

v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3 / erb-b2 receptor tyrosine kinase 3 (ERBB3) : Machine learning discoveries of 2nd order synergy in Meningiomas

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Abstract

Background : Of the four epidermal growth factor receptor (EGFR/ERBB) family of receptor tyrosine kinases, ERBB3 is one of them. It is known to form active heterodimers with other members of the ERBB family, most notably the ligand binding-impaired ERBB2. ERBB, is derived from the name of avian erythroblastic leukemia viral oncogene to which these receptors are homologous. Insufficient ERBB signaling in humans is associated with the development of neurodegenerative diseases, while excess of ERBB signaling is associated with the development of solid tumors. Meningiomas are the most common intracranial primary neoplasm in adults. Patel et al. [1] analyzed 160 tumors from all 3 World Health Organization (WHO) grades (I through III) using clinical, gene expression, and sequencing data and using unsupervised clustering analysis identified 3 molecular types (A, B, and C) that reliably predicted recurrence. Further, these groups did not directly correlate with the WHO grading system, which classifies more than half of the tumors in the most aggressive molecular type as benign. **Issue** : Increasing evidence point to the fact that meningioma classification and grading, that is based on histopathology does not always accurately predict tumor aggressiveness and recurrence behaviour and knowledge of the underlying biology of the treatment resistant meningiomas and the impact of genetic alterations in these tumors, is lacking. At the current stage more genomic studies are required to unravel the role of other genes and their interactions with other genetic factors. **Resolution** : In a recently published work Sinha [2], a frame work of a search engine was developed which can rank combinations of factors (genes/proteins) in a signaling pathway. Adapting this search engine to the Meningioma dataset, i present here 2nd order combinations of ERBB3, some of which have been known to exist via wet lab experiments, but many are yet to be tested. The reveals combinations might help oncologists/biologists test possible hypotheses that might be the causing factors in meningioma. Further, in my

[☆]ML dicoveries of ERBB3 synergy in Meningiomas

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limited grasp, if proven true, the combinations revealed by the search engine might pave way for development of gene based therapies aimed at resolving pathological issues related to meningiomas.

Keywords: ERBB3, Meningioma, Sensitivity analysis, Machine learning.

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1. Introduction

1.1. Meningioma

Meningiomas are the most common intracranial primary neoplasm in adults. They arise from the arachnoid cap cells. These arachnoid cap cells are specialized cells that make up the arachnoid mater (one of the three protective membranes covering the brain and spinal cord). The arachnoid mater is one of the three meninges. The other two that constitute the meninges are dura mater and pia mater.

1.1.1. World Health Organization (WHO) classification

The meningiomas are classified into three grades by WHO under the Central Nervous System tumours, namely, Grade I (benign), Grade II (atypical) and Grade III (anaplastic/malignant), based on histopathology or subtype (Louis et al. [3]). As of 2021, there

exists 12 histopathological meningioma subtypes according to a mini-review by Torp et al. [4]. They are meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, atypical, chordoid, clear cell and anaplastic (malignant) meningioma.

1.1.2. Historical perspective

Czarnetzki et al. [5] investigated a skull that was excavated at Steinheim/Murr (Baden-Württemberg, Germany) and consisted of a well preserved plagiocephalic cranium, with most of the facial skeleton intact. Their results of stratigraphical dating suggested the fossil specimen of *Homo steinheimensis*, was about 3,65,000 years old. In the fossile, they found that several features of the inner cranial table were consistent with a diagnosis of meningioma.

As documented in Okonkwo and Laws Jr [6], in 1614, Felix Plater, Professor of Medicine, issued a case report from the University of Basel on Caspar Bonecortius, a noble knight stating -

began to lose his mind gradually over a two year period, to such an extent that finally he was completely stupefied and did nothing rationally. He had no desire for food and ate only when forcibly fed. ... Finally after matters had gone on thus for six months, he died.

Further, the autopsy report of Plater stated the following -

a round fleshy tumor, like an acorn. It was hard and full of holes and was as large as a medium-sized apple. It was covered with its own membrane and was entwined with veins. However, it was free of all connections with the matter of the brain, so much so that when it was removed by hand, it left behind a remarkable cavity.

This was the first case in the history that documented a patient with a lesion that was most compatible with a meningioma.

Next, in a contribution by Italian scientists, Paterniti [7] documents the first contribution of Andrea Vacca' Berlinghieri in 1813 in a manuscript *Trattato di Chirurgia Pratica*, which was never published. Its discovery was made accidentally by David Giordano, who referred in detail in an article on surgeon of Pisa in *La chirurgia di Andrea Vacca' Berlinghieri*. *Riv Storia Sci MedNat*. 1927: XVIII (3-4): 75-106. The unpublished manuscript of 488 pages describes that Vacca Berlinghieri proposed and performed a most bold radical operation. After a craniectomy with five or six burr holes on the outskirts of the fungus, the tumor was removed together the dura mater from which it originated, tying the cut vessels.

In 1847, Zanobi Pecchioli, Professor of Clinical Surgery and Operative Medicine at Modena and then at Siena University, published an account of surgeries performed during 16 years, from 1832 to 1847 (16 of the 1524 reported operations involved trephining of the skull). In one of these interventions, he carried out on July 29 1835, in Siena, for the resection of a meningioma, a defined fungus of the duramater. The case was not referred in the literature by Pecchioli but was described by in Pecchioli [8]. Finally, Cushing [9] coined the modern term of "meningioma".

