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RESEARCH ARTICLE **MOLECULAR BIOLOGY**

Kim, et al: Identification of OGCT associated variants using WES

Whole-exome sequencing reveals rare genetic variations in ovarian granulosa cell tumor

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ABSTRACT

Ovarian granulosa cell tumor (OGCT) is a rare ovarian tumor that accounts for about 2-5% of all ovarian tumors. Despite the low grade of ovarian tumors, high and late recurrences are common in OGCT patients. Even though this tumor usually occurs in adult women with high estrogen levels, the cause of OGCT is still unknown. To screen genetic variants associated with OGCT, we collected normal and matched-tumor formalin-fixed paraffin-embedded (FFPE) from 11 OGCT patients and performed whole-exome sequencing (WES) using Illumina NovaSeq 6000. A total of 1,067,219 single nucleotide polymorphisms (SNPs) and 162,155 insertions/deletions (indels) were identified from 11 pairs of samples. Of these, we identified 44 tumor-specific SNPs in 22 genes and four tumor-specific indels in one gene that were common to 11 patients. We used three cancer databases (TCGA, COSMIC, and ICGC) to investigate genes associated with ovarian cancers. Nine genes (*SEC22B, FEZ2, ANKRD36B, GYPA, MUC3A, PRSS3, NUTM2A, OR8U1*, and *KRTAP10-6)* associated with ovarian cancers were found in all three databases. In addition, we identified seven rare variants with MAF $\leq$ 0.05 in two genes (*PRSS3* and *MUC3A*). Of seven rare variants, five variants in *MUC3A* are potentially pathogenic. Furthermore, we conducted gene enrichment analysis of tumor-specific 417 genes in SNPs and 106 genes in indels using cytoscape and metascape. In GO analysis, these genes were highly enriched in "selective autophagy", and "regulation of anoikis". Taken together, we suggest that *MUC3A* is implicated in OGCT development, and *MUC3A* could be used as a potential biomarker for OGCT diagnosis.

KEYWORD: Whole-exome sequencing; Ovarian granulosa cell tumor; Single-nucleotide polymorphism; Indels; Ovarian cancer

INTRODUCTION

Ovarian granulosa cell tumor (OGCT) is a rare sex cord-stromal tumor that Rokitansky first described in 1855 (1). It accounts for only 2-5% of all ovarian tumors and is estimated to occur in 0.6-1.0 per 100,000 women annually worldwide (2, 3). The incidence of OGCT is highest in postmenopausal women, especially between the ages of 50 to 55, and juvenile GCT occurs in less than 5% of pre-pubescent girls and women younger than 30 years of age (4, 5). The symptoms of OGCT are vaginal bleeding, pain abdomen, abdominal distension, menstrual abnormalities, or amenorrhea (2).

About 70-80% of OGCTs are diagnosed at stage I disease, the 10-year survival rate in stage I is 84-95%, decreases to 50-65% in stage II, and 17-33% in stages III and IV (6). Although OGCT has a low grade, high and late recurrences are common in patients with OGCT (7). Recurrence occurs in about 50% of patients, and it is known that 50-80% of patients die from recurrence (8). When recurrence occurs, the prognosis for the patient is poor, and conventional chemotherapy is not effective for recurrence (9). Although this tumor is usually known to occur in adult women with high estrogen levels, the cause of OGCT is still unclear (10).

To date, several types of research have been conducted to elucidate the pathogenesis and treatment of OGCT. Shah et al. reported that more than 95% of OGCT patients were found to have a *FOXL2* c.402C>G point mutation (C134W), which is a crucial transcription factor that regulates ovarian development and function (11-13). Interestingly, WGS revealed that the *FOXL2* (c.402C>G) mutation is specific for OGCT but not commonly found in other cancers (12). *FOXL2* regulates the crucial signaling pathways in the ovary, such as TGF-β/BMP signaling, MAP-kinase signaling, steroid signaling, PI3K/Akt signaling, involved in cell proliferation and apoptosis (14). A recent study by Alexiadis et al. reported the high frequency of the *TERT* g. -124C>T mutation in the recurrent adult GCT (15). *TERT* encodes the catalytic subunit of telomerase involved in oncogenesis. The mutation of the *TERT* promoter is a biomarker for the prognosis of various cancers, including hepatocellular carcinoma, chondrosarcoma, and primary glioblastoma (16-18). Despite efforts to understand the development and recurrence of OGCT, the pathogenesis is still insufficient. Here, we aimed to detect genetic variants involved in OGCT development in normal and matched-tumor tissues from 11 OGCT patients by whole-exome sequencing (WES).

MATERIALS AND METHODS

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Chungnam National University Hospital and complied with the tenets of the Declaration of Helsinki (2016-12-056).

Patient

A total of 11 OGCT patients from the Chungnam university hospital were included in this study. The age of patients was 27-78 years old. Patients were diagnosed at various times by individuals from 2011 to 2017. We collected normal and matched-tumor formalin-fixed paraffin-embedded (FFPE) from 11 OGCT patients. The tumor with an average size of about 10 cm (range 3.3-22.5 cm) was collected from each of the 11 patients (Table 1). According to the manufacturer's instructions, DNAs were extracted from twenty-two FFPE samples from 11 patients using the Maxwell 16 FFPE plus LEV DNA purification kit (Promega, USA). The paired normal tissue was the contralateral ovarian tissue from each patient. The pathologist then made a microscopic diagnosis of normal and tumor tissue using hematoxylin and eosin (H&E)-stained biopsy slides.

Whole-Exome Sequencing and variant calling

Preparation for capturing libraries with an Agilent SureSelect Target Enrichment Kit (Agilent, USA) followed the manufacture's protocols. The libraries were sequenced with an Illumina NovaSeq 6000 with a 2 x 150 bp paired-end read. After that, sequencing reads were aligned to the human reference genome using the Burrows-Wheeler Alignment tool (BWA 0.7.12) with -M parameters. Picard (picard-tools-1.130) was used to remove PCR duplicates, and the Genome Analysis Tool kit (GATKv3.4.0) was performed for variant calling with -T and -knownSites parameters. Here, we only used the variants more than 30 depths in coverage. Functional annotation was conducted using SnpEff (SnpEff_v4.1g) with default settings.

Cancer databases

We used The Catalogue Of Somatic Mutations In Cancer (COSMIC), International Cancer Genome Consortium (ICGC), and The Cancer Genome Atlas (TCGA) to find ovarian cancer-related genes. Three databases contain mutational signatures in the cancer genome.

Gene Set Enrichment Analysis

We performed a gene ontology (GO) enrichment analysis of the variants with tumor-specific genes to investigate the biological relevance of the candidate genes using Metascape software (https://metascape.org/gp/index.html). The significant gene sets are classified into

three classes: biological process, cellular component, and molecular function. In addition, to determine their biological functions related to cancer and associated pathway, we performed molecular and genetic interaction networks analysis using Cytoscape software (cytoscape_v3.7.0 and ClueGO_v.2.5.7). We used the Benjamini & Hochberg (BH) adjustment to correct the p-value in ClueGO.

Pathogenic variants analysis

We used three databases to analyze the Exome Aggregation Consortium (ExAC) (n = 60,706, http://exac.broadinstitute.org/), 1000 Genomes project phase 3 database (1000 G; n = 2,504, http://www.internationalgenome.org/), and National Heart, Lung, and Blood Institute (NHLBI) (n = 6,503, http://evs.gs.washington.edu/EVS/) to investigate the rare variants in the general population. We collected nonsynonymous variants with MAF $\leq$ 0.05, shared by 11 patients. In addition, we performed a pathogenic analysis of the variants to predict protein functional effects using Sorting Intolerant From Tolerant (SIFT) (http://sift.jcvi.org) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) tools.

RESULTS

Subjects and Whole-exome sequencing

We recruited 11 patients from the Chungnam university hospital. The mean age was 56 (range 27-78) years. The size of the tumor is an average of 10.00 cm (Table 1). We obtained 22 fresh-frozen samples, including 11 normal and matched- tumor FFPE from OGCT patients for WES. On Illumina NovaSeq 6000 platform with 150 bp paired-end reads, WES data were generated with an average of 128 Gb sequences. The post-alignment average read depth of the whole-exome sequencing was 258X and 169.7X in tumor and normal samples, respectively. Sequencing quality for Q30 value was 91.5% and 92.8% in tumor and normal tissues, respectively (Table S1).

Identification of OGCT related variants

A total of 1,067,219 single nucleotide polymorphisms (SNPs) and 162,155 insertions/deletions (indels) were identified from WES data of 22 samples. To identify OGCT related variants, we collected 29,998 SNPs and 3,437 indels, shared by 11 patients (Table 2). In the variant calling step, we selected only the variants with at least 30 depth coverage to eliminate possible errors in library preparation and sequencing data production and to determine the substantial variants in OGCT. As a result, variants with 31.7 minor depth and 417 average depth were selected. To identify OGCT related variants, we identified 7,957 SNPs and 234 indels in the exonic region (Table 2). Of these, we identified 4110 nonsynonymous

variants, including missense, nonsense, and unknown variants, and 137 frameshift indels, including nonsense and unknown variants that could affect protein functions (Table 3). To analyze the variants associated with OGCT development and recurrence, we focused on 44 tumor-specific nonsynonymous variants in 22 genes (*PABPC3*, *ZNF595*, *MUC3A*, *OR2T4*, *SEC22B*, *PRSS3*, *NBPF14;NBPF19;NBPF26;NBPF9*, *FEZ2*, *ANKRD36C*, *ANKRD36B*, *GYPA*, *PRIM2*, *VWDE*, *CFTR*, *NUTM2A*, *MUC6*, *OR8U1;OR8U8*, *GOLGA6L3*, *TPSD1*, *NPIPB15*, *SHC2*, and *KRTAP10-6*) and four tumor-specific frameshift indels in *ZNF595* (Table 3). *PABPC3* encodes a protein that binds to the poly (A) tail and regulates mRNA stability. Previous studies reported that WES reveals high-risk frameshift mutations and somatic mutations for *PABPC3* in breast cancer patients (19, 20) and malignant ovarian germ cell tumors, respectively (21). *ZNF595* encodes a protein belonging to the C2H2 zinc finger protein family that is involved in transcriptional regulation. Recent studies revealed that zinc finger protein families are closely related to various cancer and tumor types, such as tumorigenesis or tumor suppressor genes (22). For example, overexpression of *ZNF304* transcriptionally regulates β1 integrin, resulting in metastasis of ovarian cancer (23). β1 integrin, a member of the integrin family, is involved in cell adhesion and recognition in immune response, tissue repair, and tumor cell metastasis. In addition, *ZKSCAN3* (*ZFN306*) also contributes to tumor metastasis in colorectal cancer cells, prostate cancers, and hepatocellular carcinoma (24-26). For a 5-year survival rate, *ZKSCAN3* is used for the potential prognostic marker of hepatocellular carcinoma patients. *ZKSCAN3* increases the expression of *ITGB4* (integrin β4) binding to its promoter, resulting in promoting migration, invasion, and EMP progress. *ITGB4* activates the AKT signaling pathway involved in cell proliferation (26).

