP5	5382	7257	3376	38023	30318	
CSNK1A1-PORCN-TLE2	36377	50293	37575	3836	55812	CSNK1A1-FGF4-SEN2	3374	55056	13678	34346	43962	
CSNK1A1-DVL2-FOSL1	55879	22362	36218	7242	48985	CSNK1A1-PORCN-PPP2R1A	32307	17216	8460	87	56661	
CSNK1A1-FGF4-RHOU	5893	6761	20675	42030	35006	CSNK1A1-DVL2-PPP2CA	25344	18547	15707	11312	20765	
CSNK1A1-FGF4-FZD7	6478	2389	8522	2832	23365	CSNK1A1-GSK3B-TCF7	47998	7725	1475	2546	51874	
CSNK1A1-FZD8-TLE2	27314	35709	26792	3349	48039	CSNK1A1-CTBP2-TCF7	9502	10709	2042	36079	27819	
FZD5-CSNK1A1-DAAM1	40656	23017	23552	22095	36752	BCL9-CSNK1A1-DVL1	54648	7806	27824	5947	45419	
CSNK1A1-NLK-WIF1	11282	8274	56968	38447	50254	FZD5-CSNK1A1-WNT3A	42407	33834	18047	51521	4064	
CSNK1A1-FGF4-FRZB	2699	36751	20655	26306	40111	FZD5-CSNK1A1-DKK1	3449	17141	26176	52062	1549	
CSNK1A1-DVL2-PPP2R1A	56797	35397	16667	8537	53736	CSNK1A1-FGF4-NLK	5934	47193	13185	41723	38100	
CSNK1A1-CTBP2-FBXW11	24649	2340	29673	46334	44039	FZD5-CSNK1A1-FZD1	20237	18396	37640	4153	15624	
FZD5-CSNK1A1-CSNK2A1	38103	8653	39291	8415	48804	CSNK1A1-JUN-SEN2	10922	51170	21128	28997	8938	
CSNK1A1-FGF4-WNT4	2597	7193	37885	14945	56051	CSNK1A1-PORCN-WNT5A	18048	10911	1449	21232	54808	
CSNK1A1-CTNNB1-WNT5A	26843	10192	12731	48429	51797	CSNK1A1-FGF4-FRAT1	4866	31030	2401	3401	51224	
CSNK1A1-GSK3A-TLE2	7134	50657	51617	41371	44030	CSNK1A1-CTBP2-FRAT1	8317	3924	3495	50186	56834	
APC-CSNK1A1-TCF7L1	4565	13852	30998	36714	26086	APC-CSNK1A1-FZD1	5253	14937	15529	37119	41793	
CSNK1A1-FBXW11-SLC9A3R1	49938	26269	56022	6527	51109	CSNK1A1-FZD8-KREMEN1	33831	26241	20861	32946	25109	
APC-CSNK1A1-WNT2	16640	5458	43640	16393	21928	CSNK1A1-CTBP2-TLE2	35858	2736	40345	38840	40218	
CSNK1A1-CTBP2-DIXDC1	26364	1158	23736	9780	15204	CSNK1A1-DVL2-NKD1	54028	5607	19606	1199	29562	
CSNK1A1-CTNNB1-CXXC4	9644	43667	50701	46639	11963	CSNK1A1-FGF4-WNT2B	6487	2504	13514	43449	50217	
CSNK1A1-FGF4-WNT3A	5838	44710	40803	39001	56918	FZD5-CSNK1A1-WNT5A	13867	12121	25578	55880	42025	
FZD5-CSNK1A1-CTNNB1	21396	2265	23803	20237	29433	BCL9-CSNK1A1-SLC9A3R1	46365	4520	48658	40569	3204	
CSNK1A1-FGF4-TCF7	4052	6701	482	18613	56965	CSNK1A1-CTBP2-FZD6	24448	2668	14692	37435	18181	
APC-BCL9-CSNK1A1	52297	5829	37925	18570	37069	APC-CSNK1A1-FZD8	10455	26921	27436	37958	39658	
CSNK1A1-CTBP2-FZD8	23069	3773	29385	47288	18564	CSNK1A1-CTNNB1-FZD7	19234	6487	43359	13715	36679	
APC-CSNK1A1-DKK1	2622	8697	2312	32876	38829	CSNK1A1-FBXW11-LRP6	53577	8575	29750	36656	56168	
CSNK1A1-GSK3A-KREMEN1	6573	24688	52114	44210	53821	CSNK1A1-TCF7-TLE2	45610	9957	48526	53367	35758	
BCL9-CSNK1A1-LRP6	48795	5310	8417	38640	27537	CSNK1A1-DVL2-SEN2	51226	36936	45861	18243	49683	
APC-CSNK1A1-FBXW11	4161	12339	6766	10742	50724	APC-CSNK1A1-GSK3B	22497	5941	47689	46089	20278	
CSNK1A1-WNT3-WNT5A	37235	26881	9370	45751	49582	CSNK1A1-FOXN1-TLE2	7302	12368	41632	26789	37910	
CSNK1A1-LRP6-WNT2B	51938	7845	40652	47883	47032	APC-CSNK1A1-FRZB	3856	4803	47020	21585	14752	
FZD5-CSNK1A1-CTBP2	38663	29860	3143	21998	52722	CCND3-CSNK1A1-FBXW4	20682	45470	7827	41609	1368	
CSNK1A1-PYGO1-TLE1	89	408	36983	15330	39183	CSNK1A1-GSK3B-LRP6	56301	2025	7366	15018	40522	
CSNK1A1-CTNNB1-FRAT1	28981	54038	15633	458	42561	CSNK1A1-CTBP2-SLC9A3R1	36027	20	39513	30626	47319	
APC-CSNK1A1-SEN2	3444	41167	28465	13264	35065	CSNK1A1-FGF4-WNT2	13317	24582	27380	41739	22979	
APC-CSNK1A1-TCF7	7736	33700	27024	12562	36468	CSNK1A1-LRP6-WNT5A	47653	10651	9505	52387	23450	
CSNK1A1-JUN-PITX2	29961	18458	34169	55719	14194	CSNK1A1-GSK3A-SFRP4	4191	50809	54823	9605	42733	
FZD5-CSNK1A1-FOSL1	20891	913	56996	13269	20956	CSNK1A1-CTNNB1P1-WIF1	38552	24332	29614	9954	36686	
CSNK1A1-GSK3B-SFRP1	49751	2699	30945	23770	50545	CSNK1A1-SLC9A3R1-WNT5A	12722	2435	1118	45619	41911	
CSNK1A1-FGF4-FZD1	4440	32172	14449	14756	36664	BCL9-CSNK1A1-FZD8	38516	7226	30008	39633	29940	
CSNK1A1-FZD8-MYC	56708	29228	1057	5642	49312	CSNK1A1-TCF7-TCF7L1	36595	9507	39234	38395	56953	

Table 2: Rankings of CSNK1A1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf

PPP2R1A, CSNK1A1-DVL2-PPP2CA, BCL9-CSNK1A1-DVL1, CSNK1A1-DVL2-NKD1 and CSNK1A1-DVL2-SEN2. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

Looking at the tables above, one finds the following combinations for JUN along with CSNK1A1, to be prominent at 3rd order level - CSNK1A1-JUN-TCF7L1, CSNK1A1-JUN-TLE2, CSNK1A1-JUN-TLE1, CSNK1A1-JUN-PITX2 and CSNK1A1-JUN-SEN2.

RANKING @ t_1 USING SOBOL - 2002												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1A1-CTBP2-FZD7	31566	22309	30736	36727	30548	CSNK1A1-FBXW4-TLE1	8858	44863	28484	14112	40362	
CSNK1A1-FBXW4-WNT4	17150	33308	23879	17349	39381	CSNK1A1-CTBP2-KREMEN1	22944	41262	26386	13278	43474	
FZD5-CSNK1A1-FBXW4	20354	39251	3926	3454	42221	CSNK1A1-LRP6-RHOU	35494	34805	31586	40687	45812	
APC-CSNK1A1-DAAM1	27659	21365	6869	26069	48769	CSNK1A1-FGF4-WNT5A	19234	7567	25442	12975	45195	
CSNK1A1-JUN-TCF7L1	48736	28417	29151	42720	4277	CSNK1A1-FGF4-TLE1	34028	15885	31088	49322	7825	
CSNK1A1-CTBP2-SFRP4	34028	15885	31088	49322	7825	FZD5-CSNK1A1-FRZB	6448	25213	19977	24920	26926	
CSNK1A1-LRP6-PPP2CA	21805	35780	26361	19325	3996	CSNK1A1-CTBP2-SEN2	35393	18640	32385	44234	19529	
CSNK1A1-FGF4-PPP2R1A	19430	15108	26384	3273	35844	CSNK1A1-PORCN-SEN2	27814	41340	22240	7446	30078	
CSNK1A1-FGF4-FOSL1	31936	30526	31908	35528	15251	CSNK1A1-GSK3B-WNT2B	11273	20202	28474	7966	36728	
FZD5-CSNK1A1-FBXW11	8648	33147	26112	22304	21737	CSNK1A1-PORCN-TLE1	12005	44696	23553	11286	28512	
CSNK1A1-FBXW4-TCF7L1	42112	9817	28668	29599	18842	CSNK1A1-CTBP2-WNT2B	14279	32584	25596	18227	18296	
CSNK1A1-JUN-TLE2	37552	26081	28586	38231	8510	FZD5-CSNK1A1-GSK3B	18600	12262	15585	14274	19818	
CSNK1A1-DVL2-FZD7	34864	21555	29691	41610	6595	FZD5-CSNK1A1-FZD8	8242	45415	15215	20788	15692	
CSNK1A1-CTBP2-FOSL1	43122	17498	29136	41748	25756	CCND3-CSNK1A1-WNT3A	2952	56510	305	26398	49052	
CSNK1A1-LRP6-SLC9A3R1	27079	32490	19166	27635	7784	CSNK1A1-CTNNB1-T	43665	30982	35759	37419	14419	
CSNK1A1-CTBP2-FRZB	26340	39376	27153	12811	30783	CSNK1A1-CTBP2-CXXC4	32731	6104	30912	45061	27995	
CSNK1A1-CTBP2-DKK1	23529	38044	24536	21674	36906	CSNK1A1-PORCN-WNT4	18363	33232	26729	4216	46046	
CSNK1A1-NLK-TLE1	34554	35813	30941	38569	6273	CSNK1A1-CTBP2-WNT5A	11628	24885	28394	9281	35281	
CSNK1A1-DVL2-WNT2	36897	17141	30324	40363	14182	CSNK1A1-CTBP2-T	18730	31014	27154	26686	43290	
CSNK1A1-CTBP2-GSK3B	25428	42848	27429	21585	39514	CSNK1A1-FGF4-TCF7L1	23185	40973	26065	7839	49266	
CSNK1A1-PORCN-TCF7L1	38567	20007	29236	41635	23698	APC-CSNK1A1-FBXW4	27679	9154	10417	26292	46488	
CSNK1A1-JUN-TLE1	19600	31191	28571	18907	48659	CSNK1A1-PORCN-WNT2B	32766	32478	29427	48576	29309	
CSNK1A1-FGF4-FBXW4	18925	48950	28063	14819	46634	CSNK1A1-FGF4-LRP5	25933	56134	15030	7295	43615	
CSNK1A1-PORCN-TLE2	45135	12230	33608	45875	28904	CSNK1A1-FGF4-SEN2	33045	13835	30277	43272	14578	
CSNK1A1-DVL2-FOSL1	39808	37591	29989	43165	26253	CSNK1A1-PORCN-PPP2R1A	33540	14808	31151	43414	22297	
CSNK1A1-FGF4-RHOU	24122	43291	26893	13870	42711	CSNK1A1-DVL2-PPP2CA	36741	42674	30145	37928	5899	
CSNK1A1-FGF4-FZD7	30872	20155	30520	44434	14838	CSNK1A1-GSK3B-TCF7	36438	31687	28655	42431	7318	
CSNK1A1-FZD8-TLE2	31667	25145	30680	39984	14415	CSNK1A1-CTBP2-TCF7	38464	25739	29996	30477	13951	
FZD5-CSNK1A1-DAAM1	3364	50573	5353	18164	47676	BCL9-CSNK1A1-DVL1	1048	18774	18145	6293	46351	
CSNK1A1-NLK-WIF1	32459	19376	28696	36711	12615	FZD5-CSNK1A1-WNT3A	23292	31414	4023	7309	46564	
CSNK1A1-FGF4-FRZB	15730	35652	26773	14726	38109	FZD5-CSNK1A1-DKK1	12330	27121	12662	9172	29765	
CSNK1A1-DVL2-PPP2R1A	16325	38457	27941	16805	41980	CSNK1A1-FGF4-NLK	26759	47388	26756	25660	38122	
CSNK1A1-CTBP2-FBXW11	23018	17422	27493	18291	51489	FZD5-CSNK1A1-FZD1	6750	1016	4490	15202	29967	
FZD5-CSNK1A1-CSNK2A1	8541	11031	2822	9650	17384	CSNK1A1-JUN-SEN2	6384	23379	28366	24788	34572	
CSNK1A1-FGF4-WNT4	33314	16428	30722	35014	15930	CSNK1A1-PORCN-WNT5A	38789	23969	30418	52936	11242	
CSNK1A1-CTNNB1-WNT5A	42511	20663	32690	43619	9467	CSNK1A1-FGF4-FRAT1	33317	28589	29267	40896	9039	
CSNK1A1-GSK3A-TLE2	13398	38676	27953	23001	52309	CSNK1A1-CTBP2-FRAT1	32797	28654	30340	44090	20886	
APC-CSNK1A1-TCF7L1	28369	22215	2680	26640	48490	APC-CSNK1A1-FZD1	27824	24772	2361	28070	39038	
CSNK1A1-FBXW11-SLC9A3R1	16717	20879	27185	11762	19223	CSNK1A1-FZD8-KREMEN1	36908	36973	29107	38889	27962	
APC-CSNK1A1-WNT2	28667	24643	39561	36728	9282	CSNK1A1-CTBP2-TLE2	13560	38972	27007	10311	26766	
CSNK1A1-CTBP2-DIXDC1	36649	29759	30208	35374	5536	CSNK1A1-DVL2-NKD1	34807	20003	32979	36080	16108	
CSNK1A1-CTNNB1-CXXC4	16200	33323	25806	20043	44722	CSNK1A1-FGF4-WNT2B	20188	23715	24725	20985	50055	
CSNK1A1-FGF4-WNT3A	23841	40734	26459	22150	41207	FZD5-CSNK1A1-WNT5A	18817	36894	3076	5941	41483	
FZD5-CSNK1A1-CTNNB1	39986	17212	54803	37232	18554	BCL9-CSNK1A1-SLC9A3R1	10557	48613	21165	9456	39731	
CSNK1A1-FGF4-TCF7	31857	13749	31256	50031	12280	CSNK1A1-CTBP2-FZD6	25608	34829	26426	20502	26782	
APC-BCL9-CSNK1A1	25135	15796	26078	26679	43452	APC-CSNK1A1-FZD8	26532	18002	7651	14310	42717	
CSNK1A1-CTBP2-FZD8	20973	29794	28384	15108	31081	CSNK1A1-CTNNB1-FZD7	20241	33129	26088	26072	34516	
APC-CSNK1A1-DKK1	18766	14382	7118	20275	44632	CSNK1A1-FBXW11-LRP6	20440	36804	26367	7460	22152	
CSNK1A1-GSK3A-KREMEN1	14101	4583	26563	18329	39465	CSNK1A1-TCF7-TLE2	30781	9702	37973	40213	27967	
BCL9-CSNK1A1-LRP6	13672	27381	17905	15144	42398	CSNK1A1-DVL2-SEN2	34333	26702	29547	40131	17867	
APC-CSNK1A1-FBXW11	27134	21114	19532	27942	45263	APC-CSNK1A1-GSK3B	22105	25680	5871	25440	51299	
CSNK1A1-WNT3-WNT5A	31744	30946	30951	37138	31476	CSNK1A1-FOXN1-TLE2	31935	18561	30496	28879	29914	
CSNK1A1-LRP6-WNT2B	38393	35904	31134	31663	44866	APC-CSNK1A1-FRZB	26020	14813	5951	16122	34755	
FZD5-CSNK1A1-CTBP2	17113	40220	2353	19883	38901	CCND3-CSNK1A1-FBXW4	2944	52988	4900	4754	56552	
CSNK1A1-PYGO1-TLE1	13052	40144	28229	9557	42141	CSNK1A1-GSK3B-LRP6	45069	21241	28790	38086	10397	
CSNK1A1-CTNNB1-FRAT1	18102	39146	26580	20946	33174	CSNK1A1-CTBP2-SLC9A3R1	33679	25358	31687	42664	22596	
APC-CSNK1A1-SEN2	34573	39489	48358	30213	7489	CSNK1A1-FGF4-WNT2	31624	1945	30697	43203	18362	
APC-CSNK1A1-TCF7	37060	46411	56682	30638	5642	CSNK1A1-LRP6-WNT5A	35518	46181	28613	39154	15733	
CSNK1A1-JUN-PITX2	9621	18540	22340	12819	49548	CSNK1A1-GSK3A-SFRP4	43317	33051	30344	39363	21783	
FZD5-CSNK1A1-FOSL1	52341	1015	51653	36235	53778	CSNK1A1-CTNNB1P1-WIF1	10478	41370	27469	15853	27701	
CSNK1A1-GSK3B-SFRP1	24448	29886	24235	4957	42540	CSNK1A1-SLC9A3R1-WNT5A	23466	29587	27210	21571	43523	
CSNK1A1-FGF4-FZD1	12395	44700	25390	16990	36088	BCL9-CSNK1A1-FZD8	39214	28527	49370	49357	5290	
CSNK1A1-FZD8-MYC	40693	26729	29108	42831	11129	CSNK1A1-TCF7-TCF7L1	36712	26788	31154	43473	15625	

Table 3: Rankings of CSNK1A1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - 2002