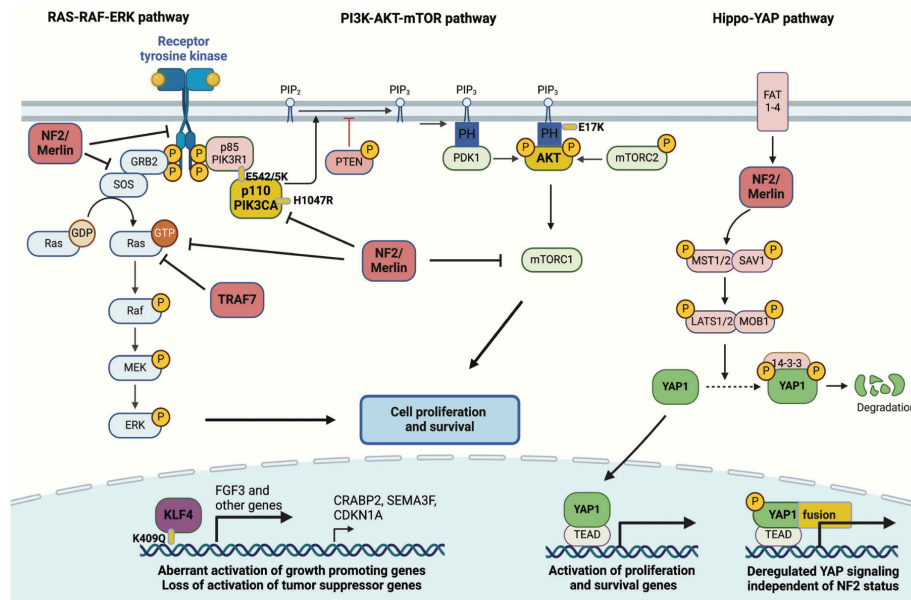


Figure 1: A schematic diagram of different pathways in different meningiomas, as provided by Szulzewsky et al. [12] under CC-BY Attribution 4.0 International license (<https://creativecommons.org/licenses/by/4.0/>)

1.1.3. Pathophysiology

Meningiomas arise from arachnoidal cap cells, most of which are near the vicinity of the venous sinuses, and this is the site of greatest prevalence for meningioma formation. The dural venous sinuses (also called dural/cerebral/cranial sinuses) are venous sinuses (channels) found between the periosteal and meningeal layers of dura mater in the brain. They receive blood from the cerebral veins, and cerebrospinal fluid (CSF) from the subarachnoid space via arachnoid granulations. They mainly empty into the internal jugular vein. Cranial venous sinuses communicate with veins outside the skull through emissary veins. These communications help to keep the pressure of blood in the sinuses constant. (contributors [10] and Pamir et al. [11]) A schematic diagram for different pathways in different meningiomas has been provided in figure 1.

1.2. erb-b2 receptor tyrosine kinase 3 (ERBB3)

ERBB-1/2/3/4 all belong to the family of ERBB proteins that contains receptor tyrosine kinases (RTKs) which are cell receptors and mutations in which lead to several signalling cascades that have numerous effects on protein expression. L-Tyrosine or tyrosine (symbol Tyr or Y) or 4-hydroxyphenylalanine is one of the 20 standard amino acids that are used by cells to synthesize proteins. Cell surface/membrane/transmembrane receptors embedded in the plasma membrane of cells. A tyrosine kinase can transfer a phosphate group from ATP to the tyrosine residues of specific proteins inside a cell

and functions as an on/off switch in many cellular functions. Basically a kinase is an enzyme that catalyzes the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates, a process known as phosphorylation, where the high-energy ATP molecule donates a phosphate group to the substrate molecule.

Kraus et al. [13] detected a related DNA fragment distinct from the epidermal growth factor receptor and ERBB2 genes by reduced stringency hybridization of v-erbB to normal genomic human DNA. Characterization of the cloned DNA fragment mapped the region of v-erbB homology to three exons with closest identity of 64% and 67% to a contiguous region within the tyrosine kinase domains of the epidermal growth factor receptor and ERBB2 proteins, respectively. Based on cDNA cloning which predicted 148-kDa transmembrane polypeptide with structural features identifying it as a member of the ERBB gene family, they named the gene as ERBB3. They mapped it to human chromosome 12q13 and showed its expression as a 6.2-kilobase transcript in a variety of normal tissues of epithelial origin. Further, they observed elevated ERBB3 mRNA levels in certain human mammary tumor cell lines. Their findings suggested that increased ERBB3 expression might play a role in some human malignancies.

Epidermal growth factor (EGF), transforming growth factor α (TGF- α), and amphiregulin are structurally and functionally related growth regulatory proteins. These secreted polypeptides all bind to the 170-kDa cell-surface EGF receptor, activating its intrinsic kinase activity. Amphiregulin only partially competes with EGF for binding EGF receptor, and it does not induce anchorage-independent growth of normal rat kidney cells (NRK) in the presence of TGF- β . It also appears to abrogate the stimulatory effect of TGF- α on the growth of several aggressive epithelial carcinomas that overexpress EGF receptor. These findings suggest that amphiregulin may interact with a separate receptor in certain cell types. Plowman et al. [14] reported the cloning of another member of the human EGF receptor (HER) family of receptor tyrosine kinases, which they named "HER3/ERBB3." The cDNA was isolated from a human carcinoma cell line, and its 6-kilobase transcript was identified in various human tissues. Further, they generated peptide-specific antisera that recognized the 160-kDa HER3 protein when transiently expressed in COS cells.

Northern blot analysis by Katoh et al. [15], revealed that 6.2-kb c-erbB3 transcript was expressed in all gastric cancer cell lines examined, and that 1.4-kb c-erbB3 transcript was expressed as highly as 6.2-kb transcript in MKN45 cells. Their sequence analysis of erbB3-S cDNA showed that this 1.4-kb c-erbB3 mRNA encoded a secreted receptor and further analysis of partial genomic structure of c-erbB3 gene revealed that the exon specific to secreted receptor was identical with the 5' portion of the intron in c-erbB3 gene. Thus they concluded that c-erbB3 gene encoded a secreted as well as transmembrane receptor tyrosine kinase due to alternative splicing.

