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Risk Variants Associated With Normal Pressure Hydrocephalus

Genome-Wide Association Study in the FinnGen Cohort

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Abstract

Background and Objectives

Large-scale genome-wide studies of chronic hydrocephalus have been lacking. We conducted a genome-wide association study (GWAS) in normal pressure hydrocephalus (NPH).

Methods

We used a case-control study design implementing FinnGen data containing 473,691 Finns with genotypes and nationwide health records. Patients with NPH were selected based on *ICD-10* G91.2 diagnosis. To select patients with idiopathic NPH (iNPH) for sensitivity analysis, we excluded patients with a potentially known etiology of the condition using an algorithm on their disease history. The controls were the remaining non-hydrocephalic participants. For a replication analysis, the NPH cohort from UK Biobank (UKBB) was used.

Results

We included 1,522 patients with NPH (mean age 72.2 years, 53% women) and 451,091 controls (mean age 60.5 years, 44% women). In the GWAS comparing patients with NPH with the controls, we identified 6 gene regions significantly ($p < 5.0e-8$) associated with NPH that replicated in a meta-analysis with UKBB (NPH n = 173). The top loci near the following genes were rs7962263, *SLCO1A2* (odds ratio [OR] 0.71, 95% CI 0.65–0.78, $p = 1.0e-14$); rs798495, *AMZ1/GNA12* (OR 1.29, 95% CI 1.20–1.39, $p = 2.9e-12$); rs10828247, *MLLT10* (OR 0.77, 95% CI 0.71–0.83, $p = 1.5e-11$); rs561699566 and rs371919113, *CDCA2* (OR 0.76, 95% CI 0.70–0.82, $p = 1.5e-11$); rs56023709, *C16orf95* (OR 1.24, 95% CI 1.16–1.33, $p = 3.0e-9$); and rs62434144, *PLEKHG1* (OR 1.23, 95% CI 1.14–1.32, $p = 1.4e-8$). In the sensitivity analysis comparing only patients with iNPH (n = 1,055) with the controls (n = 451,091), 4 top loci near

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Glossary

AD = Alzheimer disease; **BAB** = blood-arachnoid barrier; **BBB** = blood-brain barrier; **BCSFB** = blood-CSF barrier; **eQTL** = expression quantitative trait loci; **GTEx** = Genotype-Tissue Expression; **GWAS** = genome-wide association study; ***ICD-10*** = *International Classification of Diseases, Tenth Revision*; **iNPH** = idiopathic NPH; **MAF** = minor allele frequency; **LD** = linkage disequilibrium; **NPH** = normal pressure hydrocephalus; **OR** = odds ratio; **PIP** = posterior inclusion probability; **PRS** = polygenic risk score; **PSP** = progressive supranuclear palsy; **QC** = quality control; **sNPH** = secondary NPH; **TBI** = traumatic brain injury; **T2D** = type 2 diabetes; **UKBB** = UK Biobank.

the following genes remained significant: rs7962263, *SLCO1A2* (OR 0.70, 95% CI 0.63–0.78, p = 2.1e-11); rs10828247, *MLLT10* (OR 0.74, 95% CI 0.62–0.82, p = 4.6e-10); rs798511, *AMZ1/GNA12* (OR 1.28, 95% CI 1.17–1.39, p = 1.7e-8); and rs56023709, *C16orf95* (OR 1.28, 95% CI 1.17–1.39, p = 1.7e-8).

Discussion

We identified 6 loci significantly associated with NPH in the thus far largest GWAS in chronic hydrocephalus. The genes near the top loci have previously been associated with blood-brain barrier and blood-CSF barrier function and with increased lateral brain ventricle volume. The effect sizes and allele frequencies remained similar in NPH and iNPH cohorts, indicating the identified loci are risk determinants for iNPH and likely not explained by associations with other etiologies. However, the exact role of these loci is still unknown, warranting further studies.

