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Review Article

Genetics of Hydrocephalus (HC)

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Abstract: Genetic hydrocephalus is a neurological condition in which the cerebrospinal fluid (CSF) flows with subsequent and it results in enlargement of the cerebral ventricular cavities. The common cause of the congenital hydrocephalus is the variation in the L1CAM gene, and there is the narrow passage between the third and fourth ventricles. It is suggesting that hydrocephalus is more complicated than the simple CSF , and are many factors which are associated with the genetics of hydrocephalus, the major two factors are the i) telomeres proximity ii) and the more content of Adenine and Thymine [A, T] in the human CH as compared to the other nervous disorders. It is also suggesting that genetics of hydrocephalus is a crucial birth defect, and its genetics is still not completely understood, so it is the most important clinical feature. There are about 43 mutant loci associated with the animals and human hydrocephalus. Among them 9 are associated with animal models and 1 with the human. The most important hydrocephalus gene products are the growth factors, cytokines and many cellular signal pathways in the starting stage of brain development. In this study we will aim to understand the abnormalities in brain cause by the abnormal cellular functioning, and all these cellular events results congenital hydrocephalus. All these studies show that it is the mandolin type of disease with reference to the cellular, molecular genetics, physiological and pathological studies.

Keywords: Congenital hydrocephalus, CSF circulation, Neuro-developmental disorders.

INTRODUCTION

Genomic hydrocephalus is an important medical condition which is characterized by the abnormality in the flow and the disturbance during desorption of the cerebrospinal fluid [CSF] which results in the ventricular dilation [1]. Due to this disorder abnormalities in birth rate also increases [2]. Human hydrocephalus is much more complex as compared to the simple disorder of [CSF] and it also has the many other collection of heterogenous and multifactorial disorders [3]. There are also many factors cause the pathogenesis of hydrocephalus and shows adverse effects [4-6]. Hydrocephalus is a genetic defect and shows many developmental defects [7-12]. And all these are occurring after the development of brain and ventricles. The study of genetic of hydrocephalus is not completely understood yet so, it is thought that is may occur during the specific time when the neural tube is differentiated and proliferation in brain [13, 14]. It may be syndromic and non syndromic, if it is syndromic then it is difficult to explain the defective gene. And if is non syndromic then it is cause by specific faulty gene [15, 16]. Human hydrocephalus is a collection of a heterogeneous complex and multiple conditions, while being often thought of as a singular disorder. An increase in the cerebral ventricular size and/or subarachnoid space is referred to as hydrocephalus. It is brought on by an imbalance between cerebrospinal fluid production, circulation, and resorption (CSF). This does not include primary cerebral atrophy-related ventriculomegaly. CSF flow blockage is the primary cause of the majority of cases of hydrocephalus [17, 18]. Many experimental works also conducted on mice and mouse to study the genetics of hydrocephalus [19, 20]. Many factors also contribute to cause the hydrocephalus i.e, drinking of alcohol during pregnancy [21, 22], intracerebral hemorrhage, [23-25], and bombardment of X ray radiation during pregnancy [26-28].

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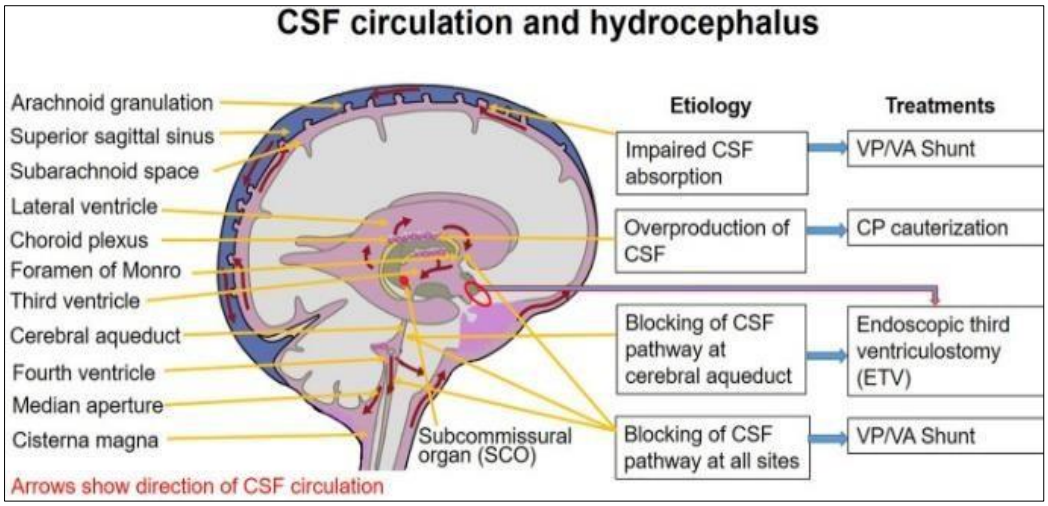


Figure 1 Hydrocephalus and therapeutic options. CP: choroid plexus; CSF: cerebrospinal fluid; EVT: endoscopic third ventriculostomy; VA: ventriculoatrial; VP: ventriculoperitoneal [28]

Genetics of HC (Hydrocephalus)

Hereditary hydrocephalus is the more common of the two types of hydrocephalus, and it is most likely the result of abnormal brain development and disrupted cellular function, emphasizing the critical roles that congenital hydrocephalus genes play during brain development. Recurrence risk for congenital hydrocephalus, excluding Xlinked hydrocephalus, is generally low [29, 30]. Congenital hydrocephalus affects 0.5-2.5:1000 total births. Congenital hydrocephalus is a collection of developmental disorders [10, 31, 32]. Determining Identifying the genetic cause of hydrocephalus is critical in determining outcome and plays a role in genetic counselling. The risk of recurrence of congenital hydrocephalus varies greatly depending on the cause [20, 33-43]. Recurrence risk for non-NTD and nonXlinked hydrocephalus is estimated to be 1- 4 percent in subsequent children. These risks will be reduced as we gain a better understanding of the genetic causes of hydrocephalus and improve genetic testing [44]. Despite shunting, the clinical presence of additional congenital malformations or cytogenetic abnormalities has a negative impact on the prognosis for intellectual development in hydrocephalus patients [45].Hydrocephalus may occur as a primary malformation or in conjunction with other complex brain malformations such as neural tube defects, X-linked hydrocephalus (part of the clinical spectrum of CRASH syndrome), or Dandy-Walker syndrome [46-48]. Hydrocephalus can also be found in genetic syndromes with multiple systemic malformations (such as occurring with chromosomal abnormalities or other mendelian disorders). Trisomy 13, trisomy 18, and trisomy 9 are the most common chromosomal abnormalities associated with congenital hydrocephalus [49, 50]. Many mammals have been observed to have hydrocephalus.

