Supplementary File S1: Search strings used to retrieve articles for the databases

PubMed

1. (H+/K+ ATPase OR ATP4A OR ATP4B) AND (autoimmune gastritis OR atrophic gastritis OR acid secretion disorder) AND (trafficking OR sorting OR β-subunit glycosylation)
2. (H+/K+ ATPase OR ATP4A OR ATP4B) AND (AP-1 OR AP-2 OR adaptor proteins OR SNARE OR Rab OR endosomal sorting OR trafficking)
3. (H+/K+ ATPase OR ATP4A OR ATP4B) AND (mutation OR variant OR dysfunction OR channelopathy) AND (sorting OR trafficking OR localization OR vesicle)
4. (Parietal cell) AND (H+/K+ ATPase OR gastric proton pump) AND (tubulovesicle OR apical membrane OR recycling OR sorting)

Wiley online

1. "H+/K+ ATPase" OR "gastric proton pump" OR ATP4A OR ATP4B
2. (protein sorting OR trafficking OR vesicular transport OR endocytosis OR exocytosis OR membrane targeting OR trans-Golgi OR adaptor proteins OR Rab OR SNARE)
3. ("H+/K+ ATPase" OR "gastric proton pump") AND (trafficking OR sorting) AND (mutation OR variant)
4. (H+/K+ ATPase OR gastric proton pump) AND (protein sorting OR trafficking) AND ("proton pump inhibitor" OR PPI OR SCH-28080)

African Journal Online

1. H+/K+ ATPase OR gastric proton pump
2. ATP4A OR ATP4B
3. gastric ATPase AND protein trafficking
4. gastric ATPase AND sorting OR localization

Supplementary File S2: Data extraction sheets for the included studies

Authors	**Title of Article**	**Experimental Model**	**Medium**	**Sample Size**	**Sorting Protein Investigated**	**Type of experimental intervention**	**Method Used in Assay**	**Key findings**	**DOI**
Heitzmann and Warth[48]	"No Potassium, No Acid: K^+ Channels and Gastric Acid Secretion"	In vitro studies utilizing isolated gastric parietal cells from animal models.	In vitro (electrophysiological recordings, ion flux measurements, and pharmacological interventions)	Not specified; the study employed multiple cell preparations and experimental replicates.	KCNE2 and KCNQ1 potassium channels	1. Pharmacological inhibition using specific blockers and inhibitors. 2. Electrophysiological recordings to measure ion channel activity. 3. Gene expression analysis to assess the presence and function of potassium channels.	1. Patch-clamp electrophysiology to measure ion channel currents. 2. Ion flux measurements to assess potassium and chloride movement. 3. Western blotting to detect protein expression levels. 4. Immunohistochemistry to visualize protein localization within cells.	1. The gastric H^+/K^+-ATPase actively transports protons into the lumen, creating a highly acidic environment essential for digestion. 2. Potassium channels, specifically KCNE2 and KCNQ1, are localized in the luminal membrane of parietal cells. 3. These potassium channels facilitate the recycling of K^+ ions back into the lumen, maintaining the electrochemical gradient necessary for sustained acid secretion. 4. Inactivation or dysfunction of these potassium channels impairs gastric acid secretion and disrupts the architecture of the	10.1152/physiol.00016.2007

Sahoo et al.[33]	Gastric Acid Secretion from Parietal Cells Is Mediated by a Ca^{2+} Efflux Channel in the Tubulovesicle	Mouse (murine) parietal cells (as well as genetically modified mice) and ex vivo/parietal cell preparations	In vivo (mouse models) + ex vivo / isolated cells (i.e. in vitro in isolated organelles and cells	The paper does not report a single "sample size" in the sense of n = X for all experiments, as multiple assays were done (biochemical, patch clamp, imaging, etc.). For example, they used "three independent acid secretion assays"	The principal protein of interest is **TRPML1** (also called ML1) — a lysosomal / tubulovesicular Ca^{2+} channel	Overexpression of ML1 in parietal cells (transgenic)	Whole-endolysosomal / tubulovesicle patch clamp / electrophysiology (ion current measurements)	TRPML1 (ML1) functions as a **Ca^{2+} efflux channel** on tubulovesicle (TV) membranes, which is activated in a PKA-dependent manner in response to histamine stimulation.	10.1016/j.devcel.2017.04.003