All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

RANKING @ t_1 USING SOBOL - MARTINEZ												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1A1-CTBP2-FZD7	33268	11828	6448	19326	56029	CSNK1A1-FBXW4-TLE1	24498	5861	43353	48199	46265	
CSNK1A1-FBXW4-WNT4	21502	52930	8543	32700	10282	CSNK1A1-CTBP2-KREMEN1	34887	2984	15075	26075	37944	
FZD5-CSNK1A1-FBXW4	27533	51976	2191	12746	21935	CSNK1A1-LRP6-RHOU	27996	7737	1446	23990	14100	
APC-CSNK1A1-DAAM1	6308	3917	9565	25289	40677	CSNK1A1-FGF4-WNT5A	17317	3438	16557	42025	30659	
CSNK1A1-JUN-TCF7L1	56402	21678	40854	35544	40582	CSNK1A1-FGF4-TLE1	50141	14289	1579	17055	42641	
CSNK1A1-CTBP2-SFRP4	44416	36413	1920	4513	48659	FZD5-CSNK1A1-FRZB	22692	18682	56822	55298	6613	
CSNK1A1-LRP6-PPP2CA	42454	18402	25345	47495	4538	CSNK1A1-CTBP2-SEN2	38749	36141	2497	16914	40484	
CSNK1A1-FGF4-PPP2R1A	23603	17704	17458	38201	8185	CSNK1A1-PORCN-SEN2	237	31277	21830	41359	18275	
CSNK1A1-FGF4-FOSL1	42045	529	1485	3037	46681	CSNK1A1-GSK3B-WNT2B	30189	23709	30335	11241	13351	
FZD5-CSNK1A1-FBXW11	9233	54622	54939	55489	4033	CSNK1A1-PORCN-TLE1	4139	48680	6866	34294	16668	
CSNK1A1-FBXW4-TCF7L1	54316	440	43549	18203	57026	CSNK1A1-CTBP2-WNT2B	5751	26813	13649	42063	45127	
CSNK1A1-JUN-TLE2	53308	33159	44441	47162	42366	FZD5-CSNK1A1-GSK3B	5330	57027	56301	55942	368	
CSNK1A1-DVL2-FZD7	36450	11657	1937	24333	15205	FZD5-CSNK1A1-FZD8	1610	8475	55242	55855	2381	
CSNK1A1-CTBP2-FOSL1	51511	11283	3515	18073	56450	CCND3-CSNK1A1-WNT3A	27407	21026	33109	36618	45870	
CSNK1A1-LRP6-SLC9A3R1	15892	18686	8690	34461	4168	CSNK1A1-CTNNB1-T	45258	41598	9151	2804	39618	
CSNK1A1-CTBP2-FRZB	2133	1594	25191	30397	37892	CSNK1A1-CTBP2-CXXC4	46105	8098	960	7556	56796	
CSNK1A1-CTBP2-DKK1	19025	6381	51996	42157	21708	CSNK1A1-PORCN-WNT4	39148	56389	5371	51550	11271	
CSNK1A1-NLK-TLE1	56242	25711	3977	25404	37414	CSNK1A1-CTBP2-WNT5A	9289	37103	7483	11014	25436	
CSNK1A1-DVL2-WNT2	46507	12274	5803	23436	56057	CSNK1A1-CTBP2-T	21631	35350	23537	8094	21777	
CSNK1A1-CTBP2-GSK3B	22569	7399	12833	10779	42102	CSNK1A1-FGF4-TCF7L1	20721	12841	15556	28909	22687	
CSNK1A1-PORCN-TCF7L1	55575	17635	5491	2770	56404	APC-CSNK1A1-FBXW4	35097	5399	5924	21292	54042	
CSNK1A1-JUN-TLE1	26147	31094	56162	7942	28470	CSNK1A1-PORCN-WNT2B	51145	2966	1646	6984	51942	
CSNK1A1-FGF4-FBXW4	9110	31751	16365	34491	6012	CSNK1A1-FGF4-LRP5	3205	32201	9668	10559	3324	
CSNK1A1-PORCN-TLE2	48652	7052	89	25723	56653	CSNK1A1-FGF4-SEN2	24207	8179	4108	18555	39643	
CSNK1A1-FGF4-RHOU	49069	30818	1971	14661	36417	CSNK1A1-PORCN-PPP2R1A	51187	35349	570	23329	56565	
CSNK1A1-FGF4-FZD7	5830	17010	28223	32523	31936	CSNK1A1-DVL2-PPP2CA	41750	26193	8024	25997	50825	
CSNK1A1-FZD8-TLE2	26542	20534	5021	7104	44246	CSNK1A1-GSK3B-TCF7	19985	30246	41277	38376	46826	
CSNK1A1-FZD8-TLE2	31342	1554	1123	21208	27265	CSNK1A1-CTBP2-TCF7	43689	40342	22510	648	51720	
FZD5-CSNK1A1-DAAM1	25588	20787	55537	55140	5934	BCL9-CSNK1A1-DVL1	16549	23845	56038	41352	7601	
CSNK1A1-NLK-WIF1	30129	8991	3923	16574	38964	FZD5-CSNK1A1-WNT3A	5535	18798	2545	22509	37152	
CSNK1A1-FGF4-FRZB	18109	2905	34814	46973	16820	FZD5-CSNK1A1-DKK1	29234	53678	54840	53548	43392	
CSNK1A1-DVL2-PPP2R1A	23473	8665	16871	29059	40409	CSNK1A1-FGF4-NLK	33126	51525	21458	16463	3732	
CSNK1A1-CTBP2-FBXW11	23355	13073	20148	44709	8203	FZD5-CSNK1A1-FZD1	2931	27635	52243	41438	2552	
FZD5-CSNK1A1-CSNK2A1	5523	20838	55091	55579	6725	CSNK1A1-JUN-SEN2	26039	14625	56664	31948	45083	
CSNK1A1-FGF4-WNT4	49051	39260	7419	16537	47375	CSNK1A1-PORCN-WNT5A	54650	52431	7732	2602	47701	
CSNK1A1-CTNNB1-WNT5A	47102	35469	2582	14269	55324	CSNK1A1-FGF4-FRAT1	33332	23738	1508	20212	46452	
CSNK1A1-GSK3A-TLE2	21078	39746	53320	21373	2478	CSNK1A1-CTBP2-FRAT1	28319	3546	1989	19053	44487	
APC-CSNK1A1-TCF7L1	38636	4135	6864	25428	52970	APC-CSNK1A1-FZD1	39665	7793	7199	15940	14749	
CSNK1A1-FBXW11-SLC9A3R1	26208	9401	24346	47600	22499	CSNK1A1-FZD8-KREMEN1	49936	408	2369	10980	50255	
APC-CSNK1A1-WNT2	14500	38448	405	32011	18136	CSNK1A1-CTBP2-TLE2	19014	23578	49102	51196	7662	
CSNK1A1-CTBP2-DIXDC1	46670	2836	10130	14475	53477	CSNK1A1-DVL2-NKD1	53518	26394	8999	25622	47570	
CSNK1A1-CTNNB1-CXXC4	7008	15549	17934	37365	23157	CSNK1A1-FGF4-WNT2B	8837	16912	16674	44411	19417	
CSNK1A1-FGF4-WNT3A	6477	3833	52826	48955	3436	FZD5-CSNK1A1-WNT5A	20740	17402	2764	5824	25387	
FZD5-CSNK1A1-CTNNB1	9885	37117	53717	51541	39359	BCL9-CSNK1A1-SLC9A3R1	13745	53342	56010	29790	3939	
CSNK1A1-FGF4-TCF7	31041	5816	805	19224	23439	CSNK1A1-CTBP2-FZD6	12915	16583	6779	24388	30145	
APC-BCL9-CSNK1A1	32163	6346	28474	52424	48126	APC-CSNK1A1-FZD8	30377	7232	13159	17929	44649	
CSNK1A1-CTBP2-FZD8	31050	24995	23539	30076	7754	CSNK1A1-CTNNB1-FZD7	14015	40119	19180	2624	10353	
APC-CSNK1A1-DKK1	36829	3214	11174	23106	47230	CSNK1A1-FBXW11-LRP6	9603	13939	41251	38504	34976	
CSNK1A1-GSK3A-KREMEN1	18459	2597	9014	31785	38606	CSNK1A1-TCF7-TLE2	42996	42080	9937	11633	34753	
BCL9-CSNK1A1-LRP6	5007	26156	56668	44375	732	CSNK1A1-DVL2-SEN2	28527	2367	4558	21265	33808	
APC-CSNK1A1-FBXW11	35632	38614	9751	31501	47775	APC-CSNK1A1-GSK3B	24578	11963	21668	31233	33069	
CSNK1A1-WNT3-WNT5A	50961	25271	5377	14710	39891	CSNK1A1-FOXN1-TLE2	25803	22769	4943	21807	33663	
CSNK1A1-LRP6-WNT2B	53420	38086	5856	15991	54324	APC-CSNK1A1-FRZB	29949	7021	9611	35394	13559	
FZD5-CSNK1A1-CTBP2	39830	26528	31316	18842	13925	CCND3-CSNK1A1-FBXW4	51222	50466	11492	38172	47352	
CSNK1A1-PYGO1-TLE1	16140	950	47497	47768	29193	CSNK1A1-GSK3B-LRP6	56502	10533	43799	5789	45969	
CSNK1A1-CTNNB1-FRAT1	28273	26319	15003	28465	5552	CSNK1A1-CTBP2-SLC9A3R1	26932	37894	2423	19966	56907	
APC-CSNK1A1-SEN2	27990	30738	38441	15554	12496	CSNK1A1-FGF4-WNT2	42029	4351	675	6395	50265	
APC-CSNK1A1-TCF7	41272	26483	35260	37340	41163	CSNK1A1-LRP6-WNT5A	39970	32402	13929	9265	29540	
CSNK1A1-JUN-PTX2	19943	44766	31705	22479	6181	CSNK1A1-GSK3A-SFRP4	49487	21530	3128	18851	57052	
FZD5-CSNK1A1-FOSL1	29277	6430	50537	35536	55927	CSNK1A1-CTNNB1P1-WIF1	26195	24309	48507	48555	5275	
CSNK1A1-GSK3B-SFRP1	1063	15226	43852	28107	10923	CSNK1A1-SLC9A3R1-WNT5A	2293	26469	11695	42889	36449	
CSNK1A1-FGF4-FZD1	3145	4310	9494	34934	22010	BCL9-CSNK1A1-FZD8	9429	36357	48005	49652	18334	
CSNK1A1-FZD8-MYC	51089	54986	3255	6829	56137	CSNK1A1-TCF7-TCF7L1	50783	53467	10797	5676	29420	

Table 4: Rankings of CSNK1A1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - martinez

6.3.2. Examining the behaviour of TCF-CSNK1A1-X combinations

The WNT pathway regulates the steady state level of β -catenin, a transcriptional coactivator for the TCF3/ LEF1 family of DNA binding proteins. Lee et al. [27] demonstrated that TCF3 could inhibit β -catenin turnover via its competition with AXIN and adenomatous polyposis for β -catenin binding. TCF3 is a substrate for both glycogen

synthase kinase (GSK3) and CK1 ϵ , and phosphorylation of TCF3 by CK1 ϵ stimulated its binding to β -catenin, an effect reversed by GSK3. They observed that TCF3 synergized with CK1 ϵ to inhibit β -catenin degradation, whereas CKI-7, an inhibitor of CK1 ϵ , reduced the inhibitory effect of TCF3. Finally, they also provided evidence that CK1 ϵ stimulated the binding of DVL to GSK3 binding protein (GBP) in extracts. Along with evidence that a significant amount of TCF protein was nonnuclear, their findings suggested that CK1 ϵ could modulate WNT signaling in vivo by regulating both the β -catenin-TCF3 and the GBP-DVL interfaces. Looking at the tables above, one finds the following combinations for members of TCF family along with CSNK1A1, to be prominent at 3rd order level - CSNK1A1-JUN-TCF7L1, CSNK1A1-FBXW4-TCF7L1, CSNK1A1-PORCN-TCF7L1, APC-CSNK1A1-TCF7L1, CSNK1A1-FGF4-TCF7, APC-CSNK1A1-TCF7, CSNK1A1-FGF4-TCF7L1, CSNK1A1-GSK3B-TCF7, CSNK1A1-CTBP2-TCF7, CSNK1A1-TCF7-TLE2, and CSNK1A1-TCF7-TCF7L1. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.3.3. Examining the behaviour of PP2A-CSNK1A1-X combinations

CKI and protein phosphatase 2A (PP2A or PPP2R1A) act as positive and negative regulators of the WNT pathway, respectively. Gao et al. [28] showed that both CKI δ and CKI ϵ interacted directly with DVL1, and that CKI phosphorylated multiple components of the WNT-regulated β -catenin degradation complex in vitro, including DVL1, adenomatous polyposis coli (APC), AXIN, and β -catenin. It was observed that CKI abrogated β -catenin degradation in *Xenopus* egg extracts. Notably, CKI decreased, whereas inhibition of CKI increased, the association of PP2A with the β -catenin degradation complex in vitro. The ability of CKI to induce secondary body axes in *Xenopus* embryos was reduced by the B56 regulatory subunit of PP2A, and kinase-dead CKI ϵ acted synergistically with B56 in inhibiting WNT signaling. Their data suggested that CKI phosphorylated and destabilized the β -catenin degradation complex, likely through the dissociation of PP2A, thus providing a mechanism by which CKI stabilized β -catenin and propagated the WNT signal.

Looking at the tables above, one finds the following combinations for members of PPP2A family along with CSNK1A1, to be prominent at 3rd order level - CSNK1A1-LRP6-PPP2CA, CSNK1A1-FGF4-PPP2R1A, CSNK1A1-DVL2-PPP2R1A, CSNK1A1-PORCN-PPP2R1A and CSNK1A1-DVL2-PPP2CA. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.3.4. Examining the behaviour of LRP-CSNK1A1-X combinations

LDL-receptor-related proteins 5 and 6 (LRP-5/6) are key receptors required for transmission of WNT/ β -catenin signaling in metazoa. Using a protein modification screen for regulators of LRP6, Davidson et al. [29] described the identification of *Xenopus* Casein kinase 1 γ (CK1 γ). Their gain-of-function and loss-of-function experiments showed that CK1 γ was both necessary and sufficient to transduce LRP6 signaling in vertebrates and *Drosophila* cells. In *Xenopus* embryos, CK1 γ was required dur-

ing antero-posterior patterning to promote posteriorizing WNT/ β -catenin signaling. CK1 γ was observed to associate with LRP6, which had multiple, modular CK1 phosphorylation sites. WNT treatment induced the rapid CK1 γ -mediated phosphorylation of these sites within LRP6, which, in turn, promoted the recruitment of the scaffold protein AXIN.

Looking at the tables above, one finds the following combinations for members of LRP family along with CSNK1A1, to be prominent at 3rd order level - CSNK1A1-LRP6-PPP2CA, CSNK1A1-LRP6-SLC9A3R1, BCL9-CSNK1A1-LRP6, CSNK1A1-LRP6-WNT2B, CSNK1A1-LRP6-RHOU, CSNK1A1-FGF4-LRP5, CSNK1A1-FBXW11-LRP6, CSNK1A1-GSK3B-LRP6 and CSNK1A1-LRP6-WNT5A. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.3.5. Examining the behaviour of CTNNB1-CSNK1A1-X combinations

Deregulation of the WNT pathway results in the accumulation of β -catenin in the nucleus, often leading to cancer. Normally, cytoplasmic β -catenin associates with APC and AXIN and is continuously phosphorylated by GSK3 β , thus marking it for proteasomal degradation. WNT signaling prevents GSK3 β from phosphorylating β -catenin, thus causing its stabilization. Amit et al. [30] studied the regulation of β -catenin phosphorylation and degradation by the WNT pathway. Using mass spectrometry and phosphopeptide-specific antibodies, they showed that a complex of AXIN and CKI induced β -catenin phosphorylation at a single site, i.e serine 45 (S45). They observed that CKI inhibition suppresses this phosphorylation in vivo. Further, it was observed that CKI phosphorylation created a priming site for GSK3 β and is both necessary and sufficient to initiate the β -catenin phosphorylation-degradation cascade. WNT3A signaling and DVL overexpression suppressed S45 phosphorylation, thereby precluding the initiation of the cascade.

Looking at the tables above, one finds the following combinations for CTNNB1 along with CSNK1A1, to be prominent at 3rd order level - CSNK1A1-CTNNB1-WNT5A, CSNK1A1-CTNNB1-CXXC4, FZD5-CSNK1A1-CTNNB1, CSNK1A1-CTNNB1-FRAT1, CSNK1A1-CTNNB1-T and CSNK1A1-CTNNB1-FZD7. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.3.6. Examining the behaviour of APC-CSNK1A1-X combinations

In the absence of a WNT signal, CK1 and GSK3 β phosphorylate cytosolic β -catenin, thereby flagging it for recognition and destruction by the ubiquitin/proteasome machinery. Phosphorylation occurs in a multiprotein complex that includes the kinases, β -catenin, AXIN, and the APC protein. Ha et al. [31] observed that CK1 ϵ and GSK3 β phosphorylated APC, which increased its affinity for β -catenin. Crystal structures of phosphorylated and nonphosphorylated APC bound to β -catenin revealed a phosphorylation-dependent binding motif generated by mutual priming of CK1 and GSK3 β substrate sequences. AXIN was shown to act as a scaffold for substrate phosphorylation by these kinases. Phosphorylated APC and AXIN bound to the same surface of, and competed

directly for, β -catenin. The structural and biochemical data suggested a novel model for how APC functions in β -catenin degradation.

Looking at the tables above, one finds the following combinations for APC along with CSNK1A1, to be prominent at 3rd order level - APC-CSNK1A1-DAAM1, APC-CSNK1A1-TCF7L1, APC-CSNK1A1-WNT2, APC-BCL9-CSNK1A1, APC-CSNK1A1-DKK1, APC-CSNK1A1-FBXW11, APC-CSNK1A1-SEN2, APC-CSNK1A1-TCF7, APC-CSNK1A1-FBXW4, APC-CSNK1A1-FZD1, APC-CSNK1A1-FZD8, APC-CSNK1A1-GSK3B and APC-CSNK1A1-FRZB. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.4. Conserved machine learning rankings for tested CSNK1D-X-X combinations

A total of 2415, 3rd order combinations involving CSNK were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 6, 7 and 8 show the rankings for the same combinations as in table 5, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

NOTE - We consider the same factors which acted in combination for CSNK1A1, in the previous sections, as we have evidence of literature that have verified the existence of combinatorial synergy with CSNK1A1. Here we see if there exists combinations for CSNK1D, or not.

6.4.1. Examining the behaviour of DVL-CSNK1D-X combinations

Looking at the tables above, one finds the following combinations for members of DVL family along with CSNK1D, to be prominent at 3rd order level - BCL9-CSNK1D-DVL1 and CSNK1D-DVL2-LEF1. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.4.2. Examining the behaviour of TCF-CSNK1D-X combinations

Looking at the tables above, one finds the following combinations for members of TCF family along with CSNK1D, to be prominent at 3rd order level - CSNK1D-FGF4-TCF7L1, CSNK1D-FGF4-TCF7, CSNK1D-PORCN-TCF7, CSNK1D-PPP2R1A-TCF7L1, CSNK1D-PPP2R1A-TCF7, CSNK1D-FOXN1-TCF7L1, CSNK1D-JUN-TCF7L1, CSNK1D-FOXN1-TCF7, CSNK1D-JUN-TCF7, CSNK1D-GSK3A-TCF7L1 and CSNK1D-LRP6-TCF7. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

RANKING @ t_i USING HSIC - LINEAR												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1D-FGF4-SEN2	12	15434	36642	38886	8419	CSNK1D-FGF4-FOSL1	30	6054	51426	42593	32863	
CSNK1D-FGF4-TCF7L1	44	18859	55201	32920	17618	CSNK1D-FGF4-WNT5A	59	12095	43366	47094	42796	
CSNK1D-FGF4-WNT3A	62	3435	29950	56252	22054	CSNK1D-FGF4-LRP5	68	8358	23265	46644	15156	
CSNK1D-FGF4-PPP2R1A	72	17401	22364	53716	30729	CSNK1D-FGF4-WNT2B	82	23581	20638	52449	10903	
CSNK1D-FGF4-WNT4	98	6482	43663	41124	12062	CSNK1D-FGF4-SFRP1	103	1452	48498	52465	14299	
CSNK1D-FGF4-TCF7	114	16725	32161	19689	28545	CSNK1D-FGF4-SFRP4	120	325	44939	34338	20617	
CSNK1D-FGF4-RHO	137	7470	45846	49163	20155	CSNK1D-FGF4-FRAT1	154	4058	50213	49903	6296	
CSNK1D-FGF4-NLK	182	13641	35785	54873	12126	CSNK1D-FGF4-GSK3B	194	12598	37191	52378	26164	
CSNK1D-FGF4-LEF1	219	1576	38743	22056	7921	CSNK1D-FGF4-FZD7	220	17662	38625	44699	22997	
CSNK1D-PORCN-SEN2	254	26488	43944	21480	22511	CSNK1D-SFRP1-WNT2B	268	48716	36593	46538	17001	
AES-AXIN1-CSNK1D	336	51649	23870	47953	1427	CSNK1D-FOXN1-LEF1	437	1005	10226	23334	20989	
CSNK1D-FGF4-FZD8	505	12071	27989	37578	9827	CSNK1D-FZD2-LEF1	522	392	1270	40271	30141	
CSNK1D-FGF4-KREMEN1	529	10037	50110	50880	28493	CSNK1D-FSHB-LEF1	553	21733	36403	3295	16135	
CSNK1D-FOSL1-FZD1	568	999	47773	10250	51091	CSNK1D-PORCN-WNT2B	573	51683	44617	47981	16208	
CSNK1D-FOXN1-SEN2	624	4830	5783	7469	36423	CSNK1D-GSK3A-LEF1	723	313	2418	21648	1291	
CSNK1D-FGF4-WNT3	740	18961	36184	50414	8143	CSNK1D-FGF4-TLE1	799	22825	47823	41761	7069	
CSNK1D-JUN-LEF1	823	6859	47543	11454	29458	CSNK1D-PPP2R1A-WNT5A	992	931	1207	30631	56811	
FZD5-CCND3-CSNK1D	1013	2704	4480	48146	19	CSNK1D-PORCN-TLE2	1050	41629	52347	39317	20436	
CSNK1D-FGF4-FZD6	1063	5699	37365	32586	26789	CSNK1D-PORCN-TCF7	1115	16160	38935	28820	29405	
CSNK1D-FOXN1-KREMEN1	1122	3656	11331	13933	38262	CSNK1D-PPP2R1A-TCF7L1	1128	12625	3602	38061	56712	
CSNK1D-FOXN1-PPP2CA	1252	17427	16752	21509	34632	CSNK1D-CXXC4-FZD1	1263	2919	24873	24770	29960	
CSNK1D-FOXN1-WNT2B	1328	17615	2986	7052	5219	CSNK1D-CTNNB1-T	1338	17969	13628	49746	36181	
CSNK1D-FOXN1-FZD8	1359	10239	4066	27563	3347	CSNK1D-PPP2R1A-TCF7	1430	4169	153	38743	7414	
CSNK1D-FGF4-LRP6	1476	6459	24160	48759	14140	CSNK1D-PORCN-SLC9A3R1	1596	41508	51420	34746	16992	
CSNK1D-FGF4-SLC9A3R1	1680	16334	34504	26928	33064	CSNK1D-FOXN1-TCF7L1	1701	17694	5920	17923	11937	
CSNK1D-TLE1-TLE2	1724	21275	41549	44598	15361	CSNK1D-WNT1-WNT2B	1760	3377	3805	17345	50447	
CSNK1D-FOXN1-FZD7	1784	13446	5253	17028	40495	CSNK1D-FOXN1-MYC	1836	2577	20627	16019	40465	
CSNK1D-SFRP1-SFRP4	1855	34480	36277	39100	23037	CSNK1D-PORCN-SFRP1	1945	41776	54231	29005	26519	
CSNK1D-FGF4-PPP2CA	2103	20756	11349	39534	15407	CSNK1D-FOXN1-SLC9A3R1	2107	11939	2569	12418	40459	
CSNK1D-PORCN-FBXW4	2224	25065	31330	23189	19480	CSNK1D-JUN-TCF7L1	2260	26231	56724	39559	1567	
CSNK1D-FOXN1-FZD1	2304	904	14917	34472	44382	CSNK1D-FGF4-FSHB	2441	17927	45150	34061	11599	
CSNK1D-FZD6-SFRP4	2540	1448	2060	26618	40843	FZD5-CCND2-CSNK1D	2569	50084	31913	44030	55296	
CSNK1D-GSK3A-SFRP4	2717	1830	17275	20425	6307	CSNK1D-WNT3-WNT3A	2727	49625	22336	55596	44252	
CSNK1D-JUN-WNT3A	2740	3878	56083	44551	46162	CSNK1D-CXXC4-FRAT1	2744	18327	34701	8594	2661	
CSNK1D-NLK-WNT4	2750	2726	9906	45186	25621	CSNK1D-WNT1-WNT2	2884	830	8568	25186	5895	
CSNK1D-FOXN1-RHO	2891	4517	7734	29359	18640	CSNK1D-PORCN-PPP2R1A	2896	17111	34991	43683	19157	
CSNK1D-PORCN-WNT5A	2899	17376	34214	55252	32946	CSNK1D-FGF4-PYGO1	2967	23307	41918	28164	3925	
CSNK1D-GSK3A-SEN2	3013	17698	1355	31846	6960	CSNK1D-FOXN1-TCF7	3058	2324	2856	25009	48032	
CSNK1D-FGF4-PITX2	3093	11417	24874	53815	30793	CSNK1D-FGF4-WIF1	3202	18099	34798	40988	22019	
CSNK1D-FOXN1-LRP5	3219	4054	11922	50036	24583	CSNK1D-JUN-TCF7	3439	2738	31647	25028	51027	
CSNK1D-FOSL1-FRZB	3460	9515	54696	17041	40782	CSNK1D-GSK3A-WNT2B	3478	33755	3658	52438	24593	
CSNK1D-FRAT1-FZD1	3569	4219	52992	30046	47083	CSNK1D-WNT1-WNT4	3618	317	9161	25363	16241	
CSNK1D-NLK-WNT3A	3672	3466	7618	26301	5357	CSNK1D-GSK3A-WNT2	3764	1816	4728	34640	8679	
CSNK1D-FOXN1-PITX2	3778	6280	4678	21772	36345	CSNK1D-FOXN1-LRP6	3780	5416	14616	20732	36025	
CSNK1D-JUN-WNT2B	3782	39855	36594	49047	2280	BCL9-CSNK1D-DVL1	3917	28513	23552	3666	9410	
FZD5-CSNK1D-WNT5A	3923	32577	23307	47873	6444	CSNK1D-JUN-PYGO1	3934	1849	39438	23725	46933	
CSNK1D-SFRP1-WNT5A	3998	16473	29590	51130	13720	CSNK1D-JUN-SEN2	4050	19615	50185	29822	41231	
CSNK1D-GSK3A-PPP2CA	4064	22624	794	37163	9946	CSNK1D-FOXN1-GSK3B	4159	13828	5801	31044	53930	
CSNK1D-GSK3A-KREMEN1	4185	9426	5865	52232	3987	CCND3-CSNK1D-FGF4	4247	56969	5553	44696	25096	
BCL9-CSNK1D-FOSL1	4412	39895	11612	3219	55102	CSNK1D-FZD2-PPP2CA	4453	21686	1861	42323	46897	
CSNK1D-SFRP1-WNT3A	4551	19558	52514	48069	19184	CSNK1D-LRP6-RHO	4592	17007	12476	52979	3340	
CSNK1D-CTBP2-LEF1	4610	223	28103	22239	7005	BCL9-CSNK1D-SEN2	4632	37058	3181	4534	51855	
CSNK1D-FOXN1-WNT3A	4647	1495	8738	24005	46405	CSNK1D-DVL2-LEF1	4662	5034	10825	440	37937	
CSNK1D-JUN-TLE2	4736	22202	35404	30933	11826	CCND3-CSNK1D-WNT5A	4753	43030	22446	46977	51854	
CSNK1D-FOSL1-FZD7	4768	31561	48499	37364	37254	CSNK1D-NLK-SEN2	4773	12377	9957	43796	3597	
CSNK1D-SFRP1-TLE2	4922	46547	38030	46678	31499	CSNK1D-GSK3A-TCF7L1	5032	24389	11966	40967	20883	
CSNK1D-PITX2-SFRP4	5096	37446	11233	10582	41257	CSNK1D-FZD2-LRP5	5122	962	3101	54072	26208	
CSNK1D-GSK3A-RHO	5141	8223	4832	44949	10510	CSNK1D-CTNNB1-FRZB	5197	24993	56239	40597	28537	
CSNK1D-FGF4-MYC	5235	14215	44901	39123	23202	CSNK1D-JUN-WNT4	5251	20001	51942	21538	52316	
BCL9-CSNK1D-EP300	5259	34971	18070	4629	41428	CSNK1D-FOXN1-PPP2R1A	5317	3754	8571	14144	18670	
FZD5-CCND1-CSNK1D	5355	24059	52933	18167	50576	CSNK1D-FZD2-SFRP4	5362	1855	17483	13582	54971	
CSNK1D-FOXN1-WNT4	5440	3392	11967	26112	53280	APC-BTRC-CSNK1D	5442	10883	12646	22647	6204	
CSNK1D-CTBP2-SFRP4	5542	334	31924	37036	44498	CSNK1D-LRP6-TCF7	5593	12297	32989	31678	26667	