Animal Models

Animal hydrocephalus models are histopathological similar to humans and can be used to study the genetics and pathogenesis of brain damage [51-59]. It has been well documented in animal models that congenital hydrocephalus is a genetic disease in the majority of cases. In addition, many congenital hydrocephalus loci have been identified and mapped in animal models.

Mouse Model

Genetics of hydrocephalus also observed in mouse which results from the genetic deletion of Rho family guanosine triphosphatase 3 (Rnd3), and the aqueductal stenosis [60]. This [Rnd3] helps in regulation of the cell migration and cytoskeleton of the cell. Due to the deletion of the [Rnd3] gene hydrocephalus increase in size and there is the severe obstruction, as well as increase the size of third and fourth ventricle. Due to the deficiency of the Rnd3 Notch signaling activity increase and this can be resolved by stopping this Notch activity [61].

Rat Model

Rat have also been under observation, and there are about three main Texas strain related to rat hydrocephalus which are HTX, LEW/Jms, and 6-aminonicotinamide [6- AN] [62]. HTX rats cause the cerebral aqueduct closure and form hydrocephalus. The second type LEW/Jms cause defect in early age before the pulmonary maturation [63]. And the 6-AN- type of hydrocephalus is similar to walker syndrome. Among all three HTX is well studied congenital hydrocephalus, because it enlarges the ventricles during late gestation which results the cerebral aqueduct and subcommissural organ [SCO] type of abnormalities. The SCO is the key structure for the flow of CSF. By keeping view human hydrocephalic fetus also smaller SCO. SO due to the low level of SCO ventricle size in HTX rat's increase [64].

Mice Model

Congenital hydrocephalus is a polygenic trait in mice, which is develop by the presence of strain associated genetic modifiers. And it also observes that C57BL strain more common for recognizing the hydrocephalus as compared to other strains of mice [65]. Genetic background has large impact on experimental studies. E.g nm1504- or fyn deficient mice on C57BL severe hydrocephalus [66]. In L1 deficient gene there is severe hydrocephalus when exposing with C57BL/6 strain [67]. Hydrocephalus in mutant mice having Naglu least related to previous strain of C57BL/6 [68].

Human Hydrocephalus Model

In humans hydrocephalus may be related to the abnormal brain development, and when the cellular functioning is improper, so it leads to the pathogenesis of hydrocephalus [69]. It is studied that about 40% patient of hydrocephalus related to the genetic etiology [70], and there are more than 100 genes are discover which describe the hydrocephalus [71], and 5-15% genetic hydrocephalus related to the X-linked hydrocephalus [72, 73]. There are almost four pair of which cause the human hydrocephalus due to the mutation in them , the most common among them is [L1CAM] known as L1 cell adhesion molecule, and the other three are multiple PDZ domain proteins (MPDZ), and coiledcoil domain- containing protein 88c (CCDC88C), sigma 2 subunit of the adapter protein 1 complex (AP1S2), [74-76]. These genes may be expressed as autosomal or Xlinked fashion. The X-linked human gene L1CAM is located at the AP1S2 and Xq28 [77]. The mechanism of L1 gene is not known clearly. But neural cell membrane protein and L1 protein plays the important role during the development of brain [78]. When the neural adhesion start the L1 gene mediates the function of cell to cell adhesion, which cause the axon bundling, synaptogenesis, growth cone morphology, and pathfinding [79]. It also cause the agenesis of the corpus callosum, aqueduct of Silvius, fusion of thalami, nonfunctioning of corticospinal tracts [80].

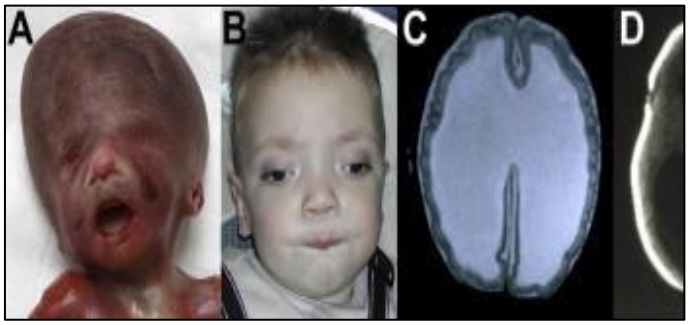
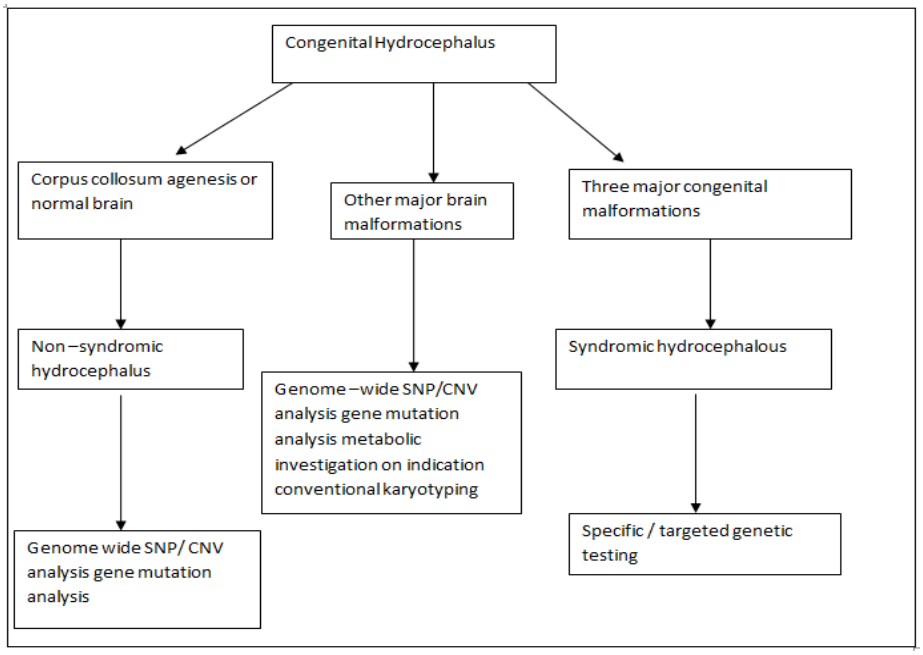