Sagia et al.[9]	Distinct trafficking routes of polarized and non-polarized membrane cargoes in Aspergillus nidulans	The fungus Aspergillus nidulans (a filamentous fungus) was used, examining membrane cargoes (transporters, SNAREs) in fungal hyphae / germlings.	Mostly in vivo within living fungal cells (i.e., the intact organism / hyphae) plus live imaging and genetic perturbations. Also use of mutant and repressed genetic strains (genetically manipulated fungus)	Because multiple experiments and imaging/colocalization quantifications were done, there is not a single uniform "n." For example, in one COPII repression experiment the authors report n = 101, 158, 163, 256, 126 for different COPII component repressions (SarA, Sec12, Sec24, Sec13, Sec31, respectively) in counting cells for localization phenotypes.	SynA: a polarized R-SNARE (localizes preferentially to apical membrane)	Genetic repression of conventional secretion machinery (e.g. repressible alleles for COPII components, Golgi / TGN maturation proteins) to disrupt canonical secretory pathway	Live cell fluorescence imaging / confocal / spinning disk microscopy to track localization and dynamics of the cargo proteins (UapA, SynA)	**Distinct trafficking routes**: The two cargoes (SynA and UapA) follow separate secretory routes. SynA trafficking depends on the canonical Golgi route, whereas UapA bypasses some Golgi / late secretion requirements.	10.7554/eLife.103355

Zhang et al.[4]	*H^+/K^+ ATPase expression in human parietal cells and gastric acid secretion in elderly individuals*	Human subjects (parietal cells from gastric mucosa biopsies)	Ex vivo / tissue samples (parietal cell ultrastructure by electron microscopy; mRNA / protein measurements	50 participants total: 19 in younger group (20–59 years) and 31 in elder group (≥ 60 years)	They are not focusing on a "sorting protein" per se, but rather **H^+/K^+ ATPase** (the proton pump in parietal cells) (α-subunit mRNA, β-subunit protein	Observational comparison between age groups (young vs elderly); measurement of ultrastructure and expression without experimental perturbation	Electron microscopy (EM) to assess ultrastructure in parietal cells	No significant morphological differences in parietal cell ultrastructure (mitochondria proportion, tubulovesicular system) between younger and elderly groups	10.1111/1751-2980.12055
Kawasaki-Nishi et al.[31]	Arg-735 of the 100-kDa subunit a of the yeast V-ATPase is essential for proton translocation	Yeast (Saccharomyces cerevisiae), specifically the vacuolar H^+-ATPase (V-ATPase) complex in yeast cells	In vivo (yeast whole cells), plus biochemical preparations / membrane assays (isolated membranes)	The paper does not state a sample "n = X" overarching sample size; rather, multiple mutants and assays (ATPase activity, proton translocation) were measured repeatedly.	The paper investigates the 100-kDa subunit a of V-ATPase (in yeast, called Vph1p), focusing on a conserved Arg-735 residue within it.	They made site-directed point mutations at Arg-735 (substitutions to Asn, Glu, Gln, Lys) and also mutated Arg-799. These mutant alleles were expressed in yeast and assayed for proton translocation, ATP hydrolysis, and complex assembly.	Measurement of ATPase activity (hydrolysis of ATP) in membrane preparations or whole cells	Mutation of Arg-735 (to Asn, Glu, or Gln) yields V-ATPase complexes that assemble normally but are completely devoid of proton transport activity and ATPase-coupled proton translocation	10.1073/pnas.221291798

