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Alzheimer's Disease Susceptibility Genes in Malignant Breast Tumors

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Abstract

Background: Cognitive problems have been reported in breast cancer patients after chemotherapy. A small group of older breast cancer survivors carrying the APOE4 gene, receiving chemotherapy, was at increased risk of long-term impairment of brain function. We have analyzed the expression of APOE and the next 23-ranked Alzheimer's disease (AD) susceptibility genes in malignant breast tumors. We wished to determine if these 24 genes might be related to breast cancer.

Methods: To identify the most important AD susceptibility genes, we consulted the ALZGENE database (www.alzgene.org/) which displays this information and regularly updates it. To analyze the effect of AD susceptibility genes on breast cancer, we used The Cancer Genome Atlas (TCGA). We analyzed TCGA data with cBioPortal for Cancer Genomics. cBioPortal provides visualization, analysis, and download of large-scale cancer genomic data sets. cBioPortal can analyze APOE in breast tumors but cannot distinguish its three alleles: E2, E3, and E4.

Results: About 1.6% of the tumors had APOE amplification (copy number alteration). Two percent of the tumors had CD33 alterations. None of the tumors had APOE mutations. Two tumors had CD33 missense mutations of unknown significance. Expression heatmap shows that over- or underexpression of APOE and CD33 was correlated in most of the tumors. APOE alteration significantly co-occurred with CD33 and CD2AP.

Conclusion: Alterations of certain cancer genes tend to co-occur, indicating that they may work in tandem to drive tumor formation and development. This may be the case with the co-occurring alterations of APOE, CD33, and CD2AP. It would be important to know which APOE allele(s) were co-occurrent with CD33 and CD2AP and whether co-occurrence in the tumor predicted increased risk of AD. This information could help in identification of specific risk factors for breast cancer-related cognitive decline in older women, which has important implications for oncology care.

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Conflicts of interest

There are no conflicts of interest.

Keywords

cBioPortal; co-occurrence; dementia; The Cancer Genome Atlas

INTRODUCTION

Dementia, cognitive difficulties, and breast cancer are related, especially in older women. For example, a link may exist between markers of biological aging and cognitive performance in older survivors of breast cancer. However, a 6-year observational cohort study identified no detrimental effect of endocrine therapy on cognitive function in survivors of early-stage breast cancer, compared with those who were not receiving endocrine therapy.[1]

Among women treated for early-stage breast cancer an average of 4 years previously, both high DNA damage and low telomerase activity appear to be related to worse executive functioning. High DNA damage is associated with worse memory, and low telomerase activity is associated with worse attention and motor speed.[2]

High DNA damage and low telomerase activity could be the result of chemotherapy and have nothing to do with aging or markers of normal biological aging. There are not enough data in the literature currently to comment on whether these two markers are associated with cognitive function in cancer survivors not treated with chemotherapy. Cognitive changes and deficits in patients with cancer and in remission can be linked to the direct effects of cancer itself, nonspecific factors, or other illnesses unrelated to the treatments or combination of treatments administered.[3]

Cognitive problems have been reported in breast cancer patients after chemotherapy.[4] A small group of older breast cancer survivors carrying the APOE4 gene, receiving chemotherapy, was at increased risk of long-term impairment in brain function.[5] In addition, the frequency of APOE4 in early-onset breast cancer survivors is increased (odds ratio: 2.15).[6] While APOE is ranked the number one Alzheimer's disease (AD) susceptibility gene, many others have been identified in genome-wide association studies (GWAS).[7]

AD genes might have roles in cancer biology.[8] For example, Feng *et al.* investigated the genetic relationship between AD and cancer using GWAS summary statistics. They found a significant positive genetic correlation between AD and five cancers combined: colon, breast, prostate, ovarian, and lung.[9] Malik *et al.* have identified a relationship between CD33, AD, and acute myeloid leukemia.[10]

In the current study, we analyzed the expression of APOE and the next 23-ranked AD susceptibility genes in malignant breast tumors. We wished to determine if these 24 genes might be related to AD, as well as to tumor pathology.

METHODS

The mean age of 816 patients with breast cancer studied was 59 ± 13. Seventy-three percent were white, 11% black, 7% Asian, and 9% unclassified. 60% had invasive ductal carcinoma,

16% had invasive lobular carcinoma, 11% had mixed ductal–lobular carcinoma, and 13% had other histologies. Nine percent were Stage I, 56% Stage II, and 14% Stage III.

