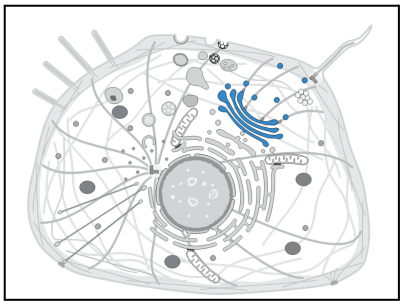
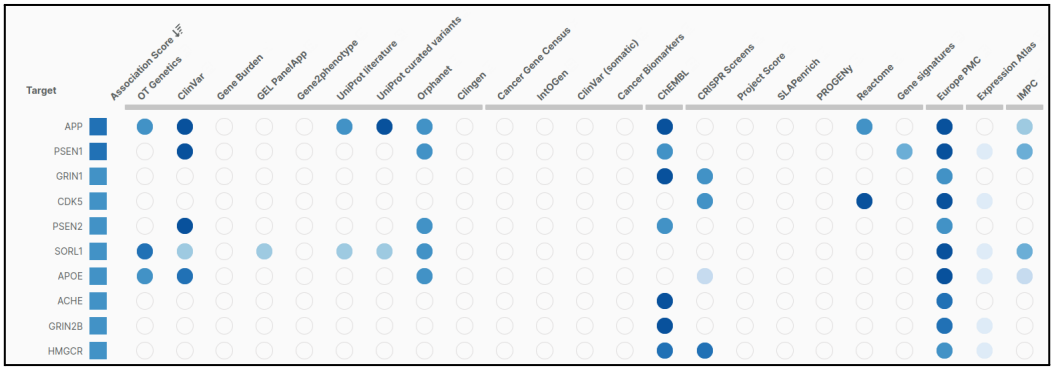
ALZHEIMER'S DISEASE: A Comprehensive Exploration

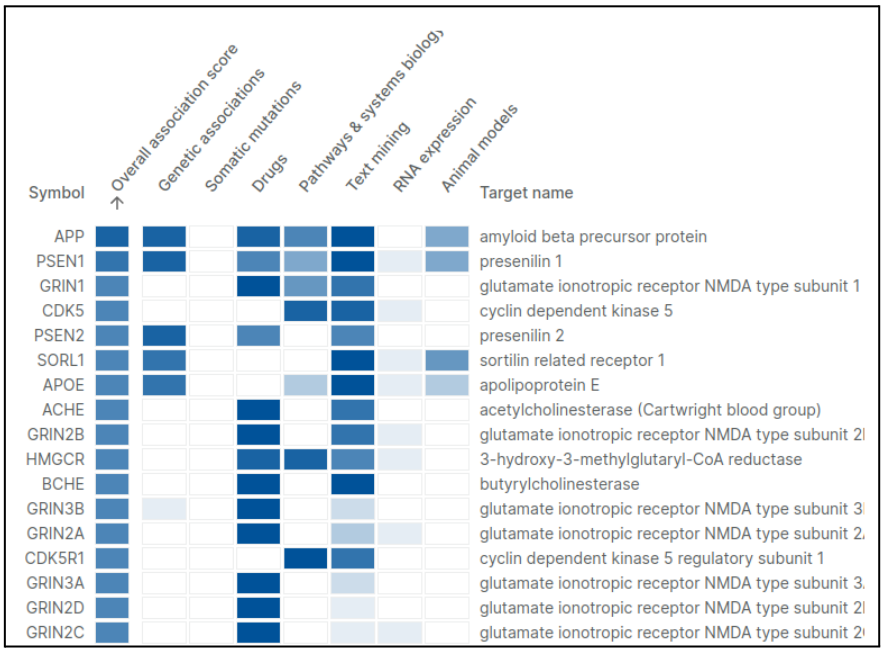
by Jana Moreno and Eloi Vilella

The diseases and phenotypes associated with the APP gene are visually represented in a bubble chart. Notably, Alzheimer's disease takes the forefront, characterized by progressive memory loss and cognitive decline. Other associations include Cerebral Amyloid Angiopathy (CAA), Hereditary Cerebral Hemorrhage with Amyloidosis-Dutch type (HCHWA-D), Hereditary Cerebral Alzheimer's disease is intricately linked to 8270 target associations, with the amyloid beta precursor protein (APP) standing out as the most prominently associated target. This association is substantiated by various experimental models, including genetic associations, drugs, pathways & systems biology, text mining, and animal models. Notably, somatic mutations fail to reinforce this association, while RNA expression exhibits comparatively lower support.