Figure 2: Patients with congenital SH. A. trisomy 9, B. 6p25 terminal deletion due to de novo unbalanced translocation 46,XY,der(6)t(6;13)(p25;q34), C. MRI scan of the brain in patient with pathogenic L1CAM gene mutation, D. CT scan of the brain in patient with Micospe [79]



Congenital hydrocephalus in clinical practice [75, 23]

Syndromic and Non Syndromic Hydrocephalus

Hydrocephalus has two forms syndromic and non syndromic [81]. Hence , no proper agreement has been made which classify genetic syndromic patient that lack the major clinically features. For example, L1CAM gene considered as both syndromic and non syndromic [82, 83]. It is prefer to distinguish between both types of syndromes in the phenotypes of clinical phenotype characterize by brain , as well as physical abnormalities. When the genetic basis and syndrome identified, then hydrocephalus are associate with syndrome i.e L1CAM link hydrocephalus.

Hydrocephalus causes: Hydrocephalus is completely extrinsic event and acting upon structure of brain. It can be idiopathic molecular syndrome identifiable in clinic. In a recent series there is about 411 infants associated with hydrocephalus, among them 175 are extrinsic cause of the condition. Most common cause is prematurity-associated intraventricular hemorrhage [84]. The other 236 patients had no clear extrinsic cause , and 28 has identifiable genetic cause syndrome. Mechanism , development , pathology, physiology of hydrocephalus: Ventricle dilation of cerebral disturbed the functioning of CFS flow which is observed in many animals, and in most cases subarachnoid space, defective development of cerebral is observed [85].

Effected individuals or patient may have severe developmental delay and the radiographic findings of hydrocephalus [86]. The developmental and morphological changes in brain ventricles have clearly studied in the three major rats models , which are suffering from congenital hydrocephalus and these rats are mutant by LEW/Jms ,HTX, 6- aminonicotinamide (6-AN)- induced. This study reveal that it is related to the Walker syndrome. The major morphological and developmental changes in the brain ventricular system have been well studied in three major rat models of congenital hydrocephalus which are 6-aminonicotinamide (6-AN)-induced, LEW/Jms and HTX mutant rats. This study reveal that it is related to the Walker syndrome. The two models of gene , LEW/Jms and HTX mutant rat were selected as identical for studying the genetics of hydrocephalus in postnatal duration. It is also studied that LEW/Jms rats shows minute aqueductal stenosis, but before the pulmonary maturation it has been reveals the hydrocephalus [87].

However, in HTX rats fetus shows the secondary closure of aqueduct , which cause the defects in hypothalamus [88,89] and cell proliferation, and apoptotic cell death [90,91]. So , the HTX rat shows the loss of secretory cells of SCO. Due to the reduction of SCO glycoprotein proceed the aqueduct close and the lateral side of ventricles in HTX rat expand [92,93]. Although, it has also reveal that microglia (resident mononuclear phagocytes of the brain) in the brain of animals hydrocephalus models. In one experiment brain tissues were studiedwhich are taken from ten hydrocephalic and ten non hydrocephalic and controls with immunohistochemically , antibodies against MHC and CD68 antigen [94]. The lectin histochemistry was done with tomato lectin. The CD68 and tomato lectin shows the hydrocephalus cases which have the positive macrophages along the ependymal lining of lateral ventricles especially in the occipital horn. The macrophage response known by the ependymal lining of ventricles and around its nearby area shows the sensitivity of both age of fetus and hydrocephalus [95]. The molecular etiology of hydrocephalus: The disruption of neural cell membrane proteins, which play an important role during brain development, is one of the possible mechanisms leading to the pathogenesis of hydrocephalus. The L1 protein, which is encoded by the human Xlinked hydrocephalus gene, is a member of the immunoglobulin superfamily of neural cell adhesion molecules [96].

It is expressed in neurons and Schwann cells and appears to be required for brain development and function. Hirschsprung's disease (HSCR) is distinguished by the absence of ganglion cells in the distal bowel and the presence of hypertrophic nerve trunks [97]. Several patients with X-linked hydrocephalus and HSCR have been reported to have a mutation in the L1CAM gene. As a result, decreased L1CAM may play a role in the development of HSCR [98]. X-linked hydrocephalus is a neurological disorder characterized by aqueduct stenosis and hydrocephalus. This condition contributes to male predominance in congenital hydrocephalus. It is estimated that X-linked hydrocephalus accounts for about 2-5% of all non syndromic congenital hydrocephalus [U5]. Since the early 1960s, this condition has been recognized. The most common genetic form of congenital hydrocephalus, X-linked hydrocephalus, affects approximately 1:30000 male births [99].

The disease gene is passed down from mothers to sons. In addition to varying degrees of hydrocephalus, there may be hypoplasia of the corticospinal tracts (characterized by the absence of medullary pyramids), corpus callosal agenesis, hypoplasia of the anterior cerebellar vermis, and thalami fusion. Aspects of Environment and risk factors attained through environmental forces in the pathogenesis of Hydrocephalus: With observance to the environment and acquired elements, alcohol intake, diabetes, hypertension, inflammation, aging, and sleep apnea are curious risk factors for iNPH development [100-102].Alcohol intake indicate a correlation with iNPH development possibly due to ethanolinduced decrease in beating frequency of motile cilia and consequent abnormality on the ependymal cells of ventricles [103, 104] .Although iNPH patients present with increased bitterness of diabetes, the causal relationship has not been concluded [105].The

hypothetical pathogenesis may be attributed to high concentration of sugar and increased fluid viscosity in CSF.