To identify the most important AD susceptibility genes, we consulted the ALZGENE database (http://www.alzgene.org/) which displays this information and regularly updates it.[7] The 695 genes in the database were identified in 1395 studies. As expected, APOE and its three alleles (E2, E3, and E4) were number one [Table 1].

To analyze the effect of AD susceptibility genes on breast cancer, we used The Cancer Genome Atlas (TCGA). TCGA is a project, begun in 2005, to catalog genetic mutations responsible for cancer, employing genome sequencing, and bioinformatics. We used cBioPortal for cancer genomics to analyze data in TCGA. cBioPortal provides visualization, analysis, and download of large-scale cancer genomic data sets.[11] cBioPortal can analyze APOE in breast tumors but cannot distinguish its three alleles: E2, E3, and E4. No Institutional Review Board (IRB) or other approval was needed since TCGA data are public, are unrestricted, and may be accessed and analyzed by anyone.

Gene expression is quantitated as fragments per kilobase of transcript per million mapped reads upper quartile, which is an RNA-Seq-based expression normalization method.[12]

Simple statistics were calculated to identify patterns of mutual exclusivity or co-occurrence. For each pair of query genes (e.g. APOE and CD33), an odds ratio (OR) is calculated (Equation 1) that indicates the likelihood that the events in the two genes are mutually exclusive or co-occurrent across the selected cases.

$$OR = (A \times D) / (B \times C) \quad (1)$$

Where A = number of cases altered in both genes; B = number of cases altered in APOE but not CD33; C = number of cases altered in CD33 but not APOE; and D = number of cases altered in neither gene. Each pair was then assigned to one of three categories indicative of a tendency toward mutual exclusivity, of a tendency toward co-occurrence, or of no association. To determine whether the identified relationship is significant for a gene pair, Fisher's exact test was performed.[11]

RESULTS

APOE was the highest ranking AD gene. Table 1 shows the first 24 AD genes from the ALZGENE database, numbered by rank.

APOE alterations significantly co-occurred with CD33 and CD2AP. Table 2 shows these and other significantly co-occurrent altered AD genes in 816 breast tumor samples. *P* values are Bonferroni adjusted. Q value is derived from the Benjamini–Hochberg false discovery rate correction procedure for multiple comparisons.[13] We are unable to determine whether these alterations were related to cognition. In addition, the large number of cases altered in neither gene [i.e., variable D in Equation 1 and Column 3 in Table 2] actually drives the final odds

ratio, meaning the value given by Equation 1 was at a higher chance to be quite biased. It is not a static for co-occurrence anymore; it is a measure of (or at least highly correlated to) no alterations in both.

About 1.6% of the tumors had APOE amplification (copy number alteration). Two percent of the tumors had CD33 alterations. Although we were unable to distinguish the APOE alleles, we did find that none of the tumors, and therefore none of the alleles, had APOE mutations. Two tumors had CD33 missense mutations of unknown significance. Expression heatmap shows that over- or underexpression of APOE and CD33 was correlated in most of the tumors. We were unable to determine whether over- or underexpression affected cognition. Figure 1 shows an Oncoprint of the APOE gene and CD33 gene in 816 breast tumors.

Alteration did not affect overall survival ($P = 0.592$ logrank test) or disease-free progression. Nor did alteration affect overall survival ($P = 0.947$ logrank test) or disease-free progression in the 11 AD genes that significantly co-occurred. Figure 2 shows the distribution of alterations in 24 AD genes among 816 breast cancers.

Figure 3 shows that APOE mRNA significantly co-expressed with APOC1 mRNA in 812 breast cancers. The APOC1 insertion allele, in combination with APOE E4, is a risk factor for AD.[14]

Figure 4 illustrates APOE, CD2AP, and their network of neighboring genes, including PIK3CA, the second most commonly mutated gene in breast cancer (TP53 is the most common). An arrow signifies a directed interaction, and a line signifies an undirected interaction. A blue arrow signifies control of state of change. The brown lines signify targeted by drug. As indicated in the figure, serum albumin affects the APOE gene. Low serum albumin levels are associated with worse cognition.[15] We were unable to determine if tumor APOE gene expression affects serum APOE levels.

DISCUSSION

Desikan *et al.* have used APOE allele and other genotype information for genetic assessment of age-associated AD risk and development and validation of a polygenic hazard score.[16] The polygenic hazard score combines the effects of more than two dozen genetic variants, most associated by themselves with only a small risk of AD. The polygenic score is better at predicting which cognitively normal older adults will go on to develop Alzheimer's dementia than APOE E4 alone.