The experimental models that support this association are genetic associations, drugs, pathways systems biology, text mining and animal models. We can observe that somatic mutations do not support this association, and RNA expression has lower support.



In-Depth Focus on APP: Clinical Perspectives

Zooming in on APP, there are 25 clinical candidates and/or approved drugs specifically targeting APP for the treatment of Alzheimer's disease. These candidates span different phases, with Phase III clinical trials listed on clinicaltrials.gov and Phase IV trials securing approval from the Food and Drug Administration.

Disease/phenotype	Targets	Drug	Modality	Mechanism of action (MoA)	Phase	Status	Start Date	Source
Alzheimer disease	APP	ADUCANUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase IV	N/A	N/A	FDA
Alzheimer disease	APP	TRAMIPROSATE	Small molecule	Beta amyloid A4 protein stabiliser	Phase III	Unknown status	2006	ClinicalTrials.gov
Alzheimer disease	APP	BAPINEUZUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Completed	2007	ClinicalTrials.gov
Alzheimer disease	APP	DONANEMAB	Antibody	Beta amyloid A4 protein disrupting agent	Phase III	Active, not recruiting	2020	ClinicalTrials.gov
Alzheimer disease	APP	SOLANEZUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Completed	2009	ClinicalTrials.gov
Alzheimer disease	APP	GANTENERUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Completed	2014	ClinicalTrials.gov
Alzheimer disease	APP	LECANEMAB	Antibody	Beta amyloid A4 protein inhibitor	Phase III	Active, not recruiting	2019	ClinicalTrials.gov
Alzheimer disease	APP	BAPINEUZUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Completed	2007	ClinicalTrials.gov
Alzheimer disease	APP	BAPINEUZUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Terminated	2009	ClinicalTrials.gov
Alzheimer disease	APP	ADUCANUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Active, not recruiting	2020	ClinicalTrials.gov
Alzheimer disease	APP	ADUCANUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Recruiting	2022	ClinicalTrials.gov
Alzheimer disease	APP	VALILTRAMIPROSATE	Small molecule	Beta amyloid A4 protein stabiliser	Phase III	Active, not recruiting	2021	ClinicalTrials.gov
Alzheimer disease	APP	LECANEMAB	Antibody	Beta amyloid A4 protein inhibitor	Phase III	Recruiting	2020	ClinicalTrials.gov
Alzheimer disease	APP	GANTENERUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Completed	2010	ClinicalTrials.gov
Alzheimer disease	APP	DONANEMAB	Antibody	Beta amyloid A4 protein disrupting agent	Phase III	Recruiting	2021	ClinicalTrials.gov
Alzheimer disease	APP	SOLANEZUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Completed	2009	ClinicalTrials.gov
Alzheimer disease	APP	GANTENERUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Terminated	2018	ClinicalTrials.gov
Alzheimer disease	APP	ADUCANUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Terminated	2015	ClinicalTrials.gov
Alzheimer disease	APP	CRENEZUMAB	Antibody	Beta amyloid A4 protein inhibitor	Phase III	Terminated	2016	ClinicalTrials.gov
Alzheimer disease	APP	GANTENERUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Terminated	2020	ClinicalTrials.gov
Alzheimer disease	APP	SOLANEZUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Terminated	2013	ClinicalTrials.gov
Alzheimer disease	APP	BAPINEUZUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Terminated	2009	ClinicalTrials.gov
Alzheimer disease	APP	GANTENERUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Terminated	2021	ClinicalTrials.gov
Alzheimer disease	APP	CRENEZUMAB	Antibody	Beta amyloid A4 protein inhibitor	Phase III	Terminated	2017	ClinicalTrials.gov
Alzheimer disease	APP	BAPINEUZUMAB	Antibody	Beta amyloid A4 protein binding agent	Phase III	Terminated	2008	ClinicalTrials.gov

