Supplemental Information

AUTOPHAGOPATHIES: FROM AUTOPHAGY GENE POLYMORPHISMS TO PRECISION MEDICINE FOR HUMAN DISEASES

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Supplementary tables

Table S1. List of autophagy-related genes and regulators investigated in this study.

I. ULK1/2 complex
- *ULK1*
- *ULK2*
- *ATG13*
- *RB1CC1*
- *ATG101*
- *SMCR8*
- *TBC1D14*
- *WDR41*
- *C9orf72*

IRGM

II. PtdIns3K complex
- *PIK3C3/VPS34*
- *PIK3R4/VPS15*
- *BECN1*
- *ATG14*
- *UVRAG*
- *AMBRA1*
- *MCL1*
- *NRBF2*
- *RUBCN*
- *RUBCNL*
- *SH3GLB1/BIF-1*
- *VMP1*

III. ATG9 complex
- *ATG2A*
- *ATG2B*
- *ATG9A*
- *ATG9B*
- *WIPI1*
- *WIPI2*
- *WDR45B*
- *WDR45*
- *ZFYVE1/DFCP1*

IV. ATG12 conj
- *ATG5*
- *ATG7*
- *ATG10*
- *ATG12*
- *ATG16L1*
- *ATG16L2*

TP53INP2

V. LC3 conjugation system
- *EGR1*
- *MAP1LC3A*
- *MAP1LC3B*
- *MAP1LC3B2*
- *MAP1LC3C*
- *GABARAP*
- *GABARAPL1*
- *GABARAPL2*
- *GABARAPL3*
- *ATG3*
- *ATG4A*
- *ATG4B*
- *ATG4C*
- *ATG4D*

VI. Autophagy receptors
- *CALCOCO2*
- *DRAM1*
- *FUNDC1*
- *NBR1*
- *NCOA4*
- *NUFIP1*
- *NIPSNAP1*
- *NIPSNAP2*
- *OPTN*
- *SQSTM1*
- *TAX1BP1*
- *TOLLIP*
- *UBQLN2*
- *WDFY3/ALFY*

- *LAMP1*
- *LAMP2*
- *CHMP2B*

Tables S2-S7. Association between common genetic polymorphisms in the autophagy-related genes and human diseases (risk, prognosis, theragnosis). *ATG* SNP (single-nucleotide polymorphism) and their functional annotation (promoter, 5', 3', missense mutations, transcription factor, and miRNA binding sites) were retrieved using PubMed, litvar [1], HaploReg [2,3], and GTEX [4] (eQTLs).

Table S2. ULK1/2 complex.

Table S3. PtdIns3K Complex.

Table S4. ATG9 system.

Table S5. LC3-conjugation system.

Table S6. ATG12-conjugation system.

Table S7. Autophagy receptors.


Related to theragnosis (side effects, toxicity, efficacy), overall survival (OS), and progression-free survival (PFS).


Related to bacterial infection or 
viral infection or 
parasite infection


Related to air pollution or 
coal exposure, or 
smoking.


Related to aging 
Related to autoimmune and autoinflammatory diseases.

Abbreviations: ALS-FTD, amyotrophic lateral sclerosis, and frontotemporal dementia; Alt, alternate allele; ccRCC, clear cell renal cell carcinoma; CD, Crohn disease; exp, expression; (eQTL): eQTL in different tissue of that affected by the disease; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; LD, linkage disequilibrium; MAF, minor allele frequency in European (Eur) or Asian (As) populations; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; Ref, reference allele; SLE, systemic lupus erythematosus.

Table S2. *ULK1/2* complex – AUTOPHAGY.

Gene	SNP (rs)	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ULK1 **NM_003565.1** **93 eQTL**	rs9481	A	G	86%	10	**TUBERCULOSIS** [5] Protective	Asians	3'UTR	(eQTL)
	rs7138581	G	C	13%	5	RISK and SEVERITY	Asians	3'UTR	(eQTL)
	rs12297124	G	T	8%	4	**TUBERCULOSIS** [6] Protective	Asians	Intronic	(eQTL) ↑ exp[6]
	rs7300908	C	T	2% As 8%	1		Asians	Intronic	(eQTL) ↑ exp[6]
	rs4964879	G	A	10%	1	**ANKYLOSING SPONDYLITIS** [7] Protective	Asians	Intronic	eQTL- Nerve
	rs11246867	G	A	6%	23	Age-related **MACULAR DEGENERATION** [8] Theragnostic (anti-VEGF)	Europeans	5' *ULK1*	
	rs3088051	T	C	29%	1			3'UTR	(eQTL)
						CROHN DISEASE [9] Complications	Oceanians		
	rs7488085	T	G	6%	23	**CROHN DISEASE** [9] Protective	Oceanians	Intronic	(eQTL)
	rs10902469	G	C					5' *ULK1*	(eQTL)
	rs10902472	C	T			**ASTHMA** [10]	Americans	Intronic	(eQTL)
	rs7487166	A	G	81%	12	**ASTHMA** [10]	Americans	Intronic	(eQTL)
	rs9652059	T	C			**ANKYLOSING SPONDYLITIS** [7]	Asians		
	rs11616018	C	T			**ASTHMA** [10]	Americans	synonymous	eQTL - colon
						CROHN DISEASE [9] Weak association	Oceanians		
	rs7953348	C	T			**CROHN DISEASE** [9] Weak association	Oceanians	Intronic	(eQTL)
						NON SMALL CELL LUNG CANCER (NSCLC) [11] Theragnostic (Platinum-based chemotherapy)	Asians		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ULK1 **NM_003565.1** **93 eQTL**	[rs12303764](#)	T	G	36%	1	**CROHN DISEASE** [9,12] **NSCLC** [11] Theragnostic (platinum-based chemotherapy)	Europeans, and Oceanians Asians	Intronic	eQTL - colon
	CANCERS. Thirty-six missense somatic mutations of *ULK1* are co-occurring with mutations in a large number of ULK1 interactors or substrates. Of the mutations, 50% in the ULK1 kinase domain are predicted to affect protein stability and kinase activity (S184F, D102N, and A28V). Consistently, *ULK1* acts as an oncogene in gastric cardiac adenocarcinoma. Silencing *ULK1* can significantly suppress cancer cell proliferation, migration and invasion [13,14].								
	[rs55815560](#)	C	T	1%	1	**SCHIZOPHRENIA** [15] A highly heritable psychiatric disorder, combining these 4 SNPs. No variant was individually statistically significant	Europeans	**MISSENSE** S665L	
	[rs145279005](#)	C	T	1%	1			**MISSENSE** A705V	
	[rs145451295](#)	C	T	1%	2			**MISSENSE** T242I	
	[rs188342389](#)	C	T	0%	6			**Intron** ***MMP17 missense***	
ULK2 **NM_014683** **1450 eQTL**	[rs281357](#)	T	C	64%	1	**PARKINSON DISEASE** [16]	American GWAS	Intronic	eQTL-Nerve
	[rs281366](#)	C	T	3%	3	**ACUTE LYMPHOBLASTIC LEUKEMIA** [17] Theragnostic (asparaginase-associated pancreatitis)	Europeans	5' *ULK2*	(eQTL)
ATG13 **NM_014741** **4655 eQTL**	[rs7484002](#)	A	G	17%	130	↑ **DNA damage** [18]	Asians	Intronic	eQTL- Skin ↓ exp [18]
	[rs10838611](#)	G	C	57%	2	**BREAST CANCER** (TNBC) [19] Theragnostic (asparaginase-associated pancreatitis)	Asians	3'-UTR	
	[rs4565870](#)	T	C	30%	5	**SELECTIVE IMMUNOGLOBULIN A DEFICIENCY** [20]	European GWAS		eQTL
	[rs35619591](#)	G	A	1%	1	**TYPE 2 DIABETES** [21] Insulin processing	European American GWAS	**MISSENSE** G433R	
RB1CC1/FIP200 **NM_014781** **68 eQTL**	[rs1129660](#)	A	G	21%	19	**COLORECTAL CANCER** [22] Bad theragnosis (anti-VEGF)	Europeans	synonymous	
	SCHIZOPHRENIA Rare duplications of the *RB1CC1* gene is enriched in European patients [23,24]								

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
SMCR8 **NM_144775** **1,354 eQTL**	rs1563634	T	C	67%	12	**BREAST CANCERS** [25]	Europeans	5' *SMCR8*	eQTL-Breast
	rs8080966	C	T	31%	81	**CHILDHOOD APRAXIA OF SPEECH** [26]	American GWAS	**MISSENSE** P524L	eQTL- Brain
	rs12939757	A	G			**NEURAL TUBE DEFECTS** [27] Low maternal folate intake	Americans	3' *SMCR8*	eQTL- Brain
	rs921986	C	T			**OVARIAN CANCER** [28]	American GWAS	3' *SMCR8*	eQTL- ovary
	rs12952556	T	C					3' *SMCR8*	eQTL- ovary
TBC1D14 **NM_020773** **746 eQTL**	rs10804990	G	A	62%	3	**CORONARY HEART DISEASE** [29]	American GWAS	Intronic	eQTL- Artery
WDR41 **NM_018268** **10007 eQTL** **ULK1 partner**	rs163016	A	T	40%	41	**MYOPIA** [30]	World	Intronic	(eQTL)
	rs163030	A	C	48%	83	**CAUDATE VOLUME** [31] Brain region implicated in common neurological and psychiatric disorders	American GWAS	Intronic	eQTL - Brain
	rs163035	A	G					Intronic	eQTL - Brain
	rs335636	A	G					Intronic	eQTL - Brain
	rs335632	C	T	1%	1	**HEART eQTL** [32]	Genome-wide eQTL mapping Europeans		eQTL
	rs33204	C	T	40%	28	**MYOPIA** [30]	World	**MISSENSE** V326I	(eQTL)
	rs10514104	T	C	18%	14	Age-related **HEARING IMPAIRMENT** [33]	European GWAS	Intronic	eQTL - Brain ↓ exp [33]