Table 5: Rankings of CSNK1D-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear

6.4.3. Examining the behaviour of PP2A-CSNK1D-X combinations

Looking at the tables above, one finds the following combinations for members of PPP2A family along with CSNK1D, to be prominent at 3rd order level - CSNK1D-FGF4-PPP2R1A, CSNK1D-FOXN1-PPP2CA, CSNK1D-FGF4-PPP2CA, CSNK1D-

RANKING @ t_i USING HSIC - RBF												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1D-FGF4-SEN2	2542	27165	19967	35638	32914	CSNK1D-FGF4-FOSL1	3694	6645	6799	4138	45840	
CSNK1D-FGF4-TCF7L1	4541	25809	20278	40264	36271	CSNK1D-FGF4-WNT5A	16991	26760	1497	11585	17580	
CSNK1D-FGF4-WNT3A	866	6634	43990	20734	56058	CSNK1D-FGF4-LRP5	8844	18263	430	12232	23605	
CSNK1D-FGF4-PPP2R1A	3004	29048	12442	15684	23801	CSNK1D-FGF4-WNT2B	2842	20288	7801	35728	43120	
CSNK1D-FGF4-WNT4	2044	17655	11902	17351	48590	CSNK1D-FGF4-SFRP1	17187	352	5460	18719	36092	
CSNK1D-FGF4-TCF7	2578	13286	34	28753	54402	CSNK1D-FGF4-SFRP4	6151	154	43125	29798	22993	
CSNK1D-FGF4-RHO	3836	6390	11977	25185	40250	CSNK1D-FGF4-FRAT1	4624	3572	29726	25608	46279	
CSNK1D-FGF4-NLK	5343	27561	8638	8497	51980	CSNK1D-FGF4-GSK3B	2870	6165	39093	37995	35649	
CSNK1D-FGF4-LEF1	16885	889	16278	22379	29256	CSNK1D-FGF4-FZD7	3708	1492	23721	12408	17016	
CSNK1D-PORCN-SEN2	5664	26748	24402	26200	37885	CSNK1D-SFRP1-WNT2B	7873	54928	11692	34070	52974	
AES-AXIN1-CSNK1D	33513	47832	7845	51708	6743	CSNK1D-FOXN1-LEF1	6150	3755	45826	20298	28446	
CSNK1D-FGF4-FZD6	1068	28301	13813	37144	30865	CSNK1D-FZD2-LEF1	38842	5216	13377	4337	12007	
CSNK1D-FGF4-KREMEN1	2147	22653	25065	18882	43497	CSNK1D-FSHB-LEF1	55374	14244	35230	8216	18460	
CSNK1D-FOSL1-FZD1	14359	1015	37515	5753	14234	CSNK1D-PORCN-WNT2B	8595	53305	9816	26691	42121	
CSNK1D-FOXN1-SEN2	1289	8520	39455	7070	25852	CSNK1D-GSK3A-LEF1	6720	14350	53714	3942	23987	
CSNK1D-FGF4-WNT3	2419	18531	38096	22623	37111	CSNK1D-FGF4-TLE1	1651	32994	23493	5014	41934	
CSNK1D-JUN-LEF1	20901	8723	38740	12713	27687	CSNK1D-PPP2R1A-WNT5A	27528	4279	14277	4265	42405	
FZD5-CCND3-CSNK1D	4293	24482	51150	40471	36385	CSNK1D-PORCN-TLE2	12595	39793	26325	7235	43651	
CSNK1D-FGF4-FZD6	6737	6408	6417	30228	39254	CSNK1D-PORCN-TCF7	4035	1408	266	23788	31209	
CSNK1D-FOXN1-KREMEN1	3060	1922	41865	30003	8137	CSNK1D-PPP2R1A-TCF7L1	34388	5648	48876	25681	52823	
CSNK1D-FGF4-PPP2CA	677	25144	54449	22625	44186	CSNK1D-CXXC4-FZD1	7144	1734	27303	7250	11481	
CSNK1D-FOXN1-WNT2B	2477	5135	39962	11954	23525	CSNK1D-CTNNB1-T	51919	2142	9666	39801	16008	
CSNK1D-FGF4-FZD8	484	13507	45944	36021	49258	CSNK1D-PPP2R1A-TCF7	34317	14103	3740	45791	33515	
CSNK1D-FGF4-LRP6	18101	5680	13351	25149	10621	CSNK1D-PORCN-SLC9A3R1	26693	34397	22670	453	31614	
CSNK1D-FGF4-SLC9A3R1	10617	29302	26992	4647	42618	CSNK1D-FOXN1-TCF7L1	1853	19094	49475	40364	5085	
CSNK1D-TLE1-TLE2	28280	37833	12666	39269	5835	CSNK1D-WNT1-WNT2B	3674	5014	26127	3017	32922	
CSNK1D-FOXN1-FZD7	2580	12602	43323	15316	39137	CSNK1D-FOXN1-MYC	463	3569	42774	40411	28606	
CSNK1D-SFRP1-SFRP4	5865	32490	29157	40625	43609	CSNK1D-PORCN-SFRP1	36889	38723	2444	15209	50430	
CSNK1D-FGF4-PPP2CA	3187	47005	13018	23779	39413	CSNK1D-FOXN1-SLC9A3R1	9628	8268	42958	15342	21726	
CSNK1D-PORCN-FBXW4	5373	20376	20328	22365	50987	CSNK1D-JUN-TCF7L1	22113	18400	27177	33962	5630	
CSNK1D-FOXN1-FZD1	186	1437	42030	14270	8269	CSNK1D-FGF4-FSHB	8876	10878	93	40281	25736	
CSNK1D-FZD6-SFRP4	28948	9871	56626	33341	10920	FZD5-CCND3-CSNK1D	2174	48901	29308	29035	26999	
CSNK1D-GSK3A-SFRP4	3312	9861	54850	25114	31433	CSNK1D-WNT3-WNT3A	4832	51374	56476	26830	11649	
CSNK1D-JUN-WNT3A	3991	7790	52423	12387	1862	CSNK1D-CXXC4-FRAT1	14134	8276	23947	22453	12908	
CSNK1D-NLK-WNT4	1538	21775	47534	6449	28873	CSNK1D-WNT1-WNT2	3841	8374	55936	27925	28491	
CSNK1D-FOXN1-RHO	3693	1529	28226	32793	21419	CSNK1D-PORCN-PPP2R1A	16940	28022	22571	2476	54099	
CSNK1D-PORCN-WNT5A	17071	12074	1312	10487	50936	CSNK1D-FGF4-PYGO1	35224	24194	35705	42726	4974	
CSNK1D-GSK3A-SEN2	679	19695	54356	47357	23687	CSNK1D-FOXN1-TCF7	526	3006	24338	37412	29080	
CSNK1D-FGF4-PITX2	21808	22200	7826	55044	47261	CSNK1D-FGF4-WIF1	2570	27850	35517	16644	26870	
CSNK1D-FOXN1-LRP5	3643	4399	15957	9681	3346	CSNK1D-JUN-TCF7	19796	346	649	20621	7941	
CSNK1D-FOSL1-FRZB	19966	5694	21191	35654	5540	CSNK1D-GSK3A-WNT2B	537	38319	50713	23870	15104	
CSNK1D-FRAT1-FZD1	30515	10291	41362	5174	7792	CSNK1D-WNT1-WNT4	2475	13139	28187	2712	22029	
CSNK1D-NLK-WNT3A	12770	9632	43802	42949	37641	CSNK1D-GSK3A-WNT2	1633	16051	53761	28401	27543	
CSNK1D-FOXN1-PITX2	11143	1695	49037	55776	7145	CSNK1D-FOXN1-LRP6	13480	3544	42500	13963	13814	
CSNK1D-JUN-WNT2B	36826	33885	13766	40492	6501	BCL9-CSNK1D-DVL1	43892	32546	30461	1264	19067	
FZD5-CSNK1D-WNT5A	10782	25515	25535	29067	55122	CSNK1D-JUN-PYGO1	46732	424	46278	41608	30058	
CSNK1D-SFRP1-WNT5A	7931	18053	3281	19001	33260	CSNK1D-JUN-SEN2	2653	23718	38996	40186	21869	
CSNK1D-GSK3A-PPP2CA	1046	40897	47094	14850	34061	CSNK1D-FOXN1-GSK3B	1758	13445	40737	47921	44449	
CSNK1D-GSK3A-KREMEN1	1238	5197	49343	17131	39680	CCND3-CSNK1D-FGF4	53833	56236	13403	31362	5509	
BCL9-CSNK1D-FOSL1	47904	42624	47654	3433	45846	CSNK1D-FZD2-PPP2CA	3053	36451	19189	15273	40108	
CSNK1D-SFRP1-WNT3A	1694	2663	18831	24025	39031	CSNK1D-LRP6-RHO	9238	26733	38518	37191	35303	
CSNK1D-CTBP2-LEF1	8883	17823	28631	13435	18163	BCL9-CSNK1D-SEN2	44308	43457	33874	30051	32611	
CSNK1D-FOXN1-WNT3A	174	2450	50841	26734	14997	CSNK1D-DVL2-LEF1	53540	4763	36760	14495	51756	
CSNK1D-JUN-TLE2	17254	7221	33658	28649	27279	CCND3-CSNK1D-WNT5A	26184	41606	8103	12634	19595	
CSNK1D-FOSL1-FZD7	39520	47576	23109	9945	26122	CSNK1D-NLK-SEN2	2789	23569	46292	12953	16278	
CSNK1D-SFRP1-TLE2	13034	42315	14660	41421	27119	CSNK1D-GSK3A-TCF7L1	789	29786	54140	26077	36093	
CSNK1D-PITX2-SFRP4	4175	45358	33459	4847	37993	CSNK1D-FZD2-LRP5	31249	14000	540	14876	15989	
CSNK1D-GSK3A-RHO	557	7015	53157	22185	43573	CSNK1D-CTNNB1-FRZB	15856	15227	48531	37431	9414	
CSNK1D-FGF4-MYC	4085	24182	15055	21582	25623	CSNK1D-JUN-WNT4	23623	7470	42887	14337	2015	
BCL9-CSNK1D-EP300	52623	25888	25234	6007	31047	CSNK1D-FOXN1-PPP2R1A	783	2341	30370	5693	20193	
FZD5-CCND1-CSNK1D	4682	17735	35223	18136	46595	CSNK1D-FZD2-SFRP4	8632	6917	25028	10001	13916	
CSNK1D-FOXN1-WNT4	712	1876	41088	1961	29254	APC-BTRC-CSNK1D	2236	12178	36083	5029	45903	
CSNK1D-CTBP2-SFRP4	5497	10895	29317	34539	10978	CSNK1D-LRP6-TCF7	5176	36559	1881	36347	12983	

Table 6: Rankings of CSNK1D-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf

GSK3A-PPP2CA, CSNK1D-PPP2R1A-WNT5A, CSNK1D-PPP2R1A-TCF7L1, CSNK1D-PPP2R1A-TCF7, CSNK1D-PORCN-PPP2R1A, CSNK1D-FZD2-PPP2CA and CSNK1D-FOXN1-PPP2R1A. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

RANKING @ t_i USING SOBOL - 2002												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1D-FGF4-SEN2	45011	27585	30267	41354	22081	CSNK1D-FGF4-FOSL1	31433	17351	34702	49796	3779	
CSNK1D-FGF4-TCF7L1	25851	23703	28531	9955	26240	CSNK1D-FGF4-WNT5A	27276	41074	28302	22360	34593	
CSNK1D-FGF4-WNT3A	26097	37629	27746	14081	26558	CSNK1D-FGF4-LRP5	2955	43397	25413	16078	42368	
CSNK1D-FGF4-PPP2R1A	16041	36350	23034	23038	36186	CSNK1D-FGF4-WNT2B	28074	51541	15533	12033	30048	
CSNK1D-FGF4-WNT4	31095	19365	29428	42965	30788	CSNK1D-FGF4-SFRP1	17254	46015	24945	24496	39736	
CSNK1D-FGF4-TCF7	47373	33208	33019	35060	24479	CSNK1D-FGF4-SFRP4	39876	11006	32217	32622	17395	
CSNK1D-FGF4-RHO	12115	29224	26900	15818	35002	CSNK1D-FGF4-FRAT1	43307	19656	33814	44501	13085	
CSNK1D-FGF4-NLK	11305	41185	24087	8932	35872	CSNK1D-FGF4-GSK3B	4128	7853	22532	14175	38412	
CSNK1D-FGF4-LEF1	35712	40912	31537	37596	9192	CSNK1D-FGF4-FZD7	38718	29241	32518	33630	10048	
CSNK1D-PORCN-SEN2	26180	49740	24174	6964	30394	CSNK1D-SFRP1-WNT2B	14464	28189	8702	8326	25216	
AES-AXIN1-CSNK1D	17614	20399	2658	23007	32892	CSNK1D-FOXN1-LEF1	18416	22419	26392	15687	40976	
CSNK1D-FGF4-FZD8	10015	39491	25159	24198	38526	CSNK1D-FZD2-LEF1	31519	19029	30167	30946	20994	
CSNK1D-FGF4-KREMEN1	21369	16424	25622	19556	47905	CSNK1D-FSHB-LEF1	17557	28861	26741	15958	23463	
CSNK1D-FOSL1-FZD1	33939	40307	29863	45255	32407	CSNK1D-PORCN-WNT2B	39627	20751	32331	36708	28715	
CSNK1D-FOXN1-SEN2	22145	41275	26967	5135	47598	CSNK1D-GSK3A-LEF1	36973	16169	28985	41996	5916	
CSNK1D-FGF4-WNT3	29097	5562	41695	44969	27058	CSNK1D-FGF4-TLE1	31338	33282	28628	47096	30909	
CSNK1D-JUN-LEF1	25658	26247	28008	9195	29514	CSNK1D-PPP2R1A-WNT5A	26135	44357	28294	20860	36948	
FZD5-CCND3-CSNK1D	46351	3330	50103	35023	9366	CSNK1D-PORCN-TLE2	40721	9512	29575	32383	21204	
CSNK1D-FGF4-FZD6	18376	27935	24677	23494	47063	CSNK1D-PORCN-TCF7	10132	38975	27387	12057	30165	
CSNK1D-FOXN1-KREMEN1	31821	16389	28671	30403	11306	CSNK1D-PPP2R1A-TCF7L1	25967	41054	27430	10798	32868	
CSNK1D-FOXN1-PPP2CA	18148	46116	27668	8407	45131	CSNK1D-CXXC4-FZD1	15838	20986	27843	15827	35450	
CSNK1D-FOXN1-WNT2B	34971	36541	30580	44435	4295	CSNK1D-CTNNB1-T	42761	39366	30573	52126	13625	
CSNK1D-FOXN1-FZD8	31892	7178	33756	49005	20364	CSNK1D-PPP2R1A-TCF7	41472	28978	28805	36435	24561	
CSNK1D-FGF4-LRP6	54180	13585	31741	41058	14672	CSNK1D-PORCN-SLC9A3R1	22475	41256	24969	21096	28384	
CSNK1D-FGF4-SLC9A3R1	43276	13827	31871	40076	15155	CSNK1D-FOXN1-TCF7L1	35334	23957	30050	36064	4998	
CSNK1D-TLE1-TLE2	19455	40358	5030	19470	26781	CSNK1D-WNT1-WNT2B	42719	30480	50555	50603	27503	
CSNK1D-FOXN1-FZD7	25311	49876	23413	8098	36669	CSNK1D-FOXN1-MYC	44307	29810	29915	52115	22248	
CSNK1D-SFRP1-SFRP4	32021	30603	35439	41782	29994	CSNK1D-PORCN-SFRP1	30977	7376	32969	50220	26759	
CSNK1D-FGF4-PPP2CA	45504	35247	32816	42764	13525	CSNK1D-FOXN1-SLC9A3R1	23368	50212	27896	7855	37916	
CSNK1D-PORCN-FBXW4	40912	20587	30104	44920	20175	CSNK1D-JUN-TCF7L1	40981	24954	29837	33199	13509	
CSNK1D-FOXN1-FZD1	36474	18523	28735	38842	16102	CSNK1D-FGF4-FSHB	37586	23188	30054	39574	14949	
CSNK1D-FZD6-SFRP4	37025	20562	29540	31061	17840	FZD5-CCND3-CSNK1D	39639	19905	41415	55029	16947	
CSNK1D-GSK3A-SFRP4	38998	40109	29848	46577	10900	CSNK1D-WNT3-WNT3A	36262	46174	50463	43303	12247	
CSNK1D-JUN-WNT3A	41685	14518	29055	33675	22133	CSNK1D-CXXC4-FRAT1	34042	35885	29812	41264	26139	
CSNK1D-NLK-WNT4	41521	25413	31966	31421	31114	CSNK1D-WNT1-WNT2	14398	26421	6595	6539	29319	
CSNK1D-FOXN1-RHO	31392	16873	29114	44729	3759	CSNK1D-PORCN-PPP2R1A	38585	10367	29409	42259	26713	
CSNK1D-PORCN-WNT5A	33173	15133	30807	39641	18354	CSNK1D-FGF4-PYGO1	41090	20740	34158	34168	20857	
CSNK1D-GSK3A-SEN2	45946	48851	30360	53837	19511	CSNK1D-FOXN1-TCF7	21839	33109	27126	21035	52156	
CSNK1D-FGF4-PITX2	45761	16034	33072	48233	21295	CSNK1D-FGF4-WIF1	34683	24427	28639	39649	25219	
CSNK1D-FOXN1-LRP5	38778	34796	30801	41436	16166	CSNK1D-JUN-TCF7	16160	32149	27332	23912	43544	
CSNK1D-FOSL1-FRZB	31318	38355	31685	44774	22524	CSNK1D-GSK3A-WNT2B	9527	37019	28419	11178	37958	
CSNK1D-FRAT1-FZD1	20960	29768	28275	10710	43347	CSNK1D-WNT1-WNT4	20721	8116	11826	6782	37040	
CSNK1D-NLK-WNT3A	15647	31281	25207	25693	26652	CSNK1D-GSK3A-WNT2	37628	15354	32710	30271	18583	
CSNK1D-FOXN1-PITX2	18384	31000	27911	15993	34137	CSNK1D-FOXN1-LRP6	12836	27102	27262	5010	34889	
CSNK1D-JUN-WNT2B	35800	33697	28958	34580	16565	BCL9-CSNK1D-DVL1	5169	2531	9866	16638	46496	
FZD5-CSNK1D-WNT5A	21298	15129	1430	366	40105	CSNK1D-JUN-PYGO1	24772	39437	27678	10274	47704	
CSNK1D-SFRP1-WNT5A	11269	25479	3686	15976	27188	CSNK1D-JUN-SEN2	19786	39894	26516	17689	39326	
CSNK1D-GSK3A-PPP2CA	38964	24815	30788	42585	4984	CSNK1D-FOXN1-GSK3B	33934	15919	31085	51592	27046	
CSNK1D-GSK3A-KREMEN1	20093	40861	28185	15145	51111	CCND3-CSNK1D-FGF4	25501	41888	19350	4356	36845	
BCL9-CSNK1D-FOSL1	10419	8445	20713	5953	54355	CSNK1D-FZD2-PPP2CA	40401	31133	29816	40542	23445	
CSNK1D-SFRP1-WNT3A	19952	32710	12566	7366	35990	CSNK1D-LRP6-RHO	34637	26415	30562	44183	17446	
CSNK1D-CTBP2-LEF1	35436	36626	30114	35212	1936	BCL9-CSNK1D-SEN2	7894	55225	16856	28157	9757	
CSNK1D-FOXN1-WNT3A	36731	14201	28962	47587	13902	CSNK1D-DVL2-LEF1	37733	42004	32019	35022	16190	
CSNK1D-JUN-TLE2	35323	15737	30487	31236	19521	CCND3-CSNK1D-WNT5A	26753	51792	5466	20864	48578	
CSNK1D-FOSL1-FZD7	25294	25065	27511	18532	28438	CSNK1D-NLK-SEN2	40143	16432	28881	34696	27936	
CSNK1D-SFRP1-TLE2	14852	25401	8318	13409	27386	CSNK1D-GSK3A-TCF7L1	23592	41249	27328	22703	35101	
CSNK1D-PITX2-SFRP4	26609	44292	24260	17256	33381	CSNK1D-FZD2-LRP5	21506	19923	24132	16640	35889	
CSNK1D-GSK3A-RHO	11202	8387	26821	3303	37553	CSNK1D-CTNNB1-FRZB	35537	12277	40549	47197	15377	
CSNK1D-FGF4-MYC	24133	31913	27203	19416	39013	CSNK1D-JUN-WNT4	24170	35809	26365	15414	39425	
BCL9-CSNK1D-EP300	3311	5825	20711	3984	45817	CSNK1D-FOXN1-PPP2R1A	39046	11003	29491	48744	12072	
FZD5-CCND1-CSNK1D	14887	40746	19201	997	4727	CSNK1D-FZD2-SFRP4	35660	24193	30365	46109	21000	
CSNK1D-FOXN1-WNT4	23873	38225	27206	12028	40601	APC-BTRC-CSNK1D	42702	43953	47146	33780	8438	
CSNK1D-CTBP2-SFRP4	35574	12520	29543	31811	17639	CSNK1D-LRP6-TCF7	14059	30348	28213	14212	32048	