Asano et al.[47]	The cavity structure for docking the K^+-competitive inhibitors in the gastric proton pump	Heterologous expression in HEK-293 cells expressing gastric H^+/K^+-ATPase mutants, plus membrane preparations / vesicles for biochemical assays	In vitro / cell culture + biochemical membrane assays (isolated membranes, vesicles)	They report replicate experiments (e.g. "four experiments" for Rb^+ transport assays)	he gastric H^+/K^+-ATPase α-subunit (especially residue Tyr-801 in transmembrane segment 5) and its interaction with K^+-competitive inhibitors (SCH 28080)	Site-directed mutagenesis of Tyr-801 (to alanine, serine, leucine, phenyl etc)	$^{86}Rb^+$ transport assays (to mimic K^+ flux)	Mutants at Tyr-801 (e.g. Y801A, Y801S) retained ion transport / ATPase activity but had 60–80× lower sensitivity (i.e. much weaker inhibition) to SCH 28080 compared to wild type in Rb^+ transport assays	10.1074/jbc.M308934200
Abe et al.[50]	Gastric proton pump with two occluded K^+ engineered with sodium pump-mimetic mutations	Recombinant / mutant **gastric H^+/K^+-ATPase** expressed in suitable systems (likely heterologous expression for structural determination)	In vitro structural biology (crystallography, cryo-EM) and biochemical / crystallographic analyses	Not a sample "n = …" — multiple structural determinations (crystal & cryo-EM) and mutant constructs. The cryo-EM structure is resolved to 2.6 Å resolution with the quintuple mutant.	The **gastric H^+/K^+-ATPase** (proton pump) is the main protein of interest; specifically engineered mutants to bind two K^+ ions (mimicking the Na^+/K^+ pump)	Site-directed mutagenesis: multiple amino acid substitutions (e.g. Lys791 → Ser, Glu820 → Asp, Tyr340 → Asn, Glu936 → Val, Tyr799 → Trp) to engineer K^+-binding capacity at a second site.	- X-ray crystallography (for various mutant constructs)	- The wild-type gastric H^+/K^+-ATPase normally binds a **single** K^+ in its K^+-occluded E2-P form, unlike Na^+/K^+-ATPase which binds two K^+ ions at sites I and II	10.1038/s41467-021-26024-1

Young et al.[3]	Structure and function of H+/K+ pump mutants reveal Na+/K+ pump mechanisms	Recombinant gastric H^+/K^+-ATPase mutants expressed in suitable systems (likely heterologous expression for structural determination)	In vitro structural biology (crystallography, cryo-EM) and biochemical / crystallographic analyses	Not a sample "n = …" — multiple structural determinations (crystal & cryo-EM) and mutant constructs. The cryo-EM structure is resolved to 2.6 Å resolution with the quintuple mutant.	The gastric H^+/K^+-ATPase (proton pump) is the main protein of interest; specifically engineered mutants to bind two K^+ ions (mimicking the Na^+/K^+ pump)	Site-directed mutagenesis: multiple amino acid substitutions (e.g. Lys791 → Ser, Glu820 → Asp, Tyr340 → Asn, Glu936 → Val, Tyr799 → Trp) to engineer K^+-binding capacity at a second site.	X-ray crystallography (for various mutant constructs)	The wild-type gastric H^+/K^+-ATPase normally binds a single K^+ in its K^+-occluded E_2-P form, unlike Na^+/K^+-ATPase which binds two K^+ ions at sites I and II. By introducing five targeted mutations (K791S, E820D, Y340N, E936V, Y799W), the authors engineered a mutant H^+/K^+ pump that occludes two K^+ ions (i.e. two separate densities at the two cation-binding sites) in its 2.6 Å cryo-EM structure. This demonstrates that structural constraints / specific residues prevent the wild-type pump from	10.1038/s41467-022-32793-0