Furthermore, we investigated 22 genes for whether the genes were related to OGCT using three cancer-related databases (TCGA, ICGC, and COSMIC) that contain cancer-associated genes across all cancer types. We found nine genes (*SEC22B*, *FEZ2*, *ANKRD36B*, *GYPA*, *MUC3A*, *PRSS3*, *NUTM2A*, *OR8U1*, and *KRTAP10-6)* in all three databases, which were highly associated with ovarian cancer (Figure 2). *FEZ2* is a family of FEZ proteins involved in axonal growth in *Caenorhabditis elegans*. FEZ proteins are involved in neuronal development, neurological disorders, viral infection, and autophagy. *FEZ1* is a tumor suppressor gene and is implicated in ovarian carcinogenesis. *FEZ1* was evaluated as a prognostic and diagnostic marker for ovarian neoplasia (27). *NUTM2A* (NUT family member 2A), also known as *FAM22A*, reported that *YWHAE-NUTM2A* fusion transcript is associated with aggressive endometrial stromal sarcomas (28). *SEC22B*, a member of the *SEC22* family of vesicle-

trafficking proteins, is involved in the membrane fusion of vesicle trafficking between the endoplasmic reticulum (ER) and Golgi apparatus, secretory autophagy, and antigen cross-presentation (29). Several studies have reported that *SEC22B* is highly related to tumorigenesis that the mutations in *SEC22B* were found in various cancers. Interestingly, the fusion of *SEC22B*-NOTCH2 activates the NOTCH pathway to the proliferation and survival of tumor cells in aggressive breast cancers and mantle cell lymphoma (30-32).

Enrichment and pathway analysis

To understand the functional relevance, we analyzed the gene ontology of 507 genes (16 overlapping genes in SNPs and indels), including 417 and 106 genes in tumor-specific SNPs and tumor-specific indels, respectively, in cellular compounds (CC), molecular functions (MF), and biological processes (BP) through metascape analysis (Figure 3; Table S2). The most significantly enriched gene set in the cellular component is "extracellular matrix (23 genes)", "clathrin-coated pit (16 genes)", "autophagosome (8 genes)", and "ciliary base (10 genes)" (Figure 3A). For the molecular function, "inorganic molecular entity transmembrane transporter activity (31 genes)" and "protein kinase binding (29 genes)" showed the most significantly enriched (Figure 3B). The most significant gene set enrichment is "response to starvation (20 genes)", "chloride transmembrane transport (21 genes)", "selective autophagy (31 genes)", and "regulation of cell morphogenesis (43 genes)" in the biological process (Figure 3C). Interestingly, two candidate genes (*SEC22B* and *FEZ2*), which were highly associated with ovarian cancer in three cancer databases, were identified in the term "selective autophagy". In addition, we performed gene-gene interaction analysis using ClueGO (p-value <0.05; Benjamini-Hochberg). The genes were highly enriched in "selective autophagy (9 genes)", "cellular component assembly in morphogenesis (9 genes)", "regulation of anoikis (4 genes)", and "regulation of cell morphogenesis (17 genes)" (Figure 4; Table S3).

Pathogenic variants in OGCT

To identify pathogenic variants in OGCT, we collected variants with MAF less than 0.05 using the 1,000 genomes project database, NHLBI exome sequencing project (ESP), and ExAC database (http://exac.broadinstitute.org). Of the 16 variants in nine genes found in three cancer databases, we identified seven nonsynonymous SNPs, except unknown variants with MAF ≤ 0.05, including five SNPs (p.Thr343Ile, p.Met357Ile, p.Glu364Ala, p.Glu364Asp, and p.Ser366Thr) in *MUC3A* and two SNPs (p.Ser7Asn and p.Gly8Val) in *PRSS3* (Table 4). In investigating rare functional variants using the public database, Allele Frequency Aggregator

(ALFA), we confirmed that the seven selected variants have an infrequent MAF of 0.0092 on average in the Asian population (Table 4) (33).

PRSS3 is a member of the trypsin family of serine proteases. The serine proteases are secreted by several enzymes that promote tumor growth and metastatic progression in various cancers, including lung adenocarcinoma, prostate cancer, and pancreatic cancer (34, 35). Interestingly, the expression of *PRSS3* showed a significant increase in epithelial ovarian cancer tissue compared to normal ovarian samples at mRNA and protein levels (36). *MUC3A* is a member of the membrane mucin gene family that encodes secreted and membrane bounding epithelial glycoproteins and also referred to as a potent modifier of epidermal growth factor receptor (EGFR) and is known to lead to poor prognosis by upregulated and downregulated expression of programmed cell death-ligand 1 (PD-L1) in non-small cell lung cancer (37). In addition, we used SIFT and polyphen-2 program to analyze seven variants for the potentially deleterious effects. Of these, two SNPs (p.Ser7Asn and p.Gly8Val) in *PRSS3* were predicted to be tolerant or benign in the SIFT and Polyphen-2 (Table 4). 5 SNP variants in *MUC3A* were predicted to be “unknown” in SIFT and Polyphen-2 (Table 4).

DISCUSSION

Today, high throughput next-generation sequencing (NGS) is a technology that helps make genetic testing faster and cheaper. Whole-exome sequencing (WES), one of the NGS technologies, is widely used to investigate the genetic variations and mechanisms of rare diseases and cancers. Although exons account for only about 2% of the human genome, exons contain approximately 85% of the mutations in Mendelian disorders with significant effects (38, 39).

In ovarian cancer, there are various factors to increase the risks, such as aging, obesity, hormone therapy after menopause, and smoking. However, the development and causes of ovarian granulosa cell tumor (OGCT) is still unclear. OGCT accounts for about 5% of ovarian cancers, but the prognosis is poor due to a high recurrence rate of over 50%. Thus, early diagnosis and treatment using genetic mutations are important.

Several studies tried to understand the mechanism of occurrence for ovarian granulosa cell tumors (OGCTs) using NGS sequencing. *FOXL2* mutation (C134W) was found using whole-transcriptome paired-end RNA sequencing and whole-genome sequencing (13, 40). The *FOXL2* is strongly expressed in granulosa cells as one of the earliest markers of ovarian differentiation. *FOXL2* C134W mutation is the loss of function mutation that is prevalent in adult OCCT patients. Two *TERT* promoter mutations (C228T and C250T) might be a biomarker of OGCT using whole-exome sequencing and targeted sequencing (15). These two mutations are involved in telomerase activation in several cancers, including central nervous system tumors, hepatocellular carcinomas, bladder cancers, and thyroid cancers. Significantly, they are hot-spot mutations found in about 15.9% of ovarian clear cell carcinomas.

Mucins protect epithelial tissues against external environments under normal physiological conditions (41). The mucins are a family of O-glycoproteins that play an important role in epithelial cell regeneration, cell adhesions, immune response, and cell signaling. Reduced expression levels of several mucin genes, including *MUC3*, *MUC4*, and *MUC5B* in patients with Crohn's disease, suggest primary or early mucosal defect of these genes (42). Chauhan et al. showed that *MUC13* is more overexpressed in malignant ovarian tumors than in benign ovarian tumors (43). *MUC16* is overexpressed in epithelial ovarian cancer and used as a biomarker (CA125) (44-46). On the other hand, the expression of *MUC3* and *MUC4* was significantly reduced as the cancer stage increased (47). *MUC3A* plays a role in the pathogenesis and progression of cancers (48). Abnormal overexpression of *MUC3A* in

clear-cell renal cell carcinoma (ccRcc), breast, pancreatic, gastric, colorectal, appendiceal, and prostate cancer is associated with poor prognosis (49-52). The abnormal expression of *MUC3A* is highly associated with a poor prognosis in many tumor types, although the roles of *MUC3A* in cancer development are not yet clear. In addition, hypomethylation contributes to the expression of *MUC3A* in cancer cells (53). The methylation status of *MUC3A* is also utilized as an epigenetic diagnostic marker for carcinogenic risk and prognosis in cancer patients.

Gene enrichment analysis showed that tumor-specific variants are highly enriched in anoikis and autophagy pathways. Anoikis resistance represents a critical and distinguishing feature underlying the aggressiveness of ovarian cancer cells. Several studies reported that enhanced anoikis resistance is closely related to activating the Src/Akt/Erk signaling pathway, which is a critical cellular process including aggressiveness and tumorigenicity (54, 55). In addition, autophagy has been implicated in both tumor suppression and growth, and regulates oncogenic protein substrates and angiogenesis (56, 57). Autophagy can inhibit cancer by preventing angiogenesis in prostate, breast, and colon cancer cells. Cai et al. reported that a high rate of metabolism and autophagy is associated with increased anoikis resistance, and blocking these metabolic pathways significantly increases anoikis and inhibits tumor development *in vitro* and *in vivo* (54).

CONCLUSION

In summary, we identified five rare variants for the potentially deleterious effects in *MUC3A* though WES. Our findings suggest that *MUC3A* may contribute to OGCT development, although little is known about the functional role of *MUC3A* in cancer pathology. It also suggests that *MUC3A* may be used as a potential biomarker for OGCT. For this, further investigation with more tumor samples is required to understand the development of OGCT.

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TABLES AND FIGURES

Table 1. Clinical characteristics of patients with OGCT

Patient no	Tumor	Normal	Age	Date of diagnosis	Size of tumor
1	**T1**	**N1**	50	15-08-21	14
2	**T2**	**N2**	54	16-12-30	7.6
3	**T3**	**N3**	78	17-03-03	10
4	**T4**	**N4**	63	17-04-26	2.7
5	**T5**	**N5**	63	17-08-18	6.5
6	**T6**	**N6**	43	11-03-02	7
7	**T7**	**N7**	56	11-12-29	7.5
8	**T8**	**N8**	52	13-08-05	3.3
9	**T9**	**N9**	58	14-02-14	18
10	**T10**	**N10**	73	15-03-17	11
11	**T11**	**N11**	27	15-03-13	22.5

Table 2. The number of candidate variants in OGCT patients

Variant	SNPs			Indels		
	Normal	**Common**	**Tumor**	**Normal**	**Common**	**Tumor**
Intragenic						
Exonic	22 (10)	7877 (4170)	58 (27)	2 (2)	228 (188)	4 (1)
Intronic	70 (66)	15993 (6105)	346 (300)	35 (35)	2319 (1831)	83 (78)
Exonic; Splicing	-	5 (5)	-	-	25 (23)	-
Splicing	-	33 (33)	-	-	56 (47)	-
5”UTR	2 (2)	649 (555)	4 (4)	-	86 (84)	6 (6)
3”UTR	5 (5)	923 (778)	11 (10)	-	114 (108)	9 (8)
5”UTR;3”UTR	-	2 (2)	1 (1)	-	-	-
Intergenic	17 (9)	1330 (459)	33 (22)	4 (3)	156 (91)	4 (4)
Upstream;Downstream	-	27 (24)	-	-	7 (5)	-
Upstream	6 (6)	381 (277)	15 (11)	-	62 (55)	4 (4)
Downstream	1 (1)	172 (124)	6 (5)	-	19 (19)	3 (2)
ncRNA exonic	5 (4)	839 (378)	31 (20)	1 (1)	82 (70)	1 (1)
ncRNA splicing	-	2 (2)	-	-	1 (1)	-
ncRNA intronic	10 (9)	1091 (406)	30 (25)	2 (2)	120 (93)	3 (2)

ncRNA exonic; splicing	-	1 (1)	-	-	1 (1)	-
Total variants	**138**	**29,325**	**535**	**44**	**3,276**	**117**
(Total Genes)	112	13,319	425	43	2,616	106

