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Genetic Underpinnings of Cerebral Edema in Acute Brain Injury: An Opportunity for Pathway Discovery

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Abstract

Cerebral edema constitutes an important contributor to secondary injury in acute brain injury. The quantification of cerebral edema in neuroimaging, a well-established biomarker of secondary brain injury, represents a useful intermediate phenotype to study edema formation. Population genetics provides powerful tools to identify novel susceptibility genes, biological pathways and therapeutic targets related to brain edema formation. Here, we provide an overview of the pathogenesis of cerebral edema, introduce relevant genetic methods to study this process, and discuss the ongoing research on the genetic underpinnings of edema formation in acute brain injury. The epsilon 2 and 4 variants within the Apolipoprotein E *(APOE) gene* are associated with worse outcome after traumatic brain injury and intracerebral hemorrhage, and recent studies link these polymorphisms to inflammatory processes that lead to blood-brain barrier disruption and vasogenic edema. For the Haptoglobin gene (*HP*), the Hp 2–2 genotype associates with worse outcome after acute brain injury, whereas the haptoglobin Hp 1–1 genotype correlates with increased edema in the early phases of intracerebral hemorrhage. Another important protein in cerebral edema is aquaporin 4, coded by the *AQP4* gene. *AQP4* mutations contribute to the formation of cytotoxic edema, and further genetic research is necessary to help elucidate the mediating mechanism. Findings supporting the target genes outlined above require replication in larger samples and evaluation in non-white populations. These next steps will be significantly facilitated by the rapid changes observed in the field of population genetics, including large international collaborations, open access to genetic data, and significant reductions in the cost of genotyping technologies.

Keywords

Stroke; Hemorrhagic stroke; Intracerebral hemorrhage; Ischemic stroke; Traumatic brain injury; Brain edema; Stroke genetics

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Introduction

Diseases involving acute brain injury, including intracerebral hemorrhage (ICH), ischemic stroke, and traumatic brain injury (TBI), are associated with elevated mortality and morbidity [1]. Stroke is a leading cause of death and adult disability worldwide, while TBI is a contributing factor to a third of all injury-related deaths in the United States [1–4]. For a given patient, the total burden of brain injury corresponds to the sum of the primary and secondary injury components. The primary brain injury is directly related to the mechanisms of the underlying disease and occurs immediately after its onset. The term secondary injury encompasses several biological processes that occur hours to days after the primary insult, either as a direct consequence of the anatomical changes produced by this insult (hydrocephalus and compressive injury) or related to the pathophysiological responses to it (inflammation ad circulatory changes) [5].

The delayed and longer time window of secondary injury provides an appealing opportunity to deploy treatments aimed to reduce the final disability burden related to acute brain injury. One promising final pathway of secondary injury is cerebral edema, a biological process that leads to an increase in brain volume and intracranial pressure, sometimes followed by decreased cerebral perfusion, herniation, and death [1, 5, 6]. Observational studies indicate that cerebral edema is an independent predictor of mortality in TBI and ICH [7] [8]. Understanding the pathophysiology of cerebral edema is key to identifying therapeutic targets of secondary brain injury. Population genetics provides powerful tools to identify novel susceptibility genes, biological pathways and therapeutic targets involved in acute brain injury and edema formation. Thus far, the application of genomic analyses to neuroimaging phenotypes of acute brain injury has been limited by limited sample sizes and incomplete harmonization across the existing data. However, with the creation of large research consortia capable of assembling extremely large sample sizes and the implementation of accurate automated imaging pipelines, the ability to apply genomic analyses to neuroimaging markers has become a reality [3]. In this review, we provide a brief overview of relevant concepts related to population genetics and genomic medicine, review the pathogenesis of cerebral edema, and discuss relevant studies on the genetic underpinnings of edema formation post-acute brain injury.