Table 7: Rankings of CSNK1D-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - 2002

6.4.4. Examining the behaviour of LRP-CSNK1D-X combinations

Looking at the tables above, one finds the following combinations for members of LRP family along with CSNK1D, to be prominent at 3rd order level - CSNK1D-FGF4-LRP6, CSNK1D-FOXN1-LRP5, CSNK1D-FGF4-LRP5, CSNK1D-FOXN1-LRP6, CSNK1D-

RANKING @ t_i USING SOBOLE - MARTINEZ											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
CSNK1D-FGF4-SEN2	55119	28784	753	23302	53897	CSNK1D-FGF4-FOSL1	39220	16866	389	23848	23132
CSNK1D-FGF4-TCF7L1	40859	12468	13114	42874	33245	CSNK1D-FGF4-WNT5A	39875	34325	26022	14242	1408
CSNK1D-FGF4-WNT3A	11042	19248	28222	21505	8886	CSNK1D-FGF4-LRP5	44011	14327	27863	30216	18989
CSNK1D-FGF4-PPP2R1A	32236	18431	4861	24170	28783	CSNK1D-FGF4-WNT2B	11099	33067	21662	18628	9514
CSNK1D-FGF4-WNT4	30931	24624	1645	40905	44453	CSNK1D-FGF4-SFRP1	24988	7332	20614	11103	14523
CSNK1D-FGF4-TCF7	56903	23341	587	8096	54144	CSNK1D-FGF4-SFRP4	51948	20558	476	17213	54793
CSNK1D-FGF4-RHOU	25547	26286	25711	24726	4948	CSNK1D-FGF4-FRAT1	56865	12006	918	21628	54532
CSNK1D-FGF4-NLK	33940	4625	12426	23698	5080	CSNK1D-FGF4-GSK3B	37094	8199	21044	25936	22668
CSNK1D-FGF4-LEF1	50110	29395	2034	27280	54041	CSNK1D-FGF4-FZD7	54587	3593	2262	16940	46019
CSNK1D-PORCN-SEN2	1456	4258	8869	32822	29157	CSNK1D-SFRP1-WNT2B	45504	25704	37754	9982	35219
AES-AXIN1-CSNK1D	35852	3680	25566	9981	7313	CSNK1D-FOXN1-LEF1	32374	24326	23110	46046	3210
CSNK1D-FGF4-FZD8	23206	13656	45564	53305	9821	CSNK1D-FZD2-LEF1	29724	23302	1126	4556	23508
CSNK1D-FGF4-KREMEN1	24857	20786	27757	39745	8714	CSNK1D-FSHB-LEF1	19222	39228	21058	21493	6562
CSNK1D-FOSL1-FZD1	41680	37855	2054	46155	46394	CSNK1D-PORCN-WNT2B	54547	33746	2831	17934	52535
CSNK1D-FOSN1-SEN2	38843	9650	25689	48746	11032	CSNK1D-GSK3A-LEF1	27984	32214	780	18412	15578
CSNK1D-FGF4-WNT3	27141	43301	10716	18079	36761	CSNK1D-FGF4-TLE1	30313	3293	20586	21005	55995
CSNK1D-JUN-LEF1	36389	9478	48851	37502	3819	CSNK1D-PPP2R1A-WNT5A	34799	46397	27927	38367	6548
FZD5-CCND3-CSNK1D	24425	35427	11357	16458	13140	CSNK1D-PORCN-TLE2	53642	34642	1349	6256	56564
CSNK1D-FGF4-FZD6	25549	14281	21210	22546	3415	CSNK1D-PORCN-TCF7	25748	22359	21805	36766	4140
CSNK1D-FOXN1-KREMEN1	32146	2230	14527	12211	48112	CSNK1D-PPP2R1A-TCF7L1	1420	17934	41275	37855	4684
CSNK1D-FOSN1-PPP2CA	35792	53371	27044	46895	15279	CSNK1D-CXXC4-FZD1	28112	48535	48166	35007	4846
CSNK1D-FOXN1-WNT2B	40727	20657	11342	28759	54605	CSNK1D-CTNNB1-T	55697	37457	1377	24186	53282
CSNK1D-FOXN1-FZD8	40606	42498	22468	13908	52376	CSNK1D-PPP2R1A-TCF7	50128	22951	5812	8544	53759
CSNK1D-FGF4-LRP6	56364	10127	2296	23831	56682	CSNK1D-PORCN-SLC9A3R1	15731	15687	5737	23413	32643
CSNK1D-FGF4-SLC9A3R1	52818	9841	830	24865	56433	CSNK1D-FOXN1-TCF7L1	51221	5285	6459	25508	51438
CSNK1D-TLE1-TLE2	42315	43646	33134	2508	54333	CSNK1D-WNT1-WNT2B	31537	11063	42528	38828	9460
CSNK1D-FOXN1-FZD7	33029	31601	24563	26553	33641	CSNK1D-FOXN1-MYC	50924	26721	3557	20447	56671
CSNK1D-SFRP1-SFRP4	21268	21314	35721	28006	9257	CSNK1D-PORCN-SFRP1	18994	35477	42	21142	50577
CSNK1D-FGF4-PPP2CA	55329	26273	1032	21669	55925	CSNK1D-FOXN1-SLC9A3R1	33119	17256	36353	44743	32463
CSNK1D-PORCN-FBXW4	54457	32031	1944	26924	56516	CSNK1D-JUN-TCF7L1	48658	28221	1848	12654	36298
CSNK1D-FOXN1-FZD1	55202	51315	557	15388	55873	CSNK1D-FGF4-FSHB	53386	36653	4663	24262	56290
CSNK1D-FZD6-SFRP4	51105	5714	720	31166	44306	FZD5-CCND2-CSNK1D	7223	27121	23185	31108	21218
CSNK1D-GSK3A-SFRP4	47899	34099	4951	23576	49750	CSNK1D-WNT3-WNT3A	11520	29889	44430	29706	9625
CSNK1D-JUN-WNT3A	49779	33157	919	18538	52334	CSNK1D-CXXC4-FRAT1	18469	1863	38915	19191	36580
CSNK1D-NLK-WNT4	55088	4562	19617	29935	54873	CSNK1D-WNT1-WNT2	40567	28297	16569	6336	51007
CSNK1D-FOXN1-RHOU	34252	18639	2074	27005	35628	CSNK1D-PORCN-PPP2R1A	46494	24460	5959	26920	56966
CSNK1D-PORCN-WNT5A	22402	4216	2288	18135	42734	CSNK1D-FGF4-PYGO1	53782	7577	1845	21026	56561
CSNK1D-GSK3A-SEN2	52934	31036	1324	14474	42126	CSNK1D-FOXN1-TCF7	32381	26851	38448	50093	9452
CSNK1D-FGF4-PITX2	44579	43462	767	11821	46293	CSNK1D-FGF4-WIF1	43363	48941	1472	39959	56626
CSNK1D-FOXN1-LRP5	52584	42034	6817	14398	37913	CSNK1D-JUN-TCF7	22295	36468	17276	29939	515
CSNK1D-FOSL1-FRZB	41028	37740	6910	31880	54766	CSNK1D-GSK3A-WNT2B	28987	44289	19857	45245	10158
CSNK1D-FRAT1-FZD1	35866	8723	28263	47919	5986	CSNK1D-WNT1-WNT4	4934	23696	3275	40685	48358
CSNK1D-NLK-WNT3A	30261	5484	6297	36145	38245	CSNK1D-GSK3A-WNT2	44075	10874	7758	16421	56183
CSNK1D-FOSN1-PITX2	39725	19950	32730	49412	6271	CSNK1D-FOXN1-LRP6	42807	7879	23909	46855	44003
CSNK1D-JUN-WNT2B	41000	35594	890	25093	56672	BCL9-CSNK1D-DVL1	13131	24654	56866	21285	11397
FZD5-CSNK1D-WNT5A	22240	8729	8905	8361	14874	CSNK1D-JUN-PYGO1	5673	24084	17393	28564	30653
CSNK1D-SFRP1-WNT5A	46232	40726	39677	8395	43436	CSNK1D-JUN-SEN2	31303	34385	30502	38156	4556
CSNK1D-GSK3A-PPP2CA	49948	27496	4120	13149	30348	CSNK1D-FOXN1-GSK3B	44857	1620	1103	5943	42753
CSNK1D-GSK3A-KREMEN1	8331	36538	18893	45935	39059	CCND3-CSNK1D-FGF4	33645	25729	11171	4259	2969
BCL9-CSNK1D-FOSL1	6994	56975	54633	36841	20797	CSNK1D-FZD2-PPP2CA	49236	39754	539	34368	52220
CSNK1D-SFRP1-WNT3A	36490	53621	5052	7047	50254	CSNK1D-LRP6-RHOU	34336	2691	1633	17028	44197
CSNK1D-CTBP2-LEF1	48968	10726	6135	22249	56309	BCL9-CSNK1D-SEN2	7818	31418	33113	7222	1844
CSNK1D-FOXN1-WNT3A	47715	2711	5484	26364	53183	CSNK1D-DVL2-LEF1	49081	18658	2603	29361	56933
CSNK1D-JUN-TLE2	55996	3817	12011	19143	52700	CCND3-CSNK1D-WNT5A	36336	364	51360	31612	43178
CSNK1D-FOSL1-FZD7	32946	26115	27641	53780	8204	CSNK1D-NLK-SEN2	54274	1758	35987	36243	51006
CSNK1D-SFRP1-TLE2	41155	46372	37122	5380	40515	CSNK1D-GSK3A-TCF7L1	2372	2561	26389	42919	28709
CSNK1D-PITX2-SFRP4	783	12794	45331	28854	43563	CSNK1D-FZD2-LRP5	4958	19633	32139	50415	4916
CSNK1D-GSK3A-RHOU	16007	10231	17105	47130	31183	CSNK1D-CTNNB1-FRZB	51258	45759	3242	19204	39592
CSNK1D-FGF4-MYC	27747	53740	29653	32287	2134	CSNK1D-JUN-WNT4	28813	34671	41857	33835	1136
BCL9-CSNK1D-EP300	37357	52675	55940	48065	6089	CSNK1D-FOXN1-PPP2R1A	53170	6227	2620	23711	53082
FZD5-CCND1-CSNK1D	31474	38575	10040	10604	7111	CSNK1D-FZD2-SFRP4	51918	14988	1412	33035	37704
CSNK1D-FOXN1-WNT4	40130	54610	25402	49876	4689	APC-BTRC-CSNK1D	56835	26515	42490	50974	18375
CSNK1D-CTBP2-SFRP4	49397	12922	932	7503	56132	CSNK1D-LRP6-TCF7	31280	19096	22465	41381	4029

Table 8: Rankings of CSNK1D-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOLE; Implementation - martinez

LRP6-RHOU, CSNK1D-FZD2-LRP5, and CSNK1D-LRP6-TCF7. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.4.5. Examining the behaviour of CTNNB1-CSNK1D-X combinations

Looking at the tables above, one finds the following combinations for CTNNB1 along with CSNK1D, to be prominent at 3rd order level - CSNK1D-CTNNB1-T and CSNK1D-CTNNB1-FRZB. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.4.6. Examining the behaviour of APC-CSNK1D-X combinations

Looking at the tables above, one finds the following combinations for APC along with CSNK1D, to be prominent at 3rd order level - APC-BTRC-CSNK1D. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.5. Conserved machine learning rankings for tested CSNK1G1-X combinations

A total of 2415, 3rd order combinations involving CSNK1G1 were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 10, 11 and 12 show the rankings for the same combinations as in table 9, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

NOTE - We consider the same factors which acted in combination for CSNK1A1, in the previous sections, as we have evidence of literature that have verified the existence of combinatorial synergy with CSNK1A1. Here we see if there exists combinations for CSNK1G1, or not.

6.5.1. Examining the behaviour of DVL-CSNK1G1-X combinations

Looking at the tables above, one finds the following combinations for members of DVL family along with CSNK1G1, to be prominent at 3rd order level - CSNK1G1-DVL2-WNT2, CSNK1G1-DVL2-TCF7, CSNK1G1-DVL2-FBXW11, CSNK1G1-DVL2-TCF7L1, CSNK1G1-DVL2-TLE2, CSNK1G1-DVL2-SEN2, CSNK1G1-DVL2-FOSL1, CSNK1G1-DVL2-FZD1 and CSNK1G1-DVL2-FRZB. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.5.2. Examining the behaviour of TCF-CSNK1G1-X combinations

Looking at the tables above, one finds the following combinations for members of TCF family along with CSNK1G1, to be prominent at 3rd order level - CSNK1G1-DVL2-TCF7, CSNK1G1-NKD1-TCF7L1, CSNK1G1-FOXN1-TCF7L1, CSNK1G1-DVL2-TCF7L1, CSNK1G1-FZD1-TCF7L1, CSNK1G1-FGF4-TCF7L1, CSNK1G1-FOXN1-TCF7, CSNK1G1-NLK-TCF7L1, CSNK1G1-CTNNBIP1-TCF7L1, CSNK1G1-