The studies have shown the increased fluid viscosity increases the shear stress on the ventricular wall and increases the dilatation of the vasculature [106]. Hypertension and aging were also known to be potential risk factors for ventriculomegaly. The underlining mechanism was considered to be related to the decline in the glymphatic function [107]. As previously discussed, obstructive sleep apnea was commonly associated with iNPH, [108] and up to 90% of iNPH patients suffered from obstructive sleep [109]. In addition to the previously discussed pathogenic process, obstructive sleep apnea decreases oxygen intake and decreases venous return to the heart, resulting in further retrograde intracranial venous hypertension and ventricular enlargement [110].

CONCLUSION

The genetic study of hydrocephalus in humans is restricted, many hydrocephalus genetic loci have been found in animal models. This method provides researchers with important insights into the molecular etiology of damaged brains during hydrocephalus development. Furthermore, hereditary abnormalities affecting motile cilia create the groundwork for the development of hydrocephalus, and acquired risk factors enhance the development of hydrocephalus [111]. Furthermore, glymphatic system malfunction and sleep problems are becoming attractive themes in research of the pathophysiology and potential therapeutic management of hydrocephalus, particularly in iNPH. As a result, these types of investigations will aid in gaining a better knowledge of the molecular process behind hydrocephalus and will provide vital insights into the etiology of iNPH and other neurological illnesses. Other than altered CSF circulation [112] and resorption, new processes discovered via genetic research may assist to explain why patients with hydrocephalus may still undergo symptomatic progression despite functioning shunts. Finally, such knowledge will be beneficial in improving patient care in a variety of ways, as well as guiding best treatment decisions for patients as early as feasible. To summarize, several genetic loci of hydrocephalus have been defined in animal models, laying the groundwork for a better knowledge of the molecular etiology of hydrocephalus; yet, genetic study of hydrocephalus in humans remains restricted. Animal models' histopathological similarities can be used to better understand the genetics and etiology of human hydrocephalus. This review of molecular etiologies reveals a wide range of pathogenetic mechanisms. Perturbation of practically any chemical involved in early brain development, as well as sequential regulation of cerebrospinal fluid dynamics, could contribute to the aetiology of congenital hydrocephalus.

Future Prospects

It is critical to recognise that molecular genetics an , it is the only current scientific approach to studying hydrocephalus that addresses the common concern about whether an observed phenomenon is a result or a cause. Despite our understanding of hydrocephalus genetics in animal models, we know very little about the genetic and molecular mechanisms that cause human hydrocephalus. Without this information, it is impossible to say whether the pathogenesis of human hydrocephalus is comparable to that seen in animal models, and extrapolating data from animal models to humans is impractical. Attempts to identify genetic variants associated with susceptibility to genetic diseases rely on three major approaches: pedigree and sibpair linkage analysis, population association studies, and genome-wide association studies. The distinctions between these study designs reflect their origins in biological versus epidemiological traits. It would be extremely difficult, as with most common diseases, to identify and recruit large pedigrees in hydrocephalus that demonstrate hereditary transmission of this condition.

REFERENCES

1. Schurr, P. H., McLaurin, R. L., & Ingraham, F. D. (1953). Experimental Studies on the Stoll, C., Alembik, Y., Dott, B., & Roth, M. P. (1992). An epidemiologic study of environmental and genetic factors in congenital hydrocephalus. *European journal of epidemiology*, 8(6), 797-803.
2. Schurr, P. H., McLaurin, R. L., & Ingraham, F. D. (1953). Experimental Studies on the Circulation of the Cerebrospinal Fluid: And Methods of Producing Communicating Hydrocephalus in the Dog. *Journal of neurosurgery*, *10*(5), 515-525.
3. Czosnyka, M., Czosnyka, Z., Schmidt, E. A., & Momjian, S. (2003). Cerebrospinal fluid production. *Journal of neurosurgery*, 99(1), 206-207.
4. Willems, P. J. (1988). Heterogeneity in familial hydrocephalus. *American Journal of Medical Genetics*, 31(2), 471-473.
5. Price, J. R., & Horne, B. M. (1968). Family history indicating hereditary factors in hydrocephalus. *Mental Retardation*, 6(5), 40.
6. Tipton, R. E. (1971). Familial hydrocephalus. *Birth Defects Original Article Series*, 7(1), 231-231.
7. Mori, K., Shimada, J., Kurisaka, M., Sato, K., & Watanabe, K. (1995). Classification of hydrocephalus and outcome of treatment. *Brain and Development*, 17(5), 338-348.
8. Mori, K. (1990). Hydrocephalus— revision of its definition and classification with special reference to intractable infantile hydrocephalus. *Childs Nervous System*, 6(4), 198-204.
9. Mori, K. (1995). Current concept of hydrocephalus: evolution of new classifications. *Child's Nervous System*, 11(9), 523-531.
10. Haverkamp, F., Wölfle, J., Aretz, M., Krämer, A., Höhmann, B., Fahnenstich, H., & Zerres, K. (1999). Congenital hydrocephalus internus and aqueduct

