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A Bioinformatic Meta-Analysis of Genes Affected by Abnormal Alternative Splicing in Ovarian Cancer

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ABSTRACT: It's predicted that in 2023, there will be 19,710 new cases and 13,270 deaths due to ovarian cancer in the United States. Ovarian cancer (OV) is the leading cause of death among gynecological cancers and the 5th leading cause of death among all cancers in women in the United States. Early diagnosis provides the best solution to increase the survivability of ovarian cancer (OV), and genomic markers are proving to be the key to early diagnosis. Insight into some of the genomic contributors to ovarian cancer, specifically abnormal alternative splicing factors has surfaced recently. It is unknown which abnormal alternative splicing factors associated with ovarian cancer could help increase early diagnosis. I used the Alternative Splicing for Cancer Molecular Classification (AS-CMC) interface and Metascape to conduct a bioinformatic analysis of alternative splice events and the affected genes in ovarian cancer. The expression (gene expression) and custom analysis results show that most genes affected by AS events in OV encode proteins involved in cytoskeleton alteration/organization. The results from this research will help to discover biomarkers in ovarian cancer patients and contribute to early diagnosis and research on targeted therapy for OV.

KEYWORDS: Cellular and Molecular Biology; Genetics; Ovarian Cancer; Abnormal Alternative Splicing Events; Bioinformatics.

Introduction

Ovarian Cancer:

It is predicted that in 2023 there will be 19,710 new cases and 13,270 deaths due to ovarian cancer in the United States.[1] Ovarian cancer (OV) is the leading cause of death among gynecological cancers and the 5th leading cause of death among all cancers in women in the United States.[1] Abdominal swelling, urinary symptoms, pelvic pressure, shortness of breath, etc., characterize it. However, these symptoms are not consistent across all OV patients. They tend to manifest in later stages: Stages 3 or 4.[2] OV at Stages 3 and 4 is much harder to cure and survive than OV at Stages 1 or 2; therefore, finding a way to diagnose patients at these earlier stages would benefit survivability. Moreover, these symptoms are general and nonspecific which can cause them to be missed initially, further pushing the time of diagnosis. Screening for ovarian cancer typically includes radiographic imaging CT, transvaginal and abdominal ultrasound, and MRI.[2] Such screening is not done during annual gynecological check-ups; therefore, this method does not establish an early diagnosis. As a result of all of these barriers to early diagnosis of OV the abundance of deaths due to ovarian cancer stems from late-stage diagnoses.[3] Therefore, the early diagnosis of ovarian cancer could have a significant effect in increasing the survival rate of ovarian cancer patients.

Abnormal Alternative Splicing Factors in Ovarian Cancer:

Recently, there has been insight into some genomic factors of ovarian cancer specifically abnormal alternative splicing factors.[4] To elaborate, RNA splicing was first discovered to extract sequences from pre-mRNA and combine the leftover sequences.[5] When there is a deviation from this standard sequence splicing it is described as alternative splicing. Alternative splicing creates protein diversity when mRNA is being expressed from a genome.[6] Moreover, one of its more interesting functions is encoding protein variants that control cell development. Therefore, when alternative splicing events experience altered expression, it can lead to cancer.[7] Studies have outlined various protein-coding genes that undergo abnormal alternative splicing in patients with ovarian cancer such as TP53, TP73, and HMGA2.[8,9] Furthermore, 10% of AS events specific to breast and/or ovarian cancer were found to be involved in cancer cell survival from a screen of selected splice variants.[10] Although studies have shown that alternative splicing may contribute to cancer, the analysis of alternative splicing in ovarian cancer has yet to be explored in vast detail. Further research must be conducted to truly analyze the specific alternative splicing factors and the genes they influence in ovarian cancer patients. Based on previous studies the most common alternative splicing factor type that frequents patients who develop ovarian cancer is exon skip, and the genes affected are almost always protein-coding or tumor-related. Many genes that experience AS events in ovarian cancer patients have protein functions related to cellular processes/signaling, specifically actin filament/cytoskeleton alterations. This paper will further elaborate on these findings. The results from this research will help to discover biomarkers in ovarian cancer patients and contribute to increased early diagnosis of OV and research on targeted therapy for OV.

Methods

To perform an analysis of the alternative splicing factors in ovarian cancer a list of genes implicated in AS in ovarian cancer was created from the Alternative Splicing for Cancer Molecular Classification (AS-CMC) interface (https://www.pmrc.re.kr/ASCMC/).[11] AS-CMC is a data interface that allows

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researchers to explore AS events from The Cancer Genomics Atlas (TCGA). AS-CMC permits users to curate a list of AS events from a single cancer type and pan-cancer lists for relevant AS events. I used the Single Cancer AS service to explore the AS events implicated in OV cancer patients specifically.

It was decided that performing an analysis on this list of genes would be important to understand why these specific alternative splicing events in these genes were influencing ovarian cancer. Furthermore, this will provide insight into how such events serve as biomarkers for early diagnosis and targeted treatment. Subsequently, all 215 genes from the AS-CMC interface under ovarian cancer AS events were imported into Metascape (http://metascape.org) under express and custom analysis for Homo-sapiens genes.[12] Of the 215 genes from AS-CMC, Metascape found 173 Homo-sapien. The 173 genes used in the analysis can be found in Table 1.

Table 1: 173 OV Genes from AS-CMC.

