Scientific Research Publishing

Open Journal of Pathology, 2026, 16(4), 202-213
https://www.scirp.org/journal/ojpathology
ISSN Online: 2164-6783
ISSN Print: 2164-6775

Concurrent Myelomeningocele and Hydrocephalus in a 55-Year-Old Female: Genetic Insights

Andrey Frolov, Carl Lee, Carley Olson, Daniel T. Daly*

Center for Anatomical Science and Education, Department of Surgery, Saint Louis University School of Medicine, St. Louis, MO, USA
Email: *daniel.daly@health.slu.edu

How to cite this paper: Frolov, A., Lee, C., Olson, C. and Daly, D.T. (2026) Concurrent Myelomeningocele and Hydrocephalus in a 55-Year-Old Female: Genetic Insights. *Open Journal of Pathology*, **16**, 202-213.
https://doi.org/10.4236/ojpathology.2026.164021

Received: August 4, 2026
Accepted: September 13, 2026
Published: September 16, 2026

Abstract

Spina bifida (SB) is the most common congenital malformation of the central nervous system (CNS), which develops as a result of disrupted primary neurulation and neural tube closure. Myelomeningocele (MMC) is the most severe SB form and belongs to a larger group of congenital malformations known as neural tube defects (NTDs). MMC occurs when a portion of the spinal cord or nerves protrudes from an opening in the spine and may or may not be covered by meninges. MMC can be associated with hydrocephalus (HC), Arnold-Chiari II malformation, bowel and bladder dysfunction, lower limb paralysis, and pain syndromes. Despite many studies suggesting possible MMC causes such as folic acid deficiency, genetic disorders, ethnicity, and maternal health characteristics, the mechanism of MMC, particularly its concurrence with HC, is still unclear. To address such shortcomings, the whole exome sequencing (WES) of cadaveric DNA procured from the body of a 55-year-old female with concurrent MMC and HC was performed on the Illumina next-generation sequencing (NGS) platform. The bioinformatics analysis of WES data yielded 84 rare (minor allele frequency, MAF ≤ 0.01) pathologic/deleterious genetic variants, with few of the affected genes being previously linked to NTD/MMC or HC. The most interesting such genes were *ALDH1L1* and *DNAAF1* because they have been previously reported to be associated with both NTD/MMC and HC. The great extent of HC association with MMC raises a question of whether the *ALDH1L1* and *DNAFF1* mutations could, at least in some cases, underline the concurrent MMC and HC in humans.

Keywords

Spina Bifida, Myelomeningocele, Hydrocephalus, Whole Exome Sequencing,

Next Generation Sequencing, Aldehyde Dehydrogenase 1 Family Member L1, Dynein Axonemal Assembly Factor 1

1. Introduction

Spina bifida (SB) is the most common birth defect of the central nervous system (CNS) and is a member of a larger group of congenital malformations known as neural tube defects (NTDs) [1]. NTDs affect approximately 4 people per 10,000 live births in the United States, but worldwide, it is about 5 times more likely to occur [2] [3]. The probability of an individual being affected by SB has been shown to be different between ethnic groups, such as Caucasians being less likely than Hispanics to experience SB but more likely than African Americans in the United States [4] [5]. While compatible with life, SB contributes to increased mortality rates for infants and lifelong disability for those who survive [1] [6].

NTDs are caused by a disruption of the normal process of neurulation, the severity and type of which depend on the location of this disruption. SB has three major forms: spina bifida occulta, closed neural tube defects, and spina bifida aperta. Spina bifida occulta is the least severe form, with no visible external malformation, only vertebral malformation. Closed neural tube defects cover a range of conditions that usually require corrective surgery and involve malformations of the bone, fat, and connective tissue of the spine and spinal cord. Spina bifida aperta refers to two distinct subtypes of SB, namely meningocele and myelomeningocele (MMC). Meningocele is a significant malformation of the vertebral column resulting in the meninges protruding from the spine and forming a sac filled with cerebrospinal fluid. MMC is the severest and the most clinically relevant form of SB, which is presented by a portion of the spinal cord or cauda equina extending out of a lesion in the vertebral column, which may or may not be covered by meninges [1] [4] [7].