stenosis: aetiology and implications for genetic counselling. *European journal of pediatrics*, 158(6), 474-478.
11. Chahlavi, A., El-Babaa, S. K., & Luciano, M. G. (2001). Adult-onset hydrocephalus. *Neurosurgery clinics of North America*, 12(4), 753-760.
12. Czosnyka, M., Richards, H. K., Czosnyka, Z., & Pickard, J. D. (2004). Normal-pressure hydrocephalus. *Journal of neurosurgery*, 101(6), 1083-4.
13. Adams, C., Johnston, W. P., & Nevin, N. C. (1982). Family study of congenital hydrocephalus. *Developmental Medicine & Child Neurology*, 24(5), 493-498.
14. Fernell, E., Hagberg, B., Hagberg, G., & Von Wendt, L. (1986). Epidemiology of infantile hydrocephalus in Sweden: I. Birth prevalence and general data. *Acta Pædiatrica*, 75(6), 975-981.
15. Teebi, A. S., Naguib, K. K., Opitz, J. M., & Reynolds, J. F. (1988). Autosomal recessive nonsyndromal hydrocephalus. *American journal of medical genetics*, 31(2), 467-470.
16. Partington, M. D. (2001). Congenital hydrocephalus. *Neurosurgery Clinics of North America*, 12(4), 737-42.
17. Zhang, X. J., Guo, J., & Yang, J. (2020). Cerebrospinal fluid biomarkers in idiopathic normal pressure hydrocephalus Neuroimmunol. *Neuroinflammation*, 7, 109-119.
18. Silverberg, G. D., Huhn, S., Jaffe, R. A., Chang, S. D., Saul, T., Heit, G. & Rubenstein, E. (2002). Downregulation of cerebrospinal fluid production in patients with chronic hydrocephalus. *Journal of neurosurgery*, 97(6), 1271-1275.
19. Kundishora, A. J., Singh, A. K., Allington, G., Duy, P. Q., Ryou, J., Alper, S. L., & Kahle, K. T. (2021). Genomics of human congenital hydrocephalus. *Child's Nervous System*, 37(11), 3325-3340.
20. Haverkamp, F., Wölfle, J., Aretz, M., Krämer, A., Höhmann, B., Fahnenstich, H., & Zerres, K. (1999). Congenital hydrocephalus internus and aqueduct stenosis: aetiology and implications for genetic counselling. *European journal of pediatrics*, 158(6), 474-478.
21. Akata-Haga, H., Sawada, K., Ohnishi, T., & Fukui, Y. (2004). Hydrocephalus following prenatal exposure to ethanol. *Acta neuropathologica*, 108(5), 393-398.
22. Castro-Gago, M., Novo, I., & Peña, J. (1987). Maternal alcohol ingestion and neural tube defects: observation of four brothers in a family. *Brain & development*, 9(3), 321-322.
23. Schinazi, R. F., & Yao, X. (1995). Hydrocephalus induction in mice infected with herpes simplex virus type 2 after antiviral treatment. *Antiviral research*, 28(4), 291-302.
24. Stahl, W., & Kaneda, Y. (1997). Pathogenesis of murine toxoplasmic hydrocephalus. *Parasitology*, 114(3), 219-229.
25. Tsunoda, I., McCright, I. J., Kuang, L. Q., Zurbriggen, A., & Fujinami, R. S. (1997). Hydrocephalus in mice infected with a Theiler's murine encephalomyelitis virus variant. *Journal of Neuropathology & Experimental Neurology*, 56(12), 1302- 1313.
26. Aolad, H. M., Inouye, M., Hayasaka, S., Darmanto, W., & Murata, Y. (1998). Congenital hydrocephalus caused by exposure to low level X-radiation at early gestational stage in mice. *Uchu Seibutsu Kagaku*, 12(3), 256-257.
27. Aolad, H. M., Inouye, M., Darmanto, W., Hayasaka, S., & Murata, Y. (2000). Hydrocephalus in mice following Xirradiation at early gestational stage: possibly due to persistent deceleration of cell proliferation. *Journal of radiation research*, 41(3), 213-226.
28. Bay, C., Kerzin, L., & Hall, B. D. (1979). Recurrence risk in hydrocephalus. *Birth defects original article series*, 15(5C), 95-105.
29. Burton, B. K. (1979). Empiric recurrence risks for congenital hydrocephalus. *Birth Defects Original Article Series*, 15(5C), 107-115.
30. Burton, B. (1979). Recurrence risks for congenital hydrocephalus. *Clinical Genetics*, 16(1), 47-53.
31. Barros-Nunes, P., & Rivas, F. (1993). Autosomal recessive congenital stenosis of aqueduct of Sylvius. *Genetic counseling (Geneva, Switzerland)*, 4(1), 19-23.
32. Chow, C. W., McKelvie, P. A., Anderson, R. M., Phelan, E. M. D., Klug, G. L., & Rogers, J. G. (1990). Autosomal recessive hydrocephalus with third ventricle obstruction. *American journal of medical genetics*, 35(3), 310-313.
33. ABDUL-KARIM, R. A. J. A., ILIYA, F., & ISKANDAR, G. (1964). Consecutive hydrocephalus: Report of 2 cases. *Obstetrics & Gynecology*, 24(3), 376-378.
34. Game, K., Friedman, J. M., Paradice, B., & Norman, M. G. (1989). Fetal growth retardation, hydrocephalus, hypoplastic multilobed lungs, and other anomalies in 4 sibs. *American journal of medical genetics*, 33(2), 276-279.
35. Zlotogora, J., Sagi, M., & Cohen, T. (1994). Familial hydrocephalus of prenatal onset. *American journal of medical genetics*, 49(2), 202-204.
36. Zlotogora, J. (1997). Autosomal recessive diseases among Palestinian Arabs. *Journal of medical genetics*, 34(9), 765-766.
37. Zlotogora, J. (1997). Genetic disorders among Palestinian Arabs. 2. Hydrocephalus and neural tube defects. *American journal of medical genetics*, 71(1), 33-35.
38. Castro-Gago, M., Alonso, A., & EirísPuñal, J. (1996). Autosomal recessive hydrocephalus with aqueductal stenosis. *Child's Nervous System*, 12(4), 188-191.
39. Chudley, A. E., McCullough, C., & McCullough, D. W. (1997). Bilateral sensorineural deafness and hydrocephalus due to foramen of Monro obstruction in sibs: a newly described autosomal recessive disorder. *American journal of medical genetics*, 68(3), 350- 356.
40. Moog, U., Bleeker-Wagemakers, E. M., Crobach, P., Vles, J. S. H., & Schrander-Stumpel, C. T. R. M. (1998). Sibs with Axenfeld-Rieger anomaly, hydrocephalus, and leptomeningeal calcifications: A