Cho and Leahy [16] determined the 2.6 angstrom crystal structure of the entire extracellular region of human HER3 (ErbB3). The structure consists of four domains with structural homology to domains found in the type I insulin-like growth factor receptor. The HER3 structure reveals a contact between domains II and IV that constrains the relative orientations of ligand-binding domains and provides a structural basis for understanding both multiple-affinity forms of EGFRs and conformational changes induced in the receptor by ligand binding during signaling. These results also suggest new therapeutic approaches to modulating the behavior of members of the EGFR fam-

ily.

Overexpression of epidermal growth factor receptor (EGFR, ErbB1) correlates with enhanced malignant potential of many human tumor types including glioblastoma multiforme. Andersson et al. [17] analysed the expression of the EGFR family members apropos various parameters for the clinical importance of these receptors in 44 gliomas and 26 meningiomas. In gliomas, they showed that quantitative (RT)-PCR revealed the highest EGFR mRNA expression in high-grade gliomas, while ErbB2 and ErbB3 mRNA were detected only in a few high-grade gliomas. In contrast, ErbB4 expression was most pronounced in low-grade gliomas. ErbB2 protein expression was mainly seen in high-grade gliomas; ErbB3 protein expression was low in all gliomas analyzed and ErbB4 protein expression was significantly higher in low-grade gliomas than in high-grade gliomas ($P=0.007$). In meningiomas, quantitative RT-PCR revealed expression of EGFR, ErbB2, and ErbB4 mRNA in the majority of the tumors, while ErbB3 was detected in only one of the meningiomas analyzed.

ErbB family receptors mediate major cellular functions implied in tumorigenesis, though their role in meningiomas was not thoroughly studied. Meningiomas represent 30% of primary cranial tumors, are mostly benign, and prevail in the second half of life. Tumor therapy requires information about molecular alterations, and thus Laurendeau et al. [18] thus studied expression of ErbB receptor and ligand genes by real-time RT-PCR in different meningioma grades. They observed that receptors were overexpressed (ErbB1, ErbB2) or underexpressed (ErbB3, ErbB4). Ligands EGF, TGFA, AREG, DTR, BTDR were underexpressed and the neuregulins were overexpressed or underexpressed, while a strong ErbB1-ErbB2 correlation was found. HER-3/4 of the ErbB family have been detected in several cancers but lack substantial investigation in human meningiomas. Arnli et al. [19] evaluated the expression levels of HER-3/4 as potential biomarkers by immunohistochemistry and explored for association to clinical features in a large series of human meningiomas. They investigated 186 primary intracranial meningiomas from adult patients with antibodies against HER-3/4 intracellular domains. Tumors were scored with a staining index (SI) based on cytoplasmic/membranous staining intensity and on the percentage of positive cells and SIs were tested for associations with WHO malignancy grade, tumor subtype, localization, and prognosis. They observed that HER-3/4 were highly expressed in most tumors. Both cytoplasmic and membranous immunoreactivity occurred, and for HER4 nuclear immunoreactivity was observed as well. Further, HER-3/4 immunoreactivity was not associated with WHO malignancy grade, nor with recurrence or survival in adjusted analyses. Meningiomas of all grades were shown to widely express both HER-3/4 receptors. They concluded that this feature might have diagnostic value since non-neoplastic meninges were not immunoreactive.

Meningiomas arising from the arachnoid/meningeal layer, are nonresponsive to chemotherapies, with 50% showing loss of the Neurofibromatosis 2 (NF2) tumor suppressor gene. Beauchamp et al. [20] reported increased expression of several ligands in NF2-null human arachnoidal cells (ACs) and the meningioma cell line Ben-Men-1, particularly neuregulin-1/herregulin (NRG1), and confirm increased NRG1 secretion and activation of ERBB3. Conditioned-medium from NF2-null ACs or exogenous NRG1 stimulated ERBB3, EPHA2, and mTORC1/2 signaling, suggested pathway crosstalk. NF2-null cells were treated with an ERBB3-neutralizing antibody,

which led to partial downregulation of mTOR pathway activation but showed no effect on viability. Their mTORC1/2 inhibitor treatment decreased NRG1 expression and downregulated ERBB3 while re-activating pAkt T308, thus suggesting a mechanism independent of NRG1-ERBB3 but likely involving activation of another upstream receptor kinase. Transcriptomics after mTORC1/2 inhibition confirmed decreased ERBB3/ERBB4 while revealing increased expression of insulin-like growth factor receptor 1 (IGF1R). Drug treatment co-targeting mTORC1/2 and IGF1R/insulin receptor weakend pAkt T308 and showed synergistic effects on viability. Their findings indicated that NF2 loss leads to secretion/activation of NRG1-ERBB3 signaling. mTORC1/2 inhibition downregulated NRG1-ERBB3, while upregulating pAkt T308 involving IGF1R/insulin receptor and co-targeting these pathways might prove effective for treatment of NF2-deficient meningiomas.

Human meningiomas grow slowly and have a favourable prognosis; however, some are prone to recur despite their benign histology. Torp et al. [21], in their previous studies have published papers on the expression of epidermal growth factor receptor (EGFR) family, comprising ErbB1/EGFR, ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4, in human meningiomas. Their present study aimed to assess the clinicopathological significance of their concurrent expression. They report that 185 grade 1 and 2 meningiomas with robust clinical data underwent immunohistochemical analyses with antibodies against the aforementioned receptors. They observed that all meningiomas exhibited upregulation of these receptor proteins relative to normal meninges. In addition, the expression of phosphorylated/activated ErbB1/EGFR1 and phosphorylated/activated ErbB2/HER2 was significantly associated with histological malignancy grade and prognosis, respectively. The concurrent upregulation of ErbB receptors in human meningioma supported their fundamental role in the tumourigenesis of these tumours, and they could thus be exploited in diagnostics, prognosis, and ultimately, in targeted clinical interventions.

Many of the different synergies represented as combinations of genes/proteins have been experimentally tested and published. However, there are combinations that have yet to be explored. I address the problem of identifying these unexplored combinations via use of a machine learning based search engine in the next section.