SB etiology is complex and includes both genetic and nongenetic factors. As to the former, despite the SB inheritance pattern in humans being quite diverse, there is strong evidence that multiple genes may be involved, with some of the prominent genes—*VANGL1*, *VANGL2*, *FUZ*, *CELSR1*, and *TBXT*—having autosomal dominant inheritance [1]. Yet the SB recurrence patterns provide a clear indication that the SB trait is polygenic because it is underpinned by a combination of multiple genes and their respective multiple variants [8]. The most important nongenetic SB risk factors include maternal diabetes, obesity, and hyperthermia, deficiencies in folate, zinc, and B12, as well as certain antiepileptic drugs such as valproic acid [1].

MMC's almost exclusive concurrence with hydrocephalus (HC) is one of its most notable features, as HC was present in most SB aperta (MMC) cases and absent in all SB occulta cases. [9]. Such MMC and HC concurrence has a strong clinical significance because when assessed independently, the debilitating threat

of HC was comparable to that of MMC [10]. Despite a significant impact of concurrent MMC and HC on the patients' well-being, where HC alone could be an acutely life-threatening condition [11] [12], little is known about the genetic underpinnings of MMC and HC concurrence. To address this concurrent presentation, we performed a postmortem genetic screening of a 55-year-old female with a history of MMC and HC using whole exome sequencing of the respective DNA on the next-generation sequencing (NGS) platform. The results obtained highlight *ALDH1L1* and *DNAAF1* as potential genetic risk factors for the MMC and HC concurrence in humans.

2. Methods

2.1. Human Cadaveric Body Procurement

The body of a 55-year-old female was received through the Saint Louis University (SLU) Gift Body Program with signed informed consent. The self-reported medical history included surgical correction of open SB, urinary diversion (Kock pouch), kidney disease, HC (shunt removed at age 5), and seizures. The body was embalmed through the common carotid artery with a solution (1:1 ratio) of water and a mixture containing isopropyl alcohol (52%), ethylene glycol (24%), phenol (17%), formaldehyde (6%), and methanol (1%).

2.2. Anatomical Dissection

The cadaver was placed in the prone position, and a midline incision was made from the external occipital protuberance to the intergluteal cleft. The skin, subcutaneous fat, superficial and deep back muscles were dissected to expose the thoracic, lumbar, and sacral vertebrae. A laminectomy was then performed to expose the spinal canal expanding from the thoracic region as far inferiorly as possible. When supine, a midline abdominal incision and a transverse incision were made to reflect the anterior abdominal wall. Dissection of the abdominal cavity proceeded with cleaning of mesenteries, viscera, and scar tissue.

2.3. Genetic Analysis

The postmortem genetic screening by WES was performed by Omega Bioservices (Norcross, GA) on the Illumina NGS platform, and the respective bioinformatics analysis was conducted by the Genome Technology Access Center (GTAC, Washington University in St. Louis, MO) as previously described [13] [14]. Specifically, DNA was extracted from the tibia by the Paleo-DNA Laboratory (Lakehead University, Thunder Bay, Ontario, Canada), and DNA quality control prior to sequencing was performed using a TapeStation. WES was conducted by employing Illumina Nextera Rapid Capture Exome (45 Mb) on the Illumina HiSeq 2500 NGS platform with the PE 2 × 100 read format and 30× coverage depth (~4.7 GB per sample). The bioinformatics analysis was performed by GTAC using its standard data analysis pipeline, which included the identification of pathological/deleterious variants using three databases: SIFT, Polyphen-2, and Provean. To minimize

false-positive detection of such variants by a single database, the rare genetic variants were further sequentially filtered through SIFT, Polyphen-2, and Provean, thereby taking advantage of these databases having unique data repositories along with their proprietary prediction algorithms for identifying pathological/deleterious genetic variants.

3. Results

3.1. Anatomical Examination

During the dissection of the deep back, a lack of posterior elements of the vertebral column was noted (Figure 1).