Introduction

Normal pressure hydrocephalus (NPH) is a neurologic disease affecting the elderly population. Clinical symptoms include deteriorating gait and cognition function and urinary incontinence.[1,2] Two studies have indicated that iNPH may affect more than 5% of individuals older than 80 years. It is a serious and progressive brain disease associated with an increased hazard ratio for death if left untreated.[3-5] NPH is considered idiopathic (iNPH) when no obvious condition affecting CSF circulation or predisposing insults, such as hemorrhagic stroke, can be identified.[1] INPH is still likely underdiagnosed,[6] but potentially modifiable by CSF diversion.[7] In iNPH, the enlargement of the cerebral ventricles is associated with failed CSF homeostasis, primarily through mechanisms that are still mostly unknown,[8] which is also the case in secondary NPH (sNPH).

The potential genetic aspects of iNPH have gained increasing interest because of epidemiologic findings suggesting possible heritability. Up to 20% of patients with iNPH have at least 1 relative with possible or probable iNPH.[9] Previously, *SFMBT1*, *CFAP43*, *DNAH14*, and *CWH43* have been associated with iNPH.[10-13] The loss-of-function variant of *CFAP43* was found in a Japanese family with iNPH, and knockout of that gene in a mouse model resulted in a hydrocephalus phenotype and motile cilia abnormality.[12] Yang et al. discovered 2 loss-of-function deletions in *CWH43* potentially associated with iNPH through whole-exome sequencing of 53 patients with iNPH.[12] In mouse models, these *CWH43* deletions caused iNPH-related phenotypic findings, decreased numbers of ependymal cilia, and the localization of glycosylphosphatidylinositol-anchored proteins to the apical surfaces of choroid plexus and ependymal cells.[13] However, these findings only explain a small fraction of the potential genetic background of the disease.

So far, large-scale genome-wide studies in chronic hydrocephalus have been lacking. We conducted a genome-wide association study (GWAS) in NPH to identify novel risk variants associated with the condition and create hypotheses on potential pathophysiologic pathways. For this purpose, we used the data from the FinnGen research project.[14]