Zhan et al.[17]	Multidimensional Assessment of Psychiatric Adverse Events Related to Proton Pump Inhibitors: A Real-World, Pharmacovigilance Study	This is a pharmacovigilance study utilizing data from the FDA Adverse Event Reporting System (FAERS) to assess psychiatric adverse events (AEs) associated with proton pump inhibitors (PPIs)	The study employed disproportionality analysis to evaluate the risk of psychiatric AEs related to PPIs using FAERS data. Additionally, genetic correlation analyses and bidirectional Mendelian randomization (MR) analyses were conducted to explore potential causal relationships between PPI indications and psychiatric disorders	The study analyzed a total of 12.83% of all AE reports on PPIs from the FAERS database, focusing on those that reported psychiatric adverse events.	The primary focus was on psychiatric adverse events associated with five commonly prescribed PPIs: omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	The study utilized pharmacovigilance data analysis to identify and assess the risk of psychiatric AEs related to PPI use	Disproportionality Analysis: To evaluate the risk of psychiatric AEs associated with PPIs using FAERS data.	Prevalence of Psychiatric AEs: Psychiatric AEs were reported in 12.83% of all AE reports on PPIs.	10.1111/cns.70436

López-Hernández et al.[19]	"Clathrin-independent endocytic retrieval of SV proteins mediated by the clathrin adaptor AP-2 at mammalian central synapses	The study utilized mouse hippocampal neurons to investigate the mechanisms of synaptic vesicle (SV) protein retrieval	The research involved live-cell imaging and biochemical assays to analyze the endocytic retrieval of SV proteins.	The study does not specify a sample size in the traditional sense, as it involves multiple independent experiments with varying numbers of neurons.	The primary focus was on synaptic vesicle proteins, including VGLUT1, VGAT, SV2A, Syt1, Syp, and Syb2, and their retrieval mechanisms at central synapses.	The study involved genetic manipulation (e.g., AP-2µ knockout), pharmacological inhibition (e.g., clathrin inhibitors), and live-cell imaging to assess the endocytic retrieval of SV proteins	Live-cell Imaging: To monitor the endocytic retrieval of SV proteins in real-time	Clathrin-Independent Endocytosis: The study found that synaptic vesicle endocytosis in mouse hippocampal neurons occurs independently of clathrin at physiological temperatures.	10.7554/eLife.71198
Ray[8]	"UBCH5 Family Members Differentially Impact Stabilization of Mutant p53 via RNF128 Iso1 During Barrett's Progression to Esophageal Adenocarcinoma	The study utilized patient-matched esophageal tissues from normal squamous epithelium (SE), Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC) to investigate the role of E2 ubiquitin-conjugating enzymes in the stabilization of mutant p53 during BE progression to EAC	The research involved single-cell RNA sequencing, biochemical assays, and cellular models to analyze the expression and interaction of RNF128 isoforms and UBCH5 family members in esophageal cells	The study analyzed patient-matched tissue samples from multiple individuals to assess the expression patterns and interactions of RNF128 isoforms and UBCH5 family members	The primary focus was on RNF128 isoforms (Iso1 and Iso2) and UBCH5 family members (UBCH5A and UBCH5C), specifically their roles in the stabilization of mutant p53 during the progression of BE to EAC.	The study involved genetic manipulation (e.g., RNF128 isoform knockdown), pharmacological inhibition, and protein-protein interaction assays to investigate the impact of RNF128 and UBCH5 family members on mutant p53 stability	Single-Cell RNA Sequencing: To identify candidate E2 ubiquitin-conjugating enzymes involved in mutant p53 stabilization.	Isoform Switch of RNF128: During BE progression to EAC, RNF128 switches from isoform 2 (Iso2) to isoform 1 (Iso1), which stabilizes mutant p53.	10.1016/j.jcmgh.2021.08.003