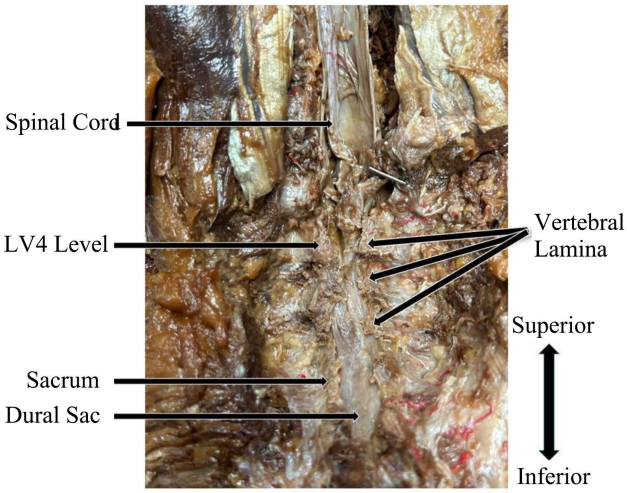

Figure 1. The lower vertebral column showcases the open midline vertebral defect associated with SB. Notice the spinal cord continues inferior to the LV2 level, which is inferior to the expected vertebral level where the conus medullaris is typically located. There was a lack of a distinct cauda equina, and it seemed that the spinal cord continued inferior to the L1/L2 level with adhesions between neural structures and the dura mater (Figure 2).

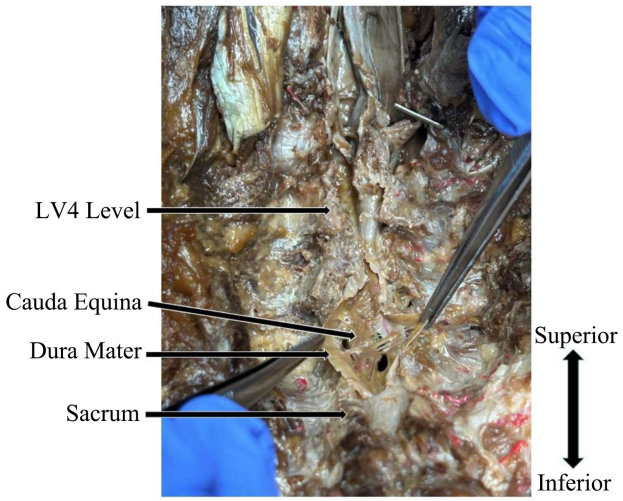

Figure 2. The lower vertebral column with the dural sac cut open. Notice the adhesion of the cauda equina to the dura.

Based on these observations and the individual's self-reported history of SB, it was concluded that the individual had MMC. During the dissection of the abdomen, a Koch's pouch was observed, consistent with the reported history of it being used in the treatment of neurogenic bladder (Figure 3). The left kidney was also noted to be absent, consistent with the medical history of kidney disease and it being removed in a prior surgery. The individual was also observed to have notably small hands and feet. Upon inspection of the head and face, the mandible was noted to protrude anteriorly in addition to a protruding forehead.

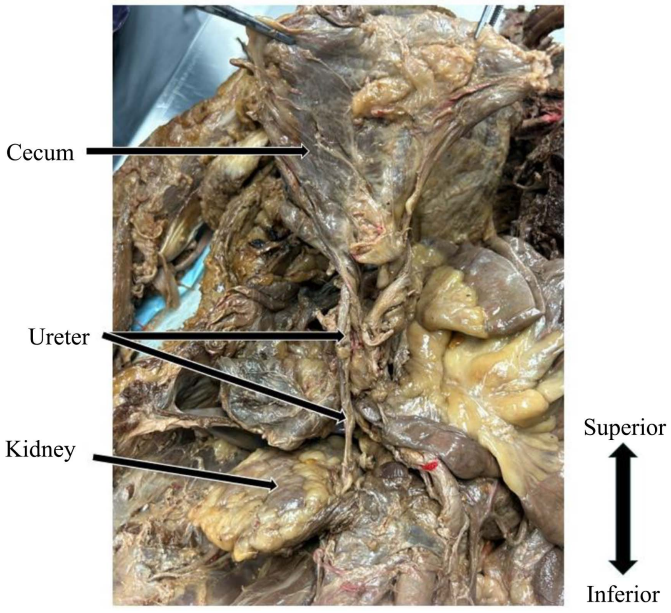

Figure 3. The abdominal cavity shows the reported history of urinary diversion. Notice the ureter directly connecting to the retracted cecum.