Population Genetics and Genomic analyses

Population genetics offers tools that help to overcome the limitations of observational studies [9][9]. Examination of inherited genetic variability may shed light on the relationship between genes, different phenotypes, and pathophysiological pathways. Since mutations are randomly distributed during meiosis, the associations between mutation and disease are not influenced by postnatal factors. This model allows for the identification of the genetic and cellular pathways involved in specific conditions. The use of genetic analysis to identify new targets and mechanisms could be a promising strategy for neurocritical care conditions, as most conditions provoke brain edema and are influenced by underlying genetic factors [10–12]. Given that genotyping techniques now capture information from the entire genome, it is possible to exhaustively investigate the cellular processes and pathways involved in brain edema formation [13].

Genetic analyses boost the turnout of the translational research cycle

Completing all stages of the translational research cycle (Figure 1), which includes identification of a pathophysiological mechanism, demonstration of its involvement in pathophysiology, and testing agents that act on this pathway, is a demanding task. Moreover, a substantial number of interventions that seemed promising in pre-clinical studies failed to show benefit in expensive and time-consuming clinical trials. Not only can population genetics identify casual relationships between mutations and phenotypes of interest, but it can also help to reduce the proportion of new treatments that do not succeed in clinical trials. A comparative study that aimed to compare clinical interventions with and without genetic support used the Informa Pharmaprojects database along with GWASdb and OMIM, two open-access resources that contain information on genetic risk factors for complex and Mendelian conditions. The authors demonstrated that selection of genetically-supported targets doubles the success of the translational research cycle [14]. New statistical methods, such as Mendelian Randomization, offer even more powerful tools to support these findings [15].

Definition of Cerebral Edema

Edema is defined as an increase in brain tissue water that occurs in both the cells and interstitial space [6]. Cerebral edema is mainly characterized as cytotoxic or vasogenic edema [16, 17]. Cytotoxic edema results from failure of homeostatic pumps, leading to an imbalanced ionic gradient. This intracellular osmotic shift causes water to move into the cells, leading to cerebral edema. Vasogenic edema involves inflammatory markers and results from blood brain barrier (BBB) disruption causing an influx of protein rich fluid into the brain [5, 18–21]. Cytotoxic and vasogenic edema closely interact with each other and mutually contribute to edema formation after acute brain injury [22]. The cascade of edema formation is shown in Figure 2.

Edema formation after intracerebral hemorrhage

The accumulation of brain edema starts a few hours after the onset of an intraparenchymal hemorrhage and peaks between 7–11 days [23, 24]. Edema formation occurs in multiple phases within this time frame. In the first few hours after ICH, clot retraction causes serum proteins to be released, creating an osmotic gradient that pulls water into the interstitial space [22, 24]. In the first few days following the initial ionic edema, neutrophils and macrophages induce inflammatory cytokines to be upregulated. Inflammatory cytokines, such as IL-Iβ, IL-6, and TNF-α, contribute to the BBB breakdown and upregulate matrix metalloproteinases (MMPs), neuropeptide substance P and bradykinins [4, 21, 22, 24, 25]. MMPs, specifically MMP-9, breakdown collagen and other basal lamina proteins integral to the BBB [26, 27]. Substance P has been shown to increase vascular permeability and edema after brain injury [28–30]. Bradykinins are linked to increased edema, vascular permeability, and BBB after ischemia and other forms of brain injury [31, 32]. Additionally, leakage of red blood cells activates a coagulation cascade that produces thrombin, which is a proinflammatory agent at high concentrations [20]. Thrombin further breaks down the BBB and works alongside complement cascade proteins that enter the parenchyma, causing

microglia activation, erythrocyte lysis, and release of hemoglobin and iron into brain matter [21, 22, 33, 34]. Toxic products of iron and hemoglobin degradation, such as free radicals, further contribute to secondary injury [4, 5, 22, 24].