Biological processes or pathways in cancer are often deregulated through different genes or by multiple different mechanisms. However, cancer gene alterations usually do not occur at random. Alterations of certain cancer genes tend to co-occur, indicating that they may work in tandem to drive tumor formation and development.[11] This may be the case with the co-occurring alterations in Table 2, especially in APOE, CD33, and CD2AP. Many other genes not included in the analysis might appear to significantly co-occur with APOE. However, these genes have a much weaker relationship to AD; therefore, the significance of the co-occurrent alterations would be uncertain.

One of the fundamental premises of cancer biology is that driver mutations occur in the tissue of origin to cause the tumor; these mutations are expected to be unique to the tumor and should not be found in the rest of the body unless the tumor has metastasized. In this study, we looked, in effect, for germline mutations predisposing toward cancer and AD, which might play into the increased risk of cancer patients for cognitive dysfunction.[17]

Cancer mortality and AD mortality increase with age, but some studies have shown an inverse relationship between the two diseases, that is, older persons with cancer have a reduced risk of AD and vice versa. However, other analyses suggest that AD and brain tumor might be positively correlated. We previously reported a significant positive correlation between AD mortality rate and malignant brain tumor mortality rate 1999–2016 in persons aged 65 years and older in (a) 1,101 US counties, $P < 0.001$ and (b) 50 US states, $P < 0.001$.[18] Moreover, glial cells may play a role in the genesis of AD.[19]

Two separate arguments relate breast cancer to AD: (1) AD genes might contribute to cognitive dysfunction in survivors and (2) AD genes might contribute to breast cancer pathology. These are very different arguments, with different data suggesting each. We think the second is more in keeping with what we have actually shown.

The first (AD genes > cognitive dysfunction in survivors) has a quick rationale. Since APOE E4 has been linked to risk of cognitive impairment in cancer survivors, other AD risk genes might also be present in cancer patients and might contribute to cognitive impairment in cancer survivors.

The second argument (AD genes might contribute to breast cancer pathology) is more cogent. To support it, we looked for AD gene mutations or copy number variations in tumor tissue. The rationale is different. In this case, we assumed that known AD genes also play roles in cancer biology. However, we could not look at the connection between tumor mutations and cognitive function with the data at hand.

Persons with one or more APOE E4 alleles, having one or more copies of the CD33 risk allele (rs3865444 C), are at increased risk of cognitive decline compared with APOE E4 carriers, no doubt reflected by the co-occurrence of APOE and CD33 alterations in the breast tumors. AD pathology is also more severe in neuroimaging studies when both APOE E4 and the CD33 risk allele are involved.[20–22] Several single-nucleotide polymorphisms in CD2AP are associated with a higher risk for AD, and CD2AP loss of function is linked to enhanced Aβ production, tau-induced neurotoxicity, and reduced blood–brain barrier integrity.[23]

It would be important to know which APOE allele (s) were co-occurrent with CD33 and CD2AP and whether co-occurrence in the tumor predicted increased risk of AD. This information could help in identification of specific risk factors for breast cancer-related cognitive decline in older women, which has important implications for oncology care; 75% of breast cancer survivors in the United States are 60 years of age and older. If more risk factors were known, perhaps a patient’s therapy and aftercare might be adjusted accordingly.[5]

A weakness in our study is that we focused on the first 24 AD susceptibility genes. We found eight pairs of genes that tended to co-occur [Table 2]. Only the co-occurrences of CD33 and CD2AP with APOE were further analyzed. We focused on these genes because AD genes below the first 24 have quite a small influence on the disease. Nevertheless, many other genes, as a result of a huge reduction in the number of tests, might appear to co-occur with APOE statistically significantly.

Another weakness is that the expressions of APOE and CD33 showed both positive and negative correlations [Figure 1]. Visually, it appears to be balanced between negative and positive cases, suggesting that the co-alteration in the two genes (i.e., positive cases) was weighing not significantly highly as opposed to being not related. This again indicates that the algorithm used to estimate co-occurrence could be significantly biased.