1.3. Insight behind the work

Across all search engines has the fundamental principle remains the same i.e to capture the pattern available in the data and based on that pattern, rank a list of queries. Different algorithms can be applied, however if the fundamental pattern is captured accurately, then the rankings will remain approximately the same, with slight variations, across the different kinds of search engines used. I use one search engine, however, vary the way the patterns are captured via use of different sensitivity methods. Each sensitivity method uses a different flavour/mathematical formulation to compute the sensitivity indices to estimate the influence of the involved factors. These involved factors are genes that play a role in cell biology, in the above research. The insight is that all methods will capture the sensitivity of the involved factors based on their recorded regulations and the search engine will rank the combination of factors based on these sensitivity indices. Since the role of involved factors are captured properly,

the search engine will give appropriate rankings to the combinations, thus capturing which gene combinations might be playing significantly in a biological phenomena. The above work shows rankings for experimentally confirmed combinations as well as unexplored/untested combinations. These rankings are not just numbers. They point to the existence of biological synergy in the form of gene combinations, whether tested in wet lab or unexplored till now. Finally, the findings suggest that the rankings are conserved across the different sensitivity methods used.

1.4. Combinatorial search problem and a possible solution

In a recently published work Sinha [2], a frame work of a search engine was developed which can rank combinations of factors (genes/proteins) in a signaling pathway. The work uses SVM package by Joachims [22] in https://www.cs.cornell.edu/people/tj/svm_light/svm_rank.html. I use the adaptation to rank 2^{nd} order gene combinations. The sensitivity package by Pujol et al. [23] was used to develop the search engine pipeline. The current research uses the Hilbert Schmidt Independence Criterion (HSIC) and SOBOL method, implemented in the sensitivity package mentioned above. I use three different kernels under the HSIC method namely, • laplace, • linear and • rbf. For SOBOL method, I use • sobol-2002, and • sobol-jansen. Each of these variants or kernels have been implemented in the sensitivity package and option has been provided in the search engine code to generate the rankings for a particular gene, using a choice of a kernel/variant at a time. Technical details about the variants and kernels can be found in references citetd in Pujol et al. [23].

2. Methods

2.1. Static data from Patel et al. [1]

Patel et al. [1] analyzed 160 meningioma samples from 140 patients, and according to the WHO histopathological classification system for meningioma, they found 121 tumors were of grade I (benign), 32 were of grade II (atypical), and 7 were of grade III (malignant). To determine whether meningiomas could be differentiated based on gene expression profiles, they used principal component analysis (PCA) on a discovery set of 97 tumors (i.e 77 WHO grade I and 20 WHO grade II). Next, they employed nonnegative matrix factorization (NMF) clustering (a unsupervised machine-learning approach) for $k = 2$ to $k = 7$ using the 1,500 genes that varied most among the tumor samples. They report that after 1,000 iterations, 3 clusters ($k = 3$) emerged as providing the best fit as determined by the consensus membership, cophenetic, and silhouette scores. They evaluated the cluster significance of the 3 subtypes using SigClust (Huang et al. [24]) and observed statistical significance between cluster boundaries, which exhibited significant differences in WHO grade representation.

2.2. Design for static data from Patel et al. [1]

The procedure begins with the listing of all C_k^n combinations for k number of genes from a total of n genes. Here n can be the choice of the biologist. k is ≥ 2 and $\leq (n - 1)$. Each of the combination of order k represent a unique set of interaction between the involved genetic factors. Since the sensitivity analysis methods require a sample for a particular observation, a steep gaussian distribution was generated with a jitter (noise) added to the deviation from the reported point measurement of 0.005. In this experiment, the distribution contained 10 measurements (including the point of measurement under consideration). This is repeated for each point of measurement.

To have an averaged ranking, the experiment was designed to run for 25 iterations. In each iteration, 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 a required format. Details of formatting the data have not been presented in the article to maintain the fluidity and brevity. Interested readers can find examples of formatting the data in the sensitivity analysis package in R. Sensitivity analysis and its relevance in systems biology have been covered in a recently published article by Sinha [25], which forms the foundation for this work. 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.

After the above sensitivity indices have been stored for each of the p^{th} combination, for a chosen sensitivity analysis method, the next step in the design of experiment is conducted. Here, the indices are averaged per combination to have a mean index value. These index values form the discriminative features for a particular combination. For a k^{th} order combination, a vector of k elements or indices forms a feature vector. Thus for C_k^n combinations there will be C_k^n vectors, each containing k elements. Next, SVM_{learn}^{Rank} Joachims [22] 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 [22]. This is followed by sorting of these scores along with the rank 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.

Note that the following is the order in which the files should be executed in R Team [26], in order, for obtaining the desired results (Note that the code will not be explained here) - • use source("extractMeningiomadata.R") • use source("manuscript-2-2.R") • use source("SVMRank-Results-S-mean.R").

2.3. Translating the pipeline into code of execution in R

The execution begins by some preprocessing of the file containing the information regarding the down regulated genes via `source("extractMeningiomadata.R")`. The library containing the sensitivity analysis methods is then loaded in the interface us-

ing the command `library(sensitivity)` (Note - this package can be downloaded for free from <https://cran.r-project.org/web/packages/sensitivity/index.html>). Next a gaussian distribution for a particular transcript level for a gene is generated to have a sample. This is needed in the computation of sensitivity index for that particular gene. A gene of particular choice is selected (in blue) and the choice of the combination is made (here $k = 2$). Later a kernel is used (here rbf for HSIC method). 25 different indices are generated which help in generating aggregate rank using these 25 indices. The Support vector ranking algorithm is employed to generate the scores for different combinations and these scores are then sorted out. This is done using the command `source("SVMRank - Results - S - mean.R")`. A file is generated that contains the combinations in increasing order of influence. Note that 1 means lowest rank and vice versa, for 2^{nd} order combinations for any gene using a particular density based sensitivity index.