new autosomal recessive syndrome. *American journal of medical genetics*, 78(3), 263-266.
41. Chalmers, R. M., Andreae, L., Wood, N. W., RAJ, R. D., & Casey, A. T. H. (1999). Familial hydrocephalus. *Journal of Neurology, Neurosurgery & Psychiatry*, 67(3), 410-411.
42. Hamada, H., Watanabe, H., Sugimoto, M., Yasuoka, M., Yamada, N., & Kubo, T. (1999). Autosomal recessive hydrocephalus due to congenital stenosis of the aqueduct of sylvius. *Prenatal diagnosis*, 19(11), 1067-1069.
43. Castro-Gago, M., Iglesias-Diz, M., Ucieda-Somoza, R., Silva-Villar, I., Codesido-Lopez, J., Viso-Lorenzo, A.,... & Eiris-Punal, J. (2001). Congenital hydranencephalic-hydrocephalic syndrome with proliferative vasculopathy: a possible relation with mitochondrial dysfunction. *Journal of Child Neurology*, 16(11), 858-862.
44. Verhagen, W. I., Bartels, R. H., Fransen, E., Van Camp, G., Renier, W. O., & Grotenhuis, J. A. (1998). Familial congenital hydrocephalus and aqueduct stenosis with probably autosomal dominant inheritance and variable expression. *Journal of the neurological sciences*, 158(1), 101-105.
45. Vincent, C., Kalatzis, V., Compain, S., Levilliers, J., Slim, R., Graia, F.,... & Petit, C. (1994). A proposed new contiguous gene syndrome on 8q consists of Branchio-Oto-Renal (BOR) syndrome, Duane syndrome, a dominant form of hydrocephalus and trapeze aplasia; implications for the mapping of the BOR gene. *Human molecular genetics*, 3(10), 1859-1866.
46. Jouet, M., Rosenthal, A., MacFarlane, J., Kenwrick, S., & Donnai, D. (1993). A missense mutation confirms the L1 defect in X–linked hydrocephalus (HSAS). *Nature genetics*, 4(4), 331- 331.
47. Owler, B. K., & Pickard, J. D. (2001). Normal pressure hydrocephalus and cerebral blood flow: a review. *Acta Neurologica Scandinavica*, 104(6), 325-342.
48. Edwards, R. J., Dombrowski, S. M., Luciano, M. G., & Pople, I. K. (2004). Chronic hydrocephalus in adults. *Brain pathology*, 14(3), 325-336.
49. Katsuragi, S., Teraoka, K., Ikegami, K., Amano, K., Yamashita, K., Ishizuka, K., & Miyakawa, T. (2000). Late onset X-linked hydrocephalus with normal cerebrospinal fluid pressure. *Psychiatry and clinical neurosciences*, 54(4), 487-492.
50. Portenoy, R. K., Berger, A., & Gross, E. (1984). Familial occurrence of idiopathic normal-pressure hydrocephalus. *Archives of neurology*, 41(3), 335-337.
51. ROBERTSON, J. M., SAMANKOVA, L., & INGALLS, T. H. (1966). Hydrocephalus and cleft palate in an inbred rabbit colony. *Journal of Heredity*, 57(4), 142-148.
52. Mori, A. (1968). Hereditary hydrocephalus in C57BL mouse. *No to shinkei= Brain and nerve*, 20(7), 695-700.
53. Silson, M., & Robinson, R. (1969). Hereditary hydrocephalus in the cat. *The Veterinary record*, 84(19), 477.
54. Taraszewska, A., & ZaleskaRutczyńska, Z. (1970). Congenital hydrocephalus in mice of strains BN and C57BL. *Polish medical journal*, 9(1), 187-195.
55. YOON, C. H., & SLANEY, J. (1972). Hydrocephalus: a new mutation in the Syrian golden hamster. *Journal of Heredity*, 63(6), 344-346.
56. Yoon, C. H., & Peterson, J. S. (1977). Linkage group II in the Syrian hamster: Linkage between hydrocephalus and cream coat color. *Journal of Heredity*, 68(6), 418-418.
57. LEIPOLD, H. W. (1977). Genetic defects in cattle: transmission and control.
58. Park, A. W., & NowosielskiSlepowron, B. J. (1979). Hydrocephalus in the laboratory rat. *Acta Morphologica Neerlandoscandinavica*, 17(3), 191-207.
59. Kohn, D. F., Chinookoswong, N., & Chou, S. M. (1984). Animal model of human disease. Congenital hydrocephalus. *The American journal of pathology*, 114(1), 184.
60. Lin, X., Liu, B., Yang, X., Yue, X., Diao, L., Wang, J., & Chang, J. (2013). Genetic deletion of Rnd3 results in aqueductal stenosis leading to hydrocephalus through up-regulation of Notch signaling. *Proceedings of the National Academy of Sciences*, 110(20), 8236-8241.
61. Zhang, J., Williams, M. A., & Rigamonti, D. (2006). Genetics of human hydrocephalus. *Journal of neurology*, 253(10), 1255-1266.
62. Oi, S., Sato, O., Yamada, H., & Matsumoto, S. (1996). Experimental models of congenital hydrocephalus and comparable clinical problems in the fetal and neonatal periods. *Child's Nervous System*, 12(6), 292-302.
63. Somera, K. C., & Jones, H. (2002). Subcommissural organ dysfunction in H-Tx rats with early-onset hydrocephalus. European journal of pediatric surgery. *Supplement*, S45- S47.
64. Meyer, G., Carmona-Calero, E., Ban, J., Me, R., Ormazabal-Ramos, C., & Ferres-Torres, R. (1994). Alterations of the subcommissural organ in the hydrocephalic human fetal brain. *Developmental brain research*, 79(2), 316-320.
65. Sweger, E. J., Casper, K. B., ScearceLevie, K., Conklin, B. R., & McCarthy, K. D. (2007). Development of hydrocephalus in mice expressing the Gi-coupled GPCR Ro1 RASSL receptor in astrocytes. *Journal of Neuroscience*, 27(9), 2309-2317.
66. Greenstone, M. A., Jones, R. W., Dewar, A., Neville, B. G., & Cole, P. J. (1984). Hydrocephalus and primary ciliary dyskinesia. *Archives of disease in childhood*, 59(5), 481-482.
67. Lindeman, G. J., Dagnino, L., Gaubatz, S., Xu, Y., Bronson, R. T., Warren, H. B., & Livingston, D. M. (1998). A specific, nonproliferative role for E2F-5 in choroid plexus function revealed by gene targeting. *Genes & development*, 12(8), 1092-1098.
68. Gorden, N. T., Arts, H. H., Parisi, M. A., Coene, K. L., Letteboer, S. J., van Beersum, S. E., & Doherty, D. (2008). CC2D2A is mutated in Joubert syndrome and interacts with the ciliopathy-associated basal body protein CEP290. *The American Journal of Human Genetics*, 83(5), 559-571