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
C9orf72 **NC_000009.12 6048 eQTL ULK1 partner**	rs774359	T	C	27%	81	**ALS-FTD** [34–36] **PROSTATE CANCER** [37]	European GWAS American European GWAS	3'UTR	eQTL - Brain
	rs2814707	C	T			**ALS-FTD** [34–36] **SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)** [38] high serum IFNK (type I IFN)	European GWAS American World GWAS	5' *C9orf72*	eQTL - Brain
	rs3849942	T	C			**ALS-FTD** [39] **PROSTATE CANCER** [37]	American GWAS European GWAS	3' *C9orf72*	eQTL - Brain
	rs3849943	C	T	75%	1	**ALS** [40]	European GWAS	3' *C9orf72*	eQTL - Brain
	rs2282241	C	A	43%	6	**ALS-FTD** [39]	American GWAS	Intronic	eQTL - Brain
	rs2492816	G	A	42%	8	**ALS** [41]	Europeans	Intronic	(eQTL)
	rs3849944	T	C			**SLE** [38] high serum IFNK	World GWAS	3' UTR	(eQTL)
	rs10812615	T	C	47%	10	**FTD** [42]	Oceanian GWAS	Intronic	eQTL- Brain
	rs10812616	T	A					Intronic	eQTL - Brain
	rs10122902	G	A	16%	9	**ALS** [43] **PROSTATE CANCER** [37]	Americans European GWAS	synonymous	(eQTL)
	rs10757665	T	C	25%	25	**PROSTATE CANCER** [37]	European GWAS	Intronic	(eQTL)
	rs10967991	C	T			**SCHIZOPHRENIA** [44]	American GWAS	5' *C9orf72*	(eQTL)
	rs12686452	T	C	21%	7	♀ **SLE** [38] high serum IFNK	World GWAS	Intronic	(eQTL)
	rs17769294	T	C	11%	10	**ALS** [43] **FTD** [42]	Oceanian GWAS Americans	**MISSENSE** N207S	(eQTL)

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
IRGM **NM_001145805 1645 eQTL**	[rs4958843](#)	T	C	9%	168	**TUBERCULOSIS** [45] ↓ RISK	Middle East	5' *IRGM*	eQTL – Lung ↑ exp [45]
	[rs1000113](#)	C	T			**CROHN DISEASE** [46] Adult-onset	Europeans	Intron	eQTL
	[rs10065172](#)	C	T			**CROHN DISEASE** [47–51]	Europeans, Asians Americans	Synonymous ***MIR196* binding seed** ↑ IRGM [52]	eQTL Lung, Colon, Blood ↑ exp [47,52] ↓ exp [48,51,53] = exp [54]
						GRAVE DISEASE [55]	Asians		
						ANKYLOSING SPONDYLITIS [56] ♀ rs4958846C-rs10065172C: RISK rs4958846T-rs10065172C: protective	Asians		
						SLE [57]	Asians		
						SEPSIS [53] ↑ mortality	Asians		
						TUBERCULOSIS [54,58,59] ↓ RISK (*population-specific* , Asians)	Asians		
	[rs11749391](#)	T	C			**CROHN DISEASE** [60]	GWAS (Europe, America, Australia)		eQTL Blood
	[rs11747270](#)	A	G			**PERIODONTITIS** [61]	Europeans	Intron	(eQTL)
						CROHN DISEASE [62] *Not population-specific* [63]	Europeans Indian* [63]		
						ULCERATIVE COLITIS* **do not exhibit Hardy-Weinberg equilibrium*	Asians		
						ARTHRITIS (CD comorbidity) [64]	Asians		
	[rs13361189](#)	T	C			**CROHN DISEASE** [47,48,51,65] ↑ CD colitis (LTF/lactoferrin and TNF)	Americans, Europeans	5' *IRGM*	**PROMOTER** eQTL - Lung Colon ↓ exp [48,51] (blood and ileum)
						SLE [57]	Asians		
						GASTRIC CANCER [66] ↓ RISK **x *H. pylori***	Asians		
						GLIOMA [67] ↑ IFNG ↑ IL4	Asians		
						GRAVE DISEASE [55]	Asians		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
IRGM **NM_001145805 1645 eQTL**	rs13361189	T	C	9%	168	**LEPROSY** [68] ↑ ***Mycobacterium leprae*** ↑ IFNG and IL4	Asians	5'UTR	eQTL - Blood
						PERIODONTITIS [61]	Europeans		
						NON-ALCOHOLIC FATTY LIVER DISEASE [69,70] CD comorbidity	Asians Europeans		
						TUBERCULOSIS [58] ↓ RISK rs10065172 rs10051924 rs13361189 >TCC	Asians		
	rs7714584	A	G			**CROHN DISEASE** [71]	European GWAS	Intron	(eQTL)
	rs72553867	C	A	4%	120	**CROHN DISEASE** [72]	Asians	**MISSENSE** T94I	
	rs9637876	C	T	9%	163	**TUBERCULOSIS** [73]	Africans	5'UTR	eQTL - lung ↑ exp [73]
						CROHN DISEASE [63]	Indians		
	rs4958846	T	C			**TUBERCULOSIS** [45,59,74] ↓ RISK	Middle East, and Asians	5' *IRGM*	eQTL - Lung ↓ exp
	rs4958847	G	A	13%	51	**CROHN DISEASE** *population-specific* (not in Asians) [64]	Europeans	Intronic	eQTL - colon
						NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) [75] CD comorbidity ↑ RISK rs4958847- rs13361189	Americans		
						ARTHRITIS [64] ↓ RISK	Asians		
						GASTRIC CANCER [66,76] ↓ RISK	Asians, and Europeans		
						GRAVE DISEASE [55]	Asians		
						PERIODONTITIS [61]	Europeans		
	rs10059011	A	C	54%	1	**METASTATIC CLEAR CELL RENAL CELL CARCINOMA ccRCC** RISK [77]	Europeans	5'UTR	(eQTL)
						TUBERCULOSIS [73]	Africans		

Table S3. PtdIns3K Complex – AUTOPHAGY_LAP.

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
PIK3C3/ **VPS34** **NM_002647** **3755 eQTL**	rs3813065	C	T	14%	42	**SLE** [78] Altered ERAP2 exp (MHC-I peptide processing enzyme) ↑ IFNA1	American GWAS	5' *PIK3C3*	eQTL – Blood ↓ Promoter
						SCHIZOPHRENIA [79] **BIPOLAR DISORDER** [79] ↑ the binding of a POU-type transcription factor	Middle East		
	rs52911	G	A	34%	47	**ESOPHAGEAL SQUAMOUS CELL CARCINOMA** [80,81] Protective	Asians, and Americans	Intronic	eQTL - Esophagus
	rs1941526	C	T	20%	83	**ALZHEIMER DISEASE** [82]	American GWAS	Intronic	eQTL - Nerve
	rs76692125	G	A	4%	1	**PANCREATIC CANCER** [83] RISK	European GWAS	Intronic	eQTL – Blood ↓ mRNA
	rs2162440	A	G	79%	25	**GASTRIC CANCER** [84,85] (GASTRIC CARDIA ADENOCARCINOMA) associated with shorter telomeres	European GWAS Asian	3' *PIK3C3* (5' MIR4318)	
	rs7235755	A	G						
PIK3R4/ **VPS15** **NM_014602** **263 eQTL**	rs10934954	C	T	20%	176	**COLORECTAL CANCER** [86]	Europeans	Intronic	eQTL - Colon
	rs2200368	A	G			Age-related **MACULAR DEGENERATION** [87]	American GWAS	Intronic	(eQTL)
	rs11713445	G	A					Intronic	(eQTL)
BECN1 **NM_003766** **157 eQTL**	rs10512488	G	A	21%	1	**TYPE 2 DIABETES** [88] **NON-HODGKIN LYMPHOMA** [89]	European GWAS, and study	Intronic	eQTL - Blood
	rs11552193	C	T	0%	1	**NSCLC** [90]	World	3'UTR	miRNA Sites
	rs60221525	C	A	6%	1	**MACHADO-JOSEPH DISEASE/** **SPINOCEREBELLAR ATAXIA TYPE 3** [91] RISK Neuroprotective	Europeans	3' *BECN1*	↑ exp [91]
	rs116943570	A	C	0%	1			3' *BECN1*	

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG14 **NM_014924 8192 eQTL – C I**	rs8015211	T	C	35%	53	**PROSTATE CANCER** [92] aggressivity not validated in an independent study	American GWAS	Intronic	eQTL Prostate
	rs8003279	A	G			**NSCLC** [11] Theragnosis (Platinum): Good	Asians	Synonymous	(eQTL)
	rs17742719	G	T	18%	8			Intronic	eQTL Lung
	rs1009647	G	A	27%	9	**NSCLC** Theragnosis (Platinum) [11] **TESTICULAR GERM CELL TUMOR** [93]	Asians European GWAS	5' ATG14	(eQTL)
UVRAG **NM_003369 1790 eQTL Autophagosome maturation – C II**	rs80191572	A	G	5%	1	**MULTIPLE SCLEROSIS** [94] Theragnosis (Copaxone)	World GWAS	Intronic	(eQTL)
	rs7111334	C	T	8%	3	**RHEUMATOID ARTHRITIS** [95] RISK	Asians	Intronic	(eQTL)
	rs7933235	A	G	8%	97	**VITILIGO** [96] LD with rs7118567 **MISSENSE** P10H	Asians	Intronic	
	rs1458836	C	T					5' *UVRAG*	eQTL - Skin
	rs7116263	C	G	8%	9	**CANCER :** Etoposide-induced cytotoxicity [97]	Americans	Intronic	(eQTL)
	rs17134573	G	A	3%	154	**CARDIOVASCULAR DISEASES** Blood lipid, body mass index [98]	American GWAS	Intronic	(eQTL)
	rs594826	G	A	6%	3			Intronic	
AMBRA1 **NM_017749.3 148 eQTL**	rs11038913	T	C	8%	1	**ARTERY DISEASE** [99] associated with blood proinsulin levels	European GWAS	Intronic	eQTL - Artery
	rs3802890	A	G	31%	1	**AUTISM** [100] protective	Europeans	Intronic	(eQTL) ↓ mRNA
	rs7130141	C	T	17%	113	**SCHIZOPHRENIA** [101,102]	European, and Asian GWAS	Intronic	eQTL - Brain
	rs7112229	C	T					Intronic	
	rs61882743	C	G					Intronic	
	rs12574668	C	A					Intronic	
	rs11819869	C	T					Intronic	