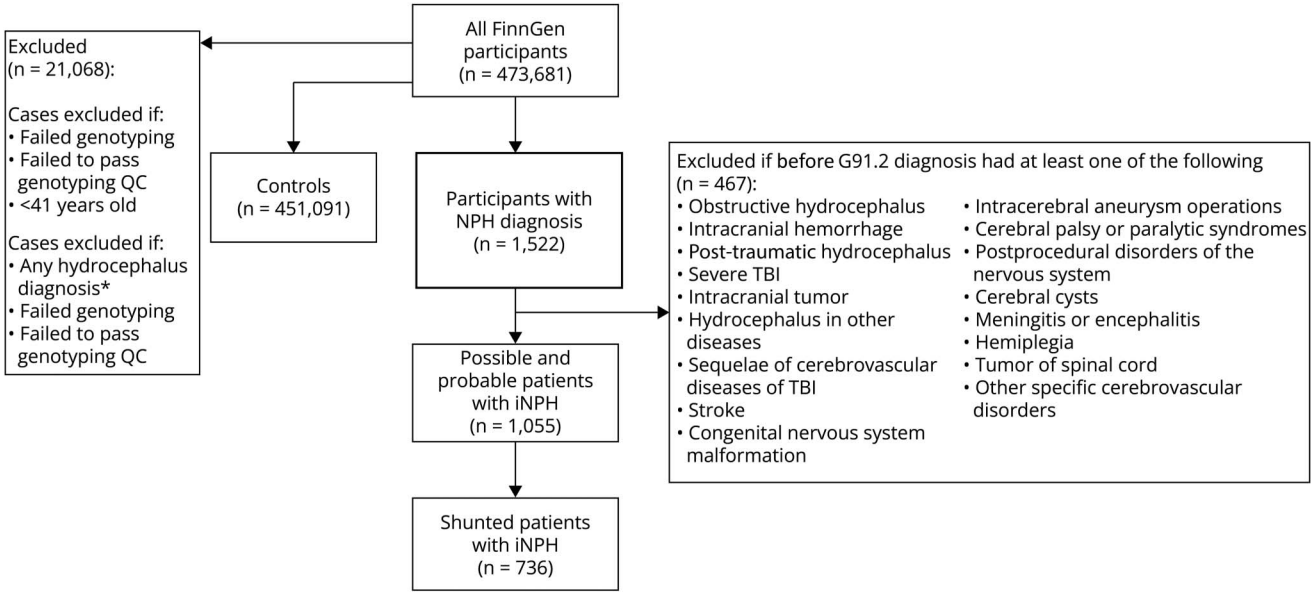
Methods

Participant Selection

FinnGen study release 11 was used for participant selection and genotype data. FinnGen (finngen.fi/en) is a public-private research project, combining genome and digital health care data of 473,681 Finns (in release 11). The FinnGen nationwide initiative aims to provide novel insights into human diseases with potential implications for medical treatments. FinnGen is a precompetitive partnership involving Finnish biobanks, their affiliated organizations (universities and university hospitals), international pharmaceutical industry partners, and the Finnish biobank cooperative FINBB. A comprehensive list of FinnGen partners can be found on the FinnGen website.

We used the *ICD-10* code G91.2 to select patients with NPH as cases. Cases were excluded if they were younger than 41 years. A sensitivity analysis was conducted including only patients with iNPH. Because the G91.2 code does not

Figure 1 Flowchart of Participant Selection for the NPH GWAS and the Exclusion of the Potential sNPH Cases for the Sensitivity Analysis With iNPH and Shunted iNPH Cohorts



GWAS = genome-wide association study; (i)NPH = (idiopathic) normal pressure hydrocephalus; QC = quality control; TBI = traumatic brain injury. *Cases of the FinnGen G6_HYDROCEPH end point.

differentiate the idiopathic form of NPH from those that have a potentially known secondary etiology for the condition, such as subarachnoid hemorrhage, brain tumor, traumatic brain injury (TBI), stroke, or meningoencephalitis,[1] we developed an iNPH selection algorithm to exclude patients with potential sNPH from the sensitivity analysis. Based on diagnoses appearing before the first diagnosis of G91.2, this algorithm excluded patients if they had obstructive hydrocephalus, intracranial hemorrhage, post-traumatic hydrocephalus, severe TBI, intracranial tumor, congenital nervous system malformation, hydrocephalus in other diseases, sequelae of cerebrovascular diseases or TBI, stroke, intracerebral aneurysm operations or other specific cerebrovascular disorders, cerebral palsy or paralytic syndromes, postprocedural disorders of the nervous system, cerebral cysts, meningitis or encephalitis, hemiplegia, or tumor of the spinal cord (Figure 1, specific disease end points in eMaterial 1). In addition, a further sensitivity analysis was conducted in patients with iNPH who underwent shunt surgery. The algorithm was developed to be in line with the international diagnostic guidelines of iNPH[1,8] to only select those patients with possible or probable iNPH for the analysis. All the patients with NPH had passed the genotyping quality control (QC). The age of the cases was defined as the age at the first G91.2 diagnosis.

The GWAS controls were the remaining FinnGen participants who did not have any hydrocephalus diagnosis, defined by the inclusion as a case in the FinnGen G6_HYDROCEPH end point. These individuals had diagnostic and demographic data presently (early 2023) available and had passed genotyping QC. The age of the controls was defined as the age at the end of follow-up, death, or when they moved abroad.

Genotyping and Association Analysis

The methods of the FinnGen study are described in detail by Kurki et al.[14] but are briefly summarized here. The individuals in the FinnGen study were genotyped using Illumina and Affymetrix chip arrays (Illumina Inc., San Diego, CA, and Thermo Fisher Scientific, Santa Clara, CA). Samples were excluded if they were duplicates or had ambiguous sex, high genotype missingness (>5%), excess heterozygosity (±4 SD), or non-Finnish ancestry. After sample exclusion, the FinnGen data set (release 11) included 473,681 individuals. Variants were excluded if they had high missingness (>2%), low Hardy-Weinberg equilibrium (p < 1e-6), or low minor allele count (<3). The samples were prephased with Eagle 2.3.5 using 20,000 conditioning haplotypes. Genotype imputation was conducted using Beagle 4.1 and a population-specific SISu v4.0 reference panel, which uses GRCh38 coordinates and includes 8,554 Finnish whole-genome sequenced individuals. Postimputation variants with an imputation INFO score <0.6 or minor allele frequency <0.0001 were excluded. The association analysis for the imputed variants was performed using regenie version 2.2.4, adjusting for sex, age, 10 principal components, and genotyping batches and, separately, for 2 additional binary FinnGen end points type 2 diabetes (T2D_WIDE) and hypertension (I9_HYPTENS). X-chromosome non-PAR region in men was coded with full dosage compensation (hemizygote men are equal to homozygote women). The statistical significance level in GWAS was set at p < 5.0e-8.[14]