69. Stoll, C., Alembik, Y., Dott, B., & Roth, M. P. (1992). An epidemiologic study of environmental and genetic factors in congenital hydrocephalus. *European journal of epidemiology*, 8(6), 797-803.
70. Haverkamp, F., Wölfle, J., Aretz, M., Krämer, A., Höhmann, B., Fahnenstich, H., & Zerres, K. (1999). Congenital hydrocephalus internus and aqueduct stenosis: aetiology and implications for genetic counselling. *European journal of pediatrics*, 158(6), 474-478.
71. Kousi, M., & Katsanis, N. (2016). The genetic basis of hydrocephalus. *Annual review of neuroscience*, 39, 409-435.
72. Haverkamp, F., Wölfle, J., Aretz, M., Krämer, A., Höhmann, B., Fahnenstich, H., & Zerres, K. (1999). Congenital hydrocephalus internus and aqueduct stenosis: aetiology and implications for genetic counselling. *European journal of pediatrics*, 158(6), 474-478.
73. Zhang, J., Williams, M. A., & Rigamonti, D. (2006). Genetics of human hydrocephalus. *Journal of neurology*, 253(10), 1255-1266.
74. Adle-Biassette, H., Saugier-Veber, P., Fallet-Bianco, C., Delezoide, A. L., Razavi, F., Drouot, N., & Laquerrière, A. (2013). Neuropathological review of 138 cases genetically tested for X-linked hydrocephalus: evidence for closely related clinical entities of unknown molecular bases. *Acta neuropathologica*, 126(3), 427-442.
75. Tarpey, P. S., Stevens, C., Teague, J., Edkins, S., O'Meara, S., Avis, T., ... & Raymond, F. L. (2006). Mutations in the gene encoding the Sigma 2 subunit of the adaptor protein 1 complex, AP1S2, cause X-linked mental retardation. *The American Journal of Human Genetics*, 79(6), 1119-1124.
76. Al-Dosari, M. S., Al-Owain, M., Tulbah, M., Kurdi, W., Adly, N., AlHemidan, A., ... & Alkuraya, F. S. (2013). Mutation in MPDZ causes severe congenital hydrocephalus. *Journal of medical genetics*, 50(1), 54-58.
77. Wang, R., Chen, H., Wang, X., Huang, S., Xie, A., & Wu, X. (2021). Prenatal diagnosis of a nonsense mutation in the L1CAM gene resulting in congenital hydrocephalus: A case report and literature review. *Experimental and Therapeutic Medicine*, 22(6), 1-6.
78. Adle-Biassette, H., Saugier-Veber, P., Fallet-Bianco, C., Delezoide, A. L., Razavi, F., Drouot, N., ... & Laquerrière, A. (2013). Neuropathological review of 138 cases genetically tested for X-linked hydrocephalus: evidence for closely related clinical entities of unknown molecular bases. *Acta neuropathologica*, 126(3), 427-442.
79. Okamoto, N., Del Maestro, R., Valero, R., Monros, E., Poo, P., Kanemura, Y., & Yamasaki, M. (2004). Hydrocephalus and Hirschsprung's disease with a mutation of L1CAM. *Journal of human genetics*, 49(6), 334-337.
80. Willems, P. J., Brouwer, O. F., Dijkstra, I., Wilmink, J., Opitz, J. M., & Reynolds, J. F. (1987). X-linked hydrocephalus. *American journal of medical genetics*, 27(4), 921-928.
81. Schrander-Stumpel, C., & Fryns, J. P. (1998). Congenital hydrocephalus: nosology and guidelines for clinical approach and genetic counselling. *European journal of pediatrics*, 157(5), 355-362.
82. Verhagen, J. M. A., Schrander-Stumpel, C. T. R. M., Krapels, I. P. C., de DieSmulders, C. E. M., Van Lint, F. H. M., Willekes, C., ... & Frints, S. G. M. (2011). Congenital hydrocephalus in clinical practice: a genetic diagnostic approach. *European journal of medical genetics*, 54(6), e542-e547.
83. Bruni, J. E., Del Bigio, M. R., Cardoso, E. R., & Persaud, T. V. N. (1988). Hereditary hydrocephalus in laboratory animals and humans. *Experimental pathology*, 35(4), 239-246.
84. Jones, H. C., Carter, B. J., Depelteau, J. S., Roman, M., & Morel, L. (2001). Chromosomal linkage associated with disease severity in the hydrocephalic HTx rat. *Behavior genetics*, 31(1), 101- 111.
85. Sheen, V. L., Basel-Vanagaite, L., Goodman, J. R., Scheffer, I. E., Bodell, A., Ganesh, V. S., & Walsh, C. A. (2004). Etiological heterogeneity of familial periventricular heterotopia and hydrocephalus. *Brain and Development*, 26(5), 326-334.
86. Miyan, J. A., Khan, M. I., Kawarada, Y., Sugiyama, T., & Bannister, C. M. (1998). Cell death in the brain of the HTx rat. *European Journal of Pediatric Surgery*, 8(S 1), 43-48.
87. Draper, C. E., Owen-Lynch, P. J., Bannister, C. M., & Miyan, J. (2001). Proliferation of cerebral cortical cells from the hydrocephalic HTx rat: an in vitro study. *European Journal of Pediatric Surgery. Supplement*, 11(1), S51-S52.
88. Mashayekhi, F., Bannister, C. M., & Miyan, J. A. (2001). Failure in cell proliferation in the germinal epithelium of the HTx rats. *European Journal of Pediatric Surgery Supplement*, 11(1), S57-S59.
89. Somera, K. C., & Jones, H. C. (2004). Reduced subcommissural organ glycoprotein immunoreactivity precedes aqueduct closure and ventricular dilatation in H-Tx rat hydrocephalus. *Cell and tissue research*, 315(3), 361-373.
90. Ulfig, N., Bohl, J., Neudörfer, F., & Rezaie, P. (2004). Brain macrophages and microglia in human fetal hydrocephalus. *Brain and Development*, 26(5), 307-315.
91. Chae, T. H., Kim, S., Marz, K. E., Hanson, P. I., & Walsh, C. A. (2004). The hyh mutation uncovers roles for αSnap in apical protein localization and control of neural cell fate. *Nature genetics*, 36(3), 264-270.
92. Kondziella, D., Qu, H., Lüdemann, W., Brinker, T., Sletvold, O., & Sonnewald, U. (2003). Astrocyte metabolism is disturbed in the early development of experimental hydrocephalus. *Journal of neurochemistry*, 85(1), 274-281.
93. Takano, T., Mekata, Y., Yamano, T., & Shimada, M. (1993). Early ependymal changes in experimental hydrocephalus after mumps virus inoculation in hamsters. *Acta neuropathologica*, 85(5), 521-525.
94. Takano, T., Rutka, J. T., & Becker, L. E. (1996). Overexpression of nestin and vimentin in ependymal cells in hydrocephalus. *Acta neuropathologica*, 92(1), 90-97.
95. Jiménez, A. J., Tomé, M., Páez, P., Wagner, C., Rodríguez, S., FernándezLlebrez, P., & Pérez-Fígares, J. M. (2001). A programmed ependymal denudation