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
MCL1 **NM_008562.3** **402 eQTL** **Inhibitor of BECN1**	rs1258188045	C	G, T	0%	1	**MEGALENCEPHALIC LEUKOENCEPHALOPATHY** [103]	Europeans	**MISSENSE** R84C	
	rs9803935	T	G	56%	36	**HNSCC** [104] **x Human papillomavirus (HPV16)**-associated oro-pharyngeal type x **SMOKING**	Americans	5' *MCL1*	(eQTL)
	rs3738485	C	G			**COLORECTAL CANCER** [105] Metastasis	Western Asians	5' *MCL1*	(eQTL)
	rs961581226	C	A	0%	1	**TUBERCULOSIS** [106]	Asians	5' *MCL1*	
	rs3831987	CC	21mer	0%	1	**LUNG CANCER in NON-SMOKER** [107] Protective **BREAST CANCER** [108] Protective	Asians	5' *MCL1*	↑ exp
NRBF2 **NM_030759** **1679 eQTL C-I**	rs10995190	G	A	14%	11	**MAMMOGRAPHIC DENSITY** [109] Putative Enhancer. **BREAST CANCER** Risk Locus Regulates NRBF2 Expression	European, and Asian GWAS	ZNF365 Intronic	
	rs10509168	T	C	52%	4			ZNF365 Intronic	
RUBCNL **NM_025113** **2581 eQTL**	rs1408184	C	T	34%	72	**ALZHEIMER DISEASE** [110]	Europeans	**MISSENSE** G152R	eQTL -Brain
	rs2478046	G	A	14%	61	**ALS** [111]	Europeans	3' *RUBCNL*	eQTL -Nerve
SH3GLB1/BIF-1 **NM_016009** ***849 eQTL***	rs263436	G	A	24%	35	**TYPE 2 DIABETES** [112]	European GWAS	intronic	
VMP1 **NM_030938** **272 eQTL** **Partner of PI3K C-I**	rs1295925	T	C	71%	32	**BREAST CANCER** [113] Protective **OSTEOSARCOMA** [114] Protective - TP53 transcriptional binding site	Asians	Intronic	eQTL - Breast

Table S4. ATG9 system – AUTOPHAGY.

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG2A **NM_015104 16 eQTL**	rs17146441	C	T	23%	2	**CROHN DISEASE** [115] Granulomas	Europeans	Intronic	(eQTL)
	rs188780113	G	A	0%	1	**KIDNEY DISEASE** [116] RISK of hyperuricemia	Asian GWAS	**MISSENSE** R478C	
ATG2B **NM_018036 318 eQTL**	rs3759601	G	C	42%	27	**BLADDER CANCER** [117] Theragnosis (BCG immunotherapy) European (not in Asian population) [118] ↓ autophagosome formation (macrophages) **HNSCC** [119] ↑ RISK pharyngeal cancer	Europeans, and Asians	**MISSENSE** Q1383E	(eQTL)
ATG9A **NM_024085 147 eQTL**	rs2382817	A	C	64%	74	**INFLAMMATORY BOWEL DISEASE** [120]	Europeans	PNKD intron	eQTL – Colon
ATG9B **NM_173681 283 eQTL** **Attributed to *NOS3***	rs7830	G	T	36%	1	**BLOOD PRESSURE** [121] **x AIR POLLUTION** - urban elderly	Asians	5' *ATG9B*	eQTL - Artery
	rs2373929	G	A	46%	1	**CORONARY ARTERY DISEASE** [122]	Middle East	Intronic	eQTL - Artery
	rs3763486	T	C	20%	2	**SKIN BASAL CELL CARCINOMA** [123] **STROKE** [124]	European GWAS Americans	5' *ATG9B*	(eQTL)
	rs3800787	G	C	40%	1	**STROKE** [124]	Americans	Intronic	
	rs3918220	C	G	0%	1			Intronic	
	rs6464119	T	C	77%	2			Intronic	eQTL - Artery
	rs11769158	A	G	88%	1			5' *ATG9B*	(eQTL)
	rs11760487	G	A	13%	2	**BONE DENSITY** [125]	Americans	Intronic	(eQTL)
	rs12666075	G	T	19%	4			Intronic	
	rs13307588	A	G	94%	2	**MYOCARDIAL INFARCTION** [126]	Europeans	Intronic	(eQTL)

Gene	variant	Ref	Alt	EUR freq	LD	Disease Susceptibility	Populations	Funct Annot	eQTL GTEX
WIPI1 **NM_017983 1114 eQTL**	rs2909207	T	C	76%	27	**Age-adjusted blood medium HDL level** [127]	European GWAS	Intronic	(eQTL)
	rs77156594	A	G	0%	1	**ANENCEPHALY** [128]	Asians	**MISSENSE** L406P	
	rs146357218	C	T	0%	1			**MISSENSE** R328Q	
WIPI2 **NM_015610 879 eQTL**	rs4720530	C	T	55%	1	**OSTEOPOROSIS** [129] RISK **x Blood lead (Pb) levels in SMOKERS**	Asian GWAS	Intronic	(eQTL) – sQTL blood
	DEVELOPMENTAL ABNORMALITIES [130] mental retardation, neurological, psychiatric, skeletal and cardiac abnormalities. homozygous (c.G745A ; pV249M). ↓ Binding of the V231M mutant to ATG16L1 (ATG12–ATG5), ↓ WIPI2 puncta, ↓ LC3 lipidation and ↓ autophagic flux.								
WDR45 **NM_007075.3 1206 eQTL**	♀ **Neurodegeneration with BRAIN IRON ACCUMULATION** [131] **BETA-PROPELLER PROTEIN-ASSOCIATED NEURODEGENERATION**[132] WDR45 mutations →↓ autophagy degradation of ferritin→↑ **iron in the brain** (basal ganglia), X-linked								
ZFYVE1/DFCP1 **NM_021260 1079 eQTL**	rs7155380	T	C	45%	25	**ALZHEIMER DISEASE** [133] Late-Onset	American GWAS	Intronic	eQTL - Brain/Nerve
	ZFYVE1/DFCP1 (WIPI2 partner) associates with lipid droplets [134].								

Table S5. LC3-conjugation system – AUTOPHAGY_LAP.

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG3 **NM_022488 98 eQTL**	rs13082005	G	A	40%	4	**NSCLC** [11] Theragnosis (Cisplatin)	Asians	Intronic	(eQTL)
ATG4A **NM_178270 309 eQTL**	rs4036579	A	G	45%	1	**CERVICAL CANCER** [135] ↑ **HPV INFECTION** RISK Transcription factor site	Asians	5' *ATG4A*	(eQTL)
	rs807182	A	C	45%	1			Intronic	(eQTL)
	rs807181	G	C	45%	2			Intronic	(eQTL)
	rs807183	G	A					Intronic	(eQTL)
	rs807185	A	T	64%	1	**LUNG CANCER** [136] RISK	Asians	Intronic	(eQTL)
	rs5973822	A	G	6%	1	**CERVICAL CANCER** [135] **CROHN DISEASE** [115] Granulomas **OVARIAN CANCER** [137]	Asians Europeans	3'UTR miRNA binding site [137]	(eQTL)
	rs7880351	G	C	45%	1	**ccRCC** [77] Theragnosis (pazopanib) ↑ OS PFS	Europeans	Intronic	(eQTL)
ATG4B **NM_013325.5 1758 eQTL**	rs3771570	C	T	13%	21	**PROSTATE CANCER** [138]	World GWAS	5' *ATG4B*	(eQTL)
	rs35320439	T	C	33%	1	**CROHN DISEASE** [139]	European, and Asian GWAS	5' *ATG4B*	(eQTL)
	rs139302128	C	T	1%	22	**ATHEROSCLEROSIS** [140] LD with rs138274580 MISSENSE N330S	European GWAS	Intronic	(eQTL)
ATG4C **NM_032852 2531 eQTL**	rs6670694	G	A	42%	96	**ccRCC** [77] Theragnosis (pazopanib) ↑ PFS	Europeans	Intronic	(eQTL)
	rs6683832	G	A	56%	33			Intronic	eQTL - Artery
						CARDIOVASCULAR DISEASE Blood FG (fibrinogen) [141]	European GWAS	Intronic	eQTL - Artery