Gene Symbol	Gene ID	Description	Protein Function (Protein Atlas)
SEC31A	22872	SEC31 homolog A, COPII coat complex component	Potential drug targets; Disease related genes; Human disease related genes:Congenital malformations:Congenital malformations of the nervous system; Predicted intracellular proteins; Transporters: Primary Active Transporters
FYN	2534	FYN proto-oncogene, Src family tyrosine kinase	Kinases:Tyr protein kinases; Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
SPAG9	9043	sperm associated antigen 9	Predicted intracellular proteins
FN1	2335	fibronectin 1	Cancer-related genes:Candidate cancer biomarkers; Disease related genes; Human disease related genes:Urinary system diseases:Kidney diseases; FDA approved drug targets:Biotech drugs; Candidate cardiovascular disease genes; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Predicted intracellular proteins; Cancer-related genes: Mutational cancer driver genes; Predicted secreted proteins
MPRIP	23164	myosin phosphatase Rho interacting protein	Predicted intracellular proteins
ICAM3	3385	intercellular adhesion molecule 3	CD markers
PTK2B	2185	protein tyrosine kinase 2 beta	Potential drug targets; Disease related genes; ENZYME proteins:Transferases; Predicted intracellular proteins; Enzymes; Kinases:Tyr protein kinases
MBNL1	4154	muscleblind like splicing regulator 1	Predicted intracellular proteins; Disease related genes
IL18BP	10068	interleukin 18 binding protein	Predicted intracellular proteins; Human disease related genes:Immune system diseases:Other immune system diseases; Disease related genes; Predicted secreted proteins
MYO9B	4650	myosin IXB	Human disease related genes:Digestive system diseases:Gastrointestinal diseases; Predicted intracellular proteins; Disease related genes
PLOD2	5352	procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	Potential drug targets; Disease related genes; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Predicted intracellular proteins; ENZYME proteins:Oxidoreductases; Enzymes
CARM1	10498	coactivator associated arginine methyltransferase 1	Cancer-related genes:Mutational cancer driver genes; Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
MAD2L2	10459	mitotic arrest deficient 2 like 2	Cancer-related genes:Candidate cancer biomarkers; Predicted intracellular proteins; Human disease related genes:Cardiovascular diseases:Hematologic diseases; Disease related genes
IFT172	26160	intraflagellar transport 172	Disease related genes; Predicted intracellular proteins; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Human disease related genes: Nervous system diseases:Eye disease; Human disease related genes:Congenital disorders of metabolism:Other congenital disorders of metabolism
MEIS3	56917	Meis homeobox 3	Transcription factors:Helix-turn-helix domains; Predicted intracellular proteins
IGFLR1	79713	IGF like family receptor 1	Predicted intracellular proteins
CA12	771	carbonic anhydrase 12	Human disease related genes:Congenital disorders of metabolism:Congenital disorders of ion transport and metabolism; Disease related genes; Enzymes; FDA approved drug targets:Small molecule drugs; ENZYME proteins:Lyases
PODNL1	79883	podocan like 1	Predicted intracellular proteins; Predicted secreted proteins
CTNND1	1500	catenin delta 1	Potential drug targets; Disease related genes; Transporters:Accessory Factors Involved in Transport; Predicted intracellular proteins; Cancer-related genes:Mutational cancer driver genes; Human disease related genes:Congenital malformations:Congenital malformations of skin
PYM1	84305	PYM homolog 1, exon junction complex associated factor	Predicted intracellular proteins
OSBPL9	114883	oxysterol binding protein like 9	Predicted intracellular proteins
MARK3	4140	microtubule affinity regulating kinase 3	Potential drug targets; Disease related genes; ENZYME proteins:Transferases; Predicted intracellular proteins; Enzymes; Kinases:CAMK Ser/Thr protein kinases
SORBS1	10580	sorbin and SH3 domain containing 1	Predicted intracellular proteins
SYTL2	54843	synaptotagmin like 2	Predicted intracellular proteins; Transporters
ANO1	55107	anoctamin 1	Predicted intracellular proteins; Transporters:Transporter channels and pores; FDA approved drug targets:Small molecule drugs; Disease related genes
RAI14	26064	retinoic acid induced 14	Predicted intracellular proteins
NUMA1	4926	nuclear mitotic apparatus protein 1	Human disease related genes:Cancers:Cancers of haematopoietic and lymphoid tissues; Cancer-related genes:Mutational cancer driver genes; Predicted intracellular proteins
PPHLN1	51535	periphilin 1	Predicted intracellular proteins
MBNL2	10150	muscleblind like splicing regulator 2	Predicted intracellular proteins
PLCB2	5330	phospholipase C beta 2	Predicted intracellular proteins; ENZYME proteins:Hydrolases; Enzymes
TPM2	7169	tropomyosin 2	Cancer-related genes:Candidate cancer biomarkers; Human disease related genes:Congenital malformations:Other congenital malformations; Disease related genes; Predicted intracellular proteins; Human disease related genes:Musculoskeletal diseases:Muscular diseases
MAGI3	260425	membrane associated guanylate kinase, WW and PDZ domain co	Predicted intracellular proteins
CCSER2	54462	coiled-coil serine rich protein 2	Predicted intracellular proteins
CLSTN1	22883	calsyntenin 1	Cancer-related genes:Candidate cancer biomarkers
ABI1	10006	abl interactor 1	Predicted intracellular proteins; Cancer-related genes; Disease related genes
NFE2L1	4779	NFE2 like bZIP transcription factor 1	Predicted intracellular proteins; Transcription factors:Basic domains
SEPTIN6	23157	septin 6	Predicted intracellular proteins
FMNL3	91010	formin like 3	Predicted intracellular proteins
RTN4	57142	reticulon 4	Predicted intracellular proteins
ARFIP1	27236	ADP ribosylation factor interacting protein 1	Predicted intracellular proteins
FLNA	2316	filamin A	Potential drug targets; Human disease related genes:Congenital malformations:Other congenital malformations; Human disease related genes:Congenital malformations:Congenital malformations of the circulatory system; Disease related genes; Transporters:Accessory Factors Involved in Transport; Human disease related genes:Congenital malformations:Congenital malformations of the nervous system; Human disease related genes:Digestive system diseases:Gastrointestinal diseases; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Predicted intracellular proteins
FLNB	2317	filamin B	Potential drug targets; Human disease related genes:Congenital malformations:Other congenital malformations; Disease related genes; Transporters:Accessory Factors Involved in Transport; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Predicted intracellular proteins
MYO18A	399687	myosin XVIIIA	Predicted intracellular proteins
ESRP1	54845	epithelial splicing regulatory protein 1	Predicted intracellular proteins; Human disease related genes:Nervous system diseases:Ear disease; Disease related genes
AP1B1	162	adaptor related protein complex 1 subunit beta 1	Potential drug targets; Disease related genes; Predicted intracellular proteins; Human disease related genes:Congenital malformations:Congenital malformations of skin; Transporters
IL15	3600	interleukin 15	Cancer-related genes:Candidate cancer biomarkers; Predicted intracellular proteins; Predicted secreted proteins
YBX3	8531	Y-box binding protein 3	Predicted intracellular proteins; Transcription factors:beta-Barrel DNA-binding domains