Edema formation in traumatic brain injury

Cytotoxic edema is present as early as 2–4 hours after TBI [21]. Impaired oxygen and glucose due to ischemia and hypoxia reduces ATP stores, disrupting the Na+/K+ ATPase function. Sodium cations flow down the electrochemical gradient, accumulating inside the cells, and drawing water into the cellular space. Aquaporins, a class of water-channel proteins located in the basolateral membranes of ependymal cells and astrocytes, colocalize with inward rectifying potassium channels. When injury occurs, water flows through the aquaporin channels and into the cell as a result of the ionic imbalance [1, 4, 6, 21]. Furthermore, the imbalanced ionic and electrochemical gradients cause the release of the excitatory neurotransmitter glutamate. Glutamate triggers pre and post synaptic neurons and leads to water influx in neighboring cells [17]. Calcium regulation is additionally impaired due to the increased cell volume. When calcium is upregulated, inflammatory pathways are triggered, contributing to the further breakdown of the BBB [17]. Vasogenic edema is also facilitated by the mechanical and vascular damage after traumatic injury. Proteins and red blood cells leaked into the parenchyma cause activation of the coagulation cascade. Thrombin acts to break down the BBB and activates microglia, cell lysis, and the release of hemoglobin, as discussed above.

APOE

Genetic variants within *APOE* may play a role in edema formation in acute brain injury. The apolipoprotein E (*APOE*) gene codes for the apolipoprotein E protein, which plays a key role in lipid transport and metabolism [35]. The epsilon variants (*ε)* are the most studied polymorphisms within *APOE.* The ε variants represent haplotypes built with genotype information from the SNPs rs429358 and rs7412. Using information from these two SNPs, *APOE-ε* variants are labeled as *APOE-ε2*, *APOE-ε3*, and *APOE- ε4*, with *APOE-ε3* being the most common allele found in the most population [36]. *APOE* is secreted by astrocytes in the central nervous system and has been shown to have BBB stabilization properties [37]. The *APOE* ε4 is associated with increased risk of cognitive decline, dementia, and Alzheimer's disease [38, 39]. Current research indicates that the *APOE* polymorphisms are also involved in many other disease processes, such as arteriosclerosis, traumatic brain injury, and intracerebral hemorrhage [35, 38, 40].

Animal studies of APOE

Animal models of acute brain injury have pointed to *APOE* as an important gene in acute brain injury and outcome. In an animal model of subarachnoid hemorrhage (SAH), *APOE*-deficient mice showed larger edema and greater BBB disruption after SAH than the wild-type mice. Additionally, there was a significant upregulation of inflammatory cytokines, such as Cyclophilin A, IL-Iβ, IL-I6, p-p65, and TNF-α, in the *APOE*-deficient mice after SAH, as well as increased MMP-9 activity. These results point to *APOE* as being directly involved in the inflammatory response that disrupts the BBB and contributes to vasogenic

edema after acute brain injury [41]. Researchers argue that *APOE* reduces the inflammatory response in an isoform-specific fashion, with *APOE-4* being the least effect of the three isoforms [41–43]. The use of an apolipoprotein peptide mimetic following head injury provides compelling evidence that *APOE* is involved in inflammation and edema formation after acute brain injury. In one study, researchers used an intravenous injection of a small peptide derived from the APOE receptor binding region in mice following TBI. This peptide has been previously shown to retain all functions of the intact protein [44]. Treatment of mice after TBI with the APOE peptide was associated with better short-term and long-term functional outcome, decreased number of injured hippocampal neurons, and reduction in TNF-α RNA [44]. In a similar study, researchers injected APOE mimetic peptide COG1410 in a subset of mice that underwent a controlled cortical impact injury to model TBI. Treatment with the peptide significantly decreased MMP-9 activity, reduced BBB disruption, reduced volume of the TBI lesion and vasogenic edema, and improved functional outcome [45].