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG4C **NM_032852** **2531 eQTL**	rs11208029	A	G	14%	109	**TUBERCULOSIS** [142]	African GWAS	Intronic	(eQTL)
	rs6587988	C	T			**CARDIOVASCULAR DISEASES** [99] Blood lipids (total cholesterol, triglycerides)	European GWAS	Intronic	eQTL - Artery 🡻 exp [143]
	rs11208030	G	A				Asians	Intronic	eQTL – Heart 🡻 exp [143]
	rs4409690	G	A			**KASHIN-BECK DISEASE** [143]		Intronic	(eQTL) 🡻 exp [143]
	rs12097658	T	C					Intronic	
ATG4D **NM_032885** **274 eQTL**	rs2304165	C	T	15%	16	**CROHN DISEASE** [115] 🡻 Granulomas	Europeans	synonymous	(eQTL)
	rs7248026	T	G	25%	31			5' *ATG4D*	(eQTL)
	rs7248036	C	T	40%	5			5' *ATG4D*	(eQTL)
	rs10439163	A	G	40%	23	**CROHN DISEASE** [115] Granulomas **CARDIOVASCULAR DISEASE** [99] Blood lipids (cholesterol and LDL)	Europeans	5' *ATG4D*	eQTL - Heart, Colon
EGR1 **NM_001964.2** **8 eQTL**	rs4902647	C	T	46%	22	**MULTIPLE SCLEROSIS** [144]	American GWAS	3' *EGR1*	(eQTL)
	rs7729723	A	G	36%	9	**CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)** [145,146] **x SMOKING**	Asians	5' *EGR1*	(eQTL)
	rs11743810	C	T	54%	7	**SCHIZOPHRENIA** [147]	Asians	Intronic	(eQTL)
GABARAP **NM_007278.1** **37 eQTL**	rs222843	T	C	38%	22	**NICOTINE DEPENDENCE** [148] **x Smoking**-induced disease **NICOTINE AND ALCOHOL DEPENDENCE** [149]	Asians, and Americans	PROMOTER (MISSENSE CLDN7)	eQTL - Brain/Nerve 🡹 exp [149]
	rs17710	A	T	15%	2	**NICOTINE DEPENDENCE** [148,149]	Americans	3'-UTR	(eQTL)

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
GABARAPL1 ***NM_031412***	**AUTISM spectrum disorder**-associated pathways. deletions of GABARAPL1 in autism [150] GABARAPL1 is the **most highly expressed gene** in the **central nervous system** among the family.								
GABARAPL2 **NM_007285 97 eQTL**	rs12599322	G	A	5%	26	**DNA DAMAGE** [18]	Asian study	RP11-77K12.8	eQTL
GABARAPL3 **NM_028287 15 eQTL**	rs6496667	C	A	20%	110	**RHEUMATOID ARTHRITIS** [151]	Asian GWAS	5' UTR	(eQTL)
MAP1LC3A **NM_181509 27368 eQTL**	rs1040747	C	G	36%	43	**CHRONIC Q FEVER** [152] ***x C. burnetii***-induced cytokine production - Protective	Europeans	3'UTR	eQTL - Blood
	rs73105013	T	C	9%	1	Age-related **MACULAR DEGENERATION** [8]	Europeans	Intronic	(eQTL)
	rs2424994	C	T	15%	1	**CORONARY ARTERY DISEASE** [99]	European GWAS	5' UTR	eQTL - Heart
	rs6088521	A	C	49%	1			5' UTR	eQTL - Heart
MAP1LC3B **NM_022818 1437 eQTL**	rs111626199	C	T	1%	4	**ACUTE MYOCARDIAL INFARCTION** [153] may abolish the binding sites for GMEB2, and ZBTB7A, ZBTB7B, ZBTB7C, and create the binding sites for GCM1-GCM2	Asians	Promoter	↓ exp [153] (luciferase)
	rs77019223	A	G	9% (1% As)	1			Promoter	↓ exp [153] (luciferase)
	rs8051218	T	C	6%	4	**ASTHMA** [10]	Americans	Intronic	(eQTL)
	rs7204722	C	T	82%	2			Intronic	(eQTL)
	rs933717	T	C	44%	26	**SLE** [154]	Asian GWAS	3' UTR	eQTL – Blood ↑ exp [154]
MAP1LC3C **NM_001004343 2 eQTL**	rs1776161	G	A	42%	1	**UTERINE LEIOMYOMAS** [155] Clinical Trial	Americans	Exon1	

Several ***cancer-associated mutations in LC3*** have been reported that either attenuate its binding to **ATG7** and subsequent lipidation (*LC3B* **Y113C**) [156] or its interaction and cleavage by **ATG4** (*LC3A* **R70C/H** rs778324131, *LC3B* **T113** rs200708875, and *LC3*C **R76C** rs776473823) [157]. These ***loss-of-function LC3 mutations*** could confer tumor-promoting features as they are reducing but not completely blocking autophagy in cells, and thus still support some level of autophagy for the continuous growth of tumor cells at later stages (melanoma/hepatocellular carcinoma) [158,159].

GABARAPs and LC3s have opposite roles in regulating ULK1 for autophagy induction [160]

Mutation of the ULK1 LC3-interacting region that disrupts the Atg8-family protein-ULK1 interaction drastically reduces ULK1 activity, autophagic degradation of SQSTM1, and phagophore formation in response to starvation. Similarly, disruption of the ATG13-Atg8-family protein interaction suppresses ULK1 activity and autophagosome formation. By reconstituting Atg8-family protein-depleted cells with individual Atg8-family members, it has been shown that: **The GABARAP subfamily (GABARAP and GABARAPL1) positively regulates ULK1 activity and autophagosome formation in response to starvation.** In contrast, the LC3 subfamily (LC3B and LC3C) negatively regulates ULK1 activity and phagophore formation.

Table S6. *ATG12*-conjugation system – AUTOPHAGY_LAP.

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG5 **NM_004849.2 509 eQTL**	[rs490010](#)	A	G	48%	20	**ccRCC** [77] Theragnosis (Pazopanib) 🡻PFS	Europeans	Intronic	(eQTL)
	[rs473543](#)	A	G			**BREAST CANCER** [161] Theragnosis (Anthracycline and/or taxane) 🡹PFS **APLASTIC ANEMIA** [162] >GG 🡻 RISK	Asians	5' *ATG5*	(eQTL)
	[rs506027](#)	**T**	**C**			**CROHN DISEASE** [163] Theragnosis (anti-TNF) 🡹 OS **SEPSIS** [164] 🡹 TNF IL1B	Europeans, and Asians	5' *ATG5* promoter	(eQTL) 🡻 exp [164] 🡹 exp [165–167]
						ASTHMA [165–167] 🡹 neutrophils	Americans, and Asians		
						APLASTIC ANEMIA [162] 🡻 RISK	Asians		
						ASTHMA [165–167] 🡹 neutrophils	Americans, and Asians		
	[rs510432](#)	T	C	44%	12	**CROHN DISEASE** [163] Theragnosis (anti-TNF) 🡹 OS	Europeans	5' *ATG5* promoter	(eQTL) 🡻 exp [164] 🡹 exp [165–167]
						HCC [168] **HBV-related diseases**	Asians		
						NSCLC EGFR* [169] Theragnosis (gefitinib) 🡹 OS PFS	Asians		
						LUNG FIBROSIS [170] 🡻 RISK x **COAL**	Asians		
						MELANOMA [171] Bad prognosis 🡻 tumor-infiltrating lymphocytes	Americans		
						SEPSIS [164] 🡹 TNF IL1B	Asians		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG5 **NM_004849.2 509 eQTL**	rs2245214	C	G	36%	11	**BLADDER CANCER** [117] ↓ autophagy (macrophages) ↓ BCG vaccine-induced trained immunity	Europeans	Intronic	(eQTL)
						MELANOMA [171] Bad prognosis ↓ tumor-infiltrating lymphocytes	Americans		
						NSCLC [172]	Europeans		
						PAGET DISEASE [173] RISK	Europeans		
						Q FEVER [152] **x *C. burnetii* infection** - Protective	Europeans		
						SLE [174,175]	American GWAS, and Europeans		
						SYSTEMIC SCLEROSIS [176]	World GWAS		
						THYROID CANCER [177]	Europeans		
	rs671116	A	G			**ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC)** [178] >TT Bad prognosis (shorter OS and PFS)	Asians	Intronic	(eQTL)
	rs633724	C	T			**ASTHMA** [10]	Americans	Intronic	(eQTL)
	rs573775	G	A	28%	1	**ASTHMA** [167]	Asians	Intronic	(eQTL) ↑ exp (PBMC) [179]
						APLASTIC ANEMIA [162]	Asians		
						BEHÇET DISEASE [179] ↓ RISK	Asians		
						SLE[175,180,181] ↑ IFNA IL10	Europeans		
						Age-related **MACULAR DEGENERATION** [8] Protective	Europeans		
	rs548234	C	T	68%	5	**HCC** [182] x Chronic **HBV (Hepatitis B virus) INFECTION**	Asian	3' *ATG5*	
						HBV INFECTION [182]			
						NEUROMYELITIS OPTICA [183] RISK of demyelination ↑T cell exp	Asians, and World		
						SLE [176,184] Protective			

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG5 **NM_004849.2 509 eQTL**	rs688810	A	G	22%	1	**NSCLC EGFR*** [169] Bad theragnosis (gefitinib)	Asians	5' *ATG5*	(eQTL)
	rs803360	G	C	48%	26	**APLASTIC ANEMIA** [162] Protective	Asians	Intronic	(eQTL)
	rs3827644	G	C	19%	31	**SYSTEMIC SCLEROSIS** [176,185]	Eaurpean GWAS, and World GWAS	Intronic	(eQTL)
	rs9372120	T	G			**MULTIPLE MYELOMA** [186] **RHEUMATOID ARTHRITIS** [187] **SYSTEMIC SCLEROSIS** [176]	Eaurpean GWAS, and World GWAS	Intronic	(eQTL)
	rs1322178	C	T			**ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC)** [178] POOR prognosis	Asians	3'ATG5	eQTL ↑ exp [178]
	rs3804329	A	G			**SYSTEMIC SCLEROSIS** [176]	World GWAS	intronic	eQTL
	rs9373839	T	C			**CROHN DISEASE** [163] Theragnosis (anti-TNF) **SYSTEMIC SCLEROSIS** [176]	Europeans, World GWAS	Intronic	(eQTL)
	rs6568431	A	C	60%	14	**HBV INFECTION** [182] **SLE** [174,175] ↑ anemia and renal involvement	Asians, Europeans, American GWAS		↑ exp [182]
						CEREBRAL PALSY [188] Protective	Asians	3' *ATG5*	↑ plasma level
	rs6937876	G	A			**SLE**[57] **NEUROMYELITIS OPTICA** [183] Protective	Asians		
	rs12201458	C	A	12%	4	**ASTHMA** [165,166]	Americans, and Asians	Intronic	
	rs2299863	T	G			↑ *ATG5* expression in nasal epithelium.		Intronic	
	rs12212740	G	A			**ASTHMA** [10,167] Protective		Intronic LD 5' of ATG5	
	rs11751513	C	A	5%	1	**ASTHMA** [165]	Americans	Intronic	
	rs17067724	A	G	1%	1	**HCC** [189] RISK	Asians	Intronic RP1-60O19.1	
	rs190825454	G	C	0% 1% As	1	**ACUTE MYOCARDIAL INFARCTION** [153]	Asians	5' *ATG5*	