GPR132	29933	G protein-coupled receptor 132	Predicted intracellular proteins; G-protein coupled receptors:GPCRs excl olfactory receptors
PQBP1	10084	polyglutamine binding protein 1	Human disease related genes:Congenital malformations:Other congenital malformations; Predicted intracellular proteins; Disease related genes
KRAS	3845	KRAS proto-oncogene, GTPase	Cancer-related genes:Candidate cancer biomarkers; Human disease related genes:Cancers:Cancers of the breast and female genital organs; Human disease related genes:Congenital malformations:Other congenital malformations; Human disease related genes:Cancers:Cancers of soft tissues and bone; Disease related genes; Cancer-related genes:Mutated cancer genes; Human disease related genes: Cancers:Cancers of the digestive system; Human disease related genes:Cancers:Cancers of the lung and pleura; RAS pathway related proteins; Predicted intracellular proteins; ENZYME proteins:Hydrolases; Enzymes; Cancer-related genes:Mutational cancer driver genes; Human disease related genes:Cancers:Cancers of haematopoietic and lymphoid tissues; Human disease related genes:Cancers:Cancers of endocrine organs; Human disease related genes:Cancers:Skin cancers; FDA approved drug targets:Small molecule drugs; Human disease related genes:Cancers:Head and neck cancers
FKBP7	51661	FKBP prolyl isomerase 7	ENZYME proteins:Isomerase; Predicted intracellular proteins; Enzymes
MFAP5	8076	microfibril associated protein 5	Human disease related genes:Cardiovascular diseases:Vascular diseases; Predicted intracellular proteins; Disease related genes; Predicted secreted proteins
CD44	960	CD44 molecule (Indian blood group)	Cancer-related genes:Candidate cancer biomarkers; Blood group antigen proteins; Predicted intracellular proteins; CD markers; Transporters; FDA approved drug targets:Small molecule drugs; Predicted secreted proteins
C1orf54	79630	chromosome 1 open reading frame 54	Predicted secreted proteins
NAALADL1	10004	N-acetylated alpha-linked acidic dipeptidase like 1	Predicted intracellular proteins; Peptidases:Metallopeptidases; Enzymes
QKI	9444	QKI, KH domain containing RNA binding	Predicted intracellular proteins; Cancer-related genes:Mutated cancer genes
KIF13A	63971	kinesin family member 13A	Predicted intracellular proteins
GNAS	2778	GNAS complex locus	Cancer-related genes:Candidate cancer biomarkers; Potential drug targets; Disease related genes; Transporters:Accessory Factors Involved in Transport; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Human disease related genes:Musculoskeletal diseases:Skeletal diseases; Predicted intracellular proteins; Cancer-related genes: Mutational cancer driver genes; Human disease related genes:Endocrine and metabolic diseases:Parathyroid diseases; Human disease related genes:Endocrine and metabolic diseases:Hypothalamus and pituitary gland diseases; Human disease related genes:Endocrine and metabolic diseases:Adrenal gland diseases
MEIS1	4211	Meis homeobox 1	Transcription factors:Helix-turn-helix domains; Predicted intracellular proteins
PICALM	8301	phosphatidylinositol binding clathrin assembly protein	Human disease related genes:Cancers:Cancers of haematopoietic and lymphoid tissues; Predicted intracellular proteins; Cancer-related genes; Disease related genes
PRDX5	25824	peroxiredoxin 5	Predicted intracellular proteins; FDA approved drug targets:Small molecule drugs; ENZYME proteins:Oxidoreductases; Enzymes
GK	2710	glycerol kinase	Potential drug targets; Disease related genes; ENZYME proteins:Transferases; Predicted intracellular proteins; Enzymes; Human disease related genes:Congenital disorders of metabolism:Congenital disorders of lipid/glycolipid metabolism
MTCH1	23787	mitochondrial carrier 1	Transporters:Electrochemical Potential-driven transporters; Predicted intracellular proteins
SOS1	6654	SOS Ras/Rac guanine nucleotide exchange factor 1	Human disease related genes:Congenital malformations:Other congenital malformations; Disease related genes; Cancer-related genes:Mutated cancer genes; Human disease related genes:Digestive system diseases:Mouth and dental diseases; RAS pathway related proteins; Predicted intracellular proteins; Cancer-related genes:Mutational cancer driver genes
CCN6	8838	cellular communication network factor 6	Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Disease related genes; Predicted secreted proteins
ANXA6	309	annexin A6	Transporters:Transporter channels and pores; Predicted intracellular proteins
OSBPL3	26031	oxysterol binding protein like 3	Predicted intracellular proteins
SCP2	6342	sterol carrier protein 2	Potential drug targets; Human disease related genes:Nervous system diseases:Neurodegenerative diseases; Disease related genes; ENZYME proteins:Transferases; Predicted intracellular proteins; Human disease related genes:Congenital disorders of metabolism:Peroxisomal diseases; Enzymes; Human disease related genes:Congenital disorders of metabolism:Congenital disorders of lipid/glycolipid metabolism
SPTAN1	6709	spectrin alpha, non-erythrocytic 1	Human disease related genes:Nervous system diseases:Epilepsy; Predicted intracellular proteins; Disease related genes
NUBP2	10101	NUBP iron-sulfur cluster assembly factor 2, cytosolic	Predicted intracellular proteins
FNIP1	96459	folliculin interacting protein 1	Predicted intracellular proteins; Disease related genes
CHTF8	54921	chromosome transmission fidelity factor 8	Predicted intracellular proteins
BMP1	649	bone morphogenetic protein 1	Potential drug targets; Disease related genes; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; ENZYME proteins:Hydrolases; Enzymes; Predicted secreted proteins
APP	351	amyloid beta precursor protein	Human disease related genes:Nervous system diseases:Neurodegenerative diseases; Disease related genes; Predicted intracellular proteins; Transporters:Transporter channels and pores; FDA approved drug targets:Small molecule drugs; Predicted secreted proteins
PCYT2	5833	phosphate cytidylyltransferase 2, ethanolamine	Potential drug targets; Disease related genes; ENZYME proteins:Transferases; Human disease related genes:Nervous system diseases:Other nervous and sensory system diseases; Predicted intracellular proteins; Enzymes
SLAIN2	57606	SLAIN motif family member 2	Predicted intracellular proteins
CMTM7	112616	CKLF like MARVEL transmembrane domain containing 7	Transporters:Transporter channels and pores
STX2	2054	syntaxin 2	Predicted intracellular proteins; Cancer-related genes:Mutated cancer genes
RTN2	6253	reticulon 2	Human disease related genes:Nervous system diseases:Other nervous and sensory system diseases; Disease related genes
TCF20	6942	transcription factor 20	Predicted intracellular proteins; Human disease related genes:Other diseases:Mental and behavioural disorders; Disease related genes
SEMA3F	6405	semaphorin 3F	Predicted intracellular proteins; Predicted secreted proteins
MARCHF8	220972	membrane associated ring-CH-type finger 8	Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
CLEC16A	23274	C-type lectin domain containing 16A	Human disease related genes:Endocrine and metabolic diseases:Diabetes; Predicted intracellular proteins; Disease related genes
GOLGA2	2801	golgin A2	Predicted intracellular proteins
MACROH2A1	9555	macroH2A.1 histone	Predicted intracellular proteins