2.4. Regarding biological insight

For the recorded gene expression values, the sensitivity indices are computed. The search engine uses the kernel based density method. The kernel method takes the data, that is in a lower dimensional plane and projects it to a higher dimensional plane, with an idea that in a higher dimensional place, there exists a dot product between the projected data. To simply state, the idea is that in a higher dimensional plane the nonlinearities between the data (in lower dimensional plane) will be captured and the data may be segregated from each other via a hyperplane. So, irrespective of the method used to measure the gene expression values, if the measurements capture biological information (to whatever extent they can), then the kernel method will be able to capture the nonlinearities/synergies, if existing and allow the sensitivity analysis method (here density based method) to estimate the strength of influence of each of the factors. Based on the sensitivity indices of combinations of a particular order, the search engine ranks the combinations. Details of search engine are provided in the published work in Sinha [2].

It is important to note that the search engine will not give insight about the mechanism of synergy between the components of a combination. However, if the synergy exists between components of an unexplored/untested combination, then the sensitivity indices will capture the influence of these components taken together (which form a combination of interest) and will rank the combination appropriately. These rankings provide insight about which combination a biologist/oncologist might want to test in a forest of combinations for a given scenario in a cell (whether normal or pathological).

3. Results & Discussion

3.1. ERBB3 related synergies

Note - ERBB3 was found to be upregulated in Type A. Upregulation was defined as Type logFC to be > 1 and $FDR \leq 0.001$, in Patel et al. [1]. Also, sorting of scores

by the machine learning algorithm were done in ascending order, i.e - top is lowest in ranking. A total of 307 2nd order combinations of ERBB3 were recorded.

3.1.1. ERBB3 - Individual genes

The following genes were found to show high rankings along with ERBB3 - malic enzyme 1 (ME1), protein kinase C zeta (PRKCZ), ribosomal protein S6 kinase A2 (RPS6KA2), ST6 beta-galactoside alpha-2,6-sialyltransferase 1 (ST6GAL1), FOS like 2, AP-1 transcription factor subunit (FOSL2), calmodulin regulated spectrin associated protein family member 3 (CAMSAP3), solute carrier family 4 member 4 (SLC4A4), immunoglobulin superfamily member 9 (IGSF9), EBF family member 4 (EBF4), solute carrier family 7 member 8 (SLC7A8), ezrin (EZR), BMP and activin membrane bound inhibitor (BAMBI), protein kinase C and casein kinase substrate in neurons 2 (PACSIN2), apolipoprotein L4 (APOL4), papilin, proteoglycan like sulfated glycoprotein (PAPLN), ring finger protein 24 (RNF24), WAP four-disulfide core domain 2 (WFDC2), fms related receptor tyrosine kinase 1 (FLT1), neurocalcin delta (NCALD), tight junction protein 3 (TJP3), RUN domain containing 3B (RUNDC3B), FA complementation group E (FANCE), phosphatase and actin regulator 1 (PHACTR1), RNA binding motif protein 24 (RBM24), ectonucleotide pyrophosphatase/phosphodiesterase family member 5 (ENPP5), glutaminyl-peptide cyclotransferase (QPCT), microtubule affinity regulating kinase 1 (MARK1), SSX family member 2 interacting protein (SSX2IP), interferon regulatory factor 6 (IRF6), ATP binding cassette subfamily G member 2 (JR blood group) (ABCG2), polypeptide N-acetylgalactosaminyltransferase 12 (GALNT12), citron rho-interacting serine/threonine kinase (CIT), ATP binding cassette subfamily C member 4 (PEL blood group) (ABCC4), G protein subunit alpha z (GNAZ), beta-1,4-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase (MGAT3), LIF interleukin 6 family cytokine (LIF), filamin C (FLNC), low density lipoprotein receptor (LDLR), argininosuccinate synthase 1 (ASS1), castor zinc finger 1 (CASZ1), EPS8 signaling adaptor L1 (EPS8L1), LARGE xylosyl- and glucuronyltransferase 1 (LARGE1), unc-79 homolog, NALCN channel complex subunit (UNC79), tetratricopeptide repeat domain 9 (TTC9), proline rich and Gla domain 4 (PRRG4), protein phosphatase 1 regulatory inhibitor subunit 1A (PPP1R1A), neuronal migration (KIAA0319), GIPC PDZ domain containing family member 2 (GIPC2), HECT and RLD domain containing E3 ubiquitin protein ligase 5 (HERC5), RasGEF domain family member 1B (RASGEF1B), cyclin dependent kinase like 2 (CDKL2), epidermal growth factor (EGF), shisa like 1 (KIAA1644), ring finger protein 157 (RNF157), solute carrier family 47 member 1 (SLC47A1), PR/SET domain 16 (PRDM16), coiled-coil domain containing 150 (CCDC150), immunoglobulin superfamily member 11 (IGSF11), scavenger receptor cysteine rich family member with 4 domains (SSC4D), astrotactin 2 (ASTN2), lipocalin 2 (LCN2), coiled-coil domain containing 81 (CCDC81), cadherin 8 (CDH8), family with sequence similarity 124 member A (FAM124A), calcium voltage-gated channel auxiliary subunit alpha2delta 1 (CACNA2D1), serine and arginine rich splicing factor 12 (SRSF12), solute carrier family 26 member 2 (SLC26A2), glutamate receptor interacting protein 1 (GRIP1), SH3 domain containing ring finger 2 (SH3RF2), STEAP2 metalloredutase (STEAP2), nucleophosmin/nucleoplasmin 2 (NPM2), actin alpha cardiac muscle 1 (ACTC1), cholinergic receptor nicotinic beta