RANKING @ t_1 USING HSIC - LINEAR												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1G1-NLK-SEN2	74	35675	3308	48520	19328	CSNK1G1-FOXN1-TLE2	226	3994	5316	18517	42187	
CSNK1G1-NLK-WNT4	321	20710	3312	50831	31403	CSNK1G1-FOXN1-KREMEN1	390	10815	10745	12917	12924	
CSNK1G1-FOXN1-SLC9A3R1	395	1314	2366	9985	14166	CSNK1G1-PORCN-SEN2	410	36322	35831	12245	17913	
CSNK1G1-FZD2-SEN2	430	26396	20526	35632	16355	CSNK1G1-FSHB-LEF1	506	19332	10676	684	44215	
CSNK1G1-DVL2-WNT2	512	22400	27124	6214	39864	CSNK1G1-FSHB-SFRP4	577	21679	6780	1575	25615	
CSNK1G1-FZD2-TLE2	600	1430	44384	54164	52337	CSNK1G1-DVL2-SEN2	708	9805	19546	23999	8201	
CSNK1G1-LRP5-SEN2	821	46576	17464	17352	30361	CSNK1G1-JUN-SEN2	855	23957	55112	11084	3256	
CSNK1G1-NKD1-PPP2CA	926	17356	35232	35369	12912	CSNK1G1-FZD2-FZD7	944	16232	24487	55399	23887	
CSNK1G1-FOXN1-PPP2R1A	960	4562	8931	10045	26824	CSNK1G1-CTNNB1P1-TCF7L1	999	13063	17121	18913	53234	
CSNK1G1-FGF4-TLE2	1023	22382	54317	54503	47054	CSNK1G1-FZD2-SFRP4	1035	1065	32773	38790	38245	
CSNK1G1-FSHB-SEN2	1054	47479	13640	1228	8996	CSNK1G1-DVL2-FOSL1	1061	14048	12622	34641	48959	
CSNK1G1-DVL2-TCF7	1070	8709	15200	25653	4958	CSNK1G1-FZD2-PPP2CA	1082	23722	6311	56537	35909	
CSNK1G1-JUN-WNT2	1087	1305	52762	5894	31347	CSNK1G1-CXXC4-FOSL1	1094	46700	26853	25310	54546	
CSNK1G1-CTNNB1P1-DKK1	1133	14650	36806	5792	53273	CSNK1G1-JUN-TCF7L1	1134	10933	47748	13909	25134	
CSNK1G1-FZD2-WNT2B	1144	10281	11030	49965	37172	CSNK1G1-CTNNB1P1-TLE2	1189	14302	22595	16694	56930	
CSNK1G1-FOXN1-TCF7L1	1194	9892	6186	28656	13545	CSNK1G1-FOXN1-FBXW4	1201	11491	20301	17590	26677	
CSNK1G1-DVL2-FBXW11	1204	11366	47774	39156	34516	CSNK1G1-GSK3B-SLC9A3R1	1210	17915	3146	1251	20930	
CSNK1G1-PGF4-KREMEN1	1239	30116	44329	46230	30098	CSNK1G1-NKD1-SEN2	1257	16631	15972	26700	19860	
CSNK1G1-FOXN1-TCF7L1	1281	8663	5550	16139	11644	CSNK1G1-T-TLE2	1289	7716	26938	1980	47468	
CSNK1G1-PORCN-TLE2	1291	31155	47884	19907	37757	CSNK1G1-PORCN-RHOU	1299	27191	33972	15284	20376	
CSNK1G1-JUN-TLE2	1365	2675	25875	17296	52928	CSNK1G1-NKD1-SFRP4	1474	513	13103	24557	6931	
CSNK1G1-FSHB-PPP2CA	1518	8523	49087	1235	27660	CSNK1G1-FOXN1-FRZB	1549	4678	4300	19697	7337	
CSNK1G1-JUN-KREMEN1	1571	14622	52390	27682	7035	CSNK1G1-FOXN1-RHOU	1587	4796	8477	31603	16974	
CSNK1G1-DVL2-TCF7L1	1594	26605	24282	21676	30138	CSNK1G1-SFRP1-WNT5A	1618	12629	47126	54603	30299	
CSNK1G1-NKD1-KREMEN1	1675	48319	35467	28250	6432	CSNK1G1-SFRP1-TLE2	1712	35952	51589	41916	56964	
CSNK1G1-JUN-FBXW4	1720	14629	26207	15285	48296	CSNK1G1-FZD1-SEN2	1791	37257	52309	26522	36929	
CSNK1G1-PORCN-SLC9A3R1	1815	10503	40046	19851	14743	CSNK1G1-CTNNB1-SEN2	1823	48308	39023	36622	2971	
CSNK1G1-CTNNB1-FBXW11	1832	37454	31263	43989	30890	CSNK1G1-CTNNB1-DAAMI	1863	29150	40706	29346	30532	
CSNK1G1-JUN-RHOU	1898	1165	55257	34817	23988	CSNK1G1-DVL2-FZD1	1899	31769	26103	8981	50719	
CSNK1G1-FZD1-TCF7L1	1928	14834	43931	28975	44251	CSNK1G1-FGF4-FOSL1	1936	28205	33826	36195	48093	
CSNK1G1-FZD2-WNT4	1942	1607	11956	46269	29169	CSNK1G1-FZD2-LEF1	1947	1417	8944	51456	47383	
CSNK1G1-GSK3A-TLE2	1958	19247	20416	54079	54261	CSNK1G1-FOXN1-FZD6	1966	10515	13241	17759	18874	
CSNK1G1-JUN-PPP2R1A	1986	10228	52696	13904	47706	CSNK1G1-JUN-PYGO1	2002	4879	55264	32395	18429	
CSNK1G1-DVL2-TLE2	2047	13079	24517	18237	55667	CSNK1G1-PORCN-TCF7L1	2073	14966	30891	15229	14200	
CSNK1G1-FGF4-SEN2	2112	49038	53530	48190	17709	CSNK1G1-JUN-TCF7	2167	22852	38657	32689	6608	
CSNK1G1-JUN-PPP2CA	2194	17201	31808	2244	24092	CSNK1G1-FZD1-FZD7	2236	8972	51512	19066	10647	
CSNK1G1-CSNK2A1-MYC	2268	42433	43512	35352	51992	CSNK1G1-PORCN-FBXW4	2284	27821	27627	9377	23266	
CSNK1G1-JUN-TCF7L1	2285	10862	41090	54745	25393	CSNK1G1-FGF4-FBXW4	2297	23073	41204	39779	38778	
CSNK1G1-FOXN1-TCF7	2327	21226	4505	21767	3917	CSNK1G1-NKD1-RHOU	2328	3565	14141	34128	1880	
CSNK1G1-FZD2-FZD8	2338	18572	33760	38917	40049	CSNK1G1-JUN-WNT2B	2402	5466	39576	33692	34944	
CSNK1G1-NLK-TCF7L1	2409	13940	8988	50696	40050	CSNK1G1-FZD2-SLC9A3R1	2430	12072	31728	53760	44963	
CSNK1G1-GSK3B-LRP6	2470	3965	12186	1024	16413	CSNK1G1-PORCN-WNT2B	2472	8559	45236	34464	18734	
CSNK1G1-CXXC4-DKK1	2488	45829	37872	27388	55403	CSNK1G1-CXXC4-FRAT1	2496	24384	49297	7946	49881	
CSNK1G1-FGF4-PPP2R1A	2535	19539	51865	57137	46652	CSNK1G1-WIF1-WNT2B	2561	1995	24404	34807	53934	
CSNK1G1-WIF1-WNT4	2582	628	24563	33380	53761	CSNK1G1-DIXDC1-WNT2B	2602	9079	34225	44850	51306	
CSNK1G1-T-WNT2B	2676	4730	9390	14824	25293	CSNK1G1-T-TCF7L1	2695	8773	21250	845	15712	
CSNK1G1-PORCN-PPP2R1A	2697	18740	49826	20704	24737	CSNK1G1-PORCN-WNT5A	2747	5935	22657	45224	29673	
CSNK1G1-PORCN-SFRP1	2795	18557	36114	17627	42050	CSNK1G1-DVL2-FRZB	2830	11776	15278	32095	12867	
CSNK1G1-JUN-SLC9A3R1	2848	7013	49399	24901	32991	CSNK1G1-JUN-WNT4	2974	622	48857	6464	4596	
CSNK1G1-FSHB-MYC	2987	47541	16749	1201	23454	CSNK1G1-NLK-WNT2B	3057	20612	364	49392	38971	
CSNK1G1-JUN-WNT5A	3068	8191	56989	38952	10438	CSNK1G1-SFRP1-WNT2B	3077	12559	37776	32807	54829	
CSNK1G1-PGF4-FRAT1	3087	3833	51164	49600	29524	CSNK1G1-CTNNB1-FRZB	3107	38284	22901	35739	3612	
CSNK1G1-CTBP2-DKK1	3146	194	46088	31304	49535	CSNK1G1-GSK3B-RHOU	3190	3405	4726	1433	8406	
CSNK1G1-CTBP2-SLC9A3R1	3240	166	52122	36860	45086	CSNK1G1-DIXDC1-RHOU	3247	13611	55894	17887	29476	
CSNK1G1-GSK3A-RHOU	3261	12094	4223	43874	25027	CSNK1G1-FZD2-WNT5A	3333	14640	38705	56952	5899	
CSNK1G1-CTNNB1P1-FOSL1	3338	21173	6659	21711	53461	CSNK1G1-FSHB-WNT2B	3357	9060	28997	6593	37362	
APC-CSNK1G1-FZD1	3390	30189	28290	1457	54900	CSNK1G1-PORCN-WNT2	3410	20366	30313	12508	34531	
CSNK1G1-CTNNB1P1-FBXW11	3415	22265	9012	12002	52077	CSNK1G1-DIXDC1-DKK1	3474	22358	26349	38523	54006	
CSNK1G1-FOXN1-FZD1	3475	2066	8269	14457	23102	CSNK1G1-FGF4-SFRP1	3511	22139	54017	39144	48106	
CSNK1G1-NKD1-WNT2	3527	1109	9218	26094	482	CSNK1G1-JUN-SFRP4	3548	4317	53039	9482	18106	
CSNK1G1-PGF4-SLC9A3R1	3554	8200	55502	49949	42703	CSNK1G1-PYGO1-TLE2	3565	24569	56894	5227	16188	
CSNK1G1-PGF4-WNT4	3583	9743	47387	43850	34383	CSNK1G1-FOXN1-WNT3A	3634	7199	9792	30313	10861	
CSNK1G1-FSHB-T	3636	19798	35345	312	15515	CSNK1G1-GSK3A-SEN2	3671	35222	2760	48687	25616	

Table 9: Rankings of CSNK1G1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear

JUN-TCF7L1, CSNK1G1-PORCN-TCF7L1, CSNK1G1-JUN-TCF7 and CSNK1G1-T-TCF7L1. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

RANKING @ t_i USING HSIC - RBF												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1G1-NLK-SEN2	34480	34469	25805	4202	8014	CSNK1G1-FOXN1-TLE2	3512	4562	37294	11299	13219	
CSNK1G1-NLK-WNT4	37117	32429	26444	1650	27288	CSNK1G1-FOXN1-KREMEN1	7103	1710	43024	36832	31611	
CSNK1G1-FOXN1-SLC9A3R1	4227	955	39936	15459	33468	CSNK1G1-PORCN-SEN2	13585	41454	10606	1967	17443	
CSNK1G1-FZD2-SEN2	16568	22383	10213	6975	36119	CSNK1G1-FSHB-LEF1	46458	5148	44690	1362	34271	
CSNK1G1-DVL2-WNT2	26581	25977	21694	30622	18019	CSNK1G1-FSHB-SFRP4	49673	9604	39425	16774	51741	
CSNK1G1-FZD2-TLE2	14214	390	12996	12800	24140	CSNK1G1-DVL2-SEN2	10060	33044	6346	24081	29517	
CSNK1G1-LRP5-SEN2	14135	47074	22615	10563	18356	CSNK1G1-JUN-SEN2	2057	43819	27038	14070	17638	
CSNK1G1-NKD1-PPP2CA	8799	37693	42013	33688	15900	CSNK1G1-FZD2-FZD7	21108	3606	11500	6373	21026	
CSNK1G1-FOXN1-PPP2R1A	3415	1125	22606	474	39586	CSNK1G1-CTNNB1P1-TCF7L1	43171	9916	19650	22573	25909	
CSNK1G1-FGF4-TLE2	12643	19305	27429	4012	34111	CSNK1G1-FZD2-SFRP4	27829	5976	9290	19601	31081	
CSNK1G1-FSHB-SEN2	41253	35360	30966	2443	33408	CSNK1G1-DVL2-FOSL1	24608	32567	25022	2699	31491	
CSNK1G1-DVL2-TCF7	15740	15189	43760	1824	49105	CSNK1G1-FZD2-PPP2CA	21192	37740	25191	13344	44898	
CSNK1G1-JUN-WNT2	10147	5580	32401	33214	37290	CSNK1G1-CXXC4-FOSL1	18872	46435	17556	11771	54033	
CSNK1G1-CTNNB1P1-DKK1	45274	12532	2085	28807	30170	CSNK1G1-JUN-TCF7L1	827	11310	28918	27910	3674	
CSNK1G1-FZD2-WNT2B	31344	5642	34740	5475	23273	CSNK1G1-CTNNB1P1-TLE2	43515	18510	14805	25265	22352	
CSNK1G1-NKD1-TCF7L1	6006	22577	49200	31622	30401	CSNK1G1-FOXN1-FBXW4	6456	4971	6852	14306	22075	
CSNK1G1-DVL2-FBXW11	14851	14553	29808	12160	18195	CSNK1G1-GSK3B-SLC9A3R1	24505	22540	7318	7896	7232	
CSNK1G1-PORCN-KREMEN1	12312	33122	8653	27029	51700	CSNK1G1-NKD1-SEN2	4079	7354	54740	12528	13804	
CSNK1G1-FOXN1-TCF7L1	2258	13561	45680	37954	10050	CSNK1G1-TLE2	15349	28608	40369	17566	47898	
CSNK1G1-PORCN-TLE2	25416	24850	21439	2281	53031	CSNK1G1-PORCN-RHOU	18456	21677	26712	34529	54262	
CSNK1G1-JUN-TLE2	3633	15390	39684	2796	27092	CSNK1G1-NKD1-SFRP4	10332	8994	35937	45547	19919	
CSNK1G1-FSHB-PPP2CA	50070	6934	23453	5427	21042	CSNK1G1-FOXN1-FRZB	4205	5593	40227	150	17600	
CSNK1G1-JUN-KREMEN1	6491	2240	25073	41585	18357	CSNK1G1-FOXN1-RHOU	5126	2277	43717	34280	32087	
CSNK1G1-DVL2-TCF7L1	8430	32795	20312	16548	46597	CSNK1G1-SFRP1-WNT5A	26848	12013	30115	7944	48214	
CSNK1G1-CTNNB1-KREMEN1	12259	40883	18405	45871	37363	CSNK1G1-SFRP1-TLE2	38330	13700	14458	10263	44078	
CSNK1G1-JUN-FBXW4	6418	15849	3058	18441	29387	CSNK1G1-FZD1-SEN2	32058	40787	30927	4374	20821	
CSNK1G1-PORCN-SLC9A3R1	33423	29599	9114	6260	50642	CSNK1G1-CTNNB1-SEN2	8473	45202	18386	8358	20498	
CSNK1G1-CTNNB1-FBXW11	8081	32056	33348	27118	24593	CSNK1G1-CTNNB1-DAAM1	13837	35555	36581	34030	48851	
CSNK1G1-JUN-RHOU	2915	263	26104	42711	34946	CSNK1G1-DVL2-FZD1	5036	24181	26002	2834	17734	
CSNK1G1-FZD1-TCF7L1	26757	20001	35110	22673	40307	CSNK1G1-FGF4-FOSL1	30497	29781	8021	11753	43558	
CSNK1G1-FZD2-WNT4	13040	11367	14247	4325	36477	CSNK1G1-FZD2-LEF1	37628	651	37780	9885	25711	
CSNK1G1-GSK3A-TLE2	21880	3846	34786	4128	44853	CSNK1G1-FOXN1-FZD6	9597	4725	31350	6692	33022	
CSNK1G1-JUN-PPP2R1A	2410	8342	5954	20586	31871	CSNK1G1-JUN-PYGO1	17775	1546	36260	46060	22759	
CSNK1G1-DVL2-TLE2	25707	7774	19195	28772	13026	CSNK1G1-PORCN-TCF7L1	19446	5592	14959	30431	50377	
CSNK1G1-FGF4-SEN2	4616	45273	3041	10902	17063	CSNK1G1-JUN-TCF7	2531	27001	37335	13108	9426	
CSNK1G1-JUN-PPP2CA	3740	31530	16470	29436	25461	CSNK1G1-FZD1-FZD7	42202	2356	44114	48791	35670	
CSNK1G1-CSNK2A1-MYC	46238	56607	42725	857	38125	CSNK1G1-PORCN-FBXW4	10477	26670	1604	31235	52570	
CSNK1G1-FGF4-TCF7L1	3125	11336	9840	33926	40511	CSNK1G1-FGF4-FBXW4	20873	40154	1525	33082	24319	
CSNK1G1-FOXN1-TCF7	6103	15997	49902	11757	46472	CSNK1G1-NKD1-RHOU	7968	13163	45029	45281	48042	
CSNK1G1-FZD2-FZD8	22757	27942	6185	40310	30385	CSNK1G1-JUN-WNT2B	7913	15753	39919	50228	16435	
CSNK1G1-NLK-TCF7L1	38665	6811	44713	7792	48500	CSNK1G1-FZD2-SLC9A3R1	28704	8977	9734	10319	26207	
CSNK1G1-GSK3B-LRP6	44943	8879	13860	8331	10201	CSNK1G1-PORCN-WNT2B	15765	2688	26141	22189	56019	
CSNK1G1-CXXC4-DKK1	18870	49739	2762	48160	29218	CSNK1G1-CXXC4-FRAT1	10676	6045	28407	52045	39223	
CSNK1G1-FGF4-PPP2R1A	8938	29139	2598	16353	38899	CSNK1G1-WIF1-WNT2B	38910	5666	25272	47015	36127	
CSNK1G1-WIF1-WNT4	16896	27273	7830	48279	26589	CSNK1G1-DIXDC1-WNT2B	56105	5718	34204	36658	46240	
CSNK1G1-T-WNT2B	7308	15374	20596	23413	32785	CSNK1G1-T-TCF7L1	2357	14811	41736	25166	36605	
CSNK1G1-PORCN-PPP2R1A	16024	19421	9392	5370	55173	CSNK1G1-PORCN-WNT5A	8541	17540	20517	6560	46815	
CSNK1G1-PORCN-SFRP1	27236	23068	16848	13318	54516	CSNK1G1-DVL2-FRZB	11203	3943	12156	18643	14086	
CSNK1G1-JUN-SLC9A3R1	8199	8824	12860	16832	13385	CSNK1G1-JUN-WNT4	3575	5	23478	28885	6190	
CSNK1G1-FSHB-MYC	43747	46283	35580	1289	17413	CSNK1G1-NLK-WNT2B	53434	5922	42619	33337	50690	
CSNK1G1-JUN-WNT5A	1627	9471	37716	21278	33763	CSNK1G1-SFRP1-WNT2B	46506	17719	30569	35787	55375	
CSNK1G1-FGF4-FRAT1	3622	6775	28403	42516	41038	CSNK1G1-CTNNB1-FRZB	9877	40304	14569	3677	31442	
CSNK1G1-CTBP2-DKK1	12379	37559	2412	41433	4051	CSNK1G1-GSK3B-RHOU	31434	1254	24292	12304	14579	
CSNK1G1-CTBP2-SLC9A3R1	25333	8891	16800	22800	25629	CSNK1G1-DIXDC1-RHOU	49459	11518	16506	41618	49774	
CSNK1G1-GSK3A-RHOU	19387	9576	34864	29016	31935	CSNK1G1-FZD2-WNT5A	20419	29433	26502	7708	18760	
CSNK1G1-CTNNB1P1-FOSL1	35395	8179	16803	17088	24295	CSNK1G1-FSHB-WNT2B	43414	19138	41449	6694	6668	
APC-CSNK1G1-FZD1	7749	26824	42227	42495	14246	CSNK1G1-PORCN-WNT2	21543	32722	24973	9534	56929	
CSNK1G1-CTNNB1P1-FBXW11	40429	22735	27221	29186	11089	CSNK1G1-DIXDC1-DKK1	26769	29764	1454	44361	36145	
CSNK1G1-FOXN1-FZD1	1030	2372	37367	366	6405	CSNK1G1-FGF4-SFRP1	15656	24142	6725	14523	42132	
CSNK1G1-NKD1-WNT2	6387	6428	51082	8449	39348	CSNK1G1-JUN-SFRP4	6927	6984	24622	46197	4920	
CSNK1G1-FGF4-SLC9A3R1	10241	16030	4176	25778	44518	CSNK1G1-PYGO1-TLE2	21495	24434	29013	7562	53728	
CSNK1G1-FGF4-WNT4	8298	17662	14155	26871	50395	CSNK1G1-FOXN1-WNT3A	7916	4786	40233	7694	33821	
CSNK1G1-FSHB-T	51659	22786	44198	2191	56498	CSNK1G1-GSK3A-SEN2	17955	35543	38041	9692	22046	

Table 10: Rankings of CSNK1G1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf

6.5.3. Examining the behaviour of PPP2A-CSNK1G1-X combinations

Looking at the tables above, one finds the following combinations for members of PPP2A family along with CSNK1G1, to be prominent at 3rd order level - CSNK1G1-NKD1-PPP2CA, CSNK1G1-FOXN1-PPP2R1A, CSNK1G1-FSHB-PPP2CA, CSNK1G1-JUN-PPP2R1A, CSNK1G1-JUN-PPP2CA, CSNK1G1-FGF4-PPP2R1A, CSNK1G1-