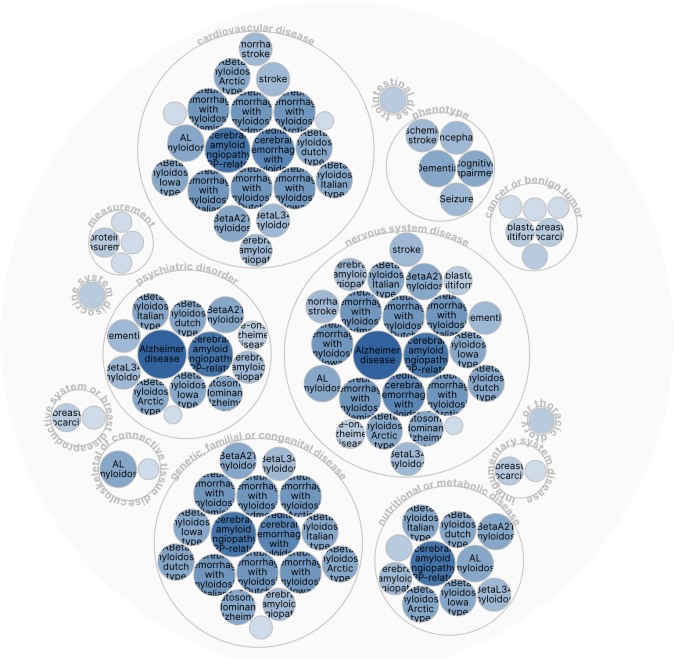
Among the clinical candidates, a diverse array of antibodies (e.g., ADUCANUMAB, BAPINEUZUMAB, DONANEMAB, SOLANEZUMAB, GANTENERUMAB, LECANEMAB, CRENEZUMAB) and small molecules (e.g., TRAMIPROSATE, VALILTRAMIPROSATE) are in various stages of development. Their statuses range from active development and participant recruitment to completed or terminated trials.
Hemorrhage with Amyloidosis-Iowa type (HCHWA-I), and APP Amyloidosis – a spectrum of diseases caused by amyloid protein buildup, resulting in brain damage and cell death.

Subcellular Localization: The Golgi Apparatus

Lastly, the subcellular location of APP is pinpointed to the Golgi Apparatus, further enhancing our understanding of its intricate involvement in cellular processes.

****Associated Diseases: Bubbles****

The bubble representation of every disease or phenotype associated with APP gene shows the following:



- **Alzheimer's disease:** The most common disease associated with the APP gene, Alzheimer's disease is a neurodegenerative disorder that causes progressive memory loss and cognitive decline.

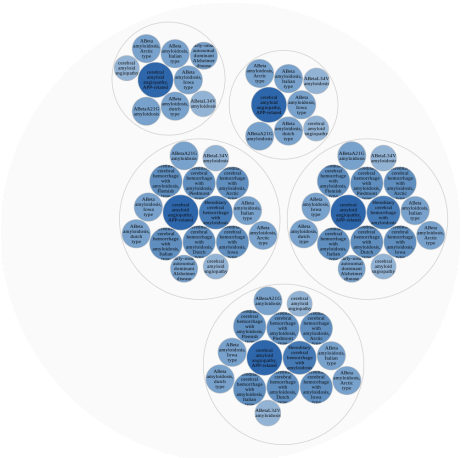
- **Cerebral amyloid angiopathy (CAA):** CAA is a condition in which amyloid proteins build up in the walls of blood vessels in the brain. This can lead to stroke, bleeding in the brain, and other problems.
- **Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D):** HCHWA-D is a rare genetic disorder that causes amyloid proteins to build up in the blood vessels of the brain, leading to stroke and bleeding in the brain.

- **Hereditary cerebral hemorrhage with amyloidosis-Iowa type (HCHWA-I):** HCHWA-I is another rare genetic disorder that causes amyloid proteins to build up in the blood vessels of the brain, leading to stroke and bleeding in the brain.

- **Beta-amyloid precursor protein (APP) amyloidosis:** This is a general term for a group of diseases caused by the buildup of amyloid proteins in the body. Amyloid proteins are abnormal proteins that can form plaques and tangles in the brain, leading to damage and cell death.