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG7 **NM_001144912 5828 eQTL**	rs8154	T	C	31%	1	**NSCLC (EGFR*)** [169] Theragnosis (Gefitinib) **BREAST CANCER** [190] Bad prognostic ↓ PFS and OS	Asians	Synonymous methylation meQTL [190]	eQTL – Lung ↑ exp [190]
	rs1375206	C	G	60%	36	**ASTHMA** [167] ↓serum IL8 levels **PARKINSON DISEASE** [191]	Asians	Intronic	(eQTL)
	rs2594972	A	G			**CEREBRAL PALSY** [188]	Asians	Intronic	(eQTL sQTL)
	rs2594966	G	A			**ISCHEMIC STROKE**[192]	Asian GWAS	Intronic	(eQTL sQTL)
	rs2594973	C	G					Intronic	(eQTL sQTL)
	rs2606736	C	T			**ccRCC** [193] ↓ RISK (> 55 years old)	Asians	Intronic	(eQTL) sQTL – Lung Blood
	rs6442260	G	A	36%	5	**ccRCC** [193] ↓ RISK (≤ 55 years old)		Intronic	(eQTL) sQTL – Blood
	rs1470612	C	T	18%	77	**CEREBRAL PALSY** [188]	Asians	Intronic	(eQTL)
	rs11706903	C	A			**SLE** [57]	Asians	Intronic	eQTL blood
	rs2594971	G	A	65%	45	**ASTHMA** [167] ↓serum IL8 levels	Asians	5' *ATG7*	(eQTL)
	rs2594975	T	C	51%	1	**MYOCARDIAL INFARCTION** [194] ↑ binding of transcription factor	Asians	5' *ATG7*	
	rs7635838	T	C	59%	35	**CARDIOVASCULAR DISEASE** [99] Blood lipids (HDL)	Europeans	Intronic	(eQTL)
	rs2447607	C	G,T	59%	14	**Systolic BLOOD PRESSURE** [99]	Europeans	Intronic	eQTL muscle
	rs36117895	T	C	3%	56	**HUNTINGTON DISEASE** [195]	Europeans	**MISSENSE** V471A	(eQTL)
	rs4684776	T	C	18%	77	**ISCHEMIC STROKE** [192]	Asian GWAS	Intronic	eQTL

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG10 **NM_001131028 16437 eQTL**	rs1864182	C	A	58%	11	**BREAST CANCER** [196] Protective	Asians	**MISSENSE** P220H	eQTL - Lung
						NSCLC [197] Poor survival **NSCLC EGFR*** [169] Theragnosis (gefitinib) 🡻 RISK for acquired RESISTANCE. 🡹 RISK of primary RESISTANCE	Asians		
						 **LUNG FIBROSIS** [170] Protective **x COAL**	Asians		
						MELANOMA [171] 🡹 tumor-infiltrating lymphocytes (TILs)	Americans		
	rs1864183	C	T	49%	22	**HCC** [189]	Asians	**MISSENSE** T212M	eQTL - Lung
						 **HNSCC** RISK to develop laryngeal cancer [119] **NPC**, Bad Theragnosis (radiotherapy) [198]	European, and Asians		
						NSCLC  Poor survival[197] Theragnosis (Platinum) [11]	Asians		
						 **PAGET DISEASE** [173] Protective	Europeans		
						TUBERCULOSIS [199] 🡹 IL8	Asian GWAS		
	rs4703533	C	G	39%	4	 **HNSCC NPC** [198] Bad Theragnosis (radiotherapy)	Asians	Intronic	
	rs10036653	A	T	20%	1	**NSCLC** [200] 🡻 RISK of brain metastasis **NSCLC EGFR*** [169] Theragnosis (gefitinib) 🡻 acquired resistance 🡹 PFS 🡹 OS	Asians	5' *ATG10*	eQTL – Lung 🡹 OCT4 binding [169]
	rs10514231	C	T	66%	1	**BREAST CANCER** [196] Protective **HCC** [189] Protective **NSCLC** [197] Poor survival **HNSCC NPC** [198] Bad Theragnosis (radiotherapy)	Asian studies, and GWAS	Intronic	eQTL - Lung, Breast 🡹 exp [189]
	rs9447453	C	A	11%	1	 Delayed age of **MENOPAUSE** [201]	American GWAS	5' *ATG10*	

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG10 **NM_001131028 16437 eQTL**	rs324913	T	C	47%	18	**ECZEMA HERPETICUM** [202] ↓ IFNG	Americans	Intronic	eQTL -Skin
	rs1485587	A	G			**ALZHEIMER DISEASE** [203]	American GWAS	Intronic	eQTL - Brain
	rs891159	G	A	22%	43			Intronic	eQTL - Brain
	rs4703879	A	G						eQTL - Brain
	rs7707921	T	A			**BREAST CANCER** [204]	European GWAS	Intronic	eQTL - Breast
	rs73134739	T	C			**BREAST CANCER** [205]	Asian GWAS	Intronic	eQTL - Breast
ATG12 **NM_004707 268 eQTL**	rs26532	C	A	78%	1	**NSCLC** [200] RISK of brain metastasis	Asians	Intronic	eQTL - Brain
	rs26537	T	C	40%	5	**HNSCC** [206] **HCC** [189]	Asians	Intronic	eQTL ↑ exp [206]
	rs26538	C	T			**NSCLC EGFR*** [169] Bad prognosis ↓ PFS **LUNG FIBROSIS** [170] **x COAL** - Protective	Asians	Intronic	eQTL - Lung ↓ exp [169]
	rs1058600	C	T	23%	12	**NSCLC** [207] Theragnosis (radiotherapy)	Americans	3'UTR	eQTL - Lung
ATG16L1 **NM_030803 2507 eQTL**	rs2289476	C	A	6%	25	**CROHN DISEASE** [208–210] **x SMOKING**	European, and American GWAS	Intronic	(eQTL)
	rs4663402	A	T	4%	18	**HNSCC** [206] **HCC** [189]	Asians	Intronic	eQTL - Esophagus
	rs4663421	G	C			♀ **ANKYLOSING SPONDYLITIS** [211]	Asians	Intronic	(eQTL)
	rs6758317	C	T	18%	3			Intronic	(eQTL)
	rs6754677	G	A	62%	8	**CROHN DISEASE** [64]	Asians	Intronic	(eQTL)
	rs78835907	G	A	5%	1	**PROSTATE CANCER** [212] Bad prognostic	Asians		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG16L1 **NM_030803** **2507 eQTL**	**rs2241880**	A	G	53%	71	♀ **CARDIOVASCULAR DISEASE** [213] RISK in postmenopausal women *Carotid intima-media thickness*	South Americans	**MISSENSE** T300A	eQTL - Colon Thyroid
						LUNG CANCER Good prognosis ↓ metastasis [200] **x SMOKING –** Protective [214] **NSCLC EGFR*** Bad theragnosis (Gefitinib) [169]	Asians, and Europeans		
						COPD [182]	Asians		
						♂ **CROHN DISEASE** [64,208–210,215] **x SMOKING** LD with 11 other pubmed cited rs: [216] rs10210302, rs6752107, rs6431654, rs6431660, rs12994997, rs3828309, rs2289474, rs2289472, rs2241879, rs3792109, rs1045100 **x BISPHENOL A** levels are correlated with systemic CD inflammatory response with dysbiotic microbiota [217]	European GWAS American GWAS and Asians European		
						PREMATURE DELIVERY [218]	Europeans		
						UROPATHOGENIC *E. coli* [219] Protective	Americans		
						HBV INFECTION [220]	South Asians		
						BURULI ULCER [221,222] x *Mycobacterium ulcerans* Protective	African study, and GWAS		
						RHEUMATOID ARTHRITIS [223] *ATG16L1* rs2241880 x *ATG16L2* rs11235604 (C/T) *ATG16L1* rs6758317 x *ATG16L2* rs11235604 (C/T)	Asians		
						PSORIASIS [224]	Europeans		
						PAGET DISEASE RISK [173]	Europeans		
						BREAST CANCER RISK [225]	Africans		
						THYROID CANCER [226] Protective ↓ RISK, Good prognosis	Europeans		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG16L1 **NM_030803** **2507 eQTL**	[rs2241880](#)	A	G	53%	71	**HNSCC (Oral)** [119]	Europeans	**MISSENSE** T300A	eQTL - Colon Thyroid
						MELANOMA [171] >GG Good prognosis (earlier stage), >AG Younger age	Americans		
						COLORECTAL CANCER ↑ RISK [227] Good prognosis (↑ survival, ↓ metastasis) ↑ IFN (indep. of autophagy, MAVS dep)[228]	Europeans Americans		
						GASTRIC CANCER [66,229] **x *H. Pylori* INFECTION** Good Prognosis ↑ tumor apoptosis [230]	Asians- Europeans Americans		
						HCC [231] (Comorbidity HCC and cirrhosis) RISK-based surveillance in cirrhosis. Protective: **HBV**-related HCC [232]	Europeans Asians		
	[rs13005285](#)	T	G	66%	8	**PSORIASIS** [224]	Europeans	Intronic	eQTL - Skin
	[rs10751215](#)	T	C	47%	33	**Metastatic ccRCC** [77]	Europeans	Intronic	(eQTL)
	[rs10898880](#)	C	A			**NSCLC** Theragnosis (radiotherapy) [207] ↑ *ATG16L2* ↓ autophagosome ↑ inflammation	Americans	5' *ATG16L2*	(eQTL) ↑ exp [207]
	[rs11605818](#)	A	G	2%	1	**SLE** [233]	European GWAS	Intronic	
ATG16L2 **NM_033388** **222 eQTL**	[rs11235604](#)	C	T	0% As 10%	1	**CROHN DISEASE** [234–236] Protective **SLE** [237–239] with IgA nephropathy or lupus nephritis **NSCLC EGFR*** [169] Bad Theragnosis (Gefitinib) **CORONARY ARTERY DISEASE** [240] **RHEUMATOID ARTHRITIS** [223]	Asian GWAS Asian GWAS Asians Asian GWAS Asians	**MISSENSE** R220W *Asian-specific*	↓ exp
	[rs11235667](#)	A	G	0% As 11%	1	**SLE** [239] YY1, and FOXA binding sites	Asian GWAS	3' *ATG16L2*	
CHMP2B ***NM_014043*** ***7278 eQTL***	[rs1002765](#)	G	A	11%	1	**ATROPHIC GASTRITIS** [241] precancerous **x *H. pylori* INFECTION** **GASTRIC CANCER** [241] **x *H. pylori* INFECTION**	Asians	Intronic not specific MIR4795	(eQTL)