3.2. Genetic Screening

Following a very stringent filtering process [13] [14], 84 genes with rare (minor allele frequency, MAF ≤ 0.01) pathological/deleterious variants were identified (Table 1). Only three genes—*HLA-DRB5*, *NPIPA5*, and *PRAMEF10*—had homozygous variants, whereas the other genes had heterozygous ones.

Table 1. Genes with rare pathological/deleterious variants associated with the present case.

Gene	Protein
ALDH1L1	Aldehyde Dehydrogenase 1 Family Member L1
ANK3	Ankyrin 3
ARMH1	Armadillo-Like Helical Domain Containing 1
ASTL	Astacin-Like Metalloendopeptidase
BNIPL	BCL2 Interacting Protein Like
BUB1B	BUB1 Mitotic Checkpoint Serine/Threonine Kinase B

Continued

C22orf42	Chromosome 22 Open Reading Frame 42
CAPN11	Calpain 11
CCDC151	Coiled-Coil Domain-Containing Protein 151/Outer Dynein Arm Docking Complex Subunit 3 (ODAD3)
CCDC88B	Coiled-Coil Domain Containing 88B
CCPG1	Cell Cycle Progression 1
CDKL4	Cyclin Dependent Kinase Like 4
CDRT1	F-Box and WD Repeat Domain Containing 10B (FBXW10B)
CEP350	Centrosomal Protein 350
CES5A	Carboxylesterase 5A
COL20A1	Collagen Type XX Alpha 1 Chain
COMP	Cartilage Oligomeric Matrix Protein
CPA2	Carboxypeptidase A2
CST1	Cystatin SN
DLX3	Distal-Less Homeobox 3
DNAAF1	Dynein Axonemal Assembly Factor 1
DOCK11	Dedicator of Cytokinesis 11
DUOX2	Dual Oxidase 2
FIG4	FIG4 Phosphoinositide 5-Phosphatase
FUT1	Fucosyltransferase 1 (H Blood Group)
GJD2	Gap Junction Protein Delta 2
GUCY2F	Guanylate Cyclase 2F, Retinal
HLA-DQB1	Major Histocompatibility Complex, Class II, DQ Beta 1
HLA-DRB5	Major Histocompatibility Complex, Class II, DR Beta 5
HMX2	H6 Family Homeobox 2
HS6ST1	Heparan Sulfate 6-O-Sulfotransferase 1
IQUB	IQ Motif and Ubiquitin Domain Containing
KCNE1	Potassium Voltage-Gated Channel Subfamily E Regulatory Subunit 1
LCT	Lactase
LECT2	Leukocyte Cell-Derived Chemotaxin 2
LRP5L	LDL Receptor Related Protein 5 Like (Pseudogene)
LTBP1	Latent Transforming Growth Factor Beta Binding Protein 1
LTBP4	Latent Transforming Growth Factor Beta Binding Protein 4
MFSD14B	Major Facilitator Superfamily Domain Containing 14B
MICALL2	MICAL Like 2