2 subunit (CHRNA2), cytochrome P450 family 3 subfamily A member 4 (CYP3A4), NHS like 3 (KIAA1522), FHF complex subunit HOOK interacting protein 1A (FAM160A1), ankyrin repeat domain 33B (ANKRD33B), lysine demethylase 1B (KDM1B), phytanoyl-CoA 2-hydroxylase interacting protein like (PHYHIPL), protein phosphatase 1 regulatory subunit 36 (PPP1R36), calcium voltage-gated channel auxiliary subunit beta 2 (CACNB2), serine peptidase inhibitor, Kunitz type 1 (SPINT1), sodium voltage-gated channel beta subunit 3 (SCN3B), serpin family B member 8 (SERPINB8), myosin IA (MYO1A), phytanoyl-CoA 2-hydroxylase interacting protein (PHYHIP), RAB3B, member RAS oncogene family (RAB3B), OTU deubiquitinase 7A (OTUD7A), CDC42 binding protein kinase gamma (CDC42BPG), anoctamin 5 (ANO5), cilia and flagella associated protein 46 (CFAP46), angiopoietin like 7 (ANGPTL7), interferon stimulated exonuclease gene 20 (ISG20), membrane bound glycerophospholipid O-acyltransferase 1 (MBOAT1), bisphosphoglycerate mutase (BPGM), cold shock domain containing C2 (CSDC2), radial spoke head component 9 (RSPH9), carboxylesterase 4A (CES4A), ciliary microtubule associated protein 3 (CIMP3 / PIFO), solute carrier organic anion transporter family member 2A1 (SLCO2A1), solute carrier family 35 member G1 (SLC35G1), potassium voltage-gated channel subfamily A member 2 (KCNA2), LRRN4 C-terminal like (LRRN4CL), G protein-coupled receptor 4 (GPR4), endoplasmic reticulum to nucleus signaling 1 (ERN1), transmembrane protein 125 (TMEM125), WSC domain containing 1 (WSCD1), transmembrane protein 30B (TMEM30B), synemin (SYMN), calpain 12 (CAPN12), family with sequence similarity 162 member B (FAM162B), coiled-coil serine rich protein 1 (CCSER1), MAF bZIP transcription factor F (MAFF), RNA binding motif protein 11 (RBM11), transcobalamin 2 (TCN2), insulin induced gene 1 (INSIG1), natural killer cell cytotoxicity receptor 3 ligand 1 (NCR3LG1), family with sequence similarity 78 member B (FAM78B), FAT atypical cadherin 4 (FAT4), solute carrier family 6 member 9 (SLC6A9), laminin subunit beta 3 (LAMB3), ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), AFDN divergent transcript (AFDN-DT), sterol regulatory element binding transcription factor 2 (SREBF2), family with sequence similarity 120A2, pseudogene (FAM120A2P / C9orf129) and SEC14 like lipid binding 6 (SEC14L6).

Using the adaptation of the above mentioned search engine, I was able to tabulate 2nd order combinations of ERBB3 with these genes, that were reported to be upregulated in Patel et al. [1].

Table 1 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in table 2 generated from analysis of the ranks in table 1.