RANKING @ t_1 USING SOBOL - 2002											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
CSNK1G1-NLK-SEN2	14817	11675	2225	15674	28868	CSNK1G1-FOXN1-TLE2	21537	42757	2336	15141	32041
CSNK1G1-NLK-WNT4	7646	8437	104	10192	43063	CSNK1G1-FOXN1-KREMEN1	12568	9848	1206	5693	56612
CSNK1G1-FOXN1-SLC9A3R1	29604	29598	56041	56960	9679	CSNK1G1-PORCN-SEN2	43281	37454	56745	49095	6460
CSNK1G1-FZD2-SEN2	11142	28642	7792	15597	42963	CSNK1G1-FSHB-LEF1	38254	27148	47701	53981	4899
CSNK1G1-DVL2-WNT2	27910	12643	15697	4994	46665	CSNK1G1-FSHB-SFRP4	49169	3805	44567	32085	3551
CSNK1G1-FZD2-TLE2	42543	28177	42687	36354	12646	CSNK1G1-DVL2-SEN2	22798	50683	12430	15447	46966
CSNK1G1-LRP5-SEN2	20952	26227	18132	5105	9267	CSNK1G1-JUN-SEN2	49955	51075	54767	43231	2180
CSNK1G1-NKD1-PPP2CA	2818	12720	1066	16639	39238	CSNK1G1-FZD2-FZD7	7158	42378	658	9668	56103
CSNK1G1-FOXN1-PPP2R1A	26102	33906	21109	71	51037	CSNK1G1-CTNNB1P1-TCF7L1	28112	7321	13375	27783	55812
CSNK1G1-FGF4-TLE2	38171	54018	38464	53649	27611	CSNK1G1-FZD2-SFRP4	23075	10268	7269	4789	48739
CSNK1G1-FSHB-SEN2	47318	7617	44202	35329	27387	CSNK1G1-DVL2-FOSL1	13304	16111	11364	20166	55668
CSNK1G1-DVL2-TCF7	22581	2224	18751	13174	56823	CSNK1G1-FZD2-PPP2CA	7371	1821	2940	12583	54147
CSNK1G1-JUN-WNT2	43215	54139	50622	48011	1250	CSNK1G1-CXXC4-FOSL1	25168	1437	11571	16056	25721
CSNK1G1-CTNNB1P1-DKK1	12140	38448	9541	5556	54479	CSNK1G1-JUN-TCF7L1	6017	14337	20145	21380	48232
CSNK1G1-FZD2-WNT2B	43957	8905	55685	37469	3334	CSNK1G1-CTNNB1P1-TLE2	25127	3237	10881	7849	46732
CSNK1G1-NKD1-TCF7L1	44067	52737	54968	47023	15857	CSNK1G1-FOXN1-FBXW4	27569	27578	1117	197	47485
CSNK1G1-DVL2-FBXW11	32525	55485	49860	43897	62	CSNK1G1-GSK3B-SLC9A3R1	17837	1282	3936	19428	55642
CSNK1G1-FGF4-KREMEN1	49711	51438	57107	44900	43052	CSNK1G1-NKD1-SEN2	8054	22379	116	14940	56704
CSNK1G1-FOXN1-TCF7L1	24011	53828	1796	3138	42955	CSNK1G1-T-TLE2	33761	15546	56982	41993	4590
CSNK1G1-PORCN-TLE2	7372	47733	19657	27924	17147	CSNK1G1-PORCN-RHOU	13901	19785	413	8056	50675
CSNK1G1-JUN-TLE2	6833	1066	4928	11587	56004	CSNK1G1-NKD1-SFRP4	10766	6807	490	4170	32258
CSNK1G1-FSHB-PPP2CA	45864	55377	47231	36646	7302	CSNK1G1-FOXN1-FRZB	16921	42333	17206	26037	35243
CSNK1G1-JUN-KREMEN1	6923	4884	26325	13483	55790	CSNK1G1-FOXN1-RHOU	22734	36628	1885	6243	38820
CSNK1G1-DVL2-TCF7L1	34613	54955	38410	43971	335	CSNK1G1-SFRP1-WNT5A	30598	12429	52931	54526	8133
CSNK1G1-CTNNB1-KREMEN1	8399	6622	8923	3958	38591	CSNK1G1-SFRP1-TLE2	36104	28241	56956	55279	6687
CSNK1G1-JUN-FBXW4	13976	51841	1693	18282	49989	CSNK1G1-FZD1-SEN2	46940	54887	56179	52112	3649
CSNK1G1-PORCN-SLC9A3R1	33650	47676	46612	33574	30645	CSNK1G1-CTNNB1-SEN2	47712	45420	46499	43561	3144
CSNK1G1-CTNNB1-FBXW11	1940	20675	21938	18791	49322	CSNK1G1-CTNNB1-DAAM1	12750	37186	12892	1955	43684
CSNK1G1-JUN-RHOU	7215	6024	2384	13893	54958	CSNK1G1-DVL2-FZD1	35203	16601	30820	51262	6952
CSNK1G1-FZD1-TCF7L1	13950	21245	2033	8324	25283	CSNK1G1-FGF4-FOSL1	8963	28835	12476	27024	48361
CSNK1G1-FZD2-WNT4	7022	898	12245	15373	35027	CSNK1G1-FZD2-LEF1	13090	29157	20896	15256	44016
CSNK1G1-GSK3A-TLE2	43557	47135	32471	29032	1778	CSNK1G1-FOXN1-FZD6	15112	29912	14213	23427	38252
CSNK1G1-JUN-PPP2R1A	17390	9694	2316	9148	46335	CSNK1G1-JUN-PYGO1	39719	47416	54841	47973	10949
CSNK1G1-DVL2-TLE2	36214	52629	39421	48657	6369	CSNK1G1-PORCN-TCF7L1	8742	30765	16154	23864	24961
CSNK1G1-FGF4-SEN2	2157	16345	1663	19346	36353	CSNK1G1-JUN-TCF7	43538	48608	50508	47527	4924
CSNK1G1-JUN-PPP2CA	49728	12194	55667	43794	1187	CSNK1G1-FZD1-FZD7	42817	7109	51146	49529	157
CSNK1G1-CSNK2A1-MYC	18695	1708	3446	13091	35254	CSNK1G1-PORCN-FBXW4	23515	9545	10526	23569	26078
CSNK1G1-FGF4-TCF7L1	47918	55844	55366	54508	35878	CSNK1G1-FGF4-FBXW4	44225	4355	54630	48647	959
CSNK1G1-FOXN1-TCF7	34219	34310	44976	35510	7051	CSNK1G1-NKD1-RHOU	40596	5950	54719	48495	7475
CSNK1G1-FZD2-FZD8	50007	14985	56494	47469	1059	CSNK1G1-JUN-WNT2B	12092	24688	5587	16813	56343
CSNK1G1-NLK-TCF7L1	44331	44573	53183	44188	4910	CSNK1G1-FZD2-SLC9A3R1	21480	38407	5615	17975	40405
CSNK1G1-GSK3B-LRP6	6438	18957	418	9590	54912	CSNK1G1-PORCN-WNT2B	8407	8013	15451	27068	11666
CSNK1G1-CXXC4-DKK1	29722	16090	47827	56588	1654	CSNK1G1-CXXC4-FRAT1	27618	3778	3433	676	48257
CSNK1G1-FGF4-PPP2R1A	48874	4935	46376	33919	6326	CSNK1G1-WIF1-WNT2B	13733	56852	4680	24169	53252
CSNK1G1-WIF1-WNT4	53996	12035	47320	37468	7141	CSNK1G1-DIXDC1-WNT2B	12114	7749	26029	14404	44639
CSNK1G1-T-WNT2B	39877	28951	37196	37502	2391	CSNK1G1-T-TCF7L1	33501	6689	34325	48942	815
CSNK1G1-PORCN-PPP2R1A	15949	51267	916	23706	44599	CSNK1G1-PORCN-WNT5A	10356	8876	25975	28454	18185
CSNK1G1-PORCN-SFRP1	7246	7363	14462	20174	36420	CSNK1G1-DVL2-FRZB	30588	38887	41771	49656	1919
CSNK1G1-JUN-SLC9A3R1	43202	5406	55467	38845	7125	CSNK1G1-JUN-WNT4	33107	46065	50016	51102	7862
CSNK1G1-FSHB-MYC	10008	29873	20279	26881	48302	CSNK1G1-NLK-WNT2B	49065	6850	56800	44447	6716
CSNK1G1-JUN-WNT5A	21479	39247	6333	24156	52648	CSNK1G1-SFRP1-WNT2B	34525	31075	56473	56358	3840
CSNK1G1-FGF4-FRAT1	23308	12898	577	6288	40499	CSNK1G1-CTNNB1-FRZB	11010	41399	10677	9362	28958
CSNK1G1-CTBP2-DKK1	36737	50084	41906	46380	7431	CSNK1G1-GSK3B-RHOU	41655	54814	54139	46702	874
CSNK1G1-CTBP2-SLC9A3R1	2953	39509	10302	16583	49929	CSNK1G1-DIXDC1-RHOU	16058	1799	7780	18030	48278
CSNK1G1-GSK3A-RHOU	47412	26494	53128	51332	7632	CSNK1G1-FZD2-WNT5A	50135	56267	44911	41731	22635
CSNK1G1-CTNNB1P1-FOSL1	28695	47395	40486	51217	12008	CSNK1G1-FSHB-WNT2B	6562	41743	11739	18943	50322
APC-CSNK1G1-FZD1	32683	26130	40629	37958	20743	CSNK1G1-PORCN-WNT2	50216	4601	38088	29252	9325
CSNK1G1-CTNNB1P1-FBXW11	27997	6997	10059	3785	44390	CSNK1G1-DIXDC1-DKK1	5009	2538	5529	18100	16388
CSNK1G1-FOXN1-FZD1	11929	3765	872	10484	55805	CSNK1G1-FGF4-SFRP1	54991	41009	55503	37797	21039
CSNK1G1-NKD1-WNT2	15676	18894	5930	17029	46372	CSNK1G1-JUN-SFRP4	42953	29268	37702	44736	6880
CSNK1G1-FGF4-SLC9A3R1	7617	19617	897	10351	45255	CSNK1G1-PYGO1-TLE2	17136	9155	11518	17890	32040
CSNK1G1-FGF4-WNT4	18545	9815	5216	15463	13843	CSNK1G1-FOXN1-WNT3A	18175	14967	2698	926	50456
CSNK1G1-FSHB-T	6318	9942	3904	6835	49975	CSNK1G1-GSK3A-SEN2	9667	52049	9371	22981	45654

Table 11: Rankings of CSNK1G1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - 2002

PORCN-PPP2R1A and CSNK1G1-FZD2-PPP2CA. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

RANKING @ t_1 USING SOBOL - MARTINEZ												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1G1-NLK-SEN2	1023	28963	23752	12006	13662	CSNK1G1-FOXN1-TLE2	4073	26473	32009	15332	6483	
CSNK1G1-NLK-WNT4	9882	34667	14911	20141	31237	CSNK1G1-FOXN1-KREMEN1	4187	16379	10411	17376	49738	
CSNK1G1-FOXN1-SLC9A3R1	11281	33656	17132	33702	26731	CSNK1G1-PORCN-SEN2	15610	15039	24692	32268	17031	
CSNK1G1-FZD2-SEN2	23323	8023	15244	20763	9314	CSNK1G1-FSHB-LEF1	8757	48545	39614	32449	13625	
CSNK1G1-DVL2-WNT2	2134	29301	54842	50984	15101	CSNK1G1-FSHB-SFRP4	39476	50249	41873	33694	14579	
CSNK1G1-FZD2-TLE2	21805	41649	20523	9228	19247	CSNK1G1-DVL2-SEN2	2829	8071	56530	44158	5270	
CSNK1G1-LRP5-SEN2	430	22598	40400	16862	29795	CSNK1G1-JUN-SEN2	53562	32056	34894	40476	27708	
CSNK1G1-NKD1-PPP2CA	19784	21076	9213	14040	31099	CSNK1G1-FZD2-FZD7	20133	14733	25644	20740	34303	
CSNK1G1-FOXN1-PPP2R1A	2180	53719	33104	7285	38261	CSNK1G1-CTNNBIP1-TCF7L1	5806	12198	11262	5166	48378	
CSNK1G1-FGF4-TLE2	8296	22216	32082	2863	23370	CSNK1G1-FZD2-SFRP4	3975	35697	43472	32265	3691	
CSNK1G1-FSHB-SEN2	32972	50887	28581	8306	20113	CSNK1G1-DVL2-FOSL1	8083	52720	54665	44734	52383	
CSNK1G1-DVL2-TCF7	1931	11355	48637	47697	45338	CSNK1G1-FZD2-PPP2CA	6902	15684	9374	21259	4565	
CSNK1G1-JUN-WNT2	26112	36147	34970	53598	32760	CSNK1G1-CXXC4-FOSL1	3540	41011	53892	1277	30939	
CSNK1G1-CTNNBIP1-DKK1	3286	20741	29442	46391	49878	CSNK1G1-JUN-TCF7L1	20659	31359	42235	11222	25258	
CSNK1G1-FZD2-WNT2B	16988	38740	33148	19223	15749	CSNK1G1-CTNNBIP1-TLE2	3609	28632	45678	10368	21084	
CSNK1G1-NKD1-TCF7L1	25433	42313	19013	1420	12490	CSNK1G1-FOXN1-FBXW4	2305	4668	32121	14002	38175	
CSNK1G1-DVL2-FBXW11	18902	31099	45042	20063	7907	CSNK1G1-GSK3B-SLC9A3R1	13151	10808	29139	7865	15618	
CSNK1G1-FGF4-KREMEN1	23388	19547	27651	18744	8543	CSNK1G1-NKD1-SEN2	5658	19388	11502	16684	22979	
CSNK1G1-FOXN1-TCF7L1	20619	35523	15458	17164	22105	CSNK1G1-TLE2	21536	24813	30561	665	19587	
CSNK1G1-PORCN-TLE2	23956	39888	45808	29516	4037	CSNK1G1-PORCN-RHOU	156	28220	17621	19760	27625	
CSNK1G1-JUN-TLE2	3654	15612	6612	7680	23323	CSNK1G1-NKD1-SFRP4	3477	44788	33518	12420	52257	
CSNK1G1-FSHB-PPP2CA	40612	43508	22826	3439	25861	CSNK1G1-FOXN1-FRZB	757	4827	25287	8957	51220	
CSNK1G1-JUN-KREMEN1	21900	17437	22609	16420	7910	CSNK1G1-FOXN1-RHOU	2715	42081	23816	12990	28874	
CSNK1G1-DVL2-TCF7L1	35932	38409	51352	32104	7019	CSNK1G1-SFRP1-WNT5A	18728	41171	27916	27826	21302	
CSNK1G1-CTNNB1-KREMEN1	7668	39456	50237	10228	44604	CSNK1G1-SFRP1-TLE2	30635	31136	34280	5452	10126	
CSNK1G1-JUN-FBXW4	35891	19352	22587	4046	48570	CSNK1G1-FZD1-SEN2	44823	32702	37344	23873	20064	
CSNK1G1-PORCN-SLC9A3R1	9278	49182	53553	52071	36096	CSNK1G1-CTNNB1-SEN2	42637	17246	37340	28255	10424	
CSNK1G1-CTNNB1-FBXW11	47591	47761	24648	52706	42288	CSNK1G1-CTNNB1-DAAM1	640	14671	43332	53397	11882	
CSNK1G1-JUN-RHOU	22504	10065	14728	48707	5692	CSNK1G1-DVL2-FZD1	29822	52079	42226	21023	15435	
CSNK1G1-FZD1-TCF7L1	3657	17738	32058	2877	3452	CSNK1G1-FGF4-FOSL1	3966	11339	26512	6277	5337	
CSNK1G1-FZD2-WNT4	10410	34283	49819	8764	3839	CSNK1G1-FZD2-LEF1	25439	42050	48188	18015	7710	
CSNK1G1-GSK3A-TLE2	15953	48553	26146	34236	29429	CSNK1G1-FOXN1-FZD6	465	20038	14379	3608	44811	
CSNK1G1-JUN-PPP2R1A	23606	19004	7535	6758	46881	CSNK1G1-JUN-PYGO1	15049	21562	26708	38509	8167	
CSNK1G1-DVL2-TLE2	25461	39155	51026	50993	10360	CSNK1G1-PORCN-TCF7L1	22705	5536	55332	52452	7332	
CSNK1G1-FGF4-SEN2	15585	3966	9710	959	24750	CSNK1G1-JUN-TCF7	24936	47488	33304	8067	17856	
CSNK1G1-JUN-PPP2CA	52121	39360	27268	41319	22355	CSNK1G1-FZD1-FZD7	23551	51418	20988	43171	26341	
CSNK1G1-CSNK2A1-MYC	816	53067	52527	17682	54911	CSNK1G1-PORCN-FBXW4	5765	9868	51683	56209	13206	
CSNK1G1-FGF4-TCF7L1	41064	41146	28605	3115	12570	CSNK1G1-FGF4-FBXW4	24615	51440	29249	42766	24693	
CSNK1G1-FOXN1-TCF7	28811	39294	26956	517	23711	CSNK1G1-NKD1-RHOU	13195	46913	28099	45919	38961	
CSNK1G1-FZD2-FZD8	55692	33791	38801	40579	16150	CSNK1G1-JUN-WNT2B	6543	12806	10942	2276	34250	
CSNK1G1-NLK-TCF7L1	25249	40044	11018	25277	24236	CSNK1G1-FZD2-SLC9A3R1	72	11838	29010	16078	46306	
CSNK1G1-GSK3B-LRP6	38011	14409	17563	26578	29511	CSNK1G1-PORCN-WNT2B	28382	5688	53042	54668	30496	
CSNK1G1-CXXC4-DKK1	21335	46326	26057	31544	22681	CSNK1G1-CXXC4-FRAT1	2838	20322	35155	3949	37439	
CSNK1G1-FGF4-PPP2R1A	51350	42511	16585	6456	20879	CSNK1G1-WIF1-WNT2B	2279	53121	35371	56846	2011	
CSNK1G1-WIF1-WNT4	56789	43140	52845	54585	19132	CSNK1G1-DIXDC1-WNT2B	40930	25751	23698	20111	41840	
CSNK1G1-T-WNT2B	41593	45959	12146	13197	24503	CSNK1G1-T-TCF7L1	18966	48845	25610	157	14816	
CSNK1G1-PORCN-PPP2R1A	503	35730	3044	6124	43150	CSNK1G1-PORCN-WNT5A	46413	14655	30449	49521	13435	
CSNK1G1-JUN-SFRP1	28402	40020	24656	8442	10906	CSNK1G1-DVL2-FRZB	19883	55733	37226	45418	8700	
CSNK1G1-JUN-SLC9A3R1	29086	31057	29189	10809	56936	CSNK1G1-JUN-WNT4	7327	52583	35808	38813	18150	
CSNK1G1-FSHB-MYC	16803	10241	15398	7414	1214	CSNK1G1-NLK-WNT2B	51130	36723	22493	41024	14440	
CSNK1G1-JUN-WNT5A	90	18823	34308	8819	39419	CSNK1G1-SFRP1-WNT2B	25407	48375	4565	5611	20190	
CSNK1G1-FGF4-FRAT1	17863	11935	14252	19547	33993	CSNK1G1-CTNNB1-FRZB	2473	1895	48867	55068	18412	
CSNK1G1-CTBP2-DKK1	9933	53999	48020	51075	12322	CSNK1G1-GSK3B-RHOU	12634	48456	37726	40555	19173	
CSNK1G1-CTBP2-SLC9A3R1	10860	22491	33788	2639	39302	CSNK1G1-DIXDC1-RHOU	37350	50752	24433	17248	3736	
CSNK1G1-GSK3A-RHOU	38032	48019	31225	42299	34354	CSNK1G1-FZD2-WNT5A	47509	40249	19979	4150	23159	
CSNK1G1-CTNNBIP1-FOSL1	11949	32749	12277	6351	7950	CSNK1G1-FSHB-WNT2B	24679	21316	37424	4944	42965	
APC-CSNK1G1-FZD1	21185	37153	44	28557	44726	CSNK1G1-PORCN-WNT2	44086	52040	53679	46699	15576	
CSNK1G1-CTNNBIP1-FBXW11	8978	49664	28961	11257	11947	CSNK1G1-DIXDC1-DKK1	32455	51113	13061	32408	39336	
CSNK1G1-FOXN1-FZD1	5809	24046	13888	4092	54967	CSNK1G1-FGF4-SFRP1	54217	40967	27315	4034	12736	
CSNK1G1-NKD1-WNT2	584	24793	8285	23891	20671	CSNK1G1-JUN-SFRP4	18558	44438	31265	34955	26920	
CSNK1G1-FGF4-SLC9A3R1	3812	15818	13512	15179	25323	CSNK1G1-PYGO1-TLE2	6707	43365	50722	55108	11091	
CSNK1G1-FGF4-WNT4	2235	6629	11645	21643	241	CSNK1G1-FOXN1-WNT3A	8675	49134	21528	19393	15926	
CSNK1G1-FSHB-T	25656	40734	22557	25924	2702	CSNK1G1-GSK3A-SEN2	8587	27952	42504	7797	12650	

Table 12: Rankings of CSNK1G1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - martinez

6.5.4. Examining the behaviour of LRP-CSNK1G1-X combinations

Looking at the tables above, one finds the following combinations for members of LRP family along with CSNK1G1, to be prominent at 3rd order level - CSNK1G1-LRP5-SEN2 and CSNK1G1-GSK3B-LRP6. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.5.5. Examining the behaviour of CTNNB1-CSNK1G1-X combinations

Looking at the tables above, one finds the following combinations for CTNNB1 along with CSNK1G1, to be prominent at 3rd order level - CSNK1G1-CTNNBIP1-DKK1, CSNK1G1-CTNNBIP1-KREMEN1, CSNK1G1-CTNNBIP1-FBXW11, CSNK1G1-CTNNBIP1-FOSL1, CSNK1G1-CTNNBIP1-FBXW11, CSNK1G1-CTNNBIP1-TCF7L1, CSNK1G1-CTNNBIP1-TLE2, CSNK1G1-CTNNBIP1-SEN2, CSNK1G1-CTNNBIP1-DAAM1 and CSNK1G1-CTNNBIP1-FRZB. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.5.6. Examining the behaviour of APC-CSNK1G1-X combinations

Looking at the tables above, one finds the following combinations for APC along with CSNK1G1, to be prominent at 3rd order level - APC-CSNK1G1-FZD1. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.6. Conserved machine learning rankings for tested CSNK2A1-X-X combinations

A total of 2415, 3rd order combinations involving CSNK were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 14, 15 and 16 show the rankings for the same combinations as in table 13, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

NOTE - We consider the same factors which acted in combination for CSNK1A1, in the previous sections, as we have evidence of literature that have verified the existence of combinatorial synergy with CSNK1A1. Here we see if there exists combinations for CSNK2A1, or not.

6.6.1. Examining the behaviour of DVL-CSNK2A1-X combinations

Looking at the tables above, one finds the following combinations for members of DVL family along with CSNK2A1, to be prominent at 3rd order level - CSNK2A1-DVL1-SLC9A3R1, CSNK2A1-DVL1-FBXW2, CSNK2A1-DVL1-FBXW11, CSNK2A1-DVL1-RHOU, CSNK2A1-DVL1-LRP6, CSNK2A1-DVL1-GSK3B, CCND1-CSNK2A1-DVL1 and CSNK2A1-DVL1-FRZB. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.6.2. Examining the behaviour of TCF-CSNK2A1-X combinations

Looking at the tables above, one finds the following combinations for members of TCF family along with CSNK2A1, to be prominent at 3rd order level - CSNK2A1-FGF4-