Table 3. Effects of variants in the exonic regions

Variant effect	SNPs			Indels		
	Normal	**Common**	**Tumor**	**Normal**	**Common**	**Tumor**
Nonsynonymous SNV	15 (9)	3782(2347)	35 (19)	-	-	-
Synonymous SNV	7 (3)	3826 (2571)	14 (9)	-	-	-
Unknown	-	235 (70)	9 (3)	-	57 (51)	4 (1)
Start loss	-	9 (9)	-	-	1 (1)	-
Stop loss	-	3 (3)	-	-	-	-
Stop gain	-	22 (17)	-	-	4 (4)	-
Nonframeshift insertion	-	-	-	1 (1)	53 (51)	-
Nonframeshift deletion	-	-	-	1 (1)	42 (42)	-
Frameshift insertion	-	-	-	-	33 (26)	-
Frameshift deletion	-	-	-	-	38 (28)	-
Total variants (Total Genes)	**22 (12)**	**7877 (5017)**	**58 (31)**	**2 (2)**	**228 (203)**	**4 (1)**

Table 4. Detail of rare variants with deleterious effects

Type	Gene	Position	rs_number	Ref	Alt	Genotype	Amino acid change	MAF in Asian	SIFT	HumDiv	HumVar
SNPs	*MUC3A*	chr7:100550447	rs776762595	C	T	c.1028C>T	p.Thr343Ile	0	unknown	unknown	unknown
		chr7:100550490	rs796897629	G	A	c.1071G>A	p.Met357Ile	0.009	unknown	unknown	unknown
		chr7:100550510	rs796842434	A	C	c.1091A>C	p.Glu364Ala	0.019	unknown	unknown	unknown
		chr7:100550511	rs74435283	G	C	c.1092G>C	p.Glu364Asp	0	unknown	unknown	unknown
		chr7:100550515	rs796491364	T	A	c.1096T>A	p.Ser366Thr	0.019	unknown	unknown	unknown
	PRSS3	chr9:33794809	rs201061108	G	A	c.20G>A	p.Ser7Asn	0.006	Tolerant	Benign	Benign
		chr9:33794812	rs199873220	G	T	c.23G>T	p.Gly8Val	0.012	Tolerant	Benign	Benign

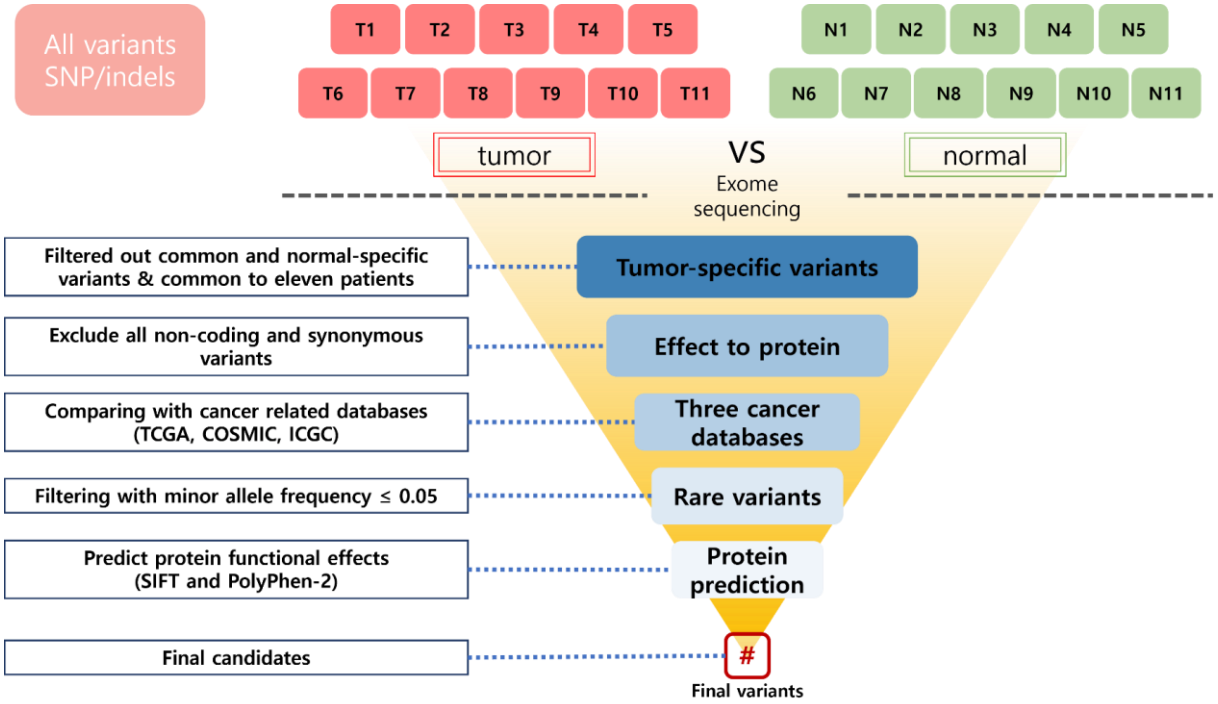


Figure 1. Comparison criteria for OGCT rare variant with 11 patients. The normal and cancer tissue isolated from 11 OGCT patients were involved in identification of rare mutation using whole-exome sequencing. Green and red boxes indicate normal and matched-tumor samples, respectively. The scope was narrowed step by step, and the critical nonsynonymous variants closely related to OGCT were finally identified by evaluating the influence of phenotype.

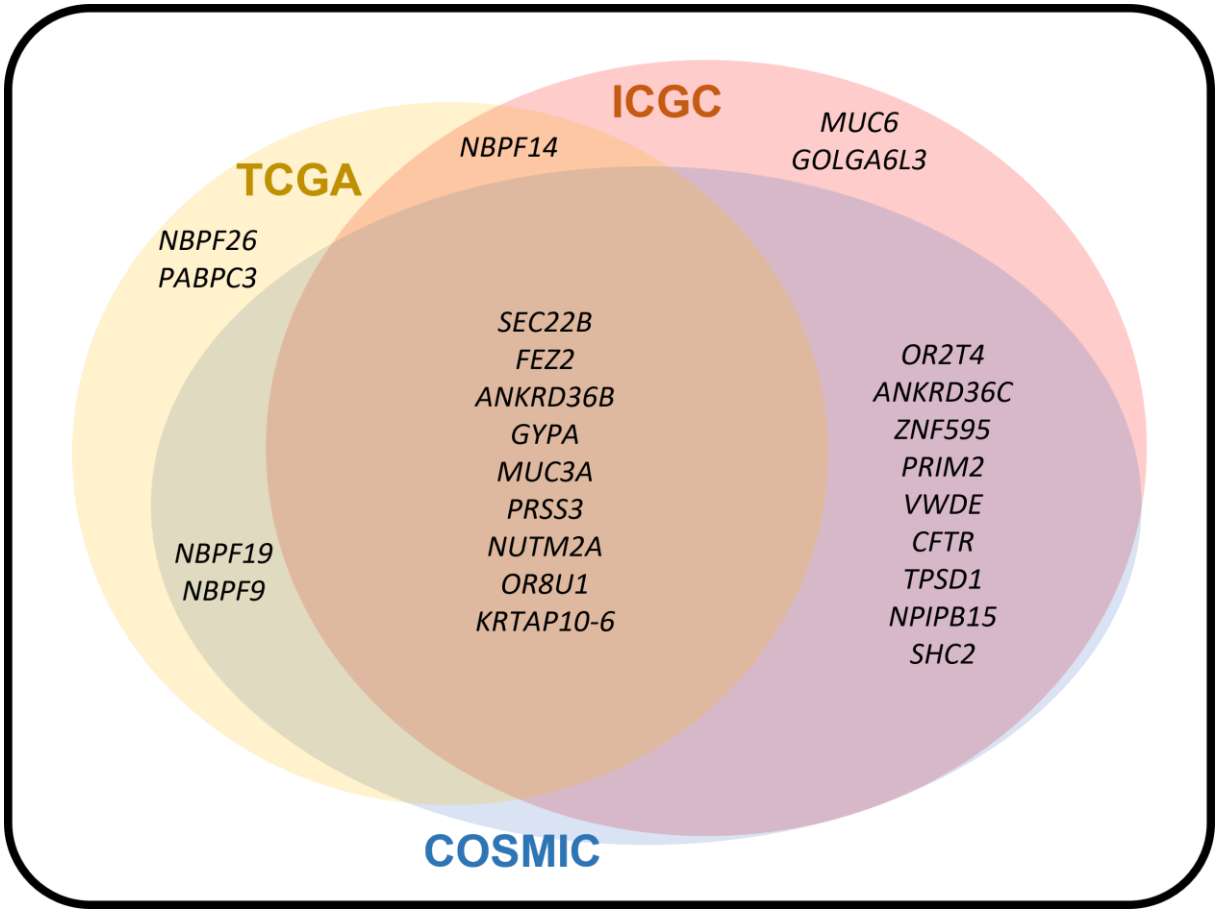
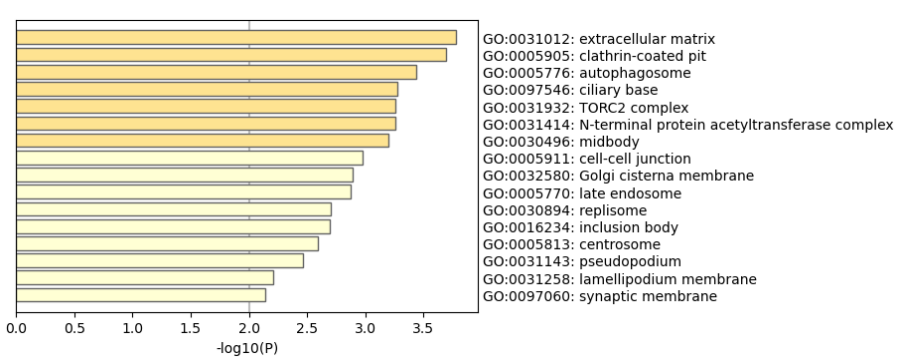
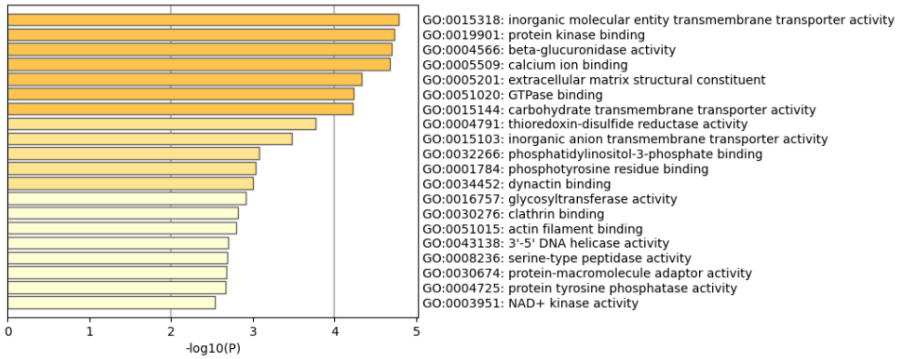


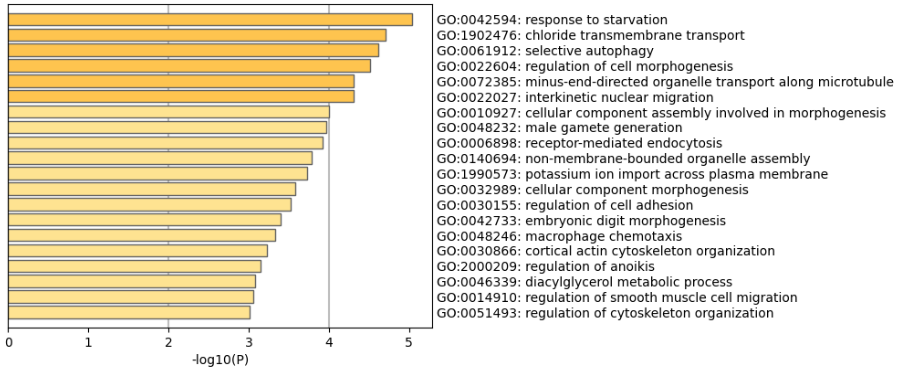
Figure 2. Venn diagram of the three cancer-related databases (ICGC, TCGA, and COSMIC). The Venn diagram shows the genes harboring tumor-specific nonsynonymous variants matched with each database, including TCGA (yellow), ICGC (pink), and COSMIC (blue) cancer genome projects. Nine were included in the common set as commonly identified genes in all databases.