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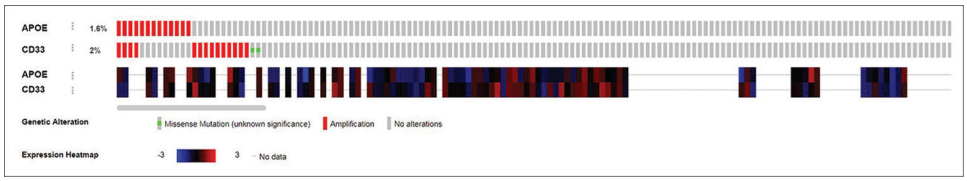

Figure 1.

Oncoprint of the APOE gene and CD33 gene in 816 breast tumors, represented by small vertical rectangles. About 1.6% of the tumors had APOE amplification (copy number alteration). Two percent of the tumors had CD33 alterations. None of the tumors had APOE mutations. Two tumors had CD33 missense mutations of unknown significance. Expression heatmap shows that over- or underexpression of APOE and CD33 was correlated in most of the tumors

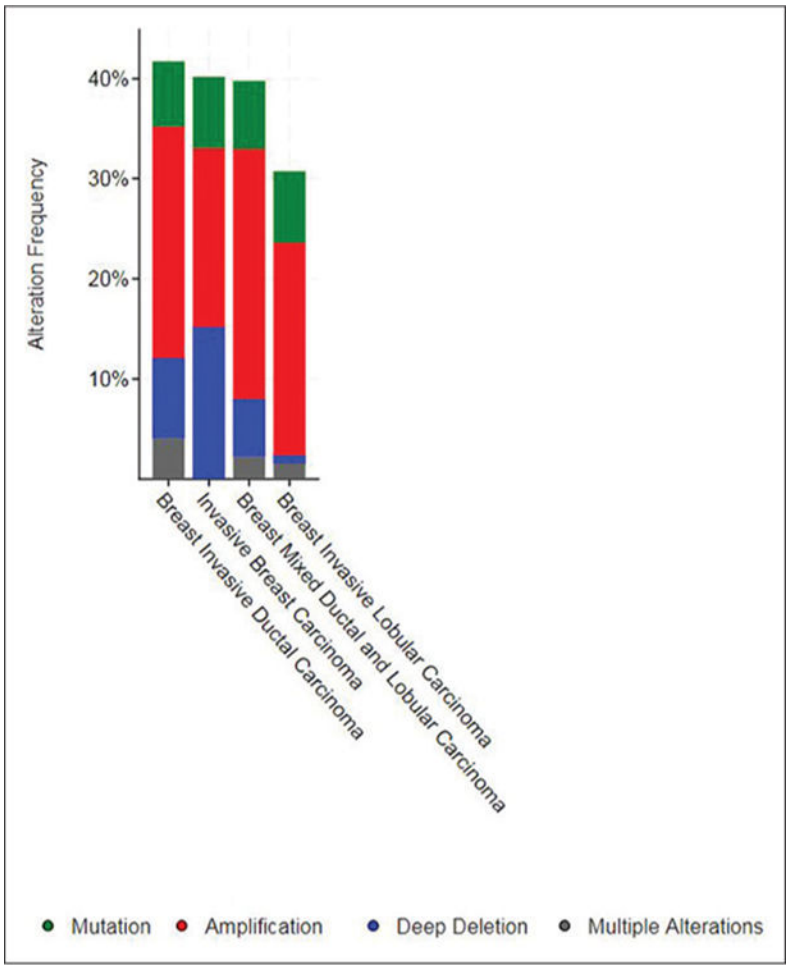

Figure 2.
Distribution of alterations in 24 Alzheimer's disease genes among 816 breast cancers