Human studies of APOE

Genetic studies in humans have yielded associations between *APOE* polymorphisms and multiple diseases and traits. Genetic studies have shown that *APOE-ε4* is a predictor of poor functional outcome after head trauma [7, 40, 46–49]. Additionally, several related studies found that the *APOE*-ε2 allele is associated with larger baseline hematoma volume, increased risk of hematoma expansion, and poor outcome and mortality in hemorrhages located in lobar regions of the brain [50] [51]. In addition, one study reported that the ε4 allele was significantly associated with midline shift and functional outcome in ICH patients [52]. This finding led to the hypothesis that the mechanism linking the *APOE* phenotype with midline shift and poor outcome was perihematomal edema [52]. Supporting this hypothesis, recent studies found an association between *APOE* polymorphisms and a number of inflammatory processes involved in the formation of cerebral edema. When the ε4 version of *APOE* is expressed in neurons, it is susceptible to proteolysis. *APOE*-ε4 is the least stable isoform and has the greatest neurotoxic effects. Cellular pathways impaired by *APO*-ε4 include mitochondrial dysfunction, amyloid B production, neurite outgrowth, neuronal apoptosis, and BBB integrity [53]. Taken in consideration with the animal research linking *APOE*-ε4 to inflammatory cytokines discussed above, it is highly probable that *APOE*-ε4 facilitates inflammatory processes that contribute to BBB and vasogenic edema after acute brain injury. Further research is needed to establish the genetic relationship between APOE and cerebral edema and the influence of *APOE*-ε4 at different time points post-acute brain injury.

Haptoglobin

Haptoglobin (Hp) is an acute-phase response protein that plays an antioxidant role by binding and neutralizing hemoglobin (Hb) in the blood [54, 55]. The bound Hp-Hb complex is cleared by CD163 scavenger receptors on macrophages, reducing cytotoxicity, edema, and neuronal damage caused by free Hb [56]. In the human genome, the *HP* gene at chromosome 16q22 is polymorphic and is represented as *Hp-1* and *Hp-2*. Individuals can either by homozygous for the *Hp*-1 allele (*Hp*-1–1), heterozygous (*Hp*-1–2), or homozygous

for the *Hp*-2 allele (*Hp*-2–2) [57]. Previous research from both animal and human studies has established that the haptoglobin polymorphism influences Hb clearance, oxidative stress, and is a risk factor for cardiovascular events [55, 58–60].

Animal studies of Haptoglobin

In one rodent study of ICH, rats with reduced blood Hp levels had significantly higher levels of oxidative brain damage and edema 24 hours after ICH induction. Additionally, rats with the *Hp* gene knocked out had severe neurological outcomes compared to wild types rodents, while rats with *Hp2* overexpression had less severe neurological deficits [54]. Additional studies support the finding that *Hp* overexpression in ICH rodent model decreases oxidative stress, reduces lesion volume, and improves neurological status [59, 61].

Human studies of Haptoglobin

Compared to *Hp*2–2, *Hp*1–1 is a superior antioxidant, binds better to hemoglobin, and is removed faster by CD163 [57]. Furthermore, a greater number of cytokines, particularly IL-6 and IL-10, are secreted when the *Hp*1-Hb complex is bound to CD163 as compared to *Hp*2-Hb [55]. While hemoglobin cytotoxicity is a deleterious process that contributes to secondary injury after intracerebral hemorrhage, the release of inflammatory cytokines also contributes to the breakdown of BBB and vasogenic edema. One genetic study that characterized patients with ICH by their Hp genotype reported a nonsignificant trend towards increased mortality when comparing persons with *Hp*-2–1 and *Hp*-2–2 versus those with *Hp*1–1. Additionally, participants with the *Hp*2 allele had significantly worse functional outcomes measured by the modified Rankin scale [62]. Interestingly, a different genetic study found that the *Hp*1–1 phenotype was associated with increased perihematomal edema (PHE) in the early stages after ICH [56]. The findings that *Hp*-1–1 acts as a better antioxidant and is associated with improved functional outcome and lower mortality after ICH, while simultaneously being associated with greater PHE, appear to be contradictory to the biological model proposed that PHE is a marker of poor functional outcome after brain injury. In order to explain this contradiction, it is hypothesized that early PHE has protective properties while Hp-Hb binding reduces prolonged inflammation, edema, and subsequently poor outcome [56]. Further genetic studies of haptoglobin and edema formation at different time points following an ICH is necessary. Moreover, it would be beneficial to study the haptoglobin phenotype in the context of TBI to gain a better understanding of its role in secondary injury.