(A)



(B)



(C)

Figure 3. GO function enrichment analysis of candidate genes in OGCT patients. GO enrichment analysis of tumor-specific genes common to 11 patients was retrieved using Metascape software. Significantly (*P*-value<0.05) enriched GO terms in cellular components (A), molecular functions (B), and biological processes (C) branches are presented. Bar chart of enriched GO term clusters; color intensity statistical significance.

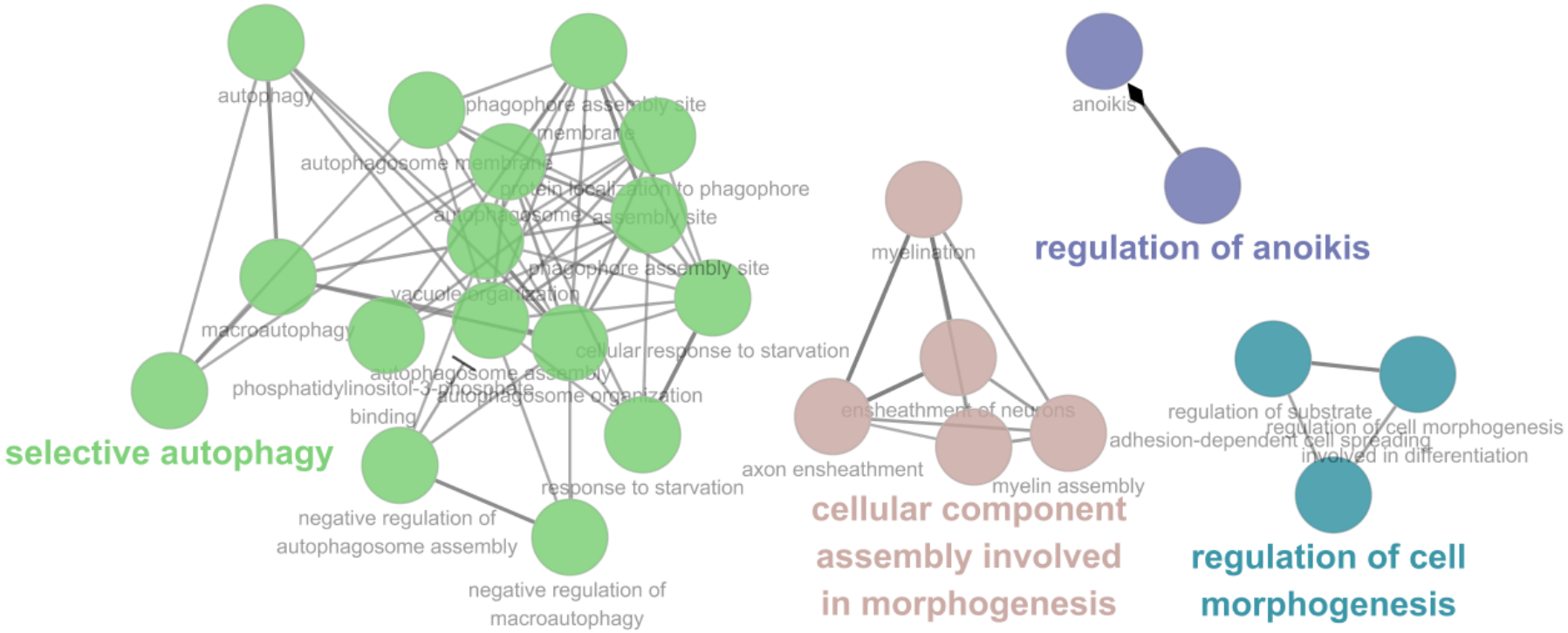


Figure 4. Gene ontology (GO) functional network analysis. Statistically significant enriched GO terms visualized by Cytoscape software add-on ClueGO plugin. *P*-value was adjusted by Benjamini–Hochberg false discovery rate (FDR). Node represents each statistically significant enriched GO term. The different size of nodes indicates the number of mapped genes in each GO term. In GO functional network analysis, the most significant and representative GO term is highlighy in bold and the offspring categories are connected with gray title.

SUPPLEMENTAL DATA

Table S1. Summary statistics of sequencing quality

	Statistics					pre-alignment statistics					post-alignment statistics							
Sample Type	**Sample name**	**AnalyzeID**	**Q20(%)**	**Q30(%)**	**GC(%)**	**total reads**	**Average Read Length (bp)**	**Total Yield (Mbp)**	**Target Regions (bp)**	**average depth (pre-alignment)**	**Initial Mappable Reads**	**% Initial Mappable Reads**	**Non-Redundant Reads**	**% Non-Redundant Reads**	**On-Target Reads**	**% On-Target Reads**	**On-Target Yield (bp)**	**mean depth (post-alignment)**
Tumor	T1	S15-47822F8	95.9	93.2	51.5	154,922,590	101.0	15,647	60,456,963	258.8	154,666,559	99.8	146,238,992	94.5	107,089,858	73.2	9519341374	157.4
	T2	S16-26915B2	94.0	90.6	48.9	146,251,212	101.0	14,771	60,456,963	244.3	144,847,864	99.0	137,360,326	94.8	100,970,699	73.5	8776113111	145.1

	T3	S17-4139B2	93.9	90.4	50.0	140,902,596	101.0	14,231	60,456,963	235.3	139,510,350	99.0	131,593,379	94.3	96,861,921	73.6	8377216650	138.5
	T4	S17-7934RG1	94.2	90.8	51.5	139,881,802	101.0	14,128	60,456,963	233.6	138,620,243	99.0	126,740,170	91.4	97,819,824	77.1	8674285663	143.4
	T5	S17-167909	93.9	90.4	49.6	137,737,678	101.0	13,911	60,456,963	230.1	136,431,002	99.0	130,239,288	95.4	88,595,630	68.0	7656389803	126.6
	T6	S11-2891RG5	96.0	93.4	50.6	141,676,368	101.0	14,309	60,456,963	236.6	141,487,308	99.8	129,578,037	91.5	98,568,622	76.0	8834348644	146.1
	T7	S11-23811F3	94.7	91.5	51.2	137,817,696	101.0	13,919	60,456,963	230.2	136,781,997	99.2	129,567,516	94.7	97,102,230	74.9	8577862313	141.8
	T8	S13-15636E	94.6	91.3	53.0	149,231,118	101.0	15,072	60,456,963	249.3	147,972,075	99.1	136,115,183	91.9	102,461,498	75.2	9127763553	150.9
	T9	S15-4531F3	95.2	92.1	51.2	186,402,720	101.0	18,826	60,456,963	311.4	185,764,683	99.6	162,876,676	87.6	121,222,036	74.4	10852812049	179.5

	T10	S14-2813F2	95.0	91.9	50.6	176,522,844	101.0	17,828	60,456,963	294.9	175,712,742	99.5	164,580,604	93.6	120,107,606	72.9	10591078346	175.1
	T11	S15-4343F3	94.5	91.0	51.0	187,438,318	101.0	18,931	60,456,963	313.1	186,651,213	99.5	172,497,815	92.4	130,551,091	75.6	11616788824	192.1
average			94.7	91.5	50.8	154,434,995	101.0	15597.5	60456963	258.0	153495094	99.3	142489817	92.9	10557736 5	74.0	9327636394	154.2
normal	N1	S15-148977	96.0	93.7	51.6	102,506,078	101.0	10,353	60,456,963	171.2	101,985,117	99.4	98,097,641	96.1	73,619,168	75.0	6519310788	107.8
	N2	S16-26915A2	95.8	93.1	49.8	101,839,794	101.0	10,285	60,456,963	170.1	101,651,545	99.8	96,068,709	94.5	70,128,238	72.9	6154444800	101.8
	N3	S17-4139A9	96.1	93.6	50.1	93,696,890	101.0	9,463	60,456,963	156.5	93,559,850	99.8	89,109,581	95.2	66,561,945	74.6	5865228861	97.0
	N4	S17-79346	95.6	92.8	50.2	97,011,068	101.0	9,798	60,456,963	162.0	96,816,305	99.7	92,012,219	95.0	67,243,231	73.0	5905584438	97.6

	N5	S17-167906	95.9	93.3	50.0	97,223,098	101.0	9,819	60,456,963	162.4	97,049,431	99.8	91,654,493	94.4	67,367,423	73.5	5908120791	97.7
	N6	S11-28911	94.5	91.3	51.4	106,083,920	101.0	10,714	60,456,963	177.2	105,034,516	99.0	98,943,908	94.2	74,664,562	75.4	6566599356	108.6
	N7	S11-23854A7	95.8	93.1	51.6	97,829,820	101.0	9,880	60,456,963	163.4	97,686,402	99.8	92,129,798	94.3	70,422,877	76.4	6284707183	103.9
	N8	S13-15636A2	96.2	93.7	52.9	99,217,586	101.0	10,020	60,456,963	165.7	99,099,123	99.8	92,198,033	93.0	71,928,473	78.0	6470534331	107.0
	N9	S14-28991	94.9	91.9	51.4	110,325,136	101.0	11,142	60,456,963	184.3	109,258,657	99.0	103,899,206	95.0	81,088,625	78.0	7178763168	118.7
	N10	S15-43944	95.0	92.0	51.1	111,616,652	101.0	11,273	60,456,963	186.4	110,682,424	99.1	105,490,521	95.3	79,443,664	75.3	7035610192	116.3
	N11	S15-4570	95.2	92.2	50.2	100,436,964	101.0	10,144	60,456,963	167.7	99,997,253	99.5	93,397,511	93.4	68,236,207	73.0	6036506480	99.8

average			95.5	92.8	50.9	101,617,001	101.0	1026 2.8	60456963.0	169.7	10116551.2	99.5	957274 20.0	94.6	7188 2219 .4	75.0	6356855490	105.1