EXOC7	23265	exocyst complex component 7	Potential drug targets; Disease related genes; Human disease related genes:Congenital malformations:Congenital malformations of the nervous system; Predicted intracellular proteins; Transporters: Transporter channels and pores
MRPL55	128308	mitochondrial ribosomal protein L55	Ribosomal proteins; Predicted intracellular proteins
VPS29	51699	VPS29 retromer complex component	Predicted intracellular proteins; Transporters
REPS1	85021	RALBP1 associated Eps domain containing 1	Human disease related genes:Nervous system diseases:Neurodegenerative diseases; Predicted intracellular proteins; Disease related genes
MAP3K7	6885	mitogen-activated protein kinase kinase kinase 7	Potential drug targets; Human disease related genes:Congenital malformations:Other congenital malformations; Disease related genes; ENZYME proteins:Transferases; Human disease related genes: Congenital malformations:Congenital malformations of the musculoskeletal system; Predicted intracellular proteins; Enzymes; Kinases:STE Ser/Thr protein kinases
PRR13	54458	proline rich 13	Predicted intracellular proteins
FAM168A	23201	family with sequence similarity 168 member A	Predicted intracellular proteins; Disease related genes
PBRM1	55193	polybromo 1	Human disease related genes:Cancers:Cancers of the urinary system; Disease related genes; Cancer-related genes:Mutated cancer genes; Predicted intracellular proteins; Cancer-related genes:Mutational cancer driver genes; Transcription factors:Other all-alpha-helical DNA-binding domains
TJP1	7082	tight junction protein 1	Predicted intracellular proteins; Transporters:Accessory Factors Involved in Transport
NEDD4L	23327	NEDD4 like E3 ubiquitin protein ligase	Potential drug targets; Disease related genes; ENZYME proteins:Transferases; Human disease related genes:Congenital malformations:Congenital malformations of the nervous system; Predicted intracellular proteins; Enzymes; Cancer-related genes:Mutational cancer driver genes
SYNE1	23345	spectrin repeat containing nuclear envelope protein 1	Human disease related genes:Nervous system diseases:Neurodegenerative diseases; Disease related genes; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Predicted intracellular proteins; Cancer-related genes:Mutational cancer driver genes; Human disease related genes:Musculoskeletal diseases:Muscular diseases
PRSS36	146547	serine protease 36	Predicted secreted proteins; Peptidases:Serine-type peptidases; Enzymes
ATP5PF	522	ATP synthase peripheral stalk subunit F6	Predicted intracellular proteins; Transporters:Primary Active Transporters
AFTPH	54812	aftiphilin	Predicted intracellular proteins
SLC35C1	55343	solute carrier family 35 member C1	Potential drug targets; Human disease related genes:Congenital disorders of metabolism:Congenital disorders of glycan/glycoprotein metabolism; Disease related genes; Transporters:Electrochemical Potential-driven transporters; Human disease related genes:Immune system diseases:Primary immunodeficiency
PTBP2	58155	polypyrimidine tract binding protein 2	Predicted intracellular proteins
FGFR1	2260	fibroblast growth factor receptor 1	Cancer-related genes:Candidate cancer biomarkers; Human disease related genes:Cancers:Cancers of the breast and female genital organs; Human disease related genes:Congenital malformations:Other congenital malformations; Disease related genes; ENZYME proteins:Transferases; Transporters:Accessory Factors Involved in Transport; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; RAS pathway related proteins; CD markers; Predicted intracellular proteins; Enzymes; Human disease related genes:Endocrine and metabolic diseases: Hypothalamus and pituitary gland diseases; Kinases:Tyr protein kinases; FDA approved drug targets:Small molecule drugs
FNBP1	23048	formin binding protein 1	Predicted intracellular proteins; Disease related genes
ITGB3BP	23421	integrin subunit beta 3 binding protein	Predicted intracellular proteins
FRMD4A	55691	FERM domain containing 4A	Human disease related genes:Congenital malformations:Congenital malformations of the nervous system; Predicted intracellular proteins; Disease related genes
KLC1	3831	kinesin light chain 1	Predicted intracellular proteins
SLK	9748	STE20 like kinase	Predicted intracellular proteins; Kinases:STE Ser/Thr protein kinases; Enzymes; ENZYME proteins:Transferases
MARK2	2011	microtubule affinity regulating kinase 2	Kinases:CAMK Ser/Thr protein kinases; Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
PDGFA	5154	platelet derived growth factor subunit A	Cancer-related genes:Candidate cancer biomarkers; Human disease related genes:Cancers:Cancers of the lung and pleura; Candidate cardiovascular disease genes; RAS pathway related proteins; Predicted intracellular proteins; Human disease related genes:Cancers:Cancers of eye, brain, and central nervous system; Predicted secreted proteins
ADD3	120	adducin 3	Human disease related genes:Nervous system diseases:Other nervous and sensory system diseases; Predicted intracellular proteins; Disease related genes
CCDC107	203260	coiled-coil domain containing 107	
TMUB2	79089	transmembrane and ubiquitin like domain containing 2	Predicted intracellular proteins
UPP1	7378	uridine phosphorylase 1	Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
MYO1B	4430	myosin IB	Predicted intracellular proteins
TRPM2	7226	transient receptor potential cation channel subfamily M membe	Transporters:Transporter channels and pores; Predicted intracellular proteins
CLASP1	23332	cytoplasmic linker associated protein 1	Predicted intracellular proteins
DCAF6	55827	DDB1 and CUL4 associated factor 6	Predicted intracellular proteins
ARHGEF1	9138	Rho guanine nucleotide exchange factor 1	Human disease related genes:Immune system diseases:Primary immunodeficiency; Predicted intracellular proteins; Disease related genes
ATP6V1C2	245973	ATPase H+ transporting V1 subunit C2	Predicted intracellular proteins; Transporters:Primary Active Transporters
PPP3CB	5532	protein phosphatase 3 catalytic subunit beta	Predicted intracellular proteins; ENZYME proteins:Hydrolases; Enzymes
TBC1D23	55773	TBC1 domain family member 23	Human disease related genes:Congenital malformations:Congenital malformations of the nervous system; Predicted intracellular proteins; Disease related genes
RELCH	57614	RAB11 binding and LisH domain, coiled-coil and HEAT repeat cor	Predicted intracellular proteins
ZFAND5	7763	zinc finger AN1-type containing 5	Predicted intracellular proteins
WNK1	65125	WNK lysine deficient protein kinase 1	Potential drug targets; Kinases; Disease related genes; ENZYME proteins:Transferases; Human disease related genes:Urinary system diseases:Kidney diseases; Human disease related genes:Nervous system diseases:Other nervous and sensory system diseases; Predicted intracellular proteins; Enzymes
EPB41L2	2037	erythrocyte membrane protein band 4.1 like 2	Predicted intracellular proteins
SMARCB1	6598	SWI/SNF related, matrix associated, actin dependent regulator o	Human disease related genes:Congenital malformations:Other congenital malformations; Disease related genes; Cancer-related genes:Mutated cancer genes; Human disease related genes:Other diseases: Others; Predicted intracellular proteins; Human disease related genes:Other diseases:Mental and behavioural disorders; Human disease related genes:Cancers:Cancers of eye, brain, and central nervous system
PLSCR1	5359	phospholipid scramblase 1	Predicted intracellular proteins; Transporters