Continued

MINDY1	MINDY Lysine 48 Deubiquitinase 1
MMP17	Matrix Metallopeptidase 17
MOK	MOK Protein Kinase
MSTN	Myostatin
NARF	Nuclear Pore Complex Interacting Protein Family Member A5
NCOR1	Nuclear Receptor Corepressor 1
NID2	Nidogen 2
NPHS2	NPHS2 Stomatin Family Member, Podocin
NPIPA5	Nuclear Pore Complex Interacting Protein Family Member A5
NRXN1	Neurexin 1
NXPE4	Neurexophilin and PC-Esterase Domain Family Member 4
PCDHA5	Protocadherin Alpha 5
PFAS	Phosphoribosylformylglycinamidine Synthase
PHF20L1	PHD Finger Protein 20 Like 1
PITPNM1	Phosphatidylinositol Transfer Protein Membrane Associated 1
PLXNA4	Plexin A4
PRAMEF10	PRAME Family Member 10
PRIMPOL	Primase and DNA-Dependent Polymerase
PSPH	Phosphoserine Phosphatase
PTGER2	Prostaglandin E Receptor 2
PTPN13	Protein Tyrosine Phosphatase Non-Receptor Type 13
PYGL	Glycogen Phosphorylase L
PYROXD2	Pyridine Nucleotide-Disulfide Oxidoreductase Domain 2
RANBP6	RAN Binding Protein 6
ROBO3	Roundabout Guidance Receptor 3
RTN4RL1	Reticulon 4 Receptor Like 1
SEC16A	SEC16 Homolog A, Endoplasmic Reticulum Export Factor
SEPTIN8	Septin 8
SF3B2	Splicing Factor 3b Subunit 2
SKA3	Spindle and Kinetochore Associated Complex Subunit 3
SLC24A4	Solute Carrier Family 24 Member 4
SOAT1	Sterol O-Acyltransferase 1
SPINK5	Serine Peptidase Inhibitor Kazal Type 5
TEKT5	Tektin 5

Continued

TGFB1I1	Transforming Growth Factor Beta 1 Induced Transcript 1
TOE1	Target of EGR1, Exonuclease
TOP3B	DNA Topoisomerase III Beta
TOR1B	Torsin Family 1 Member B
TRIM63	Tripartite Motif Containing 63
TTC36	Tetratricopeptide Repeat Domain 36
WNK4	WNK Lysine Deficient Protein Kinase 4
ZFP42	ZFP42 Zinc Finger Protein
ZNF846	Zinc Finger Protein 846
ZSCAN30	Zinc Finger and SCAN Domain Containing 30

a. Gene-to-protein name conversion was performed by using GeneCards.

4. Discussion

Based on the medical history of the donor and the results of the respective anatomical examination, the present case could be described as NTD/MMC concurrent with HC. The genetic screening by WES provided important insights into possible molecular mechanisms underlying NTD/MMC and HC concurrence in humans. The functional annotation of 84 genes with rare variants revealed three genes being linked to NTDs: *ALDH1L1* [15] [16], *DNAAF1* [17], and *DUOX2* [18] [19], whereas four genes have been associated with HC: *ALDH1L1* [20], *CCDC151* [21], *DNAAF1* [22], and *MOK* (GeneCards). Intriguingly, *ALDH1L1* and *DNAAF1* appear to be pleiotropic, as they were associated with both NTDs and HC traits. Therefore, a pleiotropic genetic component may underlie the NTD/MMC and HC concurrence in humans.

The mechanism(s) governing such concurrence could be linked to impaired folate metabolism (*ALDH1L1*) and/or disturbed motile cilia function (*DNAAF1*), with both respective pathologies engaging cerebrospinal fluid (CSF) as their mediator. Indeed, *ALDH1L1* is known as one of the key enzymes in folate metabolism, also serving as a folate transporter from CSF to cortical neurons and astrocytes [23]. The important role of *ALDH1L1* in the control of NTDs is underscored by the facts that folate supplementation during the post-conceptional period is known to prevent nearly 70% of NTDs in humans and by the *ALDH1L1* expression pattern during early CNS development in mice, where it was exclusively present in the midline [24]. Yet the CSF from rats with congenital HC was an *ALDH1L1*-deficient, which allowed identification of this enzyme as a specific HC marker [20].