Table S2. List of GO terms associated with tumor-specific genes in OGCT

(A) Cellular components

Group ID	Category	Term	Description	LogP	Log(q-value)	InTerm_InList	Symbols
1	GO Cellular Components	GO:0031012	extracellular matrix	-3.77659	-0.891	23/570	*CTSC,COL15A1,COL17A1,GLG1,MMP17,MUC4,MUC6,NID1,OVGP1,TPSAB1,HSP90B1,ADAMTSL2,POSTN,HPSE,ADAMTS20,ITIH5,FBN3,COL25A1,NAV2,COL24A1,LAMA1,EYS,MXRA7*
2	GO Cellular Components	GO:0005905	clathrin-coated pit	-3.69213	-0.891	7/70	*LDLR,ITSN1,CUBN,PICALM,AAK1,FCHO1,EPN3,BLK,PIK3C3,PTK2,GNA13,FERMT2,ATG14,WIPI2,VPS13C,WIPI1*
3	GO Cellular Components	GO:0005776	autophagosome	-3.43643	-0.850	8/101	*PEG3,PIK3C3,ATG14,WIPI2,TEX264,WIPI1,MCOLN3,MAP1LC3C*
4	GO Cellular Components	GO:0097546	ciliary base	-3.27694	-0.850	5/39	*GLI2,PRKAR1A,PRKAR1B,TULP3,FANK1,PIK3C3,ATG14,CFAP46,CFAP54,CFAP221*
5	GO Cellular Components	GO:0031932	TORC2 complex	-3.25381	-0.850	3/10	*TTI1,SMG1,PRR5L*

6	GO Cellular Components	GO:0031414	N-terminal protein acetyltransferase complex	-3.25381	-0.850	3/10	*NAA25,NAA15,NAA38*
7	GO Cellular Components	GO:0030496	midbody	-3.19835	-0.850	11/196	*ECT2,PIK3C3,SAFB,HSP90B1,PKP4,TRIOBP,ZFYVE26,EXOC2,ZFYVE19,AGAP2,ASPM*
8	GO Cellular Components	GO:0005911	cell-cell junction	-2.97449	-0.737	19/494	*AQP7,COL17A1,CXADR,ECT2,NOTCH1,VAV1,SYMPK,PKP4,PTPRU,PATJ,FERMT2,EPB41L3,FRMD4B,ADGRL3,AHI1,IQGAP3,PLEKHA7,PIKFYVE,LAMA1*
9	GO Cellular Components	GO:0032580	Golgi cisterna membrane	-2.88731	-0.713	7/95	*FUT2,B4GALT5,SCFD1,UXS1,COG3,GOLGA8IP,GOLGA8B,HOOK3*
10	GO Cellular Components	GO:0005770	late endosome	-2.8771	-0.713	13/282	*SLC31A1,DYNC1LI2,LDLR,CHMP1A,PIK3C3,PRKAR1A,PRKAR1B,MAPK3,RNF13,MCOLN3,VIPAS39,GALNTL5,PIKFYVE*
11	GO Cellular Components	GO:0030894	replisome	-2.70284	-0.629	3/15	*PRIM2,RPA1,DONSON,BCL6,TEX264*
12	GO Cellular Components	GO:0016234	inclusion body	-2.69771	-0.629	6/76	*AGL,PICALM,XRN2,FBXO7,SFMBT2,PRDM16*
13	GO Cellular Components	GO:0005813	centrosome	-2.59469	-0.617	21/615	*BICD1,CTSC,CHD3,DYNC1LI2,PRKAR1A,CIR1,KIAA0586,PATJ,CEP152,TTLL5,BICD2,UBR4,ZFYVE26,AHI1,CCDC77,HOOK*

							3,ZFYVE19,CEP295,PLEKHA7,CEP120,ASPM
14	GO Cellular Components	GO:0031143	pseudopodium	-2.46582	-0.549	3/18	*ACTN4,ACTN2,MAPK3*
15	GO Cellular Components	GO:0031258	lamellipodium membrane	-2.21213	-0.349	3/22	*NCKAP1,FERMT2,SYNE2*
16	GO Cellular Components	GO:0097060	synaptic membrane	-2.13866	-0.292	14/384	*ACTN2,DAGLA,GABRR2,PTPRD,PTPRS,ITSN1,PICALM,SLC6A5,DGKI,SLC4A8,RIMS1,SYNE1,GRIP1,CHRNA10*

(B) Molecular functions

Group ID	Category	Term	Description	LogP	Log(q-value)	InTerm_InList	Symbols
1	GO Molecular Functions	GO:0015318	inorganic molecular entity transmembrane transporter activity	-4.78765	-1.591	30/740	*AQP7,ATP4B,CFTR,SLC31A1,COX6B1,GABRR2,KCNH2,KCNJ12,FXYD3,KCNQ4,SLC6A5,SLC4A8,SLC12A7,DMAC2L,ANO7,SLC45A2,SLC38A2,MCOLN3,SLC2A9,CHRNA10,ANO2,SLC25A28,SLC12A8,CACNA2D4,PKD1L2,SLC5A11,ANO4,OTOP1,CCT8L2,KCNJ18,SLC30A9*
2	GO Molecular Functions	GO:0019901	protein kinase binding	-4.7295	-1.591	28/671	*BICD1,CBLB,ACE,KIF11,MEF2A,PPEF2,PRKAR1A,PRKAR1B,MAP2K3,PTK2,WARS1,CIR1,SLC12A7,FERMT2,ATF7,RNF13,CEP152,SHC2,FBXO7,TRIB2,GPRC5B,EXOC2,TRIM5,AGAP2,TRIM6,DUSP19,SIK1,GFRAL,LDHA*
3	GO Molecular Functions	GO:0004566	beta-glucuronidase activity	-4.69734	-1.591	3/4	*KL,HPSE,GUSBP3,AGL,GALC,OVGP1,GLB1L,IL1RAP*

4	GO Molecular Functions	GO:0005509	calcium ion binding	-4.6731	-1.591	29/713	*ACTN4,ACTN2,CBLB,CDH16,CLGN,F10, HABP2,LDLR,NID1,NOTCH1,PLCB2,PNL IPRP1,PPEF2,PRSS3,ITSN1,HSP90B1,CU BN,CELSR1,ADGRL3,HPCAL4,SYT17,LRP 1B,MCTP1,SYT15,FBN3,PKD1L2,RASEF, EYS,NOTCH2NLA*
5	GO Molecular Functions	GO:0005201	extracellular matrix structural constituent	-4.3262	-1.446	12/172	*COL15A1,COL17A1,MUC3A,MUC4,MUC 6,NID1,TUFT1,POSTN,FBN3,COL25A1,C OL24A1,LAMA1,ACTN2,BICD1,COPB1,R PL4,TPM1,CCDC6,KRT38,EPB41L3,KLHL 3,NUP54,NUP85,TLN2*
6	GO Molecular Functions	GO:0051020	GTPase binding	-4.23155	-1.446	16/294	*AP1G1,BICD1,ECT2,PICALM,NCKAP1,TR IOBP,ATG14,RIMS1,BICD2,FNBP1L,EXO C2,FGD6,RANBP17,DOCK7,FMNL2,IQG AP3*
7	GO Molecular Functions	GO:0015144	carbohydrate transmembrane transporter activity	-4.22694	-1.446	6/40	*AQP7,SLC2A3,SLC45A2,SLC2A9,SLC5A11 ,SLC2A14,SLC6A5,SLC4A8,SLC12A7,SLC3 8A2,SLC12A8,ATP4B,CFTR,COX6B1*

8	GO Molecular Functions	GO:0004791	thioredoxin-disulfide reductase activity	-3.77215	-1.043	3/7	*SELENOT,NXN,TXNRD3,ERO1B*
9	GO Molecular Functions	GO:0015103	inorganic anion transmembrane transporter activity	-3.4719	-0.856	10/153	*CFTR,GABRR2,FXYD3,SLC4A8,SLC12A7, ANO7,ANO2,SLC12A8,ANO4,CCT8L2,SLC 2A3,SLC6A5,SLC38A2,SFXN5,SLC2A14*
10	GO Molecular Functions	GO:0032266	phosphatidylinositol-3-phosphate binding	-3.07825	-0.737	5/43	*SNX13,ZFYVE26,WIPI2,WIPI1,ZFYVE19,A CTN2,TULP3,PICALM,FERMT2*
11	GO Molecular Functions	GO:0001784	phosphotyrosine residue binding	-3.03199	-0.710	5/44	*CBLB,MAPK3,VAV1,PTPN5,SHE*
12	GO Molecular Functions	GO:0034452	dynactin binding	-3.00173	-0.698	3/12	*BICD1,BICD2,HOOK3,EPB41L3,SMC3*

13	GO Molecular Functions	GO:0016757	glycosyltransferase activity	-2.91876	-0.650	13/279	*AGL,FUT2,RPN1,UGT8,UMPS,B4GALT5,UGT2A1,TIPARP,GALNTL5,STT3B,DPY19L2P2,UGT2A2,ALG1L2*
14	GO Molecular Functions	GO:0030276	clathrin binding	-2.8186	-0.612	6/72	*AP1G1,LDLR,PICALM,SYT17,EPN3,SYT15*
15	GO Molecular Functions	GO:0051015	actin filament binding	-2.79174	-0.599	11/220	*ACTN4,ACTN2,TPM1,FERMT2,TRIOBP,SYNE2,SYNE1,TLN2,FMNL2,MYOM3,IQGAP3*
16	GO Molecular Functions	GO:0043138	3”-5” DNA helicase activity	-2.70284	-0.539	3/15	*FBH1,NAV2,HELQ*
17	GO Molecular Functions	GO:0008236	serine-type peptidase activity	-2.68268	-0.539	10/194	*CTSC,ACE,DPP6,F10,HABP2,HGF,PRSS3,TPSAB1,TPSD1,PRSS3P2,MMP17,CHMP1A,CPZ,ADAM21,ADAMTSL2,PSMD14,UFSP2,ADGRG6,ADAMTS20,TRABD2A*

18	GO Molecular Functions	GO:0030674	protein-macromolecule adaptor activity	-2.67848	-0.539	13/297	*AP1G1,BICD1,UBXN8,SEC22B,EPB41L3, SYNE2,BICD2,SYNE1,GRIP1,FBXO7,TRI M5,TRIM6,DUSP19,ITSN1*
19	GO Molecular Functions	GO:0004725	protein tyrosine phosphatase activity	-2.66071	-0.533	7/104	*CDKN3,PTPRD,PTPRS,PTPRU,PTPN5,TP TE2,DUSP19,PPEF2,PHLPP2,MTMR9,PI KFYVE*
20	GO Molecular Functions	GO:0003951	NAD+ kinase activity	-2.53945	-0.458	3/17	*DGKI,NADK,DGKH*