DGUOK	1716	deoxyguanosine kinase	Potential drug targets; Disease related genes; ENZYME proteins:Transferases; Human disease related genes:Congenital disorders of metabolism:Mitochondrial diseases; Predicted intracellular proteins; Enzymes
DYRK1B	9149	dual specificity tyrosine phosphorylation regulated kinase 1B	Kinases:CMGC Ser/Thr protein kinases; Potential drug targets; Disease related genes; ENZYME proteins:Transferases; Predicted intracellular proteins; Enzymes; Human disease related genes:Endocrine and metabolic diseases:Other endocrine and metabolic diseases
SUCO	51430	SUN domain containing ossification factor	
PRMT2	3275	protein arginine methyltransferase 2	Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
RPS24	6229	ribosomal protein S24	Disease related genes; Predicted intracellular proteins; Human disease related genes:Other congenital disorders:Ribosomopathies; Ribosomal proteins; Human disease related genes:Cardiovascular diseases:Hematologic diseases
TCF7L2	6934	transcription factor 7 like 2	Disease related genes; Cancer-related genes:Mutated cancer genes; Human disease related genes:Endocrine and metabolic diseases:Diabetes; Predicted intracellular proteins; Cancer-related genes: Mutational cancer driver genes; Transcription factors:Other all-alpha-helical DNA-binding domains
EXOC1	55763	exocyst complex component 1	Transporters:Transporter channels and pores; Predicted intracellular proteins
CCDC50	152137	coiled-coil domain containing 50	Predicted intracellular proteins; Human disease related genes:Nervous system diseases:Ear disease; Disease related genes
DBNDD2	55861	dysbindin domain containing 2	Predicted intracellular proteins
TPD52L2	7165	TPD52 like 2	Predicted intracellular proteins
TCF12	6938	transcription factor 12	Human disease related genes:Congenital malformations:Other congenital malformations; Disease related genes; Predicted intracellular proteins; Transcription factors:Basic domains; Cancer-related genes: Mutational cancer driver genes; Human disease related genes:Endocrine and metabolic diseases:Hypothalamus and pituitary gland diseases
UBXN11	91544	UBX domain protein 11	Predicted intracellular proteins
EHBP1	23301	EH domain binding protein 1	Predicted intracellular proteins; Human disease related genes:Cancers:Cancers of male genital organs; Disease related genes
ALAS1	211	5'-aminolevulinate synthase 1	Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
ACP5	54	acid phosphatase 5, tartrate resistant	Potential drug targets; Disease related genes; Human disease related genes:Congenital malformations:Congenital malformations of the musculoskeletal system; Predicted intracellular proteins; ENZYME proteins:Hydrolases; Enzymes
SYNC	81493	syncoilin, intermediate filament protein	Predicted intracellular proteins
IL32	9235	interleukin 32	Predicted intracellular proteins; Predicted secreted proteins
CARD9	64170	caspase recruitment domain family member 9	Predicted intracellular proteins; Human disease related genes:Immune system diseases:Other immune system diseases; Disease related genes
MOV10	4343	Mov10 RISC complex RNA helicase	Predicted intracellular proteins; ENZYME proteins:Hydrolases; Enzymes
RABGGTA	5875	Rab geranylgeranyltransferase subunit alpha	Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
ANKRD13C-DT	11147	ANKRD13C divergent transcript	
AP1G1	164	adaptor related protein complex 1 subunit gamma 1	Potential drug targets; Predicted intracellular proteins; Transporters; Disease related genes
SUPT20H	55578	SPT20 homolog, SAGA complex component	Predicted intracellular proteins
EAF2	55840	ELL associated factor 2	Predicted intracellular proteins
RBPJ	3516	recombination signal binding protein for immunoglobulin kappa	Human disease related genes:Congenital malformations:Other congenital malformations; Predicted intracellular proteins; Transcription factors:Immunoglobulin fold; Disease related genes
GUSB	2990	glucuronidase beta	Potential drug targets; Human disease related genes:Congenital disorders of metabolism:Congenital disorders of glycan/glycoprotein metabolism; Disease related genes; Cancer-related genes:Mutated cancer genes; Predicted intracellular proteins; ENZYME proteins:Hydrolases; Enzymes; Human disease related genes:Congenital disorders of metabolism:Lysosomal storage diseases
DMKN	93099	dermokine	Predicted intracellular proteins; Predicted secreted proteins
MYOF	26509	myoferlin	Potential drug targets; Disease related genes; Predicted intracellular proteins; Human disease related genes:Cardiovascular diseases:Vascular diseases; Transporters:Transporter channels and pores
STRADA	92335	STE20 related adaptor alpha	Potential drug targets; Disease related genes; Human disease related genes:Congenital malformations:Congenital malformations of the nervous system; Predicted intracellular proteins; Enzymes; Kinases: STE Ser/Thr protein kinases
ELN	2006	elastin	Human disease related genes:Congenital malformations:Congenital malformations of the circulatory system; Disease related genes; Predicted intracellular proteins; Human disease related genes:Other congenital disorders:Chromosomal abnormalities; Human disease related genes:Congenital malformations:Congenital malformations of skin; Predicted secreted proteins
DEPDC5	9681	DEP domain containing 5, GATOR1 subcomplex subunit	Human disease related genes:Nervous system diseases:Epilepsy; Predicted intracellular proteins; Disease related genes
ITGB2	3689	integrin subunit beta 2	Human disease related genes:Immune system diseases:Primary immunodeficiency; Predicted intracellular proteins; CD markers; Disease related genes
EPOR	2057	erythropoietin receptor	Human disease related genes:Cardiovascular diseases:Hematologic diseases; Cancer-related genes:Candidate cancer biomarkers; FDA approved drug targets:Biotech drugs; Disease related genes
EPB41	2035	erythrocyte membrane protein band 4.1	Potential drug targets; Disease related genes; Transporters:Accessory Factors Involved in Transport; Predicted intracellular proteins; Human disease related genes:Cardiovascular diseases:Hematologic diseases
RALGPS2	55103	Ral GEF with PH domain and SH3 binding motif 2	Predicted intracellular proteins; Disease related genes
PPP1R9A	55607	protein phosphatase 1 regulatory subunit 9A	Predicted intracellular proteins
PHLDB1	23187	pleckstrin homology like domain family B member 1	Predicted intracellular proteins
ARHGEF10L	55160	Rho guanine nucleotide exchange factor 10 like	Predicted intracellular proteins
CAMK2D	817	calcium/calmodulin dependent protein kinase II delta	Kinases:CAMK Ser/Thr protein kinases; Predicted intracellular proteins; Enzymes; ENZYME proteins:Transferases
SORBS2	8470	sorbin and SH3 domain containing 2	Predicted intracellular proteins
ADORA1	134	adenosine A1 receptor	Transporters; G-protein coupled receptors:GPCRs excl olfactory receptors; FDA approved drug targets:Small molecule drugs; G-protein coupled receptors:Adenosine and adenine nucleotide receptors
PLB1	151056	phospholipase B1	Predicted intracellular proteins; ENZYME proteins:Hydrolases; Enzymes
TTC28	23331	tetratricopeptide repeat domain 28	Predicted intracellular proteins
SDK1	221935	sidekick cell adhesion molecule 1	Predicted intracellular proteins
PLSCR4	57088	phospholipid scramblase 4	Predicted intracellular proteins; Transporters
MYO5A	4644	myosin VA	Human disease related genes:Immune system diseases:Primary immunodeficiency; Predicted intracellular proteins; Cancer-related genes; Disease related genes