DNAAF1, on the other hand, encodes a protein that is an essential structural component of motile cilia, and its impairment serves as a causative factor in a pathological condition known as primary ciliary dyskinesia [25]. More importantly, recently obtained evidence linked some of the *DNAAF1* mutations to NTDs in humans [17] as well as to HC development in mice [22]. These data were consistent

with a key role of motile cilia in neurodevelopment via regulation of CSF flow [26] [27]. The presence of two putative mechanisms underlying NTD/MMC and HC in the present case, one mediated by folic acid deficiency and the other by ciliopathy, raises the question of their mutual dependence. One possible answer to this question could be found in the most recent publication [28], where it has been proposed that folic acid could regulate ciliogenesis, and thereby NTDs formation, by modulating the activity of reactive oxygen species-sensitive GTPase, which is required for cilia development.

5. Conclusions

The concurrence of MMC and HC could be underlined, at least in part, by pleiotropic genes responsible for both traits, with folic acid being a key mediator in the respective pathological processes.

The prenatal genetic screening for NTD/MMC and HC could benefit from the inclusion of *ALDH1L1* and *DNAAF1* genes as potential risk factors for NTD/MMC and HC concurrence.

Limitations

Since the current report was based on a postmortem, single-patient study, the respective results should be viewed as a prerequisite to an antemortem clinical research using a large cohort of patients diagnosed with concurrent NTD/MMC and HC.

Acknowledgements

We are grateful to all individuals and their families for their invaluable contribution to the SLU Gift Body Program. We also like to thank Dr. Paul Cliften (Genome Technology Access Center, Washington University in St. Louis, St. Louis, MO, USA) for his expert assistance with the bioinformatics analysis.

Funding

This study was supported by the Center for Anatomical Science and Education, SLU School of Medicine.

Disclosure

These data were presented in part as an abstract at the Anatomy Connected Meeting on March 25, 2024.

Author Contributions

All authors have read and approved the final version of the manuscript.

Ethics Statement

Throughout the study, no living human subjects were used. The cadaveric body

used in the study was received through the SLU Gift Body Program with signed informed consent from the donor. The SLU Gift Body Program abides by all rules set forth by the Uniform Anatomical Gift Act (UAGA). All work with the cadavers, as well as with any material procured from the deceased bodies, is exempt from the Institutional Review Board approval as long as the identity of the deceased individual is not revealed.

Conflicts of Interest

The authors declare that they have no competing interests.

References

[1] Hassan, A.S., Du, Y.L., Lee, S.Y., Wang, A. and Farmer, D.L. (2022) Spina Bifida: A Review of the Genetics, Pathophysiology and Emerging Cellular Therapies. *Journal of Developmental Biology*, **10**, Article 22. https://doi.org/10.3390/jdb10020022

[2] Blencowe, H., Kancherla, V., Moorthie, S., Darlison, M.W. and Modell, B. (2018) Estimates of Global and Regional Prevalence of Neural Tube Defects for 2015: A Systematic Analysis. *Annals of the New York Academy of Sciences*, **1414**, 31-46. https://doi.org/10.1111/nyas.13548

[3] Mai, C.T., Isenburg, J.L., Canfield, M.A., Meyer, R.E., Correa, A., Alverson, C.J., *et al.* (2019) National Population-Based Estimates for Major Birth Defects, 2010-2014. *Birth Defects Research*, **111**, 1420-1435. https://doi.org/10.1002/bdr2.1589

[4] Copp, A.J., Adzick, N.S., Chitty, L.S., Fletcher, J.M., Holmbeck, G.N. and Shaw, G.M. (2015) Spina bifida. *Nature Reviews Disease Primers*, **1**, Article No. 15007. https://doi.org/10.1038/nrdp.2015.7

[5] Au, K.S., Ashley-Koch, A. and Northrup, H. (2010) Epidemiologic and Genetic Aspects of Spina Bifida and Other Neural Tube Defects. *Developmental Disabilities Research Reviews*, **16**, 6-15. https://doi.org/10.1002/ddrr.93

[6] Finnell, R.H., Caiaffa, C.D., Kim, S., Lei, Y., Steele, J., Cao, X., *et al.* (2021) Gene Environment Interactions in the Etiology of Neural Tube Defects. *Frontiers in Genetics*, **12**, Article 659612. https://doi.org/10.3389/fgene.2021.659612