| RANKING INDIVIDUAL MEMBERS VS ERBB3 | | | | | | | | | |
|---|---------|--------|-----|--------|------------------|---------|--------|-----|--------|
| RANKING OF INDIVIDUAL MEMBERS W.R.T ERBB3 | | | | | | | | | |
| | laplace | linear | rbf | jansen | | laplace | linear | rbf | jansen |
| ME1 - ERBB3 | 160 | 270 | 234 | 78 | PRKCZ - ERBB3 | 274 | 273 | 207 | 122 |
| RPS6KA2 - ERBB3 | 229 | 209 | 226 | 206 | ST6GAL1 - ERBB3 | 192 | 292 | 189 | 110 |
| FOSL2 - ERBB3 | 245 | 189 | 255 | 73 | CAMSAP3 - ERBB3 | 143 | 245 | 103 | 193 |
| SLC4A4 - ERBB3 | 136 | 278 | 173 | 178 | IGSF9 - ERBB3 | 102 | 213 | 214 | 149 |
| EBF4 - ERBB3 | 157 | 199 | 263 | 109 | SLC7A8 - ERBB3 | 181 | 264 | 275 | 89 |
| BAMBI - ERBB3 | 283 | 196 | 277 | 152 | PACIN2 - ERBB3 | 121 | 259 | 217 | 177 |
| PAPLN - ERBB3 | 187 | 131 | 237 | 161 | RNF24 - ERBB3 | 164 | 177 | 205 | 202 |
| WFDC2 - ERBB3 | 234 | 80 | 231 | 242 | FLT1 - ERBB3 | 297 | 305 | 222 | 77 |
| NCALD - ERBB3 | 170 | 111 | 192 | 279 | TJP3 - ERBB3 | 85 | 198 | 167 | 256 |
| RUNDC3B - ERBB3 | 163 | 66 | 252 | 280 | PHACTR1 - ERBB3 | 227 | 184 | 193 | 82 |
| RBM24 - ERBB3 | 280 | 161 | 289 | 211 | QPCT - ERBB3 | 200 | 303 | 243 | 162 |
| MARK1 - ERBB3 | 275 | 307 | 253 | 113 | SSX2IP - ERBB3 | 144 | 183 | 228 | 159 |
| IRF6 - ERBB3 | 267 | 172 | 164 | 24 | ABCG2 - ERBB3 | 125 | 169 | 182 | 172 |
| GALNT12 - ERBB3 | 221 | 211 | 157 | 115 | CIT - ERBB3 | 253 | 187 | 142 | 92 |
| ABCC4 - ERBB3 | 177 | 248 | 82 | 198 | GNAZ - ERBB3 | 291 | 193 | 227 | 231 |
| MGAT3 - ERBB3 | 249 | 301 | 183 | 153 | LIF - ERBB3 | 214 | 296 | 175 | 81 |
| FLNC - ERBB3 | 151 | 79 | 197 | 147 | LDLR - ERBB3 | 290 | 256 | 262 | 119 |
| ASS1 - ERBB3 | 207 | 290 | 171 | 124 | CASZ1 - ERBB3 | 65 | 157 | 274 | 199 |
| EPS8L1 - ERBB3 | 199 | 154 | 150 | 158 | LARGE1 - ERBB3 | 223 | 282 | 267 | 85 |
| UNC79 - ERBB3 | 18 | 214 | 294 | 180 | TTC9 - ERBB3 | 148 | 243 | 272 | 176 |
| PRRG4 - ERBB3 | 228 | 283 | 279 | 87 | PPP1R1A - ERBB3 | 44 | 251 | 195 | 146 |
| KIAA0319 - ERBB3 | 156 | 229 | 184 | 129 | GIPC2 - ERBB3 | 250 | 268 | 265 | 114 |
| HERC5 - ERBB3 | 167 | 167 | 305 | 143 | RASGEF1B - ERBB3 | 235 | 304 | 299 | 140 |
| CDKL2 - ERBB3 | 1 | 176 | 188 | 200 | EGF - ERBB3 | 96 | 148 | 162 | 226 |
| KIAA1644 - ERBB3 | 293 | 231 | 104 | 208 | RNF157 - ERBB3 | 255 | 271 | 268 | 66 |
| SLC47A1 - ERBB3 | 155 | 219 | 282 | 74 | PRDM16 - ERBB3 | 33 | 180 | 269 | 189 |
| CCDC150 - ERBB3 | 47 | 168 | 241 | 185 | IGSF11 - ERBB3 | 147 | 178 | 203 | 184 |
| SSC4D - ERBB3 | 178 | 201 | 224 | 217 | ASTN2 - ERBB3 | 49 | 218 | 158 | 210 |
| LCN2 - ERBB3 | 288 | 49 | 165 | 249 | CCDC81 - ERBB3 | 220 | 252 | 296 | 212 |
| CDH8 - ERBB3 | 112 | 205 | 153 | 237 | FAM124A - ERBB3 | 246 | 226 | 86 | 245 |
| CACNA2D1 - ERBB3 | 174 | 277 | 258 | 68 | SRSF12 - ERBB3 | 183 | 186 | 218 | 59 |
| SLC26A2 - ERBB3 | 242 | 164 | 43 | 239 | GRIP1 - ERBB3 | 41 | 185 | 276 | 142 |
| SH3RF2 - ERBB3 | 169 | 242 | 300 | 88 | STEAP2 - ERBB3 | 284 | 204 | 133 | 190 |
| NPM2 - ERBB3 | 266 | 234 | 181 | 135 | ACTC1 - ERBB3 | 271 | 241 | 242 | 170 |
| CHRN2 - ERBB3 | 238 | 272 | 179 | 43 | CYP3A4 - ERBB3 | 300 | 188 | 172 | 191 |
| KIAA1522 - ERBB3 | 292 | 166 | 306 | 72 | FAM160A1 - ERBB3 | 189 | 145 | 290 | 54 |
| ANKRD33B - ERBB3 | 46 | 232 | 221 | 160 | KDM1B - ERBB3 | 76 | 294 | 177 | 173 |
| PPP1R36 - ERBB3 | 289 | 227 | 215 | 154 | CACNB2 - ERBB3 | 198 | 280 | 204 | 130 |
| SPINT1 - ERBB3 | 140 | 247 | 297 | 213 | SCN3B - ERBB3 | 185 | 142 | 163 | 195 |
| SERPIN8 - ERBB3 | 258 | 299 | 295 | 169 | MYO1A - ERBB3 | 13 | 258 | 169 | 175 |
| PHYHIP - ERBB3 | 243 | 81 | 148 | 288 | RAB3B - ERBB3 | 282 | 144 | 210 | 203 |
| OTUD7A - ERBB3 | 231 | 265 | 248 | 127 | ANO5 - ERBB3 | 251 | 143 | 219 | 51 |
| CFAP46 - ERBB3 | 259 | 266 | 155 | 171 | ANGPTL7 - ERBB3 | 217 | 250 | 111 | 219 |
| ISG20 - ERBB3 | 216 | 181 | 200 | 163 | MBOAT1 - ERBB3 | 90 | 238 | 235 | 156 |
| BPGM - ERBB3 | 268 | 223 | 271 | 56 | CSDC2 - ERBB3 | 305 | 162 | 76 | 272 |
| RSPH9 - ERBB3 | 190 | 135 | 198 | 196 | CES4A - ERBB3 | 186 | 279 | 239 | 167 |
| PIFO - ERBB3 | 260 | 171 | 302 | 74 | SLCO2A1 - ERBB3 | 254 | 206 | 257 | 123 |
| SLC35G1 - ERBB3 | 244 | 298 | 273 | 58 | KCNA2 - ERBB3 | 294 | 150 | 105 | 215 |
| LRRN4CL - ERBB3 | 149 | 128 | 247 | 157 | GPR4 - ERBB3 | 180 | 182 | 250 | 155 |
| ERN1 - ERBB3 | 172 | 246 | 246 | 111 | TMEM125 - ERBB3 | 171 | 163 | 116 | 227 |
| WSCD1 - ERBB3 | 176 | 222 | 261 | 192 | TMEM30B - ERBB3 | 210 | 175 | 220 | 47 |
| CAPN12 - ERBB3 | 269 | 191 | 194 | 83 | FAM162B - ERBB3 | 35 | 195 | 196 | 265 |
| CCSER1 - ERBB3 | 209 | 126 | 256 | 229 | MAFF - ERBB3 | 194 | 210 | 154 | 214 |
| RBM11 - ERBB3 | 296 | 263 | 201 | 201 | TCN2 - ERBB3 | 295 | 281 | 187 | 150 |
| INSIG1 - ERBB3 | 287 | 302 | 254 | 138 | NCR3LG1 - ERBB3 | 286 | 224 | 213 | 148 |
| FAM78B - ERBB3 | 273 | 267 | 156 | 116 | FAT4 - ERBB3 | 208 | 76 | 285 | 224 |
| SLC6A9 - ERBB3 | 299 | 297 | 212 | 186 | LAMB3 - ERBB3 | 247 | 285 | 151 | 55 |
| ENPP1 - ERBB3 | 298 | 255 | 211 | 235 | AFDN-DT - ERBB3 | 225 | 306 | 286 | 70 |
| SREBF2 - ERBB3 | 196 | 217 | 174 | 165 | C9orf129 - ERBB3 | 272 | 194 | 73 | 229 |
| SEC14L6 - ERBB3 | 201 | 107 | 159 | 260 | | | | | |

Table 1: 2nd order interaction ranking between ERBB3 VS Individual members.