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
CHMP2B **NM_014043 7278 eQTL**	rs63751126	A	C	0%	1	**ALS** [242]	Europeans	**MISSENSE** Q206H	
	rs63751048	C	T	0%	1	**FRONTOTEMPORAL DEMENTIA** [243] protein-truncating mutation	Europeans	**NONSENSE**	
	rs63750652	G	A,C	0%	1			splice acceptor	
	rs63750653	G	T	0%	1			**MISSENSE** N148T	
LAMP1 **NM_005561 74 eQTL**	rs9577229	C	T	0%	1	**TUBERCULOSIS** [199]	Asian GWAS	**MISSENSE** A204V	(eQTL)
	rs12871648	A	C	33%	1	**PARKINSON DISEASE** [244]	American GWAS	Intronic	
LAMP2 **NM_015104 820 eQTL**	rs727504953	G	A	0%	1	**DANON DISEASE** [245] cardiomyopathy, skeletal myopathy, and intellectual disability	Asians	**MISSENSE** G93R	↓ exp [245]

Table S7. AUTOPHAGY RECEPTORS

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
CALCOCO2 **NM_00583 1311 eQTL**	rs8074034	A	G	49%	26	**GLIOBLASTOMA** [246] pediatric	European GWAS	Intronic	eQTL-Brain
	rs550510	G	A	18%	14	**MULTIPLE SCLEROSIS:** Protective [247] ↑ mitophagy ↑ binding with LC3C (LIR motif) ↓ INFLAMMATION (TNF release from B cells)	Europeans	**MISSENSE** G140E	eQTL-sQTL blood Brain
	rs2303015	T	C	4%	75	**BACTERIAL PERITONITIS** [248] in patients with alcoholic cirrhosis **CROHN DISEASE** [249]	Europeans European GWAS	**MISSENSE** V272A	eQTL - Colon
DRAM1 **NM_018370 4677 eQTL** **induces the formation of the phagophore by binding SQSTM-1** [250,251]	rs7955890	C	T	11%	40	**NSCLC** [11] Theragnostic (Platinum) ↑ PFS	Asians	Intronic	eQTL - Lung
	rs17032060	G	A	1%	24			3'UTR	
	rs77694286	A	G			**TYPE 2 DIABETES** [252] higher protein intake	European GWAS	Intronic	(eQTL) ↓ exp [252]
NBR1 **NM_005899 10,959 eQTL**	rs17599948	G	C	6%	6	**PROSTATE CANCER** [253] progression to lethal cancer after radiotherapy **BREAST CANCER** [254] Rare *BRCA1* 3'UTR SNPs **NOT SPECIFIC**. Common *NBR1, NBR2,* ***BRCA1***	Americans	Intronic	eQTL – Breast, Prostate
NCOA4 **NM_005437 1231 eQTL** **FERRITINOPHAGY**	rs10740051	G	A	27%	8	**PROSTATE CANCER** [255] Coactivator for AR (androgen receptor)	African Americans	Intronic	(eQTL – sQTL)
	rs10761581	T	G	43%	7			**MISSENSE** F8V	(eQTL – sQTL)
	NCOA4 was recently identified as a cargo receptor for ferritin-based lysosomal degradation. NCOA4 depletion can eliminate iron accumulation and thus weaken ferroptosis. Cancer cells are susceptible to ferroptosis. Lower NCOA4 expression in ccRCC is associated with disease progression and poor prognosis, as well as impaired immune infiltration (CD8+ T cells) [256,257]								
NUFIP1 **NM_012345 144 eQTL** **RIBOPHAGY**	rs17066364	G	C	3% (13% As)	61	**OBESITY** [258]	Asians	Intronic LD with 5'	
	rs114280567	G	A	0% (6% As)	2	**ASTHMA** [259] x **DIISOCYANATE** occupational exposure	European GWAS	3'	

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
OPTN **NM_021980** **473 eQTL**	rs3829923	C	T	34%	3	**GLAUCOMA** [260]	Europeans	Promoter	
	rs10796021	TT	T,TC	44%	1			CCDC3	
	rs7921853	T	G	51%	1			Intronic	(eQTL)
	rs765884	T	C	28%	13			Intronic	(eQTL)
	rs11258194	T	A	3%	2	**GLAUCOMA** [261] **DIABETIC RETINOPATHY** [262]	Asians	**MISSENSE** M98K	
	rs2234968	G	A	26%	4	**GLAUCOMA** [261]	Americans, and Asians	synonymous	(eQTL)
	rs10906308	G	A	22%	18	**GLAUCOMA** [263]	Americans	Intronic	
	rs825411	A	G	54%	4	**PAGET DISEASE** [264]	European GWAS	Intronic	(eQTL)
	rs1561570	T	C	50%	3			Intronic	(eQTL)
	rs76647957	A	C	27%	3	**PAGET DISEASE** [265] Splicing (exon 5 skipping) → Truncated protein.	Americans	intronic	(sQTL)
	rs2234968	G	A					synonymous	(sQTL)
	rs10906303	A	G					intronic	(eQTL)
	Rare mutations or dysregulation of optineurin can cause several **neurodegenerative diseases**, including: amyotrophic lateral sclerosis, (rs267606929 E478G rs267606928 Q398X ↓ Ub binding), frontotemporal dementia (rs377219791 A481V, UBD, Q235*), glaucoma, (rs28939688 E50K, Insoluble Optineurin, Retinal ganglion cell apoptosis, rs75654767 R545Q Ub binding affected, rs373425395 H486R), Huntington disease, as well as inflammatory digestive disorders such as Crohn disease (reduced expression in macrophages. Innate immunity compromised) [266]								
SQSTM1 **NM_003900** **339 eQTL**	rs10277	T	C	50%	9	Age-related **MACULAR DEGENERATION** [8] Theragnosis (anti-VEGF)	Europeans	3'UTR	(eQTL)
	SQSTM1 amplification on chr.5q is linked to clear cell renal cell carcinoma [267]. Rare germinal SQSTM1 mutations are associated with **neurodegenerative diseases**, such as ALS-FTD [268], Parkinson disease, and also Paget disease of bone, metabolic diseases, obesity, and insulin resistance [269,270]								
TAX1BP1 **NM_006024** **860 eQTL**	rs11540483	T	A,C	11%	51	**HNSCC** [271]	South Americans	MISSENSE L307I	(eQTL)
	rs10214930	G	A	21%	20	**HYPOSPADIAS** [272]	European GWAS	Intronic	
	Gain of *TAX1BP1* in 7p15.2-1 was associated with larger hepatocellular carcinoma size and positivity of HCV antibody [273]								

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
TOLLIP **NM_019009 608 eQTL**	rs5743890	T	C	14%	1	**PULMONARY FIBROSIS** [274,275] ↑ mortality RISK ↓ Expression	European-American GWAS	intronic	(eQTL)
	rs111521887	C	G	20%	4			intronic	(eQTL)
	rs5743894	T	C					intronic	(eQTL)
	rs5743867	G	A	92%	18	**SEPSIS** [276] ↓ RISK >CC ↓ Secretion of TNF and IL6. **HIV INFECTION** [277] **TUBERCULOSIS** [278]	Asians	intronic	TOLLIP AS1 eQTL Lung ↑ exp [276] (PBMCs)
	rs5743899	C	T	79%	1	**HIV INFECTION** [277] **RHINOVIRUS INFECTION** [279,280] x AIR quality **TUBERCULOSIS** [278] >CC RISK for progression. **LEISHMANIASIS** [281]	Asians Europeans Asians Amazonians	intronic	
	rs3750920	C	T	46%	1	**LEISHMANIASIS** [281] **MALARIA** [283] **LEPROSY** [284] **TUBERCULOSIS** [282] Protection **PULMONARY FIBROSIS** [285] Theragnosis (N-acetylcysteine) : Good [286]	Amazonians Amazonians Mexicans Asians European GWAS Americans	synonymous	(eQTL) ↑ exp [282] (monocytes)
	rs3793964	T	C	67%	1	**LEPROSY** [287] >TT ↑ RISK ↑ *IL1RN* exp (monocytes) Potential therapeutic target for IL1-dependent diseases.	Asians	intronic	(eQTL) ↑ exp [287] (monocytes)
	rs3829223	C	T	52%	3	**PULMONARY FIBROSIS** [285]	European GWAS	intronic	eQTL