The genes were analyzed for gene summary, description, protein function, molecular function, subcellular location, development of diseases, RNA tissue category, and normal and cancer protein expression using custom analysis. Gene summary, description, and function were used to analyze the genes' functions and areas of impact. Normal and cancer protein expression was used to explore the difference in expression between cancerous and non-cancerous tissues. Lastly, the development of diseases was used to analyze which disease areas these genes impacted along with which tissues as shown through RNA tissue categories. The complete list of characteristics used for custom analysis can be found in Table 2. Metascape executes express analysis using CAME analysis, an automated analysis with 4 parts: ID conversion, gene annotation, membership search, and enrichment analysis.[12] This information is then expressed in graphs and tables, which will be discussed in this research's "Results" section.

Table 2: Custom Analysis Characteristics.

Gene Symbol
Type of Gene
Description
Gene Summary
Protein Functions (ChatGPT)
Biological Process (GO)
Molecular Function (GO)
Kinase Class (UniProt)
Protein Function (Protein Atlas)
Subcellular Location (Protein Atlas)
Developmental Disorders (DDG2P)
Drug (DrugBank)
Disease and gene associations (DisGeNET)
Disease & Drugs (ChatGPT)
Tissue Specificity (TIGER)
RNA Tissue Category (Protein Atlas)
Protein Expression Normal (Protein Atlas)
Protein Expression Cancer (Protein Atlas)
Canonical Pathways
Hallmark Gene Sets