One can also interpret the results of the table 1 graphically, with the following influences - • Individual members w.r.t ERBB3 with ERBB3 – > ME1 / PRKCZ / RPS6KA2 / ST6GAL1 / FOSL2 / CAMSAP3 / SLC4A4 / IGSF9 / EBF4 / SLC7A8 / BAMBI / PACSIN2 / PAPLN / RNF24 / WFDC2 / FLT1 / NCALD / TJP3 / RUNDC3B / PHACTR1 / RBM24 / QPCT / MARK1 / SSX2IP / IRF6 / ABCG2 / GALNT12 / CIT / ABCC4 / GNAZ / MGAT3 / LIF / FLNC / LDLR / ASS1 / CASZ1 / EPS8L1 / LARGE1 / UNC79 / TTC9 / PRRG4 / PPP1R1A / KIAA0319 / GIPC2 / HERC5 / RAS-GEF1B / CDKL2 / EGF / KIAA1644 / RNF157 / SLC47A1 / PRDM16 / CCDC150 / IGSF11 / SSC4D / ASTN2 / LCN2 / CCDC81 / CDH8 / FAM124A / CACNA2D1 / SRSF12 / SLC26A2 / GRIP1 / SH3RF2 / STEAP2 / NPM2 / ACTC1 / CHRN2 / CYP3A4 / KIAA1522 / FAM160A1 / ANKRD33B / KDM1B / PPP1R36 / CACNB2 / SPINT1 / SCN3B / SERPINB8 / MYO1A / PHYHIP / RAB3B / OTUD7A / ANO5 / CFAP46 / ANGPTL7 / ISG20 / MBOAT1 / BPGM / CSDC2 / RSPH9 / CES4A / PIFO / SLC02A1 / SLC35G1 / KCNA2 / LRRN4CL / GPR4 / ERN1 / TMEM125 / WSCD1 / TMEM30B / CAPN12 / FAM162B / CCSER1 / MAFF / RBM11 / TCN2 / INSIG1 / NCR3LG1 / FAM78B / FAT4 / SLC6A9 / LAMB3 / ENPP1 / AFDN-DT / SREBF2 / C9orf129 / SEC14L6.

4. Conclusion

Presented here are a range of multiple synergistic ERBB3 2nd order combinations that were ranked via a machine learning based search engine. Via majority voting across the ranking methods, it was possible to find plausible unexplored synergistic combinations of ERBB3-X that might be prevalent in meningioma.

Conflict of interest

There are no conflicts to declare.

Author's contributions

Concept, design, in silico implementation - SS. Analysis and interpretation of results - SS. Manuscript writing - SS. Manuscript revision - SS. Approval of manuscript - SS

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Source of Data

Data used in this research work was released in a publication in Patel et al. [1]. Permission to use, granted by PNAS.

UNEXPLORED COMBINATORIAL HYPOTHESES

Individual members w.r.t ERBB3

ME1 / PRKCZ / RPS6KA2 / ST6GAL1 / FOSL2 /
 CAMSAP3 / SLC4A4 / IGSF9 / EBF4 / SLC7A8 /
 BAMBI / PACSIN2 / PAPLN / RNF24 / WFDC2 /
 FLT1 / NCALD / TJP3 / RUNDC3B / PHACTR1 /
 RBM24 / QPCT / MARK1 / SSX2IP / IRF6 /
 ABCG2 / GALNT12 / CIT / ABCC4 / GNAZ /
 MGAT3 / LIF / FLNC / LDLR / ASS1 / CASZ1 /
 EPS8L1 / LARGE1 / UNC79 / TTC9 / PRRG4 /
 PPP1R1A / KIAA0319 / GIPC2 / HERC5 / RASGEF1B /
 CDKL2 / EGF / KIAA1644 / RNF157 / SLC47A1 /
 PRDM16 / CCDC150 / IGSF11 / SSC4D / ASTN2 /
 LCN2 / CCDC81 / CDH8 / FAM124A / CACNA2D1 /
 SRSF12 / SLC26A2 / GRIP1 / SH3RF2 / STEAP2 /
 NPM2 / ACTC1 / CHRNA2 / CYP3A4 / KIAA1522 /
 FAM160A1 / ANKRD33B / KDM1B / PPP1R36 / CACNB2 /
 SPINT1 / SCN3B / SERPINB8 / MYO1A / PHYHIP /
 RAB3B / OTUD7A / ANO5 / CFAP46 / ANGPTL7 /
 ISG20 / MBOAT1 / BPGM / CSDC2 / RSPH9 / CES4A
 PIFO / SLCO2A1 / SLC35G1 / KCNA2 / LRRN4CL /
 GPR4 / ERN1 / TMEM125 / WSCD1 / TMEM30B / CAPN12
 FAM162B / CCSER1 / MAFF / RBM11 / TCN2 /
 INSIG1 / NCR3LG1 / FAM78B / FAT4 / SLC6A9 /
 LAMB3 / ENPP1 / AFDN-DT / SREBF2 / C9orf129 / SEC14L6 ERBB3

Table 2: 2nd order combinatorial hypotheses between ERBB3 and Individual members.

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