Aquaporins

Aquaporins (AQPs) are a class of water-channel proteins, and AQP4, AQP1, and AQP9 are specifically present in the brain. AQP4, the main water channel found in the brain, is located in end-feet membranes of astrocytes adjacent to capillaries, glial limiting membranes, subependymal astrocytes and ependymal cells. AQP1 is located in the choroid plexus and plays an important role in cerebral spinal fluid production and regulation. AQP9 is located in some astrocytes and ependymal cells and functions to transfer solutes, such as glycerol and urea [63, 64].

Animal studies of Aquaporins

Several animal model studies suggest that AQPs are involved in cytotoxic edema after acute brain injury. In a mouse model of ICH, AQP4 expression was upregulated following the ICH, while AQP4 deficient mice showed worse neurological deficits, and greater edema, BBB disruption, micro-vessel damage, and neuronal death [65]. AQP4 is anchored by the α-syntrophin protein, and deletion of the α-syntrophin protein disturbs the polarization of AQP4 [64, 66]. A-syntrophin-deficient mice resulted in downregulated AQP4 expression in astrocyte perivascular membranes, as well as delayed edema formation [67]. A-syntrophin deletion also resulted in reduced astrocyte swelling after severe hypoosmotic stress and oxygen/glucose deprivation [68]. Additionally, rodent studies that used ethanol treatment after TBI and curcumin treatment after ICH showed reduced AQP4 mRNA and gene expression along with decreased cerebral edema [63, 69]. These findings support the conclusion that AQPs play an important role in cytotoxic edema formation post brain injury. Aquaporins are also implicated in vasogenic edema, as astrocytic end-feet are integral to the BBB, and AQP4 assists in the reabsorption of fluid into extracellular fluid spaces [64, 70].

Human studies of Aquaporins

While there is a growing literature of animal studies supporting AQP4 involvement in cerebral edema, the number of human studies remains limited. One genetic study looked at variations within exome 4 of the *AQP*4 gene and reported no significant variation among 102 patients with TBI [71]. However, this study was limited to only exon 4 of the *AQP*-4 gene and did not take into considerations variants that could be present on exons 1–3. Another genetic study of *AQP*4 that evaluated clinical, neuroimaging, and genetic data from 363 TBI patients identified 7 tag SNPs along the *AQP*4 gene region and found that two of them, rs3763043 and rs3875089, were associated with clinical outcome as evaluated 6 months after the traumatic event [71].

Sur1 Gene

Sur1, a sulfonylurea receptor and transmembrane protein, is coded by the *ABCC8* gene. Sur1 associates with two ion-channels: Kir6.2 and transient receptor potential melastatin 4 (Trpm4). The Sur1-Trpm4 complex is an ATP-sensitive cation channel that is not usually found in the brain, but is upregulated after trauma, ischemia, and hypoxia [72]. Previous work has shown that Sur1-Trpm4 assembles with *AQP4* to help modulate astrocyte swelling, a key factor in cytotoxic edema [73]. One study found that Sur1 was overexpressed in many cell types, particularly neurons and endothelial cells, following traumatic brain lesions [74]. Furthermore, Sur1-Trpm4 activity is associated with MMP-9 secretion, a proteinase involved in BBB breakdown and vasogenic edema [26, 27, 72]. To date, there has only been one genetic study of *ABCC8* in relation to edema formation. This study used a candidate gene approach to investigate if polymorphisms within this gene region influence edema after TBI. The investigators identified three SNPs, rs2283261, rs3819521, and rs2283258, that were significantly associated with cerebral edema, measured by CT imaging, and increased intracranial pressure. Because all three SNPs are located in non-coding regions of *ABCC8*,

the authors speculate that these SNPs may play a role in the regulation and expression of Sur1 [75].