(C) Biological processes

Group ID	Category	Term	Description	LogP	Log(q-value)	InTerm_InList	Symbols
1	GO Biological Processes	GO:0042594	response to starvation	-5.03962	-1.021	14/197	*ACAT1,ASNS,PIK3C3,MAPK3,ATG14,WIPI2,SLC38A2,MIOS,WIPI1,EIF2A,SIK1,EIF2AK4,MAP1LC3C,LOC102724428,POSTN,AGL,BCHE,LDHA,LDLR,GFRAL*
2	GO Biological Processes	GO:1902476	chloride transmembrane transport	-4.70628	-1.021	8/67	*CFTR,GABRR2,SLC4A8,SLC12A7,ANO7,ANO2,SLC12A8,ANO4,FXYD3,CD47,ACE,SLC2A3,SLC6A5,PLA2R1,SLC38A2,SLC2A9,SFXN5,SLC51B,SLC2A14,CCT8L2,SLC51A*
3	GO Biological Processes	GO:0061912	selective autophagy	-4.61147	-1.021	8/69	*MAPK3,CERS1,ATG14,WIPI2,KLHL3,TEX264,VPS13C,MAP1LC3C,PIK3C3,SEC22B,FEZ2,SCFD1,WIPI1,PIKFYVE,SMG1,VIPAS39,HGF,FBXO7,FNBP1L,MTMR9,TRIM5,TRIM6,RAB20,HOOK3,ACTN2,CHMP1A,SMARCE1,TPSAB1,TRIOBP,SUPT16H,NAV3*
4	GO Biological Processes	GO:0022604	regulation of cell morphogenesis	-4.51809	-1.021	17/309	*ACTN4,ITGA7,PTK2,PTPRD,TPM1,SEMA3E,POSTN,FERMT2,TRIOBP,RIMS1,EPB41L3,GRIP1,SYT17,FGD6,DOCK5,LARP4,F*

							MNL2,ACTN2,BCL6,COL17A1,MUC4,NID1,NOTCH1,HPSE,BMPR1A,LDLR,PTPRS,CLOCK,TRAK1,ADGRA2,TENM4,HOOK3,DOCK7,ASPM,BDKRB1,CD47,F10,HGF,MAPK3,MAP2K3,SPN,SYNE2,ELP5
5	GO Biological Processes	GO:0072385	minus-end-directed organelle transport along microtubule	-4.30501	-0.972	3/5	*BICD1,RAB6A,BICD2,HOOK3*
6	GO Biological Processes	GO:0022027	interkinetic nuclear migration	-4.30501	-0.972	3/5	*HOOK3,DOCK7,CEP120,SYNE2,ACTN4,BICD1,BLK,CFTR,MEF2A,CHMP1A,RAB6A,PICALM,ATG14,TRAK1,BICD2,FNBP1L,WIPI1,ASPM*
7	GO Biological Processes	GO:0010927	cellular component assembly involved in morphogenesis	-3.99831	-0.886	9/107	*ACTN2,MEF2A,PRKAR1A,TPM1,UGT8,ZPBP,EPB41L3,TENM4,PIKFYVE,CTSC,GALC,HGF,B4GALT5,ADGRG6*
8	GO Biological Processes	GO:0048232	male gamete generation	-3.96841	-0.886	24/590	*BCL6,CFTR,ACE,FANCA,MSH4,NOTCH1,CCNA1,CLOCK,ZPBP,XRN2,UBR2,SYNE1,MORC1,SPATA6L,STRBP,VIPAS39,TXNRD3,TDRD9,SLC2A14,CFAP54,GALNTL5,ASPM,C14orf39,DPY19L2P2,CXADR,PRKAR1A,RXFP2,EQTN*

9	GO Biological Processes	GO:0006898	receptor-mediated endocytosis	-3.92374	-0.886	14/249	*AP1G1,BICD1,LDLR,ITSN1,CUBN,PICALM,CALCRL,AAK1,PLA2R1,FCHO1,LRP1B,AHI1,FNBP1L,PIKFYVE,PIK3C3,MAPK3,EQTN,EPN3,MTMR9,MCTP1,ARHGAP12*
10	GO Biological Processes	GO:0140694	non-membrane-bounded organelle assembly	-3.78465	-0.867	18/389	*ACTN2,BICD1,KIF11,MEF2A,CHMP1A,PRKAR1A,TPM1,SMC3,CEP152,MRTO4,EIF2A,CEP295,CEP120,DEUP1,ASPM,GOLGA8IP,MCIDAS,GOLGA8B,CHD3,PATJ,DYNC1LI2,TTLL5,BICD2,CFAP46,ULK4,HOOK3,DOCK7,NAV3*
11	GO Biological Processes	GO:1990573	potassium ion import across plasma membrane	-3.72229	-0.849	6/49	*ATP4B,KCNH2,KCNJ12,SLC12A7,SLC12A8,KCNJ18,ACTN2,DPP6,FXYD3,SUMO1,KCNQ4,CCT8L2,ACTN4,BDKRB1,SLC31A1,COX6B1,SLC6A5,SLC4A8,DMAC2L,MCOLN3,SLC2A9,CHRNA10,SLC25A28,CACNA2D4,PKD1L2,OTOP1,SLC2A3,CFTR,MAPK3,RAB20*
12	GO Biological Processes	GO:0032989	cellular component morphogenesis	-3.58157	-0.784	27/744	*ACTN2,GLI2,MEF2A,NOTCH1,PRKAR1A,PTK2,PTPRD,PTPRS,TPM1,UGT8,PICALM,B4GALT5,FEZ2,SEMA3E,POSTN,NCKAP1,ZPBP,TRAK1,RIMS1,EPB41L3,GRIP1,*

							TENM4,SYT17,DOCK7,PIKFYVE,LAMA1, EIF2AK4
13	GO Biological Processes	GO:0030155	regulation of cell adhesion	-3.51805	-0.746	27/751	*ACTN4,BCL6,BLK,CBLB,CD47,FUT2,GLI 2,NID1,NOTCH1,PRKAR1A,PTK2,SPN,TP M1,VAV1,PKP4,SEMA3E,PTPRU,POSTN, NFAT5,FERMT2,TRIOBP,TMEM131L,AB CA12,GPAM,DOCK5,CARD11,LAMA1*
14	GO Biological Processes	GO:0042733	embryonic digit morphogenesis	-3.40055	-0.696	6/56	*BMPR1A,GLI2,NOTCH1,TULP3,LMBR1,T BC1D32*
15	GO Biological Processes	GO:0048246	macrophage chemotaxis	-3.33039	-0.666	5/38	*MAPK3,PTK2,MTUS1,NUP85,TAFA4*
16	GO Biological Processes	GO:0030866	cortical actin cytoskeleton organization	-3.22508	-0.635	5/40	*ECT2,NCKAP1,AKAP11,EPB41L3,FMNL2*
17	GO Biological Processes	GO:2000209	regulation of anoikis	-3.15263	-0.590	4/24	*NOTCH1,PTK2,BRMS1,SIK1*
18	GO Biological Processes	GO:0046339	diacylglycerol metabolic process	-3.08282	-0.540	4/25	*DAGLA,DGKI,GPAM,DGKH,LDLR,ATG14 ,SIK1,PIK3C3,PLCB2,SMG1,TTC7A,MTM R9,TPTE2,PIKFYVE*
19	GO Biological Processes	GO:0014910	regulation of smooth muscle cell migration	-3.05418	-0.521	7/89	*BMPR1A,ACE,TPM1,POSTN,GNA13,DOC K5,DOCK7*

20	GO Biological Processes	GO:0051493	regulation of cytoskeleton organization	-3.01088	-0.513	20/529	*ACTN2,BICD1,CD47,ECT2,CHMP1A,MAPK3,PTK2,TPM1,CELSR1,SEMA3E,PATJ,NCKAP1,FERMT2,TRIOBP,BICD2,CEP295,NAV3,IQGAP3,CEP120,WHAMMP3,ACTN4,BCL6,CXADR,KCNH2,MEF2A,PRKAR1A,HSP90B1,AKAP11,EPB41L3,SYNE2,FNBP1L,FGD6,ARHGAP12,FMNL2,AGAP2*

Table S3. List of biological network analysis with cytoscape

1D	Term	Ontology Source	Term PValue	Term PValue Corrected with Benjamini-Hochberg	Group PValue	Group PValue Corrected with Benjamini-Hochberg	GO Levels	GO Groups	% Associated Genes	Nr. Genes	Associated Genes Found
GO:0005509	calcium ion binding	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[5]	Group00	4.12	31.00	*ACTN2*, *ACTN4*, *ADGRL3*, *CBLB*, *CDH16*, *CELSR1*, *CLGN*, *CUBN*, *EYS*, *F10*, *FBN3*, *HABP2*, *HPCAL4*, *HSP90B1*, *ITSN1*, *LDLR*, *LRP1B*, *MCTP1*,

											NBPF26, NID1, NOTCH1, NOTCH2NLA, PKD1L2, PLCB2, PNLIPRP1, PPEF2, PRSS3, RASEF, SYT15, SYT17, VWDE
GO:0016266	O-glycan processing	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.00	0.01	[6, 8, 9]	Group01	9.09	6.00	*B4GALT5, GALNTL5, MUC12, MUC3A, MUC4, MUC6*

GO:0016410	N-acyltransferase activity	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.00	0.01	[5]	Group02	7.21	8.00	*BRPF3, CERS1, CLOCK, GDF1, NAA15, NAA25, SLC38A2, SMARCE1*
GO:0019901	protein kinase binding	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[5]	Group03	4.09	29.00	*ACE, AGAP2, ATF7, BICD1, CBLB, CEP152, CIR1, DUSP19, EXOC2, FBXO7, FERMT2, GFRAL, GPRC5B, KIF11, MAP2K3,*

											MEF2A, PPEF2, PRKAR1A, PRKAR1B, PTK2, RNF13, SHC2, SIK1, SLC12A7, TRIB2, TRIM5, TRIM6, TRIM6-TRIM34, WARS1
GO:0030866	cortical actin cytoskeleton organization	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[4, 7]	Group04	12.50	5.00	*AKAP11, ECT2, EPB41L3, FMNL2, NCKAP1*

GO:0031349	positive regulation of defense response	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[3, 4, 5, 6]	Group05	4.92	19.00	*AP1G1*, *CARD11*, *CD47*, *CLOCK*, *CTSC*, *GPRC5B*, *KLRC2*, *LDLR*, *MAPK3*, *MUC12*, *MUC3A*, *MUC4*, *MUC6*, *OSMR*, *PSMD14*, *TRIM5*, *TRIM6*, *TRIM6-TRIM34*, *VAV1*

GO:0031414	N-terminal protein acetyltransferase complex	GO_CellularComponent-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[3, 4, 6]	Group06	27.27	3.00	*NAA15, NAA25, NAA38*
GO:0004566	beta-glucuronidase activity	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.00	0.00	[5]	Group07	60.00	3.00	*GUSBP3, HPSE, KL*
GO:0032580	Golgi cisterna membrane	GO_CellularComponent-EBI-UniProt-	0.01	0.04	0.01	0.01	[5, 6, 7, 8, 9]	Group08	7.22	7.00	*B4GALT5, COG3, FUT2, GOLGA8B,*

		GOA-ACAP-ARAP_13.05.2021_00h00									*GOLGA8IP, SCFD1, UXS1*
GO:0048246	macrophage chemotaxis	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[4, 5, 6, 7, 8]	Group09	10.20	5.00	*MAPK3, MTUS1, NUP85, PTK2, TAFA4*
GO:0051642	centrosome localization	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13	0.01	0.04	0.01	0.01	[3]	Group10	12.12	4.00	*ASPM, BICD2, DYNC1LI2, SYNE2*

		.05.2021_00h00									
GO:0060038	cardiac muscle cell proliferation	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[4, 5, 6, 7, 8, 9]	Group11	9.80	5.00	*BMPR1A, NOTCH1, PRKAR1A, TENM4, ZFPM2*
GO:0070925	organelle assembly	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[5]	Group12	4.11	41.00	*ACTN2, AHI1, ASPM, ATG14, BICD1, CEP120, CEP152, CEP295, CFAP221, CFAP46, CFAP54, CHMP1A,*