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
TOLLIP **NM_019009 608 eQTL**	rs3168046	G	A	47%	3	**PULMONARY FIBROSIS** [285]	European GWAS	3'-UTR	eQTL/sQTL
						LUNG GRAFT DYSFUNCTION [288] ↑SERPINE1/PAI1 plasma levels	American GWAS		
	rs5744034	A	G	20%	5	**PULMONARY FIBROSIS** [285]	European GWAS ⚠	3'-UTR LD RP11-532E4.2 missense	(eQTL)
	rs5743854	G	C	88%	3	**TUBERCULOSIS:** Theragnosis (BCG VACCINATION) [289] ↓ *TOLLIP* mRNA expression (monocyte) After M. tuberculosis infection, TOLLIP-deficient monocytes ↑ IL6, ↓ bacterial replication. The TOLLIP-deficiency >G/G ↓ BCG-specific T-cell responses and ↑ susceptibility to tuberculosis infection. Activating TOLLIP may provide a novel adjuvant strategy for BCG vaccination	Americans, and South Africans	Promoter	TOLLIP AS1 eQTL
WDFY3 **NM_014991 347 eQTL**	rs76117213	G	A	1%	1	**ALZHEIMER DISEASE** [290]	American GWAS	Intronic	
	rs17009220	G	C	6%	1			Intronic	
	Heterozygous, mostly ***de novo*** **variants in WDFY3** result in a mild **NEURODEVELOPMENTAL** delay (intellectual disability, autism/hyperactivity disorder) **and opposing effects on brain size** [291]**: Loss-of-function** variants (truncating and missense) causing **haploinsufficiency** lead to **MACROCEPHALY.** In contrast, variants in the PH-domain of WDFY3 leads to **MICROCEPHALY, via dysregulation of the WNT-pathway**. Proliferating cortical neural progenitors highly express WDFY3, further supporting a role for this molecule in the regulation of neurogenesis.							

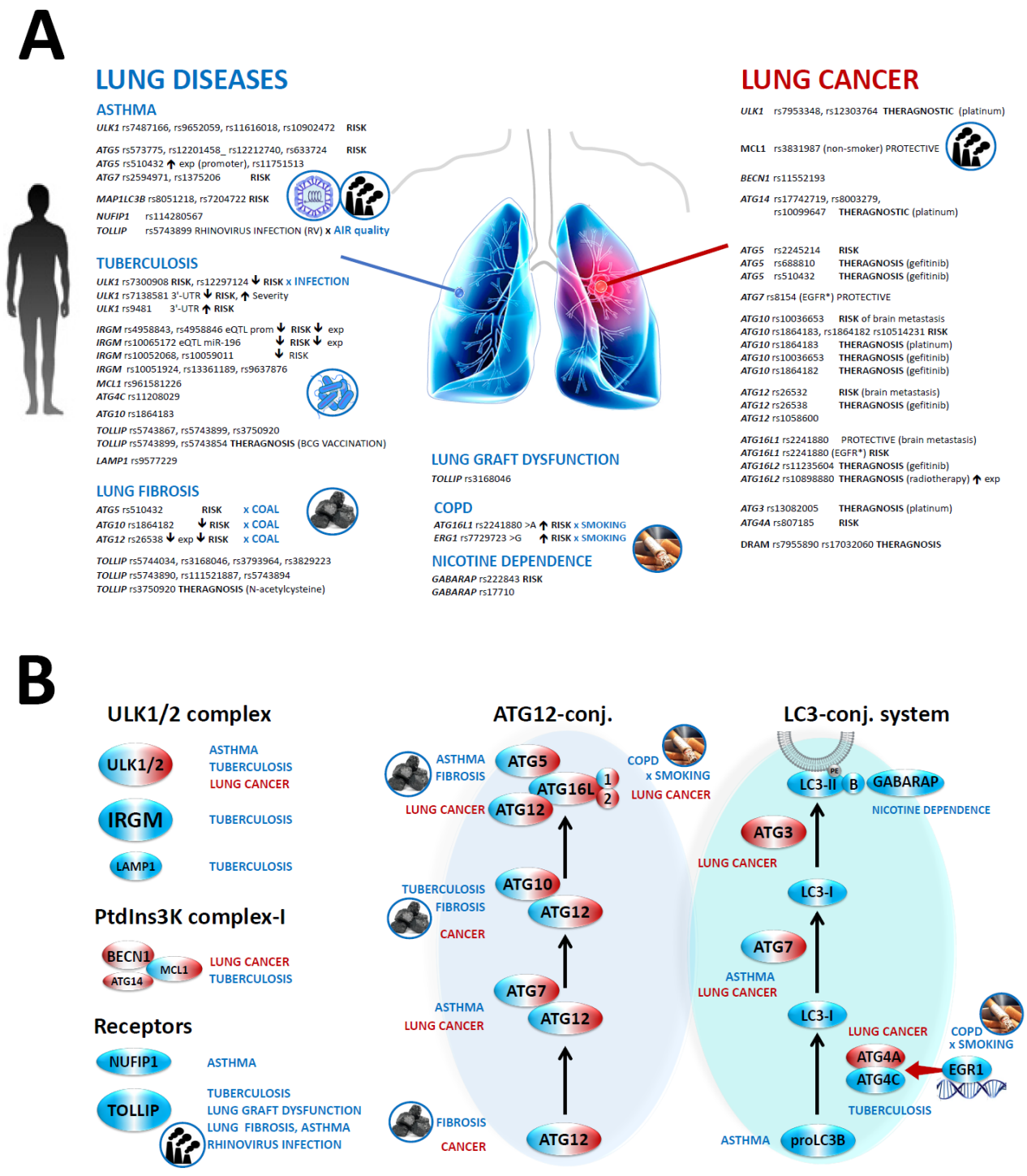


Figure S1. Autophagy deficiency in human lung diseases. (A) Summary of autophagy-related gene variations. (B) Steps of the autophagy pathway affected by SNPs. (C) Phenotypes of autophagy-deficient mouse models [146, 292-306]. CSE, cigarette smoke exposure. (Continued on next page).

C

***ulk1/2*$^{-/-}$ (DKO)**	**RESPIRATORY distress** [292]
***atg5*$^{-/-}$**	Death within 24 h of birth
***atg4b*$^{-/-}$**	**LUNG FIBROSIS** (tunicamycin [293], (bleomycin) [294]) ↑ inflammation (neutrophil infiltration)
***atg5*$^{f/f}$ *or* *atg7*$^{f/f}$** *Myeloid Cell-Specific*	**LUNG FIBROSIS** [295] ↑ IL18 (bleomycin)
***egr1* KO** 	**Smoke-induced COPD** [146] *egr1* KO ↓ ATG4B expression ↓ LC3B conversion
***map1lc3b*$^{-/-}$** 	**Smoke-induced COPD** [296]
	LUNG FIBROSIS upon aging (bleomycin) [297]
***becn1*$^{-/-}$** *Lung-Specific, Conditional* 	**LETHAL RESPIRATORY INSUFFICIENCY** [298] ↓ Lung development (branching)
Silencing *Fundc1* 	**Smoke-induced COPD** [299] Cigarette smoke (CSE) COPD mice ↑ FUNDC1. Silencing *Fundc1* → ↓ IL6 TNF ↓ CSE-induced mitophagy cell apoptosis. ↑ COPD lung function
***tollip*$^{-/-}$**	**ASTHMA** [300-302] TOLLIP is a negative regulator of innate immunity: It prevents pulmonary neutrophil recruitment in response to allergen stimulation (house dust mite), bacterial commensal infection, or rhinovirus infection, three contributors of asthma exacerbations. *tollip*-KO mice experience increased neutrophil recruitment, which exacerbates asthma.
Atg16l1 ΔWD **LAP deficient**	Lethal infection by **INFLUENZA A virus** [303] fulminant **pneumonia**, lung inflammation and high mortality
***Becn1*$^{+/-}$**	**LUNG ADENOCARCINOMAS** [304,305]
***sh3glb1* $^{-/-}$**	**SMALL CELL LUNG CARCINOMAS** [306]

Figure S1 (Continued). Autophagy deficiency in human lung diseases. (A) Summary of autophagy-related gene variations. (B) Steps of the autophagy pathway affected by SNPs. (C) Phenotypes of autophagy-deficient mouse models [146, 292-306]. CSE, cigarette smoke exposure.