Hastened pace of discovery in population genetics—The rapid advancements in population genetics research observed in recent years will bring substantial benefits to understanding the genetic factors described above. This transformation is due to many factors, including an evolving research culture that encourages collaboration and public sharing of available data; the creation of large international consortia designed to share ideas, harmonize data, and achieve large sample sizes; and novel analytical methods designed to obtain maximal benefit from Big Data. [76, 77].

Genetic studies are complex, time-consuming and costly. Making genetic data publicly accessible increases the overall impact of these studies by maximizing scientific yield of each dataset. Open access resources can be divided into 4 main categories: repositories that store already generated genetic data; large population studies with attached biobanks; disease-specific studies with genomic data available for public access; and scientific platforms that grant access to data in closed computational environments, allowing investigators to work with data without downloading them to their personal computers and local servers. Table 1 describes some of the numerous open access data resources currently available in population genetics research.

The Database of Genotypes and Phenotypes (dbGaP) sponsored by the NIH [78], the Cerebrovascular Disease Knowledge Portal (CDKP) [79] in the United States, and the European Genome-phenome Archive (EGA) [80] in Europe are three publicly available, large open access repositories. The UK Biobank [81] and the China Kadoorie Biobank [82] are successful examples of large, population-based, prospective studies that include more than 500,000 participants and provide a variety of data, ranging from genetic information to physical measurements. Regarding disease-oriented open access studies, the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study [83] is a dominant resource in Stroke research and has led to numerous sub-analyses already [84–89]. The ERICH study includes 6,000 ICH cases and matched controls, including individuals of different ethnic background. The American Heart Association Precision Medicine Platform is a scientific platform that offers public access to numerous datasets with genetic and non-genetic information. It's closed, computational environment uses Jupyter Notebooks to script, as well as Amazon Web Service to offer computational support to researchers [86]. Lastly, the *All of Us Research Program,* which is planned to start winter of 2020, will enroll at least 1 million participants in the United States from different ethnic backgrounds, providing even greater amounts of data to be used in genetic analyses [80].

Future directions—The impact of genetics on Neurocritical Care will continue to grow in coming years. Advancements in Neurocritical Care relies on many factors, with collaboration between clinicians, investigators, and research institutions being crucial. An important objective for these collaborations is to integrate genetic analyses with clinical data, such as laboratory results, neuroimaging, and vital signs, provided by Neuroscience Intensive Care Units. While public access to these data will accelerate the pace of discovery

in the field, it will inevitably raise challenges related to adequately protecting patients' privacy. [90].

Conclusions

Brain edema constitutes an important component of secondary brain injury via increased intracranial pressure and dislocation of neuroanatomical structures, sometimes with associated herniation. Given the significant association between cerebral edema with patient outcome after acute brain injury and the extended time frame of edema formation, brain edema represents an appealing target for novel therapies. In this review, we discussed a number of possible genetic loci involved in this process. *APOE-ε2* and *APOE-ε4* have been shown to be associated with outcome after TBI and ICH, and there is evidence linking these polymorphisms to inflammatory processes that lead to BBB disruption and vasogenic edema. Through its ability to bind and remove hemoglobin, haptoglobin is an important protein with antioxidant properties. The *Hp-2* allele has been associated with worse outcome after acute brain injury, while the Hp-1–1 phenotype was associated with increased edema in the early phase after ICH. Future research should be focused on studying the Hp alleles within different time points of edema formation after brain injury. Another important protein in cerebral edema is *AQP4*, which contributes to the formation of cytotoxic edema. More research is necessary to help elucidate its mechanistic properties. A summary of the genes involved in the pathogenesis of brain edema is shown in Table 2. Ascertaining novel loci related to edema formation and understanding the pathophysiology of the discussed genetic loci is crucial for the identification novel drug targets.