											DEUP1, EIF2A, EXOC2, FEZ2, GOLGA8B, GOLGA8IP, IL1RAP, KIAA0586, KIF11, MAP1LC3C, MCIDAS, MEF2A, MRTO4, NOTCH1, PIK3C3, PIKFYVE, PRKAR1A, PTPRD, PTPRS, RAB20, SCFD1, SEC22B,

											SMC3, SYNE2, TBC1D32, TPM1, WIPI1, WIPI2, ZPBP
GO:1903305	regulation of regulated secretory pathway	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.01	0.01	[5, 6, 7, 8]	Group13	5.96	9.00	*AP1G1, BLK, DGKI, KLRC2, NOTCH1, RIMS1, SLC4A8, SYT15, SYT17*
GO:2000104	negative regulation of DNA-dependent DNA replication	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13	0.01	0.04	0.01	0.01	[7, 8, 9]	Group14	17.65	3.00	*BCL6, DONSON, FBH1*

		.05.2021_00h00									
GO:0010669	epithelial structure maintenance	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[4, 6]	Group15	12.50	4.00	*CXADR*, *MUC4*, *MUC6*, *SRFBP1*
GO:0010812	negative regulation of cell-substrate adhesion	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.00	0.01	[4, 5, 6]	Group16	9.09	6.00	*ACTN4*, *BCL6*, *NOTCH1*, *POSTN*, *PTPRU*, *SEMA3E*

GO:0001784	phosphotyrosine residue binding	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.00	0.01	[5]	Group17	10.87	5.00	*CBLB, MAPK3, PTPN5, SHE, VAV1*
GO:0016234	inclusion body	GO_CellularComponent-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.01	0.01	[3]	Group18	7.69	6.00	*AGL, FBXO7, PICALM, PRDM16, SFMBT2, XRN2*
GO:0035335	peptidyl-tyrosine dephosphorylation	GO_BiologicalProcess-EBI-UniProt-	0.01	0.04	0.01	0.01	[7, 8]	Group19	6.78	8.00	*CDKN3, DUSP19, MTMR9, PTPN5,*

		GOA-ACAP-ARAP_13.05.2021_00h00									*PTPRD, PTPRS, PTPRU, TPTE2*
GO:0004725	protein tyrosine phosphatase activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[8, 9]	Group19	6.78	8.00	*CDKN3, DUSP19, MTMR9, PTPN5, PTPRD, PTPRS, PTPRU, TPTE2*
GO:0038201	TOR complex	GO_CellularComponent-EBI-UniProt-GOA-ACAP-ARAP_13	0.00	0.04	0.00	0.01	[3]	Group20	21.43	3.00	*PRR5L, SMG1, TTI1*

		.05.2021_00h00									
GO:0031932	TORC2 complex	GO_CellularComponent-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[4]	Group20	27.27	3.00	*PRR5L, SMG1, TTI1*
GO:0046339	diacylglycerol metabolic process	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[6, 7]	Group21	15.38	4.00	*DAGLA, DGKH, DGKI, GPAM*

GO:0003951	NAD+ kinase activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[7]	Group21	17.65	3.00	*DGKH, DGKI, NADK*
GO:0051020	GTPase binding	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.02	0.00	0.00	[4]	Group22	5.83	18.00	*AP1G1, ATG14, BICD1, BICD2, DGKI, DOCK7, ECT2, EXOC2, FGD6, FMNL2, FNBP1L, GOLGA8B, IQGAP3, NCKAP1,*

											PICALM, RANBP17, RIMS1, TRIOBP
GO:0031267	small GTPase binding	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[5]	Group22	5.82	16.00	*AP1G1, BICD1, BICD2, DGKI, DOCK7, ECT2, EXOC2, FGD6, FMNL2, GOLGA8B, IQGAP3, NCKAP1, PICALM, RANBP17, RIMS1, TRIOBP*
GO:0042733	embryonic digit	GO_BiologicalProcess-EBI-	0.00	0.03	0.01	0.01	[4, 5, 6, 7, 8]	Group23	10.00	6.00	*BMPR1A, GLI2, LMBR1, NOTCH1,*

	morphogenesis	UniProt-GOA-ACAP-ARAP_13.05.2021_00h00									*TBC1D32, TULP3*
GO:0060831	smoothened signaling pathway involved in dorsal/ventral neural tube patterning	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.01	0.01	[5, 6, 7, 8, 9, 10]	Group23	23.08	3.00	*GLI2, TBC1D32, TULP3*
GO:1903251	multi-ciliated epithelial cell differentiation	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13	0.00	0.03	0.01	0.01	[5, 6]	Group24	33.33	3.00	*CEP152, DEUP1, MCIDAS*

		.05.2021_00h00									
GO:0098534	centriole assembly	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.01	0.01	[4, 5, 6, 8]	Group24	10.64	5.00	*CEP120*, *CEP152*, *CEP295*, *DEUP1*, *MCIDAS*
GO:0043276	anoikis	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.01	0.01	[5]	Group25	11.43	4.00	*BRMS1*, *NOTCH1*, *PTK2*, *SIK1*

GO:2000209	regulation of anoikis	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.01	0.01	[6, 7]	Group25	15.38	4.00	*BRMS1, NOTCH1, PTK2, SIK1*
GO:0030276	clathrin binding	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[3]	Group26	8.33	6.00	*AP1G1, EPN3, LDLR, PICALM, SYT15, SYT17*
GO:0005905	clathrin-coated pit	GO_CellularComponent-EBI-UniProt-	0.00	0.03	0.00	0.00	[3, 4, 5]	Group26	9.21	7.00	*AAK1, CUBN, EPN3, FCHO1,*

		GOA-ACAP-ARAP_13.05.2021_00h00									*ITSN1*, *LDLR*, *PICALM*
GO:0072583	clathrin-dependent endocytosis	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[5, 7]	Group26	9.43	5.00	*AAK1*, *FCHO1*, *FNBP1L*, *ITSN1*, *PICALM*
GO:0016668	oxidoreductase activity, acting on a sulfur group of donors, NAD(P) as acceptor	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13	0.00	0.04	0.00	0.01	[4]	Group27	20.00	3.00	*NXN*, *SELENOT*, *TXNRD3*

		.05.2021_00h00									
GO:0047134	protein-disulfide reductase (NAD(P)) activity	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[4, 5, 6]	Group27	27.27	3.00	*NXN*, *SELENOT*, *TXNRD3*
GO:0004791	thioredoxin-disulfide reductase activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[5, 8]	Group27	50.00	3.00	*NXN*, *SELENOT*, *TXNRD3*
GO:0051647	nucleus localization	GO_BiologicalProce	0.00	0.04	0.00	0.01	[4]	Group28	14.29	4.00	*CEP120*, *DOCK7*,

		ss-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00									*HOOK3, SYNE2*
GO:0007097	nuclear migration	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[4, 5]	Group28	18.18	4.00	*CEP120, DOCK7, HOOK3, SYNE2*
GO:0022027	interkinetic nuclear migration	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-	0.00	0.03	0.00	0.01	[5, 6, 7, 8, 9, 10]	Group28	50.00	3.00	*CEP120, DOCK7, HOOK3*

		ARAP_13.05.2021_00h00									
GO:0022604	regulation of cell morphogenesis	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[4, 5]	Group29	5.20	17.00	*ACTN4, DOCK5, EPB41L3, FERMT2, FGD6, FMNL2, GRIP1, ITGA7, LARP4, POSTN, PTK2, PTPRD, RIMS1, SEMA3E, SYT17, TPM1, TRIOBP*
GO:0010769	regulation of cell morphogene	GO_BiologicalProcess-EBI-	0.01	0.05	0.00	0.01	[5, 6]	Group29	7.00	7.00	*ACTN4, DOCK5, FERMT2,*

	sis involved in differentiation	UniProt-GOA-ACAP-ARAP_13.05.2021_00h00									*POSTN, PTK2, PTPRD, TRIOBP*
GO:1900024	regulation of substrate adhesion-dependent cell spreading	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.01	[5, 6, 7]	Group29	9.68	6.00	*ACTN4, DOCK5, FERMT2, POSTN, PTK2, TRIOBP*
GO:0014812	muscle cell migration	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13	0.01	0.04	0.01	0.01	[4, 5]	Group30	7.61	7.00	*ACE, BMPR1A, DOCK5, DOCK7, POSTN, SLC6A5, TPM1*

		.05.2021_00h00									
GO:0014909	smooth muscle cell migration	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.01	0.01	[5, 6]	Group30	8.11	6.00	*ACE*, *BMPR1A*, *DOCK5*, *DOCK7*, *POSTN*, *TPM1*
GO:0014910	regulation of smooth muscle cell migration	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.01	0.01	[5, 6, 7]	Group30	9.09	6.00	*ACE*, *BMPR1A*, *DOCK5*, *DOCK7*, *POSTN*, *TPM1*
GO:0099587	inorganic ion import	GO_BiologicalProce	0.01	0.05	0.02	0.02	[4, 5, 6, 7]	Group31	6.93	7.00	*ATP4B*, *KCNH2*,

	across plasma membrane	ss-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00									*KCNJ12*, *KCNJ18*, *SLC12A7*, *SLC12A8*, *SLC31A1*
GO:0098659	inorganic cation import across plasma membrane	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.02	0.02	[5, 6, 7, 8]	Group31	6.93	7.00	*ATP4B*, *KCNH2*, *KCNJ12*, *KCNJ18*, *SLC12A7*, *SLC12A8*, *SLC31A1*
GO:1990573	potassium ion import across plasma membrane	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-	0.00	0.03	0.02	0.02	[6, 7, 8, 9]	Group31	12.50	6.00	*ATP4B*, *KCNH2*, *KCNJ12*, *KCNJ18*, *SLC12A7*, *SLC12A8*

		ARAP_13.05.2021_00h00									
GO:0055075	potassium ion homeostasis	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.02	0.02	[8]	Group31	12.50	4.00	*ATP4B, KCNH2, SLC12A7, SLC12A8*
GO:0010927	cellular component assembly involved in morphogenesis	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[3, 4, 5]	Group32	8.33	9.00	*ACTN2, EPB41L3, MEF2A, PIKFYVE, PRKAR1A, TENM4, TPM1, UGT8, ZPBP*

GO:0007272	ensheathment of neurons	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[2, 5, 6]	Group32	6.29	9.00	*ADGRG6, B4GALT5, CTSC, EPB41L3, GALC, HGF, PIKFYVE, TENM4, UGT8*
GO:0008366	axon ensheathment	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[3, 6, 7]	Group32	6.29	9.00	*ADGRG6, B4GALT5, CTSC, EPB41L3, GALC, HGF, PIKFYVE, TENM4, UGT8*
GO:0042552	myelination	GO_BiologicalProcess-EBI-UniProt-	0.01	0.04	0.00	0.00	[4, 7, 8]	Group32	6.38	9.00	*ADGRG6, B4GALT5, CTSC, EPB41L3,*

		GOA-ACAP-ARAP_13.05.2021_00h00									*GALC, HGF, PIKFYVE, TENM4, UGT8*
GO:0032288	myelin assembly	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[4, 5, 6, 8, 9]	Group32	18.18	4.00	*EPB41L3, PIKFYVE, TENM4, UGT8*
GO:0034452	dynactin binding	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13	0.00	0.03	0.00	0.00	[4]	Group33	25.00	3.00	*BICD1, BICD2, HOOK3*