Mashima et al.[43]	Involvement of vesicle-associated membrane protein 7 in human gastric epithelial cell vacuolation induced by Helicobacter pylori-produced VacA	Human gastric epithelial cell line (AGS cells)	In vitro (cell culture assays)	They used three independent replicates for some assays (e.g. mRNA expression by Northern blot)	Vesicle-associated membrane protein 7 (VAMP7), a SNARE / R-SNARE family member, in interaction with syntaxin 7 (a Q-SNARE)	siRNA knockdown of VAMP7 in AGS cells Transient transfection of a dominant-negative mutant (N-terminal domain) of VAMP7	Immunocytochemistry / fluorescence microscopy to localize VAMP7 and syntaxin 7 on vacuoles	VAMP7 localizes to the VacA-induced vacuoles in AGS gastric epithelial cells and colocalizes with syntaxin 7.	10.1128/IAI.01573-07
Lutfiah et al.[30]	H,K-ATPase and carbonic anhydrase response to chronic systemic rat gastric hypoxia	Rat (Sprague-Dawley)	In vivo (whole animal hypoxia exposure)	25 male Sprague-Dawley rats divided into 5 groups (4 hypoxia durations + 1 control)	Gastric H,K-ATPase (proton pump enzyme)	Chronic systemic hypoxia: rats placed in a hypoxia chamber (10% O_2, 90% N_2) for durations of 1, 3, 5, or 7 days; comparison with normoxia control group	Real-time RT-PCR for mRNA expression of H,K-ATPase and CA9	H,K-ATPase mRNA expression: elevated at day 1, but then drastically decreased from days 3 to 7	10.13181/mji.v24i3.1066
Liu et al.[42]	Rab7 Is Associated with Poor Prognosis of Gastric Cancer and Promotes Proliferation, Invasion, and Migration of Gastric Cancer Cells	Human gastric cancer cell lines (in vitro) plus analysis of human gastric cancer tissue specimens	In vitro (cell culture assays) and ex vivo / clinical specimen analysis (tissues)	Clinical specimens: 115 gastric cancer patients (tumor vs adjacent tissues)	Rab7, a small GT	Overexpression of Rab7 in gastric cancer cells	Immunohistochemistry (IHC) on human tissue specimens to assess Rab7 protein expression	Rab7 expression is upregulated in gastric cancer tissues compared to adjacent normal tissues, and high Rab7 expression correlates with lymph node metastasis, poorer differentiation, and worse prognosis.	10.12659/MSM.922217

Adolf et al.[39]	Proteomic Profiling of Mammalian COPII and COPI Vesicles	Mammalian cells (human cell line; semi-intact mammalian cell system)	In vitro vesicle reconstitution experiments were performed in a controlled laboratory setting using semi-intact cells and purified coat proteins.	Not explicitly specified numerically (quantitative proteomics study multiple biological replicates using SILAC-labeled mammalian cells).	COPII coat proteins (including Sec23/24 and Sec13/31 complexes) COPI coat proteins (including coatomer complex subunits) Specific focus on Sec24 isoforms (Sec24A, Sec24B, Sec24C, Sec24D) and their role in cargo selection.	Reconstitution of COPII and COPI vesicles from semi-intact mammalian cells using purified coat proteins followed by proteomic analysis (comparison of vesicles formed by different isoforms).	SILAC (Stable Isotope Labeling by Amino acids in Cell culture) for quantitative proteomics Mass spectrometry (LC-MS/MS) for protein identification and quantification In vitro vesicle formation assays using semi-intact cells and purified coat proteins	COPII vesicles formed with different Sec24 isoforms show distinct cargo compositions, indicating isoform-specific cargo selection. COPI vesicles formed from different coatomer isoforms have similar protein compositions, suggesting less specialization. The study defines core proteomes for COPII and COPI vesicles in mammalian cells. The proteomic strategy provides a comprehensive view of vesicular transport mechanisms and how coat protein paralogs influence cargo sorting.	10.1016/j.celrep.2018.12.041