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Declaration of interests

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Highlights

- Brain edema is a component of secondary brain injury.
- Mechanisms involved include inflammation, vasogenic and cytotoxic edema.
- Genes involved brain edema: Apolipoprotein E, Haptoglobin, *AQP4*, and ABCC8 (Sur1).
- Publicly accessible genetic data will help elucidate the genetic factors of edema.

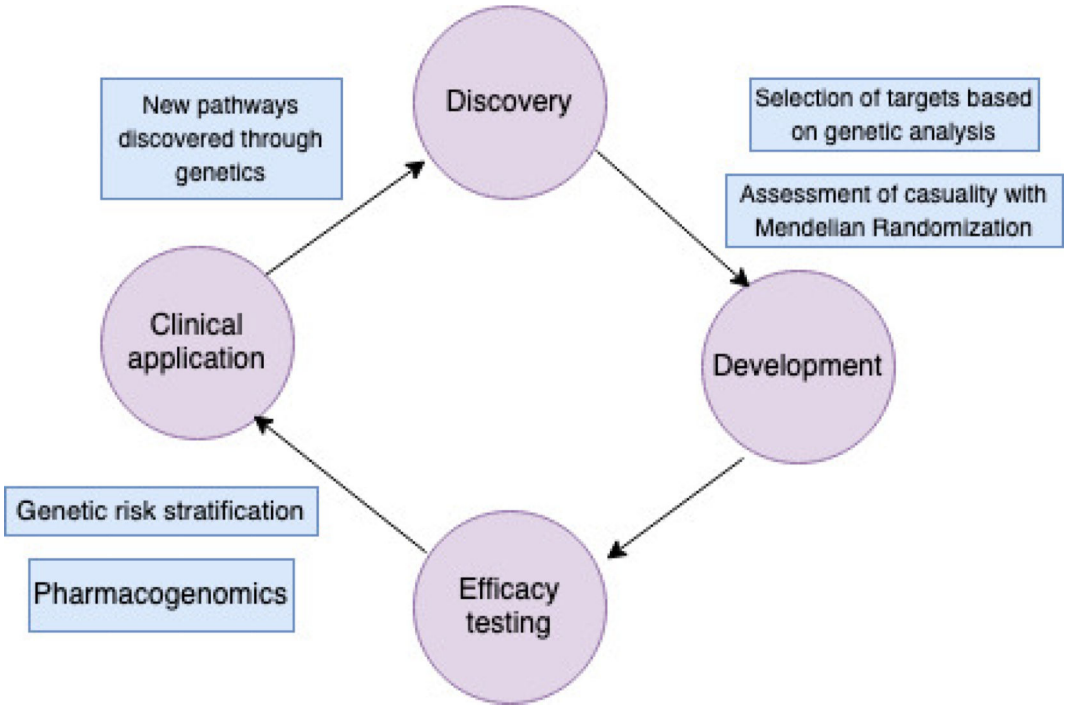

Figure 1.
The cycle of translational research.