		.05.2021_00h00									
GO:0006890	retrograde vesicle-mediated transport, Golgi to endoplasmic reticulum	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[4, 6]	Group33	8.42	8.00	*BICD2*, *COG3*, *COPB1*, *KIF11*, *RAB6A*, *SCFD1*, *SEC22B*, *TMED10P1*
GO:0006891	intra-Golgi vesicle-mediated transport	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.00	0.00	[4, 6]	Group33	11.11	4.00	*COG3*, *COPB1*, *GOLGA8B*, *RAB6A*
GO:0034067	protein localization	GO_BiologicalProce	0.01	0.04	0.00	0.00	[6]	Group33	13.33	4.00	*BICD2*, *RAB6A*,

	to Golgi apparatus	ss-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00									*TMED10P1, VPS13C*
GO:0072385	minus-end-directed organelle transport along microtubule	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.00	0.00	[5, 6, 7, 8]	Group33	60.00	3.00	*BICD1, BICD2, RAB6A*
GO:0072393	microtubule anchoring at microtubule organizing center	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-	0.00	0.04	0.00	0.00	[5, 8]	Group33	21.43	3.00	*BICD1, BICD2, HOOK3*

		ARAP_13.05.2021_00h00									
GO:0005229	intracellular calcium activated chloride channel activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.01	0.01	[8, 9, 10, 11, 12]	Group34	15.79	3.00	*ANO2*, *ANO4*, *ANO7*
GO:0098661	inorganic anion transmembrane transport	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.01	0.01	[5, 7]	Group34	8.70	8.00	*ANO2*, *ANO4*, *ANO7*, *CFTR*, *GABRR2*, *SLC12A7*, *SLC12A8*, *SLC4A8*

GO:0015103	inorganic anion transmembrane transporter activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[5, 6, 7, 8]	Group34	5.88	10.00	*ANO2*, *ANO4*, *ANO7*, *CCT8L2*, *CFTR*, *FXYD3*, *GABRR2*, *SLC12A7*, *SLC12A8*, *SLC4A8*
GO:0006821	chloride transport	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.01	0.01	[7]	Group34	8.11	9.00	*ANO2*, *ANO4*, *ANO7*, *CFTR*, *FXYD3*, *GABRR2*, *SLC12A7*, *SLC12A8*, *SLC4A8*
GO:1902476	chloride transmembrane transport	GO_BiologicalProcess-EBI-UniProt-	0.00	0.03	0.01	0.01	[6, 8]	Group34	12.12	8.00	*ANO2*, *ANO4*, *ANO7*, *CFTR*, *GABRR2*, *SLC12A7*,

		GOA-ACAP-ARAP_13.05.2021_00h00									*SLC12A8, SLC4A8*
GO:0061778	intracellular chloride channel activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.01	0.01	[8, 9, 10, 11]	Group34	15.79	3.00	*ANO2, ANO4, ANO7*
GO:0099084	postsynaptic specialization organization	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13	0.01	0.05	0.01	0.01	[5, 7]	Group35	11.11	4.00	*IL1RAP, MPP2, PTPRD, PTPRS*

		.05.2021_00h00									
GO:0097106	postsynaptic density organization	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[6, 8]	Group35	11.76	4.00	*IL1RAP, MPP2, PTPRD, PTPRS*
GO:0099150	regulation of postsynaptic specialization assembly	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.01	0.01	[5, 6, 7, 8, 9]	Group35	21.43	3.00	*IL1RAP, PTPRD, PTPRS*

GO:1904889	regulation of excitatory synapse assembly	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[6, 7, 8]	Group35	18.75	3.00	*IL1RAP, PTPRD, PTPRS*
GO:1905874	regulation of postsynaptic density organization	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.01	0.01	[5, 6, 7, 8, 9]	Group35	17.65	3.00	*IL1RAP, PTPRD, PTPRS*
GO:0097107	postsynaptic density assembly	GO_BiologicalProcess-EBI-UniProt-	0.01	0.04	0.01	0.01	[7, 8, 9]	Group35	16.67	3.00	*IL1RAP, PTPRD, PTPRS*

		GOA-ACAP-ARAP_13.05.2021_00h00									
GO:0099151	regulation of postsynaptic density assembly	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.01	0.01	[6, 7, 8, 9, 10]	Group35	23.08	3.00	*IL1RAP*, *PTPRD*, *PTPRS*
GO:0015144	carbohydrate transmembrane transporter activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13	0.00	0.02	0.00	0.00	[4, 6, 7]	Group36	15.38	6.00	*AQP7*, *SLC2A14*, *SLC2A3*, *SLC2A9*, *SLC45A2*, *SLC5A11*

		.05.2021_00h00									
GO:0051119	sugar transmembrane transporter activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[5, 7, 8]	Group36	16.00	4.00	*SLC2A14*, *SLC2A3*, *SLC2A9*, *SLC5A11*
GO:0015145	monosaccharide transmembrane transporter activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[5, 6, 7, 8, 9]	Group36	16.67	4.00	*SLC2A14*, *SLC2A3*, *SLC2A9*, *SLC5A11*

GO:0015294	solute:cation symporter activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[6, 7, 8, 9]	Group36	8.16	8.00	*SLC12A7*, *SLC12A8*, *SLC2A9*, *SLC38A2*, *SLC45A2*, *SLC4A8*, *SLC5A11*, *SLC6A5*
GO:0005402	carbohydrate:cation symporter activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[5, 7, 8, 9, 10]	Group36	18.75	3.00	*SLC2A9*, *SLC45A2*, *SLC5A11*
GO:0015149	hexose transmembrane	GO_BiologicalProcess-EBI-UniProt-	0.00	0.03	0.00	0.00	[6, 7, 8, 9, 10]	Group36	18.18	4.00	*SLC2A14*, *SLC2A3*, *SLC2A9*, *SLC5A11*

	transporter activity	GOA-ACAP-ARAP_13.05.2021_00h00									
GO:0005355	glucose transmembrane transporter activity	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[7, 8, 9, 10, 11]	Group36	18.18	4.00	*SLC2A14*, *SLC2A3*, *SLC2A9*, *SLC5A11*
GO:0000407	phagophore assembly site	GO_CellularComponent-EBI-UniProt-GOA-ACAP-ARAP_13	0.01	0.04	0.00	0.00	[2, 3, 4]	Group37	12.12	4.00	*ATG14*, *PIK3C3*, *WIPI1*, *WIPI2*

		.05.2021_00h00									
GO:0006914	autophagy	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[3, 4]	Group37	4.24	25.00	*ATG14*, *CFTR*, *DYNC1LI2*, *EIF2AK4*, *FBXO7*, *FEZ2*, *FNBP1L*, *HGF*, *KLHL3*, *MAP1LC3C*, *MAPK3*, *MTMR9*, *PIK3C3*, *PIKFYVE*, *SCFD1*, *SEC22B*, *SMG1*, *TEX264*, *TRIM5*, *TRIM6*, *TRIM6-*

											TRIM34, VIPAS39, VPS13C, WIPI1, WIPI2
GO:0034045	phagophore assembly site membrane	GO_CellularComponent-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.04	0.00	0.00	[3, 4, 5]	Group37	20.00	3.00	*ATG14, WIPI1, WIPI2*
GO:0042594	response to starvation	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.00	0.00	[3, 5]	Group37	5.22	13.00	*ACAT1, ASNS, ATG14, EIF2A, EIF2AK4, MAP1LC3C, MAPK3, MIOS, PIK3C3, SIK1,*

											SLC38A2, *WIPI1*, *WIPI2*
GO:0016236	macroautophagy	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[4, 5]	Group37	5.16	18.00	*ATG14*, *CFTR*, *DYNC1LI2*, *FEZ2*, *KLHL3*, *MAP1LC3C*, *MAPK3*, *MTMR9*, *PIK3C3*, *PIKFYVE*, *SCFD1*, *SEC22B*, *SMG1*, *TEX264*, *VIPAS39*, *VPS13C*, *WIPI1*, *WIPI2*
GO:0005776	autophagosome	GO_CellularComponent-EBI-UniProt-	0.00	0.03	0.00	0.00	[4, 5, 6]	Group37	8.16	8.00	*ATG14*, *MAP1LC3C*, *MCOLN3*, *PEG3*,

		GOA-ACAP-ARAP_13.05.2021_00h00									*PIK3C3, TEX264, WIPI1, WIPI2*
GO:0007033	vacuole organization	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[5]	Group37	5.85	11.00	*ATG14, FEZ2, HOOK3, MAP1LC3C, PIK3C3, PIKFYVE, RAB20, SCFD1, SEC22B, WIPI1, WIPI2*
GO:0009267	cellular response to starvation	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13	0.01	0.04	0.00	0.00	[4, 5, 6]	Group37	5.64	11.00	*ASNS, ATG14, EIF2AK4, MAP1LC3C, MAPK3, MIOS, PIK3C3, SIK1, SLC38A2, WIPI1, WIPI2*

		.05.2021_00h00									
GO:0061912	selective autophagy	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.02	0.00	0.00	[5, 6]	Group37	9.89	9.00	*ATG14*, *CFTR*, *DYNC1LI2*, *KLHL3*, *MAP1LC3C*, *MAPK3*, *TEX264*, *VPS13C*, *WIPI2*
GO:1905037	autophagosome organization	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[5, 6]	Group37	8.57	9.00	*ATG14*, *FEZ2*, *MAP1LC3C*, *PIK3C3*, *PIKFYVE*, *SCFD1*, *SEC22B*, *WIPI1*, *WIPI2*

GO:0000421	autophagosome membrane	GO_CellularComponent-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[5, 6, 7]	Group37	13.16	5.00	*ATG14*, *MAP1LC3C*, *MCOLN3*, *TEX264*, *WIPI1*
GO:0032266	phosphatidylinositol-3-phosphate binding	GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.00	0.03	0.00	0.00	[6]	Group37	11.63	5.00	*SNX13*, *WIPI1*, *WIPI2*, *ZFYVE19*, *ZFYVE26*
GO:0000045	autophagosome assembly	GO_BiologicalProcess-EBI-UniProt-	0.00	0.03	0.00	0.00	[6, 7]	Group37	9.00	9.00	*ATG14*, *FEZ2*, *MAP1LC3C*, *PIK3C3*, *PIKFYVE*,

		GOA-ACAP-ARAP_13.05.2021_00h00									*SCFD1, SEC22B, WIPI1, WIPI2*
GO:0016242	negative regulation of macroautophagy	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.05	0.00	0.00	[5, 6, 7, 8]	Group37	11.43	4.00	*FEZ2, SCFD1, SEC22B, SMG1*
GO:0034497	protein localization to phagophore assembly site	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13	0.00	0.03	0.00	0.00	[5, 7, 8]	Group37	30.00	3.00	*PIK3C3, WIPI1, WIPI2*

		.05.2021_00h00									
GO:1902902	negative regulation of autophagosome assembly	GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_13.05.2021_00h00	0.01	0.04	0.00	0.00	[6, 7, 8, 9]	Group37	18.75	3.00	*FEZ2*, *SCFD1*, *SEC22B*