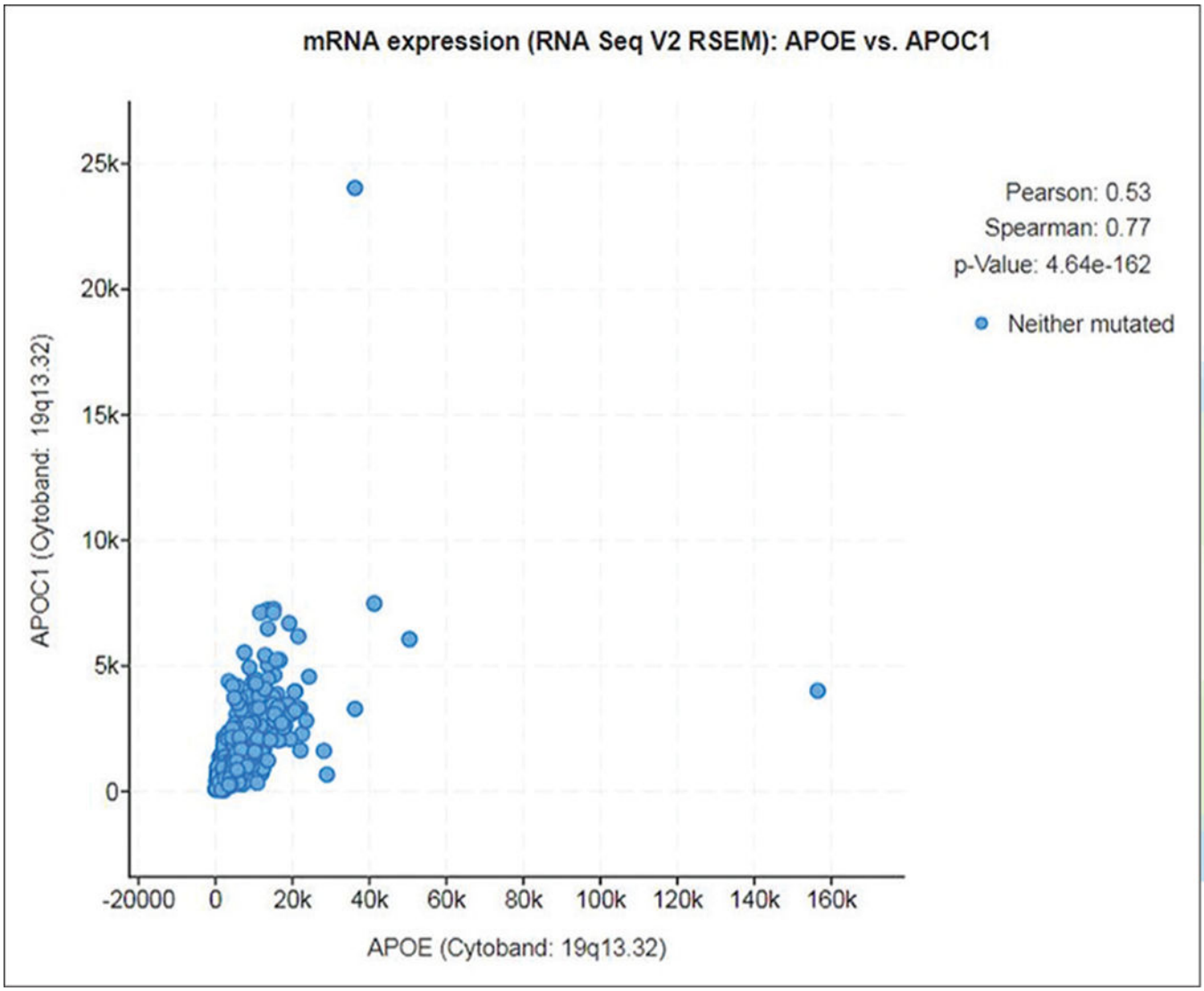

Figure 3.
APOE mRNA significantly coexpressed with APOC1 mRNA in 812 breast cancers