[7] Mohd-Zin, S.W., Marwan, A.I., Abou Chaar, M.K., Ahmad-Annuar, A. and Abdul-Aziz, N.M. (2017) Spina Bifida: Pathogenesis, Mechanisms, and Genes in Mice and Humans. *Scientifica*, **2017**, Article ID: 5364827. https://doi.org/10.1155/2017/5364827

[8] Mitchell, L.E., Adzick, N.S., Melchionne, J., Pasquariello, P.S., Sutton, L.N. and Whitehead, A.S. (2004) Spina Bifida. *The Lancet*, **364**, 1885-1895. https://doi.org/10.1016/s0140-6736(04)17445-x

[9] Paschereit, F., Schindelmann, K.H., Hummel, M., Schneider, J., Stoltenburg-Didinger, G. and Kaindl, A.M. (2021) Cerebral Abnormalities in Spina Bifida: A Neuropathological Study. *Pediatric and Developmental Pathology*, **25**, 107-123. https://doi.org/10.1177/10935266211040500

[10] Pit-ten Cate, I.M., Kennedy, C. and Stevenson, J. (2002) Disability and Quality of Life in Spina Bifida and Hydrocephalus. *Developmental Medicine & Child Neurology*, **44**, 317-322. https://doi.org/10.1111/j.1469-8749.2002.tb00818.x

[11] Ware, A.L., Kulesz, P.A., Orkisz, J.S., Arrington, C.N., Bowman, R.M. and Fletcher, J.M. (2019) Long-Term Intellectual and Fine Motor Outcomes in Spina Bifida Are Related to Myelomeningocele Repair and Shunt Intervention History. *Journal of the*

International Neuropsychological Society, **26**, 364-371.
https://doi.org/10.1017/s1355617719001176

[12] Blount, J.P., Maleknia, P., Hopson, B.D., Rocque, B.G. and Oakes, W.J. (2021) Hydrocephalus in Spina Bifida. *Neurology India*, **69**, S367-S371.
https://doi.org/10.4103/0028-3886.332247

[13] Frolov, A., Guzman, M.A., Hayat, G. and Martin, J.R. (2024) Two Cases of Sporadic Amyotrophic Lateral Sclerosis with Contrasting Clinical Phenotypes: Genetic Insights. *Cureus*, **16**, e56023. https://doi.org/10.7759/cureus.56023

[14] Jenkins, M., Frolov, A., Tan, Y., Daly, D., Lawson, C. and Martin, III, J.R. (2019) Situs Inversus Totalis in a 96-Year-Old Female Cadaver: Evidence Pointing toward the Two-Cilia Model. *Italian Journal of Anatomy and Embryology*, **124**, 230-246.
https://doi.org/10.13128/ijae-10794

[15] Franke, B., Vermeulen, S.H.H.M., Steegers-Theunissen, R.P.M., Coenen, M.J., Schijvenaars, M.M.V.A.P., Scheffer, H., *et al.* (2009) An Association Study of 45 Folate-Related Genes in Spina Bifida: Involvement of Cubilin (CUBN) and tRNA Aspartic Acid Methyltransferase 1 (TRDMT1). *Birth Defects Research Part A*: *Clinical and Molecular Teratology*, **85**, 216-226. https://doi.org/10.1002/bdra.20556

[16] Wu, L., Lu, X., Guo, J., Zhang, T., Wang, F. and Bao, Y. (2016) Association between ALDH1L1 Gene Polymorphism and Neural Tube Defects in the Chinese Han Population. *Neurological Sciences*, **37**, 1049-1054.
https://doi.org/10.1007/s10072-016-2527-8

[17] Miao, C., Jiang, Q., Li, H., Zhang, Q., Bai, B., Bao, Y., *et al.* (2016) Mutations in the Motile Cilia Gene *DNAAF*1 Are Associated with Neural Tube Defects in Humans. *G3 Genes|Genomes|Genetics*, **6**, 3307-3316. https://doi.org/10.1534/g3.116.033696