Result and Discussion

All but gene HHLA3 (a regulatory element) from the list were found to be protein-coding via the table curated by custom analysis through Metascape. The express analysis of the genes affected by AS events in OV cancer also explored diseases associated with OV cancer. According to the graph, the most common diseases associated with these genes are Strabismus, Short metatarsal, and Platyspondyly.

Genes' enriched terms and their functional roles:

The 173 genes affected by AS events in OV patients were also analyzed for enriched terms by their functional roles. The over-represented biological units (enriched terms) with the highest p-value in Figure 1 include the Actin filament-based process, diseases of signal transduction by growth factor receptors and second messengers, and positive regulation of protein localization. The corresponding gene counts of these top 3 enriched biological processes are 23, 16, and 15. Ultimately, the analysis that Figure 1 provides uncovered that actin filament-based process, diseases of signal transduction by growth factor receptors and second messengers, and positive regulation of protein localization are the enriched terms of the most relevance regarding their correlation with OV. However, further inquiry into these enriched terms is needed to uncover how they may help early diagnosis of OV and targeted therapy for OV.

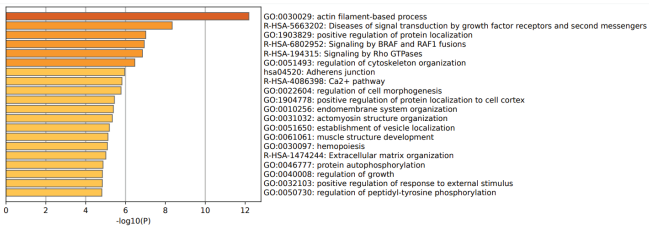

Figure 1: Bar graph of enriched terms across input gene lists, colored by p-values created using Metascape. The bar graph shows that the enriched terms with the highest p-values are actin filament-based process, diseases of signal transduction by growth factor receptors and second messengers, and positive regulation of protein localization.

Actin filament-based process pathway in OV:

The actin filament-based process pathway in OV is different than in regular tissue. Expanding cell mobility depends on reorganizing the actin cytoskeleton; this mobility is needed for OV to metastasize. In OV proteolytically active plasma membrane protrusions, or invadopodia, increase cancer cells' ability to enter vasculature.[13] The diversity of actin organization in migrating cancer cells is due to these various actin filament structures.[13] Therefore, the actin filament-based process pathway is important for ovarian cancer cells to develop and metastasize.

Diseases of signal transduction by growth factor receptors and second messengers pathway in OV:

In some cancers, including OV, a 3-member Raf kinase family is part of a signal transduction pathway that transmits growth factor-mediated proliferative signals, B-Raf being one of these kinases.[14] Depletion of B-Raf due to mutations leads to altered cell proliferation and cell survival in these cancers.[14] This information points to the explanation that AS events that affect genes that code for proteins are involved in the diseases of signal transduction by growth factor receptors and the second messenger pathway, which play a role in OV. This occurs because the mutations of these genes prevent ovarian cancer cells from experiencing cell death.

Network of the genes' enriched terms:

This was done after the genes were graphed to show a network of the enriched terms. This can be used to see the connection between the different enriched terms, the genes, and the function of the proteins they code for. Figure 2 depicts the connections between the different enriched terms found in the gene list. They are grouped by Cluster ID, which is color-coded to represent various functions/pathways most often affected by these mutations, which are listed in the key to the right of the graph. The different-sized nodes are used to represent the number of mutations affecting that function/pathway and the connections between them represent similar protein functions. This is why there are abundant connections between nodes of the same color, as these genes all code for similar proteins, and therefore, the function of these proteins is also subsequently related. This can be seen in the green cluster ID representing positive regulation of protein localization; there are numerous connections between the green nodes, but the connection begins to dwindle amongst other cluster IDs. By analyzing Figure 2, one can discover which proteins are coded for by the genes of most relevance regarding OV and classified by their function. This will help uncover which genes are of interest for targeted therapy and increase early diagnosis.

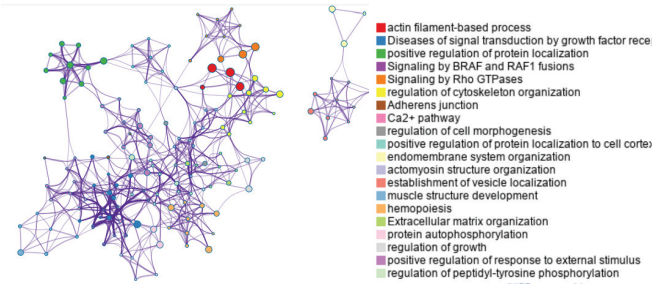

Figure 2: Network of enriched terms: colored by cluster ID, where nodes that share the same cluster-ID, are typically close to each other created using Metascape. The most prominent connections are between the actin filament-based process (red cluster ID), regulation of cytoskeleton organization (yellow cluster ID), and Signaling by Rho GTPases (orange cluster ID) enriched terms.

Observation of different cluster networks:

Off to the right, the coral cluster ID representing the establishment of the vesicle localization enriched term is solely connected to the off-white cluster ID representing the endomembrane system organization enriched term. This means these two gene functions code for similar proteins that do not connect to any other protein functions depicted. Another interesting set of nodes is made up of enriched terms: signaling by BRAF and RAF1 fusions (purple cluster ID), Diseases of signal transduction by growth factor receptors and second messengers (blue cluster ID), protein autophosphorylation (light pink cluster ID), and CA^{2+} pathway (pink cluster ID). This shows that despite these 4 nodes representing different gene functions they all have strong connections between their

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protein functions. The thicker lines connecting these 4 clusters further symbolize the extent of the connection between these nodes. This is also reflected in a couple of other sets of clusters including the actin filament-based process (red cluster ID), regulation of cytoskeleton organization (yellow cluster ID), and Signaling by Rho GTPases (orange cluster ID) enriched terms. However, these nodes are less connected than the former, which can be seen in the thinness of the connections. This means the former nodes have the most significant connection between their protein functions. These observations give us insight into which connections and enriched terms may be relevant when discussing biomarkers and genes for targeted therapy for OV.

Analysis of cluster networks:

These results may explain why these 173 genes appear to experience AS events in OV patients. One possible explanation could be that the 4 nodes with the strongest connections, signaling by BRAF and RAF1 fusions (purple cluster ID), Diseases of signal transduction by growth factor receptors and second messengers (blue cluster ID), protein autophosphorylation (light pink cluster ID), and CA^{2+} pathway (pink cluster ID), contain the set of genes that experience AS events which influence OV. Another explanation is that the green cluster ID represents positive regulation of protein localization with very thick connections and contains the genes that, when experiencing abnormal AS events, serve as the primary cause for OV. It could also be assumed that either the coral cluster ID representing the establishment of the vesicle localization enriched term and the off-white cluster ID representing the endomembrane system organization enriched term is the sole cluster IDs associated with OV or that the rest of the cluster IDs all interact together to cause OV. Lastly, the actin filament-based process (red cluster ID), regulation of cytoskeleton organization (yellow cluster ID), and Signaling by Rho GTPases (orange cluster ID) enriched terms could be the explanation. Looking into which enriched terms have the most genes will uncover the enriched terms that are of most relevance to OV and further the process of discovering the genes that can serve as biomarkers and areas for targeted therapy for OV.