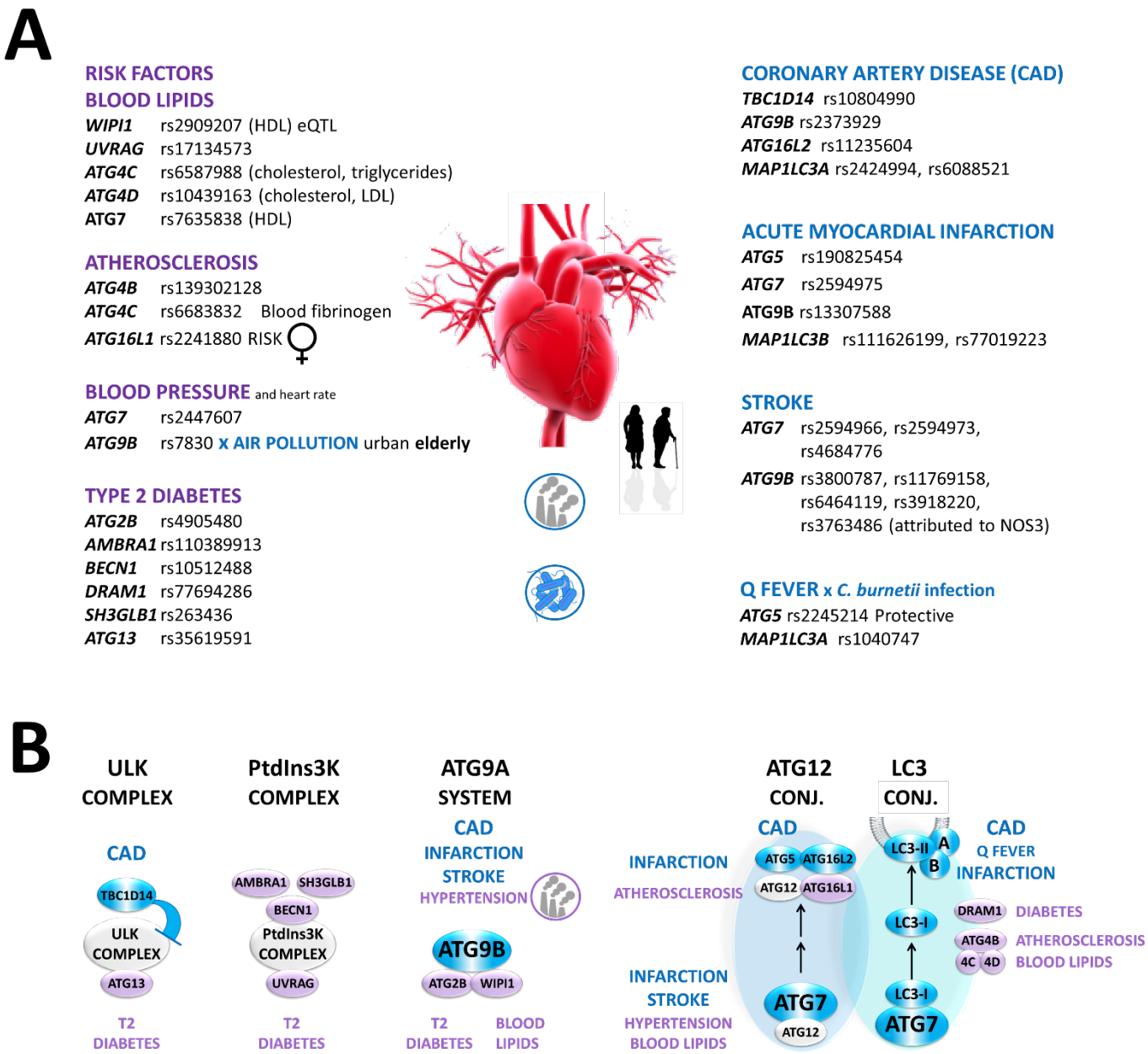
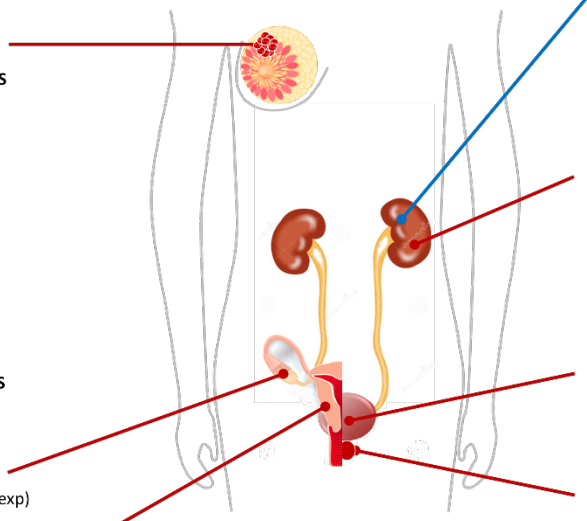


Figure S2. Autophagy deficiency in human cardiovascular diseases. (A) Summary of autophagy-related gene variations. (B) Steps of the autophagy pathway affected by SNPs. (C) Phenotypes of autophagy-deficient mouse models [307-311]. CAD, coronary artery disease.

A



MENOPAUSE

ATG10 rs9447453 **Delayed age**

BREAST CANCER

ATG13 rs10838611 **THERAGNOSIS**
ATG16L1 rs2241880 **RISK**
SMCR8 rs1563634 **RISK**

MCL1 rs3831987 **RISK**
NRBF2 rs10995190 **RISK**
NRBF2 rs10509168 **RISK**
VMP1 rs1295925 **RISK**

ATG10 rs1864182 **RISK**
ATG10 rs10514231 **RISK**
ATG10 rs7707921 **RISK**
ATG10 rs73134739 **RISK**
ATG7 rs8154 **PROGNOSIS**
ATG5 rs473543 **THERAGNOSIS**
NBR1 rs17599948 **RISK**

OVARIAN CANCER

ATG4A rs5973822 (eQTL, miRNA, ↑exp)
SMCR8 rs921986, rs12952556 eQTLs

CERVICAL CANCER

ATG4A rs5973822 (eQTL, miRNA, ↑)
ATG4A rs807181, rs807182 x HPV INFECTION RISK
ATG4A rs807183 (eQTL, ↓ exp) x HPV RISK

UTERINE LEIOMYOMAS

MAP1LC3C rs1776161

KIDNEY DISEASE

ATG2A rs188780113 MISSENSE R478C **RISK**
ATG16L1 rs2241880 MISSENSE T300A
UROPATHOGENIC E. coli
Protective

ccRCC

ATG4A rs7880351 **THERAGNOSIS** (pazopanib)
ATG4C rs6683832 **THERAGNOSIS** (pazopanib)
rs6670694
ATG5 rs490010 **THERAGNOSIS** (pazopanib)
ATG7 rs2606736
ATG16L2 rs10751215 **PROGNOSIS**
IRGM rs10059011 **RISK**

BLADDER CANCER

ATG2B rs3759601 **THERAGNOSIS** (BCG)
ATG5 rs2245214 **THERAGNOSIS** (BCG)

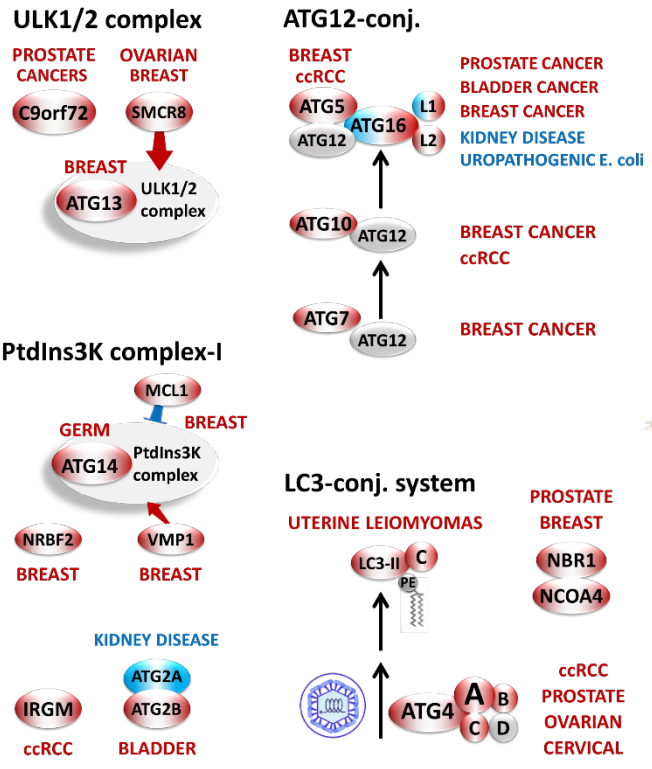
PROSTATE CANCER

ATG4B rs3771570
ATG16L1 rs78835907 **PROGNOSIS**
C9orf72 rs774359, rs3849942
rs10122902, rs10757665
ATG14 rs8015211 **PROGNOSIS** eQTL
NCOA4 rs10740051, rs10761581
NBR1 rs17599948 **THERAGNOSIS** (radiotherapy)
attributed to BRCA1

TESTICULAR GERM CELL TUMOR

ATG14 rs1009647

B



C

***atg5*$^{-/-}$** *Kidney specific* ***atg7*$^{-/-}$**	**ACUTE KIDNEY INJURY** [312,313] Cisplatin- and ischemia-reperfusion-induced
***atg5*$^{f/f}$**	**KIDNEY DISEASE AND AGING** [314]
atg16l1	**URINARY TRACT INFECTION** [315]
***Atg16l1*^{T300A}**	**URINARY TRACT UPEC INFECTION** [315] Protection: ↑ vesicle trafficking, ↓ infection. Independent of autophagy or proinflammatory cytokine responses. ↑ expression of RAB33B, which interacts with ATG16L1, as RAB27B and RAB11A → UPEC exocytosis
***optn*$^{-/-}$**	***E. Coli*-INDUCED PERITONITIS** [316]
***Becn1*$^{+/-}$** or ***atg7*$^{-/-}$** *Ovary specific*	**REDUCED FERTILITY** [317]
***atg16l1*$^{f/f}$** *Uterus specific*	**REDUCED FERTILITY** [318] Endometrial decidualization
SQSTM1 shRNA	**ccRCC growth** [267] addictive to *SQSTM1* gene gain and overexpression *(in vitro* and *in vivo)*
***atg7*$^{f/f}$** ***pten*$^{f/f}$** *Inducible prostate specific*	**PROSTATE CANCER** [319] *atg7* KO delays *pten*-deficient prostate tumor progression (evidence of ER stress)
Becn1*$^{+/-}$** ***Becn1*^{F121A} *(KI/KI)	**BREAST CANCER** [304, 320–322] ↑ ERBB2/HER2-driven tumorigenesis ERBB2/HER2 interacts with BECN1 and inhibits autophagy Somatic Allelic loss of *BECN1* is observed in over 50% of human breast cancers
***rb1cc1*$^{-/-}$** ***Rb1cc1*$^{f/+}$** *Breast specific*	**BREAST CANCER** [323]
***rb1cc1*$^{f/f}$**	**OVARIAN CANCER** [324] hyperplasia of epidermis (acanthosis)
***Becn1*$^{+/-}$**	**EARLY OVARIAN TUMORS** [325]

Figure S3. Autophagy deficiency in breast and urogenital diseases. (A) Summary of autophagy-related gene variations. (B) Steps of the autophagy pathway affected by SNPs. (C) Phenotypes of autophagy-deficient mouse models [267, 304, 312-325]. UPEC, uropathogenic *E. coli*

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