[18] Gu, Y., Zhang, Q., Guo, J., Wang, F., Bao, Y., Qiu, Z., *et al.* (2021) Higher Serum Homocysteine and Lower Thyroid Hormone Levels in Pregnant Women Are Associated with Neural Tube Defects. *Journal of Trace Elements in Medicine and Biology*, **68**, Article ID: 126814. https://doi.org/10.1016/j.jtemb.2021.126814

[19] Stoupa, A., Carré, A., Polak, M., Szinnai, G. and Schoenmakers, N. (2025) Genetics of Primary Congenital Hypothyroidism: Three Decades of Discoveries and Persisting Etiological Challenges. *European Thyroid Journal*, **14**, e240348.
https://doi.org/10.1530/etj-24-0348

[20] Requena-Jimenez, A., Nabiuni, M. and Miyan, J.A. (2021) Profound Changes in Cerebrospinal Fluid Proteome and Metabolic Profile Are Associated with Congenital Hydrocephalus. *Journal of Cerebral Blood Flow & Metabolism*, **41**, 3400-3414.
https://doi.org/10.1177/0271678x211039612

[21] Chiani, F., Orsini, T., Gambadoro, A., Pasquini, M., Putti, S., Cirilli, M., *et al.* (2019) Functional Loss of *Ccdc*151 Leads to Hydrocephalus in a Mouse Model of Primary Ciliary Dyskinesia. *Disease Models & Mechanisms*, **12**, dmm038489.
https://doi.org/10.1242/dmm.038489

[22] Ha, S., Lindsay, A.M., Timms, A.E. and Beier, D.R. (2016) Mutations in Dnaaf1 and Lrrc48 Cause Hydrocephalus, Laterality Defects, and Sinusitis in Mice. *G3 Genes|Genomes|Genetics*, **6**, 2479-2487. https://doi.org/10.1534/g3.116.030791

[23] Ikeda, L., Capel, A.V., Doddaballapur, D. and Miyan, J. (2024) Accumulation of Cerebrospinal Fluid, Ventricular Enlargement, and Cerebral Folate Metabolic Errors Unify a Diverse Group of Neuropsychiatric Conditions Affecting Adult Neocortical Functions. *International Journal of Molecular Sciences*, **25**, Article 10205.
https://doi.org/10.3390/ijms251810205

[24] Anthony, T.E. and Heintz, N. (2006) The Folate Metabolic Enzyme ALDH1L1 Is Re-

stricted to the Midline of the Early CNS, Suggesting a Role in Human Neural Tube Defects. *Journal of Comparative Neurology*, **500**, 368-383. https://doi.org/10.1002/cne.21179

[25] Ito, M., Morimoto, K., Saotome, M., Miyabayashi, A., Wakabayashi, K., Yamada, H., *et al.* (2024) Primary Ciliary Dyskinesia Caused by Homozygous *Dnaaf*1 Mutations Resulting from a Consanguineous Marriage: A Case Report from Japan. *Internal Medicine*, **63**, 2847-2851. https://doi.org/10.2169/internalmedicine.3263-23

[26] Ringers, C., Olstad, E.W. and Jurisch-Yaksi, N. (2019) The Role of Motile Cilia in the Development and Physiology of the Nervous System. *Philosophical Transactions of the Royal Society B: Biological Sciences*, **375**, Article ID: 20190156. https://doi.org/10.1098/rstb.2019.0156

[27] Kumar, V., Umair, Z., Kumar, S., Goutam, R.S., Park, S. and Kim, J. (2021) The Regulatory Roles of Motile Cilia in CSF Circulation and Hydrocephalus. *Fluids and Barriers of the CNS*, **18**, Article No. 31. https://doi.org/10.1186/s12987-021-00265-0

[28] Engelhardt, D., Petersen, J.R., Martyr, C., Kuhn-Gale, H. and Niswander, L.A. (2025) Moderate Levels of Folic Acid Benefit Outcomes for Cilia Based Neural Tube Defects. *Developmental Biology*, **520**, 62-74. https://doi.org/10.1016/j.ydbio.2024.12.019