RANKING @ t_1 USING HSIC - LINEAR												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK2A1-MYC-SEN2	13	32182	51840	11657	9637	CSNK2A1-MYC-SFRP4	47	31055	40259	11986	7067	
CSNK2A1-MYC-TCF7L1	101	9667	52256	6244	21089	AES-AXIN1-CSNK2A1	111	51086	31467	43677	53288	
CSNK2A1-T-WNT2B	184	3390	21468	32926	48474	CSNK2A1-MYC-PPP2CA	271	37740	40109	23353	26864	
CSNK2A1-CTBP1-PPP2R1A	386	22561	33967	27086	25647	CSNK2A1-MYC-WNT4	398	40617	54219	12588	16421	
CSNK2A1-MYC-TCF7	490	25022	47616	18968	2193	CSNK2A1-FSHB-SFRP4	494	33797	31035	11392	7911	
CSNK2A1-MYC-RHOU	501	22087	50879	39343	4386	CSNK2A1-T-TCF7	567	15581	6590	42077	18396	
CSNK2A1-MYC-FBXW4	629	27720	40567	7122	52935	CSNK2A1-MYC-WNT2B	662	17569	55958	14302	27991	
CSNK2A1-MYC-TLE1	666	29145	50817	19336	947	CSNK2A1-T-TCF7L1	733	7677	34582	23897	42465	
CSNK2A1-FOXN1-TCF7	736	11246	6655	11945	13187	CSNK2A1-MYC-SLC9A3R1	759	16558	36842	7846	26103	
CSNK2A1-FOXN1-WNT2B	1037	3175	7624	2538	6838	CSNK2A1-FOXN1-FZD8	1170	17750	11184	10347	9970	
CSNK2A1-FOXN1-SEN2	1233	22059	16672	4525	3145	CSNK2A1-FOXN1-FZD6	1295	29245	25754	7254	28379	
CSNK2A1-CTNNB1-FOSL1	1324	32995	31993	33693	996	CSNK2A1-T-WNT2	1378	11139	47594	23311	22414	
CSNK2A1-T-TLE2	1411	2405	38856	25977	54992	CSNK2A1-FOXN1-PPP2CA	1415	18676	25465	10950	9597	
CSNK2A1-MYC-PPP2R1A	1454	17389	25178	16938	14057	CSNK2A1-FOXN1-SFRP4	1460	20356	19876	8892	40	
CSNK2A1-FSHB-PPP2CA	1544	21794	56458	12205	17377	CSNK2A1-CTBP1-FOSL1	1581	35982	53710	47786	1954	
CSNK2A1-FSHB-WNT2B	1655	8809	48217	20614	27385	CSNK2A1-CTNNB1-TCF7	1672	33482	54660	18672	2657	
CSNK2A1-CTBP1-FZD7	1703	2164	17895	9233	54755	CSNK2A1-FOXN1-SLC9A3R1	1719	7183	9084	4971	10505	
CSNK2A1-FOXN1-PPP2R1A	1773	10252	16688	5889	9126	CSNK2A1-CTNNB1-SEN2	1797	31342	21961	12961	8045	
CSNK2A1-FGF4-PPP2R1A	1819	25704	42101	34434	17125	CSNK2A1-MYC-WNT5A	1924	52368	38656	2374	28977	
CSNK2A1-FOXN1-WNT2	2063	9719	17020	9242	1411	CSNK2A1-CTBP1-WNT2	2201	37870	53021	37011	1941	
CSNK2A1-MYC-WNT2	2230	32568	56908	16229	1729	CSNK1G1-CSNK2A1-MYC	2268	42433	43512	35352	51992	
CSNK2A1-GSK3A-SFRP4	2269	45426	45347	3867	25586	CSNK2A1-JUN-PITX2	2295	11006	48321	42767	19026	
CSNK2A1-CTNNB1-FRAT1	2318	44804	22708	39543	10094	FZD5-CSNK2A1-SEN2	2332	20735	12273	41393	25951	
CSNK2A1-FOXN1-PITX2	2356	10265	14777	12628	14201	CSNK2A1-CTNNB1-WNT4	2414	44132	33116	25592	4111	
CSNK2A1-WNT1-WNT2B	2524	14385	7157	10414	54122	CSNK2A1-FZD2-FZD7	2565	2837	56315	28772	48895	
CSNK2A1-CTBP1-TLE2	2574	40651	49439	31595	53503	CSNK2A1-FSHB-FZD7	2601	20741	19320	11749	49197	
CSNK2A1-FOXN1-GSK3B	2730	10096	8210	19805	29014	CSNK2A1-GSK3A-WNT2B	2752	9423	21413	37047	45455	
CSNK2A1-FOXN1-LRP6	2760	23273	20639	12761	26144	CSNK2A1-GSK3A-PPP2R1A	2846	28306	32715	6544	36708	
CSNK2A1-CTBP1-SEN2	2924	34117	45912	46545	6898	CSNK2A1-CTNNB1-WNT5A	3035	55445	26243	38266	23130	
CSNK2A1-FGF4-TCF7	3067	27234	51193	33410	13203	CSNK2A1-FZD2-WNT2B	3116	11239	47195	32760	3454	
CSNK2A1-NKD1-WNT2B	3148	4519	40339	22219	23905	CSNK2A1-FOXN1-WNT4	3232	23774	15633	8634	22975	
CSNK2A1-JUN-TCF7	3263	25105	52846	57067	1221	CSNK2A1-FSHB-FZD1	3426	27759	33533	13224	35693	
CSNK2A1-JUN-WNT2B	3440	1399	52127	40702	40318	CSNK2A1-FGF4-SFRP1	3465	47529	55702	41330	19744	
CSNK2A1-LEF1-TCF7L1	3467	13738	41400	53041	53144	CSNK2A1-PYGO1-WNT2	3524	34440	54530	10724	18467	
CSNK2A1-FSHB-SEN2	3609	22209	11628	8401	7649	CSNK2A1-DVL1-FBXW11	3610	6276	16364	56510	56461	
CSNK2A1-T-WNT5A	3660	45233	45887	26671	1396	CSNK2A1-MYC-PITX2	3758	35967	33879	27313	16543	
CSNK2A1-PYGO1-PPP2CA	4025	15782	45180	27270	33423	CSNK2A1-DVL1-RHOU	4065	12652	20105	53597	7814	
CSNK2A1-NKD1-PPP2R1A	4118	2001	56920	13318	8736	CSNK2A1-PORCN-SFRP4	4131	33977	12661	15057	30703	
CSNK2A1-CTNNB1-T	4140	18046	54949	26831	37101	CSNK2A1-FSHB-TCF7L1	4195	17520	18854	11543	18761	
CSNK2A1-JUN-SFRP4	4203	22709	45864	35605	32229	CSNK2A1-GSK3A-PPP2CA	4214	31336	13790	24722	34871	
CSNK2A1-GSK3A-KREMEN1	4235	23842	42754	53396	1564	CSNK2A1-FZD2-SEN2	4264	33009	54823	5421	911	
CSNK2A1-FOXN1-TLE1	4266	20295	18452	6427	9715	CSNK2A1-FSHB-LEF1	4295	17954	29380	8714	37682	
CSNK2A1-CTBP1-KREMEN1	4442	30857	51256	51490	5995	CSNK2A1-FZD2-TCF7	4766	40379	47141	22369	13184	
CSNK2A1-PYGO1-TCF7	4808	27076	33334	7691	16030	CSNK2A1-DVL1-LRP6	4823	30788	49881	34670	53880	
CSNK2A1-PORCN-TCF7	4850	31386	33280	14902	19852	CSNK2A1-FZD2-PPP2CA	4902	29491	29055	33131	4536	
CSNK2A1-PYGO1-SEN2	4917	31012	48524	12515	33413	CSNK2A1-GSK3A-RHOU	4938	37934	46583	36458	3654	
CSNK2A1-DVL1-SLC9A3R1	4980	16432	35962	54403	41159	CSNK2A1-FGF4-RHOU	5008	25194	46362	55699	23894	
FZD5-CSNK1A1-CSNK2A1	5100	3216	8691	22543	4716	CSNK2A1-FGF4-WNT5A	5228	54917	47451	35203	41872	
CSNK2A1-FZD2-TCF7L1	5254	17885	52187	20208	2379	CSNK2A1-NKD1-RHOU	5293	676	20472	46080	2722	
CCND1-CSNK2A1-MYC	5332	45803	47835	15422	49922	CSNK2A1-DVL1-GSK3B	5470	16396	27115	36734	38840	
CSNK2A1-CTBP1-DIXDC1	5484	42315	46531	44420	54509	CSNK2A1-JUN-WNT2	5498	21521	44878	22792	9510	
CSNK2A1-LEF1-SFRP4	5512	49833	36100	50127	48050	CCND1-CSNK2A1-DVL1	5522	40948	2776	26875	54578	
CSNK2A1-PORCN-PPP2R1A	5568	20810	25058	43074	9607	CSNK2A1-NKD1-TCF7L1	5618	6658	17702	27834	32704	
CSNK2A1-CTNNBIP1-DKK1	5689	36436	32863	3093	28146	CSNK2A1-FGF4-TCF7L1	5703	11207	51617	30953	5195	
CSNK2A1-FSHB-T	5815	10424	50744	7080	35089	CSNK2A1-JUN-SEN2	5821	24682	37896	29363	21988	
CSNK2A1-CTBP1-FRZB	5906	54020	49728	43068	48373	CSNK2A1-FZD2-SFRP1	5968	33591	56271	11094	34190	
CSNK2A1-FOXN1-FRAT1	5975	18588	26335	14755	2735	CSNK1G1-CSNK2A1-FBXW11	6032	34572	1132	45965	55730	
CSNK2A1-FGF4-FZD1	6048	44217	53749	54801	12677	CSNK2A1-MYC-NLK	6059	42025	55361	20925	25562	
CSNK2A1-JUN-PPP2CA	6067	21122	42758	9189	41050	CSNK2A1-FSHB-WNT2	6124	9507	15885	6738	3636	
CSNK2A1-GSK3A-SFRP1	6198	43233	46098	10386	43054	CSNK2A1-DVL1-FRZB	6206	32150	25228	42730	46311	
CSNK2A1-DVL1-FBXW2	6300	28745	4037	54096	41967	CSNK2A1-FSHB-FZD2	6334	39349	21029	16323	5662	
CSNK2A1-CTBP1-WNT2B	6360	7636	54224	13079	45632	CSNK2A1-FGF4-FBXW4	6372	24169	28837	44880	13181	
CSNK2A1-CTBP1-CXXC4	6421	43941	43074	29119	14340	CSNK2A1-FBXW11-LRP6	6459	12795	12512	33274	49844	

Table 13: Rankings of CSNK2A1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear

TCF7, CSNK2A1-JUN-TCF7, CSNK2A1-LEF1-TCF7L1, CSNK2A1-PYGO1-TCF7, CSNK2A1-PORCN-TCF7, CSNK2A1-FZD2-TCF7L1, CSNK2A1-T-TCF7, CSNK2A1-T-TCF7L1, CSNK2A1-CTNNB1-TCF7, CSNK2A1-FSHB-TCF7L1, CSNK2A1-FZD2-TCF7, CSNK2A1-NKD1-TCF7L1 and CSNK2A1-FGF4-TCF7L1. All these combinations indicate the existence of a possible synergy when they take a higher rank in the

RANKING @ t_i USING HSIC - RBF												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK2A1-MYC-SEN2	698	26688	37719	17840	33212	CSNK2A1-MYC-SFRP4	3137	18203	34840	44309	14017	
CSNK2A1-MYC-TCF7L1	3268	10141	41173	20544	17120	AES-AXIN1-CSNK2A1	39672	48590	36988	26194	17146	
CSNK2A1-T-WNT2B	38723	10644	19106	40549	37163	CSNK2A1-MYC-PPP2CA	1074	26347	29622	32938	20490	
CSNK2A1-CTBP1-PPP2R1A	51425	30212	13474	42814	33263	CSNK2A1-MYC-WNT4	4376	38940	46395	33447	19179	
CSNK2A1-MYC-TCF7	781	19559	42485	46019	12156	CSNK2A1-FSHB-SFRP4	17159	7039	55890	17829	49642	
CSNK2A1-MYC-RHOU	476	15315	41082	55249	19587	CSNK2A1-T-TCF7	11139	40799	24262	6398	28652	
CSNK2A1-MYC-FBXW4	4903	13344	34695	1270	26542	CSNK2A1-MYC-WNT2B	1714	9603	40200	31690	23030	
CSNK2A1-MYC-TLE1	13562	22303	29319	31694	13482	CSNK2A1-T-TCF7L1	26605	44985	35162	25193	37770	
CSNK2A1-FOXN1-TCF7	215	23416	42414	29565	28676	CSNK2A1-MYC-SLC9A3R1	13702	4958	47835	27410	26680	
CSNK2A1-FOXN1-WNT2B	1203	7766	40805	5216	17738	CSNK2A1-FOXN1-FZD8	255	29912	45362	18779	48225	
CSNK2A1-FOXN1-SEN2	142	13206	48212	17145	40808	CSNK2A1-FOXN1-FZD6	138	14978	35128	24657	38128	
CSNK2A1-CTNNB1-FOSL1	26592	26504	31836	43474	14209	CSNK2A1-T-WNT2	40915	37224	36704	1725	25747	
CSNK2A1-T-TLE2	42759	20833	28349	4740	25444	CSNK2A1-FOXN1-PPP2CA	278	35287	48412	13705	23060	
CSNK2A1-MYC-PPP2R1A	8973	18254	44398	29894	43896	CSNK2A1-FOXN1-SFRP4	363	18135	45540	43080	8388	
CSNK2A1-FSHB-PPP2CA	14473	24470	49869	6189	28547	CSNK2A1-CTBP1-FOSL1	48595	20470	4367	24006	8607	
CSNK2A1-FSHB-WNT2B	14373	4327	52378	10457	6308	CSNK2A1-CTNNB1-TCF7	31530	21321	30786	34753	7567	
CSNK2A1-FOXN1-FZD7	362	11023	42794	26796	28725	CSNK2A1-FOXN1-SLC9A3R1	986	3049	43332	29536	18310	
CSNK2A1-FOXN1-PPP2R1A	647	14324	25472	4074	30161	CSNK2A1-CTNNB1-SEN2	18451	38229	34476	7310	21713	
CSNK2A1-FGF4-PPP2R1A	166	29600	18823	44833	19787	CSNK2A1-MYC-WNT5A	4208	45258	25000	47595	27580	
CSNK2A1-FOXN1-WNT2	1056	20090	34851	2850	1522	CSNK2A1-CTBP1-WNT2	28304	31305	21921	11535	1886	
CSNK2A1-MYC-WNT2	1948	22451	46334	3781	9898	CSNK1G1-CSNK2A1-MYC	46238	56607	42725	857	38125	
CSNK2A1-GSK3A-SFRP4	1263	52177	43795	55690	30326	CSNK2A1-JUN-PITX2	25321	4747	44298	56844	22732	
CSNK2A1-CTNNB1-FRAT1	40906	34560	18359	47062	27181	FZD5-CSNK2A1-SEN2	11292	26637	45819	12555	33852	
CSNK2A1-FOXN1-PITX2	1130	13168	44037	50356	32422	CSNK2A1-CTNNB1-WNT4	28908	47468	40425	46495	27403	
CSNK2A1-WNT1-WNT2B	8045	25594	32444	62	44806	CSNK2A1-FZD2-FZD7	33636	1002	15242	6218	37749	
CSNK2A1-CTBP1-TLE2	50066	36049	4867	1411	19723	CSNK2A1-FSHB-FZD7	32789	11231	55533	29970	24990	
CSNK2A1-FOXN1-GSK3B	238	15019	20757	53790	26763	CSNK2A1-GSK3A-WNT2B	4036	4526	36754	54131	29491	
CSNK2A1-FOXN1-LRP6	5586	28037	33862	31143	22742	CSNK2A1-GSK3A-PPP2R1A	6662	21693	51937	52594	38018	
CSNK2A1-CTBP1-SEN2	25241	25351	27880	1822	25905	CSNK2A1-CTNNB1-WNT5A	34875	52148	5403	46302	46674	
CSNK2A1-FGF4-TCF7	52	25425	28683	39605	54030	CSNK2A1-FZD2-WNT2B	50529	27854	15045	436	11606	
CSNK2A1-NKD1-WNT2B	17855	5115	19163	36411	21386	CSNK2A1-FOXN1-WNT4	490	14187	43096	25063	20071	
CSNK2A1-JUN-TCF7	8894	46530	30809	46630	2904	CSNK2A1-FSHB-FZD1	14124	9142	52833	6616	46703	
CSNK2A1-JUN-WNT2B	35572	1820	14644	55832	35280	CSNK2A1-FGF4-SFRP1	1044	38185	15465	35338	39230	
CSNK2A1-LEF1-TCF7L1	8400	34228	31681	15033	38236	CSNK2A1-PYGO1-WNT2	6052	32583	28770	2461	39536	
CSNK2A1-FSHB-SEN2	11122	26033	53443	288	43776	CSNK2A1-DVL1-FBXW11	11873	23669	2524	43242	30015	
CSNK2A1-T-WNT5A	18871	49162	6434	9546	14718	CSNK2A1-MYC-PITX2	21651	30519	49254	52766	16814	
CSNK2A1-NKD1-PPP2CA	6422	22743	30647	42195	19402	CSNK2A1-DVL1-RHOU	6585	24060	50251	56841	33506	
CSNK2A1-PORCN-PPP2R1A	19188	9240	34119	49629	44582	CSNK2A1-PORCN-SFRP4	16519	31888	2327	45601	45214	
CSNK2A1-CTNNB1-T	50629	10136	41060	51780	31512	CSNK2A1-FSHB-TCF7L1	28512	36022	53375	46	53291	
CSNK2A1-JUN-SFRP4	17462	19428	6098	56544	24017	CSNK2A1-GSK3A-PPP2CA	8360	44268	37323	48745	27502	
CSNK2A1-GSK3A-KREMEN1	4756	10748	40012	56751	45633	CSNK2A1-FZD2-SEN2	14015	25593	34109	14375	38328	
CSNK2A1-FOXN1-TLE1	768	22849	44983	9990	15168	CSNK2A1-FSHB-LEF1	57055	1237	51589	12220	31790	
CSNK2A1-CTBP1-KREMEN1	31854	8193	3144	54939	9878	CSNK2A1-FZD2-TCF7	5580	26839	8982	36151	48517	
CSNK2A1-PYGO1-TCF7	4497	22038	26026	17251	48738	CSNK2A1-DVL1-LRP6	56336	32175	8253	43735	18355	
CSNK2A1-PORCN-TCF7	549	24654	8958	12108	39526	CSNK2A1-FZD2-PPP2CA	28548	36489	14755	4170	44758	
CSNK2A1-PYGO1-SEN2	3532	16338	31290	2453	43580	CSNK2A1-GSK3A-RHOU	3399	37045	52307	56745	39992	
CSNK2A1-DVL1-SLC9A3R1	44275	8570	38804	16178	23204	CSNK2A1-FGF4-RHOU	78	27316	34403	55447	42022	
FZD5-CSNK1A1-CSNK2A1	38103	8653	39291	8415	48804	CSNK2A1-FGF4-WNT5A	602	53194	1675	51991	37147	
CSNK2A1-FZD2-TCF7L1	48875	23683	23978	10840	45350	CSNK2A1-NKD1-RHOU	7857	1007	56328	54901	40519	
CCND1-CSNK2A1-MYC	45565	50502	21425	31301	3509	CSNK2A1-DVL1-GSK3B	22246	21600	4804	54969	51209	
CSNK2A1-CTBP1-DIXDC1	46956	37123	8717	20291	30310	CSNK2A1-JUN-WNT2	36519	26360	44355	28715	16517	
CSNK2A1-LEF1-SFRP4	4737	49980	27472	32273	29245	CCND1-CSNK2A1-DVL1	41313	45033	40356	31494	2851	
CSNK2A1-PORCN-PPP2R1A	28250	12579	11498	448	47964	CSNK2A1-NKD1-TCF7L1	18461	16904	48910	7654	40354	
CSNK2A1-CTNNB1P1-DKK1	10247	19444	19638	17406	22738	CSNK2A1-FGF4-TCF7L1	110	27867	15163	37589	34026	
CSNK2A1-FSHB-T	47446	22394	51965	1303	54042	CSNK2A1-JUN-SEN2	14777	12733	32728	5344	7111	
CSNK2A1-CTBP1-FRZB	42541	52275	2302	31289	17177	CSNK2A1-FZD2-SFRP1	31314	28960	33194	3980	37854	
CSNK2A1-FOXN1-FRAT1	1242	20577	32321	24338	27110	CSNK1G1-CSNK2A1-FBXW11	42313	26845	32557	27243	42066	
CSNK2A1-FGF4-FZD1	87	36726	114	39933	18302	CSNK2A1-MYC-NLK	11411	39046	24950	48759	18625	
CSNK2A1-JUN-PPP2CA	19891	42881	9854	51297	22060	CSNK2A1-FSHB-WNT2	17853	878	55222	3102	14025	
CSNK2A1-GSK3A-SFRP1	1584	46719	45465	33601	41778	CSNK2A1-DVL1-FRZB	23407	30241	14408	20773	35318	
CSNK2A1-DVL1-FBXW2	32812	23394	4189	44232	42783	CSNK2A1-FSHB-FZD2	5029	27255	55299	26042	39734	
CSNK2A1-CTBP1-WNT2B	44604	6714	15366	42657	5646	CSNK2A1-FGF4-FBXW4	448	26014	24455	22007	23086	
CSNK2A1-CTBP1-CXXC4	20558	27309	21582	15326	3507	CSNK2A1-FBXW11-LRP6	43842	3366	29374	34224	54258	

Table 14: Rankings of CSNK2A1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf

list of combinations.