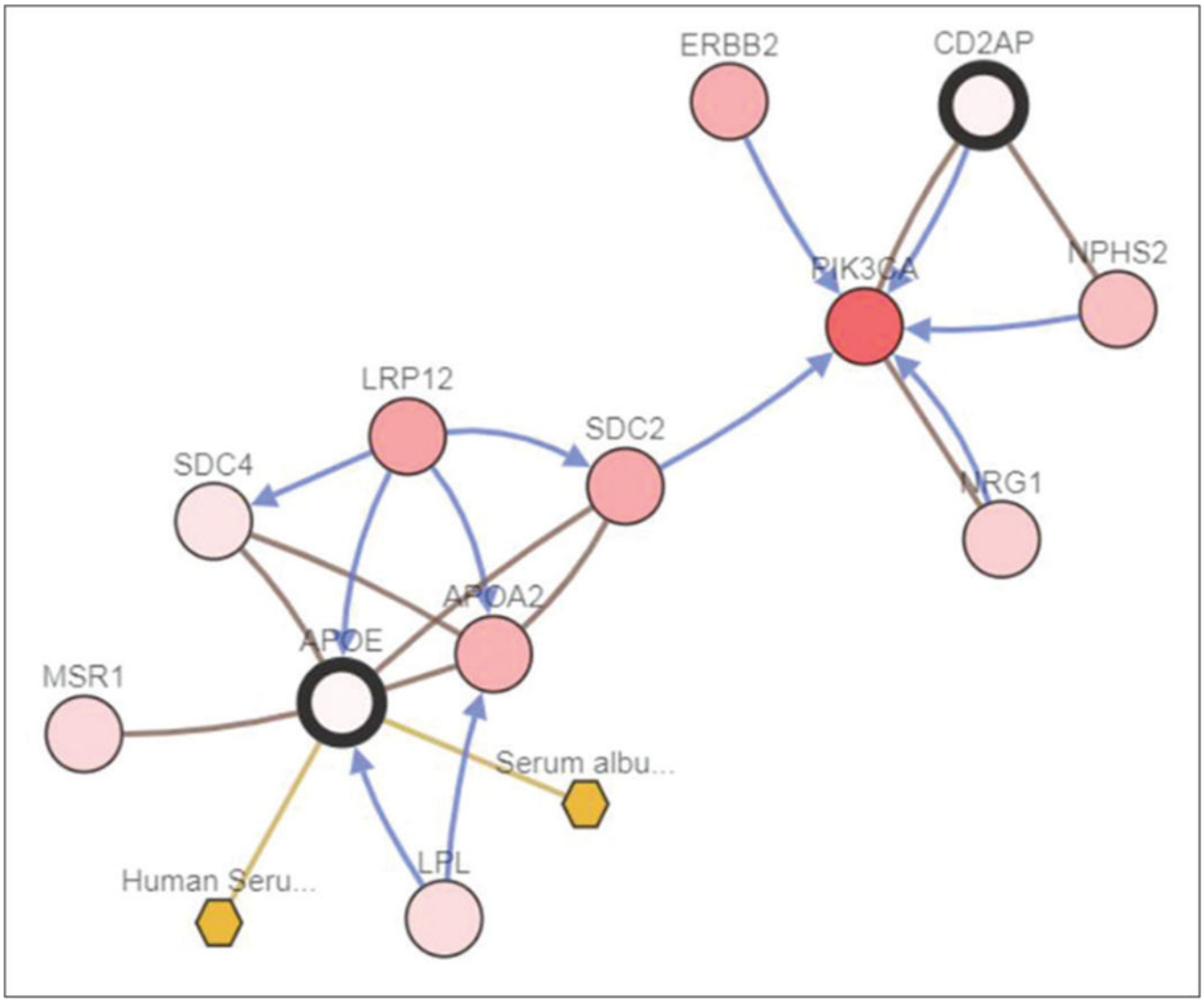

Figure 4.

APOE, CD2AP, and their network of neighboring genes, including PIK3CA, the second most commonly mutated gene in breast cancer (TP53 is the most common). An arrow signifies a directed interaction and a line signifies an undirected interaction. A blue arrow signifies control of state of change. The brown lines signify targeted by drug. Low serum albumin levels are associated with worse cognition in Alzheimer's disease patients (cBioportal.org)

Table 1.

Highest ranking Alzheimer's disease genes from the AlzGene database, numbered by rank

Rank	Gene
1	APOE
2	BIN1
3	CLU
4	ABCA7
5	CR1
6	PICALM
7	MS4A6A
8	CD33
9	MS4A4E
10	CD2AP
11	EPHA1
12	HLA-DRB1
13	PTK2B
14	SORL1
15	SLC24A4
16	RIN3
17	DSG2
18	INPP5D
19	MEF2C
20	NME8
21	ZCWPW1
22	CELF1
23	FERMT2
24	CASS4

Table 2.

Significantly co-occurrent genes in 816 breast tumor samples

A	B	Neither	A not B	B not A	Both	Log_2 OR	*P*	*Q*
CLU	PTK2B	758	2	9	47	>3	<0.001	<0.001
MS4A6A	MS4A4E	810	0	0	6	>3	<0.001	<0.001
SLC24A4	RIN3	797	6	7	6	>3	<0.001	<0.001
APOE	CD33	791	9	12	4	>3	<0.001	0.004
PTK2B	CASS4	718	44	42	12	2.221	<0.001	0.007
SLC24A4	CASS4	755	7	49	5	>3	<0.001	0.027
BIN1	SLC24A4	802	2	10	2	>3	0.001	0.046
APOE	CD2AP	789	10	14	3	>3	0.002	0.065

P values are Bonferroni adjusted, Q value is derived from the Benjamini–Hochberg false discovery rate correction procedure for multiple comparisons. OR: Odds ratio

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