precedes congenital hydrocephalus in the hyh mutant mouse. *Journal of Neuropathology & Experimental Neurology*, 60(11), 1105- 1119.
96. Wagner, C., Batiz, L. F., Rodríguez, S., Jiménez, A. J., Páez, P., Tomé, M., & Rodríguez, E. M. (2003). Cellular mechanisms involved in the stenosis and obliteration of the cerebral aqueduct of hyh mutant mice developing congenital hydrocephalus. *Journal of Neuropathology & Experimental Neurology*, 62(10), 1019-1040.
97. Ibañez-Tallon, I., Pagenstecher, A., Fliegauf, M., Olbrich, H., Kispert, A., Ketelsen, U. P., & Omran, H. (2004). Dysfunction of axonemal dynein heavy chain Mdnah5 inhibits ependymal flow and reveals a novel mechanism for hydrocephalus formation. *Human molecular genetics*, 13(18), 2133-2141.
98. Sakata-Haga, H., Sawada, K., Ohnishi, T., & Fukui, Y. (2004). Hydrocephalus following prenatal exposure to ethanol. *Acta neuropathologica*, 108(5), 393-398.
99. Kahle, K. T., Kulkarni, A. V., Limbrick Jr, D. D., & Warf, B. C. (2016). Hydrocephalus in children. *The lancet*, 387(10020), 788-799.
100. Omran, A. J. A., Saternos, H. C., Althobaiti, Y. S., Wisner, A., Sari, Y., Nauli, S. M., & AbouAlaiwi, W. A. (2017). Alcohol consumption impairs the ependymal cilia motility in the brain ventricles. *Scientific reports*, 7(1), 1-8.
101. Holth, J. K., Fritschi, S. K., Wang, C., Pedersen, N. P., Cirrito, J. R., Mahan, T. E., ... & Holtzman, D. M. (2019). The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science*, 363(6429), 880-884.
102. Ghaffari-Rafi, A., Gorenflo, R., Hu, H., Viereck, J., & Liow, K. (2020). Role of psychiatric, cardiovascular, socioeconomic, and demographic risk factors on idiopathic normal pressure hydrocephalus: a retrospective casecontrol study. *Clinical Neurology and Neurosurgery*, 193, 105836.
103. Zhang, X. J., Guo, J., & Yang, J. (2020). Cerebrospinal fluid biomarkers in idiopathic normal pressure hydrocephalus. Neuroimmunol. *Neuroinflammation*, 7, 109-119.
104. Yamada, S., Ishikawa, M., & Nozaki, K. (2021). Exploring mechanisms of ventricular enlargement in idiopathic normal pressure hydrocephalus: a role of cerebrospinal fluid dynamics and motile cilia. *Fluids and Barriers of the CNS*, 18(1), 1-11.
105. Omran, A. J. A., Saternos, H. C., Althobaiti, Y. S., Wisner, A., Sari, Y., Nauli, S. M., & AbouAlaiwi, W. A. (2017). Alcohol consumption impairs the ependymal cilia motility in the brain ventricles. *Scientific reports*, 7(1), 1-8.
106. Ghaffari-Rafi, A., Gorenflo, R., Hu, H., Viereck, J., & Liow, K. (2020). Role of psychiatric, cardiovascular, socioeconomic, and demographic risk factors on idiopathic normal pressure hydrocephalus: a retrospective casecontrol study. *Clinical Neurology and Neurosurgery*, 193, 105836.
107. Hudson, M., Nowak, C., Garling, R. J., & Harris, C. (2019). Comorbidity of diabetes mellitus in idiopathic normal pressure hydrocephalus: a systematic literature review. *Fluids and Barriers of the CNS*, 16(1), 1-6.
108. Räsänen, J., Huovinen, J., Korhonen, V. E., Junkkari, A., Kastinen, S., Komulainen, S., ... & Leinonen, V. (2020). Diabetes is associated with familial idiopathic normal pressure hydrocephalus: a case–control comparison with family members. *Fluids and Barriers of the CNS*, 17(1), 1-11.
109. Hudson, M., Nowak, C., Garling, R. J., & Harris, C. (2019). Comorbidity of diabetes mellitus in idiopathic normal pressure hydrocephalus: a systematic literature review. *Fluids and Barriers of the CNS*, 16(1), 1-6.
110. Ringstad, G., & Eide, P. K. (2020). Cerebrospinal fluid tracer efflux to parasagittal dura in humans. *Nature communications*, 11(1), 1-9.
111. Luciano, M. G., Dombrowski, S. M., Qvarlander, S., El-Khoury, S., Yang, J., Thyagaraj, S., & Loth, F. (2017). Novel method for dynamic control of intracranial pressure. *Journal of neurosurgery*, 126(5), 1629-1640.
112. Jones, H. C., Harris, N. G., Rocca, J. R., & Andersohn, R. W. (2000). Progressive tissue injury in infantile hydrocephalus and prevention/reversal with shunt treatment. *Neurological research*, 22(1), 89-96.

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