6.6.3. Examining the behaviour of PP2A-CSNK2A1-X combinations

Looking at the tables above, one finds the following combinations for members of PPP2A family along with CSNK2A1, to be prominent at 3rd order level - CSNK2A1-

RANKING @ t_1 USING SOBOL - 2002												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK2A1-MYC-SENP2	5898	9120	7738	21203	48879	CSNK2A1-MYC-SFRP4	18468	7910	3191	15042	48259	
CSNK2A1-MYC-TCF7L1	37431	43064	54354	45254	409	AES-AXIN1-CSNK2A1	18325	23757	4922	25783	12175	
CSNK2A1-T-WNT2B	14346	8714	2556	866	56003	CSNK2A1-MYC-PPP2CA	13455	56732	1328	24242	47656	
CSNK2A1-CTBP1-PPP2R1A	9565	3272	9580	22975	53995	CSNK2A1-MYC-WNT4	21742	34401	488	7129	23829	
CSNK2A1-MYC-TCF7	19743	13821	2818	11818	56749	CSNK2A1-FSHB-SFRP4	4052	10483	11365	12481	41837	
CSNK2A1-MYC-RHOU	45614	13742	53112	49853	2195	CSNK2A1-T-TCF7	41885	453	52842	43192	1378	
CSNK2A1-MYC-FBXW4	38701	49221	53963	42128	9296	CSNK2A1-MYC-WNT2B	40989	30656	53975	49615	2007	
CSNK2A1-MYC-TLE1	18169	5004	4227	177	12052	CSNK2A1-T-TCF7L1	12181	8047	5333	9116	54692	
CSNK2A1-FOXN1-TCF7	8332	7205	8216	24521	24469	CSNK2A1-MYC-CLC9A3R1	27217	34836	7872	6116	16258	
CSNK2A1-FOXN1-WNT2B	53238	9771	44983	35149	2439	CSNK2A1-FOXN1-FZD8	49203	56401	44801	39472	19441	
CSNK2A1-FOXN1-SENP2	9019	3852	10133	23930	23783	CSNK2A1-FOXN1-FZD6	37168	52306	41314	39825	20513	
CSNK2A1-CTNNB1-FOSL1	7348	26679	6679	8520	40678	CSNK2A1-T-WNT2	52287	51931	48817	48033	3417	
CSNK2A1-T-TLE2	2998	33460	16386	16657	50626	CSNK2A1-FOXN1-PPP2CA	9022	16430	12781	23632	52199	
CSNK2A1-MYC-PPP2R1A	43792	409	55826	32832	9529	CSNK2A1-FOXN1-SFRP4	14008	32657	7345	20701	33835	
CSNK2A1-FSHB-PPP2CA	8916	2500	542	374	35437	CSNK2A1-CTBP1-FOSL1	51466	6276	44543	34556	2632	
CSNK2A1-FSHB-WNT2B	56035	49999	49902	45966	16417	CSNK2A1-CTNNB1-TCF7	7581	3896	7870	16886	45112	
CSNK2A1-FOXN1-FZD7	8001	759	12282	17543	37775	CSNK2A1-FOXN1-CLC9A3R1	3259	3823	19513	19029	56600	
CSNK2A1-FOXN1-PPP2R1A	48112	40897	44318	33462	5020	CSNK2A1-CTNNB1-SENP2	7471	7301	8352	24935	46157	
CSNK2A1-FGF4-PPP2R1A	14590	280	8154	14376	57124	CSNK2A1-MYC-WNT5A	35456	22735	56665	49988	33664	
CSNK2A1-FOXN1-WNT2	3923	47496	12123	21954	54740	CSNK2A1-CTBP1-WNT2	50236	18835	44319	34339	3639	
CSNK2A1-MYC-WNT2	16135	26659	3183	7531	55194	CSNK1G1-CSNK2A1-MYC	18695	1708	3446	13091	35254	
CSNK2A1-GSK3A-SFRP4	46244	11645	56075	33851	2139	CSNK2A1-JUN-PITX2	4226	47140	759	5831	41428	
CSNK2A1-CTNNB1-FRAT1	25796	21067	5577	2152	38428	FZD5-CSNK2A1-SENP2	9757	56933	795	16736	48689	
CSNK2A1-FOXN1-PITX2	484	10646	14993	25101	56105	CSNK2A1-CTNNB1-WNT4	8106	6970	4829	17083	49554	
CSNK2A1-WNT1-WNT2B	56439	49339	39830	36489	2125	CSNK2A1-FZD2-FZD7	57035	52466	50316	41983	293	
CSNK2A1-CTBP1-TLE2	9147	35788	11366	14526	33787	CSNK2A1-FSHB-FZD7	3089	7692	3943	5213	55917	
CSNK2A1-FOXN1-GSK3B	35528	51506	42632	42029	9080	CSNK2A1-GSK3A-WNT2B	956	5727	4844	11580	53063	
CSNK2A1-FOXN1-LRP6	14518	20	1192	25846	56949	CSNK2A1-GSK3A-PPP2R1A	11380	31286	12842	24412	45687	
CSNK2A1-CTBP1-SENP2	43744	8298	33161	39128	13943	CSNK2A1-CTNNB1-WNT5A	49018	50110	52351	40046	7587	
CSNK2A1-FGF4-TCF7	48453	13899	33822	49973	14365	CSNK2A1-FZD2-WNT2B	5657	5172	380	17961	34028	
CSNK2A1-NKD1-WNT2B	25433	37	1485	5548	41572	CSNK2A1-FOXN1-WNT4	2806	435	14422	21539	41812	
CSNK2A1-JUN-TCF7	12557	52439	1511	20792	54968	CSNK2A1-FSHB-FZD1	46615	46448	50771	45908	17553	
CSNK2A1-JUN-WNT2B	46982	49168	35303	45143	14928	CSNK2A1-FGF4-SFRP1	724	12957	15455	8547	56524	
CSNK2A1-LEF1-TCF7L1	18614	1129	13381	2372	49296	CSNK2A1-PYGO1-WNT2	27842	10862	10937	6962	53007	
CSNK2A1-FSHB-SENP2	10122	25267	392	2416	51870	CSNK2A1-DVL1-FBXW11	15356	39928	19652	1792	34439	
CSNK2A1-T-WNT5A	23799	14174	1661	753	51344	CSNK2A1-MYC-PITX2	9129	7731	935	12301	36666	
CSNK2A1-NKD1-PPP2CA	35993	44148	33793	48908	1488	CSNK2A1-DVL1-RHOU	22678	41947	2301	15211	49099	
CSNK2A1-CTBP1-PPP2R1A	22699	6006	1296	8582	18490	CSNK2A1-PORCN-SFRP4	4764	55585	3453	23375	41101	
CSNK2A1-CTNNB1-T	52666	48722	39648	31301	9858	CSNK2A1-FSHB-TCF7L1	55973	47958	56151	46957	1597	
CSNK2A1-JUN-SFRP4	14451	41112	16858	24545	41381	CSNK2A1-GSK3A-PPP2CA	50785	50502	56753	49920	960	
CSNK2A1-GSK3A-KREMEN1	11355	3230	938	5098	50994	CSNK2A1-FZD2-SENP2	52978	49131	54539	42433	3789	
CSNK2A1-FOXN1-TLE1	21954	33369	6325	24019	44318	CSNK2A1-FSHB-LEF1	23163	9325	3502	903	40947	
CSNK2A1-CTBP1-KREMEN1	6552	6181	18373	22074	55772	CSNK2A1-FZD2-TCF7	47317	56054	56191	56652	43570	
CSNK2A1-PYGO1-TCF7	15569	3364	11248	16573	53552	CSNK2A1-DVL1-LRP6	45877	15195	32641	48434	16964	
CSNK2A1-PORCN-TCF7	253	20066	23705	26560	40570	CSNK2A1-FZD2-PPP2CA	52498	52415	55485	44738	17735	
CSNK2A1-PYGO1-SENP2	20706	53099	5569	21457	49132	CSNK2A1-GSK3A-RHOU	6454	4096	2365	3630	43020	
CSNK2A1-DVL1-CLC9A3R1	53263	13807	54823	50300	2024	CSNK2A1-FGF4-RHOU	6102	351	8851	577	57152	
FZD5-CSNK1A1-CSNK2A1	8541	11031	2822	9650	17384	CSNK2A1-FGF4-WNT5A	5912	1128	2119	14582	46081	
CSNK2A1-FZD2-TCF7L1	15294	353	14707	491	25701	CSNK2A1-NKD1-RHOU	28432	52475	791	7699	45703	
CCND1-CSNK2A1-MYC	35995	130	56893	53448	29416	CSNK2A1-DVL1-GSK3B	3403	21865	11550	14768	53968	
CSNK2A1-CTBP1-DIXDC1	51976	50593	32035	35231	2738	CSNK2A1-JUN-WNT2	10205	8057	21879	11928	42214	
CSNK2A1-LEF1-SFRP4	55546	17473	50709	50559	9836	CCND1-CSNK2A1-DVL1	4101	24872	1574	1354	1339	
CSNK2A1-PORCN-PPP2R1A	45314	43859	54593	47914	11717	CSNK2A1-NKD1-TCF7L1	20780	14357	675	7144	41442	
CSNK2A1-CTNNB1P1-DKK1	34814	51895	45723	42177	8806	CSNK2A1-FGF4-TCF7L1	9230	18738	1780	10884	27522	
CSNK2A1-FSHB-T	50822	4565	54740	38445	2873	CSNK2A1-JUN-SENP2	7568	864	582	2154	49741	
CSNK2A1-CTBP1-FRZB	4744	29785	13610	26986	44249	CSNK2A1-FZD2-SFRP1	358	8707	9192	5691	43838	
CSNK2A1-FOXN1-FRAT1	3262	13630	9867	23023	40813	CSNK1G1-CSNK2A1-FBXW11	22527	619	16391	25717	37891	
CSNK2A1-FGF4-FZD1	276	17331	669	16579	45250	CSNK2A1-MYC-NLK	40749	13573	35702	29709	8513	
CSNK2A1-JUN-PPP2CA	20062	6330	493	431	54018	CSNK2A1-FSHB-WNT2	1125	7249	7264	11089	40648	
CSNK2A1-GSK3A-SFRP1	10952	45294	1078	23261	54962	CSNK2A1-DVL1-FRZB	459	19798	6360	15811	52303	
CSNK2A1-DVL1-FBXW2	41797	17763	37545	55360	22648	CSNK2A1-FSHB-FZD2	1633	22635	19939	16370	37670	
CSNK2A1-CTBP1-WNT2B	3295	15706	805	8845	23881	CSNK2A1-FGF4-FBXW4	9203	19715	7306	9710	55847	
CSNK2A1-CTBP1-CXXC4	38184	6837	56901	30192	24708	CSNK2A1-FBXW11-LRP6	12906	55934	2067	15356	56033	

Table 15: Rankings of CSNK2A1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - 2002

CTBP1-PPP2R1A, CSNK2A1-MYC-PPP2R1A, CSNK2A1-FSHB-PPP2CA, CSNK2A1-FOXN1-PPP2R1A, CSNK2A1-FGF4-PPP2R1A, CSNK2A1-NKD1-PPP2CA, CSNK2A1-NKD1-PPP2R1A, CSNK2A1-PORCN-PPP2R1A, CSNK2A1-JUN-PPP2CA, CSNK2A1-MYC-PPP2CA, CSNK2A1-FOXN1-PPP2CA, CSNK2A1-GSK3A-PPP2R1A, CSNK2A1-GSK3A-PPP2CA and CSNK2A1-FZD2-PPP2CA. All these combinations indicate the

RANKING @ t_1 USING SOBOL - MARTINEZ												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK2A1-MYC-SEN2	25707	12898	3554	47825	33675	CSNK2A1-MYC-SFRP4	32089	24506	17701	13832	1328	
CSNK2A1-MYC-TCF7L1	34241	29282	18645	1856	23914	AES-AXIN1-CSNK2A1	1382	4503	10747	46198	13387	
CSNK2A1-T-WNT2B	5760	12660	53417	53139	1959	CSNK2A1-MYC-PPP2CA	641	3083	16208	54190	40209	
CSNK2A1-CTBP1-PPP2R1A	8485	5851	54850	57106	50316	CSNK2A1-MYC-WNT4	19871	31001	13262	3506	6248	
CSNK2A1-MYC-TCF7	8971	25056	6634	13626	4944	CSNK2A1-FSHB-SFRP4	6990	46178	45901	7793	15573	
CSNK2A1-MYC-RHOU	32164	4573	41446	52430	8154	CSNK2A1-T-TCF7	32693	42865	7454	24354	20983	
CSNK2A1-MYC-FBXW4	38747	33436	35263	3465	24441	CSNK2A1-MYC-WNT2B	33055	55999	36655	287	9236	
CSNK2A1-MYC-TLE1	3301	30907	4777	8124	1577	CSNK2A1-T-TCF7L1	5151	5428	30338	35936	2423	
CSNK2A1-FOXN1-TCF7	11863	6115	56630	47612	7264	CSNK2A1-MYC-CLC9A3R1	3468	23186	11607	48249	1020	
CSNK2A1-FOXN1-WNT2B	56377	38665	54391	50687	12268	CSNK2A1-FOXN1-FZD8	48413	46315	52935	6291	12792	
CSNK2A1-FOXN1-SEN2	14555	16853	56191	37447	12743	CSNK2A1-FOXN1-FZD6	6588	10061	41823	49185	11365	
CSNK2A1-CTNNB1-FOSL1	14159	29263	5533	12508	51686	CSNK2A1-T-WNT2	53657	29097	31434	39795	33739	
CSNK2A1-T-TLE2	37761	34576	29328	38292	4676	CSNK2A1-FOXN1-PPP2CA	6777	56192	42475	44384	6122	
CSNK2A1-MYC-PPP2R1A	25664	26823	22802	51070	20795	CSNK2A1-FOXN1-SFRP4	44988	20977	47958	42376	4783	
CSNK2A1-FSHB-PPP2CA	18252	39529	48641	45395	6382	CSNK2A1-CTBP1-FOSL1	55694	34498	49182	54478	10195	
CSNK2A1-FSHB-WNT2B	57093	25886	24846	4769	8081	CSNK2A1-CTNNB1-TCF7	1051	56349	54832	35478	5902	
CSNK2A1-FOXN1-FZD7	6812	31474	55953	43246	47808	CSNK2A1-FOXN1-CLC9A3R1	8707	15456	55366	51890	51278	
CSNK2A1-FOXN1-PPP2R1A	45269	55820	45196	49391	8270	CSNK2A1-CTNNB1-SEN2	7665	49515	56389	54418	11151	
CSNK2A1-FGF4-PPP2R1A	2708	11996	14685	9650	3147	CSNK2A1-MYC-WNT5A	37394	36968	36088	1047	19004	
CSNK2A1-FOXN1-WNT2	11745	7167	55396	50509	46768	CSNK2A1-CTBP1-WNT2	52495	51968	40602	37371	14060	
CSNK2A1-MYC-WNT2	26070	56747	4251	16130	26316	CSNK1G1-CSNK2A1-MYC	816	53067	52527	17682	54911	
CSNK2A1-GSK3A-SFRP4	34091	39133	20485	4011	30729	CSNK2A1-JUN-PITX2	27303	36268	42893	48996	26416	
CSNK2A1-CTNNB1-FRAT1	5810	51794	8029	23468	9661	FZD5-CSNK2A1-SEN2	9032	18062	25937	57147	24182	
CSNK2A1-FOXN1-PITX2	42869	56525	55768	53229	9861	CSNK2A1-CTNNB1-WNT4	1302	27956	45071	49285	9763	
CSNK2A1-WNT1-WNT2B	34224	30137	54159	43767	28506	CSNK2A1-FZD2-FZD7	56735	39506	34652	5900	8683	
CSNK2A1-CTBP1-TLE2	33230	39802	43760	8503	9165	CSNK2A1-FSHB-FZD7	6856	18689	18850	39695	45801	
CSNK2A1-FOXN1-GSK3B	8326	49905	54047	51644	10965	CSNK2A1-GSK3A-WNT2B	12103	52169	54990	42771	19243	
CSNK2A1-FOXN1-LRP6	5552	9594	55901	54834	4864	CSNK2A1-GSK3A-PPP2R1A	1426	6407	17691	10783	1599	
CSNK2A1-CTBP1-SEN2	26122	28357	31806	52918	10514	CSNK2A1-CTNNB1-WNT5A	15912	32149	48221	26938	16715	
CSNK2A1-FGF4-TCF7	35123	52117	32325	4544	13073	CSNK2A1-FZD2-WNT2B	12434	20338	48298	4351	778	
CSNK2A1-NKD1-WNT2B	26088	27029	12360	24175	6941	CSNK2A1-FOXN1-WNT4	13691	10110	55435	48902	11040	
CSNK2A1-JUN-TCF7	1663	14259	36086	56512	36280	CSNK2A1-FSHB-FZD1	34430	14822	30557	7690	18794	
CSNK2A1-JUN-WNT2B	55113	18243	50342	260	32860	CSNK2A1-FGF4-SFRP1	36743	54424	20977	19930	120	
CSNK2A1-LEF1-TCF7L1	19939	21094	47109	37822	17620	CSNK2A1-PYGO1-WNT2	1343	46514	39128	51687	744	
CSNK2A1-FSHB-SEN2	2358	42213	17814	39177	55018	CSNK2A1-DVL1-FBXW11	1144	37869	20966	6182	6565	
CSNK2A1-T-WNT5A	3889	52194	41219	43938	2464	CSNK2A1-MYC-PITX2	17421	12288	5142	54094	13707	
CSNK2A1-NKD1-PPP2CA	36783	42052	28232	9350	10631	CSNK2A1-DVL1-RHOU	3652	11411	13549	10475	804	
CSNK2A1-FOXN1-PPP2R1A	32525	9590	31893	25709	13680	CSNK2A1-PORCN-SFRP4	19620	17712	43043	31830	105	
CSNK2A1-CTNNB1-T	49993	28655	46959	9125	23176	CSNK2A1-FSHB-TCF7L1	47175	44476	22845	44711	15604	
CSNK2A1-JUN-SFRP4	818	29998	16317	29062	33150	CSNK2A1-GSK3A-PPP2CA	53147	43418	27751	30515	14659	
CSNK2A1-GSK3A-KREMEN1	11971	15041	18579	53795	23278	CSNK2A1-FZD2-SEN2	53269	33754	34225	35679	8436	
CSNK2A1-FOXN1-TLE1	2846	17534	30632	55614	3042	CSNK2A1-FSHB-LEF1	2869	54364	39557	33239	582	
CSNK2A1-CTBP1-KREMEN1	32191	17394	52207	56363	16597	CSNK2A1-FZD2-TCF7	40899	15897	50502	5255	24938	
CSNK2A1-PYGO1-TCF7	22495	14182	9919	4915	3730	CSNK2A1-DVL1-LRP6	34623	53684	34600	7404	15504	
CSNK2A1-PORCN-TCF7	24067	41740	38951	44434	2663	CSNK2A1-FZD2-PPP2CA	41436	45978	5837	9787	19632	
CSNK2A1-PYGO1-SEN2	3561	22661	36402	14952	3874	CSNK2A1-GSK3A-RHOU	34595	22979	15721	31577	6129	
CSNK2A1-DVL1-CLC9A3R1	53343	32839	20979	24128	17110	CSNK2A1-FGF4-RHOU	4632	14123	6119	11150	2393	
FZD5-CSNK1A1-CSNK2A1	5523	20838	55091	55579	6725	CSNK2A1-FGF4-WNT5A	10029	35718	22516	18141	333	
CSNK2A1-FZD2-TCF7L1	148	7924	54241	7307	1397	CSNK2A1-NKD1-RHOU	24589	47421	8599	21466	5498	
CCND1-CSNK2A1-MYC	25438	23184	38988	12798	13384	CSNK2A1-DVL1-GSK3B	44946	51210	27731	9073	19440	
CSNK2A1-CTBP1-DIXDC1	55549	46095	44695	50917	10443	CSNK2A1-JUN-WNT2	17755	39215	49921	4816	7330	
CSNK2A1-LEF1-SFRP4	57084	19524	51528	18319	25163	CCND1-CSNK2A1-DVL1	3753	7022	15651	7612	37340	
CSNK2A1-PORCN-PPP2R1A	21012	31151	44392	50200	9723	CSNK2A1-NKD1-TCF7L1	15686	20361	12720	55253	14422	
CSNK2A1-CTNNB1P1-DKK1	8377	45825	53769	48856	22656	CSNK2A1-FGF4-TCF7L1	4423	15097	14000	8875	2180	
CSNK2A1-FSHB-T	54571	49726	28939	52860	23604	CSNK2A1-JUN-SEN2	5638	30556	38236	42924	24270	
CSNK2A1-CTBP1-FRZB	39547	11887	53828	56894	16770	CSNK2A1-FZD2-SFRP1	41121	19107	6585	13483	7739	
CSNK2A1-FOXN1-FRAT1	5438	13233	56024	51861	48266	CSNK1G1-CSNK2A1-FBXW11	3109	25643	52608	3230	54598	
CSNK2A1-FGF4-FZD1	22381	4306	9134	11263	4372	CSNK2A1-MYC-NLK	19537	36878	26580	52384	8777	
CSNK2A1-JUN-PPP2CA	3014	53088	55530	47529	21835	CSNK2A1-FSHB-WNT2	42036	34277	26999	11757	55591	
CSNK2A1-GSK3A-SFRP1	2382	12778	14251	9522	3858	CSNK2A1-DVL1-FRZB	24368	52086	44339	6279	220	
CSNK2A1-DVL1-FBXW2	9824	7532	30398	5330	18471	CSNK2A1-FSHB-FZD2	37405	46600	33841	13079	45433	
CSNK2A1-CTBP1-WNT2B	5403	18477	11446	48700	30725	CSNK2A1-FGF4-FBXW4	5174	56706	8550	12291	9671	
CSNK2A1-CTBP1-CXXC4	14885	33435	46919	54535	19295	CSNK2A1-FBXW11-LRP6	974	53038	38336	53894	827	

Table 16: Rankings of CSNK2A1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - martinez

existence of a possible synergy when they take a higher rank in the list of combinations.

6.6.4. Examining the behaviour of LRP-CSNK2A1-X combinations

Looking at the tables above, one finds the following combinations for members of LRP family along with CSNK2A1, to be prominent at 3rd order level - CSNK2A1-

FOXN1-LRP6, CSNK2A1-DVL1-LRP6 and CSNK2A1-FBXW11-LRP6. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.6.5. Examining the behaviour of CTNNB1-CSNK2A1-X combinations

Looking at the tables above, one finds the following combinations for CTNNB1 along with CSNK2A1, to be prominent at 3rd order level - CSNK2A1-CTNNB1-FOSL1, CSNK2A1-CTNNB1-FRAT1, CSNK2A1-CTNNB1-T, CSNK2A1-CTNNBIP1-DKK1, CSNK2A1-CTNNB1-TCF7, CSNK2A1-CTNNB1-SENP2, CSNK2A1-CTNNB1-WNT4 and CSNK2A1-CTNNB1-WNT5A. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

6.6.6. Examining the behaviour of APC-CSNK2A1-X combinations

Looking at the tables above, one finds the following combinations for APC along with CSNK2A1, to be prominent at 3rd order level - APC-CSNK1G1-FZD1. All these combinations indicate the existence of a possible synergy when they take a higher rank in the list of combinations.

7. Conclusion

This manuscript studies the time behaviour of 3rd order combinations of CSNK in WNT3A stimulated HEK 293 cells. Based on the established 2nd order combinations of the CSNK, 3rd order combinations emerge using the machine learning based search engine. These 3rd order combinations might be of interest for further wet lab investigations.

Competing interests

No competing interest is declared.

Author contributions statement

SS conceived and designed the experiments; wrote the code; performed the experiments; analyzed the data; wrote the manuscript.

Availability of code

Code for time series data available at CERN based Zenodo on <https://zenodo.org/records/14637456>.

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Supplementary

The following files (ending with .txt and can be opened in R or in simple text processing program) with these names are made available with this manuscript. For CSNK, (1) **-3-odr-TP-ranking-linear.txt**, (2) **-3-odr-TP-ranking-rbf.txt**, (3) **-3-odr-TP-ranking-2002.txt**, and (4) **-3-odr-TP-ranking-martinez.txt**, contain rankings for 3rd order combinations across each time point for, HSIC (linear kernel), HSIC (rbf kernel), SOBOL (2002 implementation) and SOBOL (martinez implementation), respectively.

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