Network of enriched terms by p-value:

Figure 3 displays the same interactions except classified by the p-value of each enrichment term. Here you can see that the enriched terms with lower p-values are more closely gathered together than the terms with high p-values. This explains that these genes are most likely to influence OV, as genes are abundant with these enriched terms. This supports the idea that sets of nodes connected and close to each other interact with one another to influence OV. Rather than one cluster representing an enriched term being the source of genes that, when experiencing AS events, contribute to OV. The actin filament-based process seems to have the lowest p-value; yet again, it is an influential enriched term regarding OV.

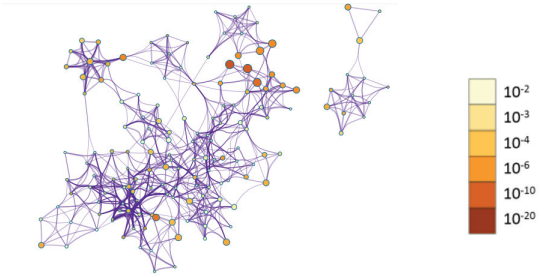

Figure 3: Network of enriched terms: colored by p-value, where terms containing more genes tend to have a more significant p-value created using Metascape. Actin filament-based process is characterized as the term with the lowest p-value and the most relevance.

Discussion:

The express and custom analysis results show that most genes that are affected by AS events in OV code for proteins associated with cellular processes and cellular signaling, specifically actin filament/cytoskeleton alterations. In Figure 1, the enriched terms with high p-values depict actin filament-based process, diseases of signal transduction by growth factor receptors and second messengers, and positive regulation of protein localization. This means that the likelihood of significance of these enriched terms is high. All three phenotypes are associated with actin filament/cytoskeleton alterations.

Furthermore, Figure 2 brings to light a different set of phenotypes with protein functions that are closely related and, therefore, could contribute to OV: actin filament-based process (red cluster ID), regulation of cytoskeleton organization (yellow cluster ID), and Signaling by Rho GTPases (orange cluster ID). Figure 2 also brings insight into 4 other enriched terms: signaling by BRAF and RAF1 fusions (purple cluster ID), Diseases of signal transduction by growth factor receptors and second messengers (blue cluster ID), protein autophosphorylation (light pink cluster ID), and CA^{2+} pathway (pink cluster ID). As these clusters are densely connected and close to each other, it is reasonable to consider the relevance of these genes in their relationship to OV. Signaling by BRAF and RAF1 fusions pertains to activating downstream signaling.[15] Protein autophosphorylation and the CA^{2+} pathway are also related to cellular signaling.[16]

However, the 3 closely connected enriched terms found in Figure 2 (actin filament-based process, regulation of cytoskeleton organization, and Signaling by Rho GTPases), contain the lowest p-values in Figure 3, so it is more likely that those genes, when affected by abnormal AS events influence OV. These 3 enriched terms are all involved with altering the cytoskeleton. This discovery concludes that genes associated with changing the cytoskeleton can be biomarkers for targeted therapy concerning OV. However, it remains to be seen why this connection exists and whether other studies have similar findings to cement this conclusion.

A study of 17 proteins involved in cytoskeleton modulation and their role in ovarian cancer further supports these findings. Ovarian carcinomas rapidly increase and the cell spheroids produced by the primary tumor are very adhesive.[17] These mechanisms, cellular proliferation, and adhesion rely on MT-dynamics (microtubules a key component of the cytoskel-

eton influence) to manage spindle dynamics and transport of adhesion molecules to the plasma membrane.[17] Consequently, when genes that code for proteins with similar functions experience abnormal alternative splicing events proper MT dynamics could be interrupted. This can lead to improper function and the formation of spindles during cell division eventually leading to cancer.[17] Furthermore, microtubules play a role in transporting proteins that promote cell adhesion. Ovarian cancer is known to have highly adhesive spheroids, so abnormal management of such proteins could further incite ovarian cancer.

A study on the CD44 gene, its activation of RhoGTPase signaling and cytoskeleton function, and its influence on tumor progression further supports my analysis.[18] RhoGTPase signaling and cytoskeleton function encoding genes experiencing alternative splicing events were the most correlated to ovarian cancer in my bioinformatic analysis. This study further elaborates on this correlation specifically concluding that coordinated HA-mediated CD44 activation of RhoPase signaling and cytoskeleton could be an underlying mechanism of tumor cell behaviors, including adhesion growth and survival.[18] These studies support the conclusion that when genes that code for proteins involved in altering the cytoskeleton experience AS events, OV closely follows.

Another study identified the expression of mitotic kinesin as a biomarker for the outcome of ovarian cancer.[19] This was discovered through an experiment that measured KIF14 mRNA, a kinesin-encoding gene, in 122 ovarian cancer tumor samples. KIF14's control over cytokinesis leads to increased cell proliferation and tumor growth.[19] This study further confirms the link between genes that code for proteins that alter the cytoskeleton and OV and validates these genes as biomarkers for OV and areas for targeted therapy for OV.

Conclusion

The results of this analysis point to the explanation that the expression of proteins involved in cytoskeleton alteration/organization may serve as biomarkers for ovarian cancer diagnosis and as an area for targeted ovarian cancer therapy. Ovarian cancer is an area of significant concern due to its high mortality rate; these results serve as a specific jumping-off point for further research to successfully uncover distinct biomarkers for early diagnosis of OV and areas for targeted therapy for OV to combat this issue. Only 173 genes that experienced AS events in OV were used in this study; a wider range of genes should be explored to exhaust other connections, possible biomarkers, and targets. Clinical trials and experiments producing new data are also needed to confirm and further investigate the connection between these genes experiencing AS events and OV.

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