****Associated Diseases: Therapeutic Areas, Genetic Familial or congenital diseases****

The next bubble representation shows that phenotype specific on **genetic familial or congenital diseases** can be caused by a variety of factors, including:



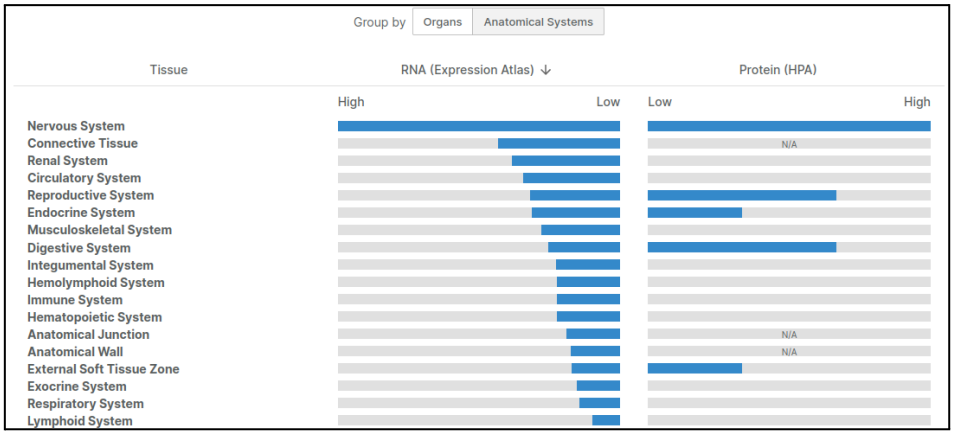
- **Genetics:** Some phenotypes specific to genetic familial or congenital diseases are caused by mutations in genes that are passed down from parents to their children. These mutations can be inherited from one parent or from both parents.

- **Environment:** Other phenotypes specific to genetic familial or congenital diseases are caused by environmental factors, such as exposure to toxins or chemicals.

- **A combination of genetics and environment:** Some phenotypes specific to genetic familial or congenital diseases are caused by a combination of genetics and environment.

****APP Expression in Anatomical Systems: A Comprehensive Overview****

Examining the anatomical expression of APP across systems, the Nervous System emerges as the primary hub, hosting the highest number of tissues and proteins. It is followed by the Connective Tissue, Renal System, and Circulatory System. The Endocrine System, on the other hand, exhibits the lowest number of tissues and proteins.



****Comparative Genomics****

Species	Homology type	Homologue	Query %id	Target %id
Human	within species paralog	APLP2	50.130	51.398
Human	within species paralog	APLP1	30.260	35.791
Chimpanzee	ortholog one2one	APP	95.974	95.850
Macaque	ortholog one2one	APP	97.273	99.734
Mouse	ortholog one2one	App	96.623	96.623
Rat	ortholog one2one	App	96.493	96.871
Rabbit	ortholog one2one	APP	97.013	97.139
Guinea Pig	ortholog one2one	APP	97.013	97.013
Dog	ortholog one2one	APP	96.883	96.883
Pig	ortholog one2one	APP	95.454	97.739
Tropical clawed frog	ortholog one2one	app	85.325	85.436
Zebrafish	ortholog one2many	appa	17.273	68.557
Zebrafish	ortholog one2many	appb	61.818	68.588
Drosophila melanogaster (Fruit fly)	ortholog one2many	Appl	27.143	23.483
Caenorhabditis elegans (PRJNA13758)	ortholog one2many	apl-1	24.286	27.259

The table shows the species, homology type, homologue, query id, and target xid of various proteins. The homology type column shows that the proteins listed are either orthologs or paralogs of human APLP2. The orthologs are found in chimpanzees, macaques, mice, rats, rabbits, guinea pigs, dogs, pigs, frogs, zebrafish, and fruit flies. The paralogs are found in humans.

In summary, the text presents a thorough examination of Alzheimer's disease, shedding light on various aspects such as the crucial involvement of the APP gene, its practical implications in a medical context, connections with other illnesses, where it is situated within cells, and how it compares across different genomes. The discoveries help build a complete picture of Alzheimer's disease, covering its details from the smallest molecular level to broader clinical viewpoints.