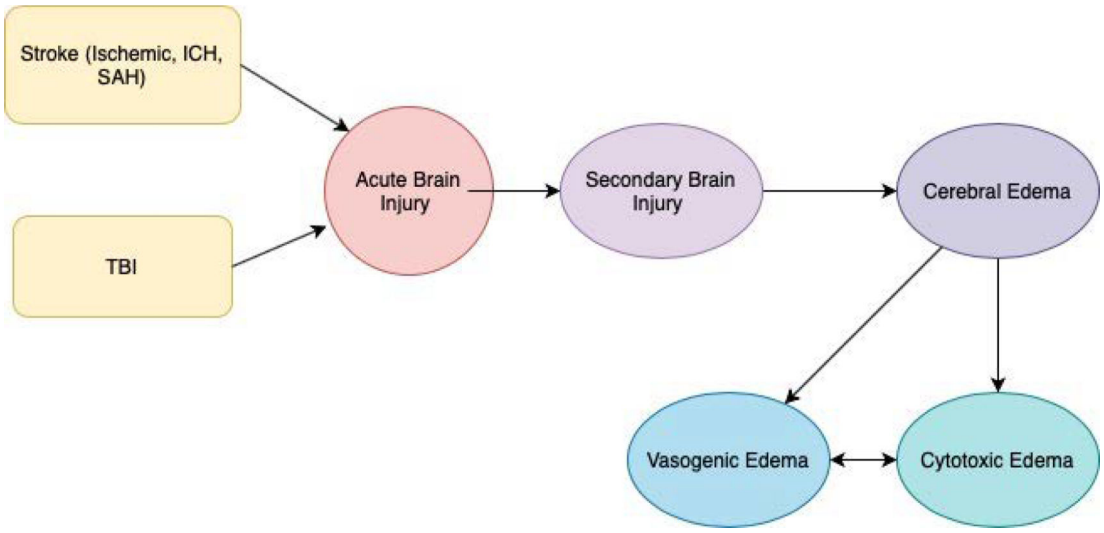

Figure 2.

Pathophysiological cascade leading to brain edema formation.

ICH – Intracerebral Hemorrhage, SAH – subarachnoid hemorrhage, TBI – traumatic brain injury

Table 1.

Open access data resources

Ref.	Name	Website	Resource type	Sample size	Access type
[81]	UK Biobank	https://www.ukbiobank.ac.uk/	Observational study	500,000	Open
[79]	Million Veteran Program	https://www.research.va.gov/mvp/	Observational study	1 million	Restricted
[80]	All of Us	https://allofus.nih.gov/	Observational study	1 million	Open
[82]	China Kadoorie Biobank	https://www.ckbiobank.org/	Observational study	500,000	Restricted
[78]	dbGAP	https://www.ncbi.nlm.nih.gov/gap/	Repository	-	Open
[83]	EGA	https://ega-archive.org/	Repository	-	Open
[84]	MIMIC-III	https://mimic.physionet.org/	Database	61,532	Open
[85]	eICU-CRD	https://eicu-crd.mit.edu/	Database	200,000	Open

Acronyms: UK = United Kingdom, dbGAP = Database of Genotypes and Phenotypes, EGA = European Genome-phenome Archive, MIMIC-III = Medical Information Mart for Intensive Care-III, eICU-CRD = eICU Collaborative Research Database.

Table 2.

Genes involved in the pathophysiology of brain edema.

Gene	Principal role	Other diseases related	Potential mechanism of edema formation
APOE	lipid transport and metabolism [46]	cognitive decline, dementia, and Alzheimer's disease [87, 91], arteriosclerosis, traumatic brain injury, and intracerebral hemorrhage [82, 86, 88]	inflammatory response that disrupts the BBB and contributes to vasogenic edema after acute brain injury [92]
Hp	acute-phase response and antioxidant role by binding and neutralizing hemoglobin in the blood [72, 93]	cardiovascular events [58, 60]	oxidative stress [54], the release of inflammatory cytokines, the breakdown of BBB [55]
AQP	the main water channel found in the brain, cerebral spinal fluid production and regulation	Epilepsy [94], neurological autoimmune diseases[95], diabetes, artherosclerosis[96], cancer [97], peripheral nerves system damage[98]	cytotoxic and vasogenic edema, BBB disruption, micro-vessel damage, and neuronal death[65]
Sur1	upregulation after trauma, ischemia, and hypoxia [99]	diabetes[99], hypoglycemia[100], autoimmune diseases[101]	modulation of astrocyte swelling, a key factor in cytotoxic edema, BBB breakdown and vasogenic edema[73]

APOE – the apolipoprotein gene, *Hp*- haptoglobin gene, BBB – blood-brain barrier, *AQP*- aquaporin gene, *Sur1*- a sulfonylurea receptor and transmembrane protein gene