Finnish enrichment refers to the ratio of allele frequency in Finnish Europeans over that in non-Finnish non-Swedish non-Estonian Europeans and is based on gnomAD 2.1 data.

Fine-Mapping

Fine-mapping was conducted to determine credible sets of potentially causal genetic variants. FINEMAP and SuSiE methods[15,16] were used to fine-map genome-wide significant loci of the NPH GWAS. The credible sets displayed are SuSiE–fine-mapped credible sets for each phenotype, and it shows the variant with the highest posterior inclusion probability (PIP) within each set as the leading variant. Preprocessing was performed by defining a 3-Mb window around each lead variant, merging overlapping regions and adjusting window size if necessary. Linkage disequilibrium (LD) computation computed in-sample dosage LD using LDstore2 for each fine-mapping region. Fine-mapping was conducted with the maximum number of 10 causal variants in a locus.

Heritability and Genetic Correlation

Both the narrow-sense heritability (h^2; the variance explained by the additive effects of the variants) and the pair-wise genetic correlations between NPH and all the FinnGen R11 end points were calculated using ldsc[17] and the Finnish LD panel.

Colocalization

Potential colocalization of credible set leading variants and for LD partners with r^2 >0.6 to expression quantitative trait loci (eQTL) were assessed using the Genotype-Tissue Expression (GTEx) Portal (V8), ROSMAP, and CommonMind eQTL catalogs[18-20] and, for other genome-wide significant disease traits, using the Open Targets Genetics database,[21] which uses UK Biobank (UKBB), FinnGen, and GWAS catalogs. Gene expression in different tissues (using GTEx V8 data) and the expression in the brain at different ages (using BrainSpan Atlas data)[22] were assessed for protein encoding genes within 250 kb of the fine-mapped credible set leading variants. The FUMA GENE2FUNC tool[23] was used to generate the gene expression matrices that were then plotted using R.[24]

Polygenic Risk Score

Polygenic risk scores (PRSs) of all FinnGen R11 participants for a UKBB-derived end point "volume of ventricular CSF (normalized to head size)"[25] (PGS catalog number PGS001070) were precalculated by FinnGen using PRScs.[26] Odds, with 95% CIs, of being a case in a binary end point were calculated in binned PRS quantiles (strata) in R using fisher.test, taking the expected counts from the combined 40–60 PRS percentile bins.

Meta-Analysis

Meta-analysis of the initial significantly associated leading variants of NPH in the FinnGen cohort together with the UKBB cohort (NPH cases defined with *ICD-10* G91.2 and the rest without *ICD-10* G91.2 as controls) was performed in R (version 4.3.2) using meta::metagen that uses inverse variance for pooling.[27]

Standard Protocol Approvals, Registrations, and Patient Consents

Study subjects in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, separate research cohorts, collected before the enactment of the Finnish Biobank Act (in September 2013) and the start of FinnGen (in August 2017), were collected based on study-specific consents and transferred to the Finnish biobanks after approval by Fimea (Finnish Medicines Agency), the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) statement number for the FinnGen study is Nr HUS/990/2017. The full FinnGen study approval and Biobank Access Decisions are listed in eMaterial 2.

UKBB comprises phenotype data from 500,000 volunteer participants from the UK population aged between 40 and 69 years, during recruitment in 2006–2010. Data for all participants have been linked with national Hospital Episode Statistics. UKBB has approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank approval. The analyses for this study have been conducted under UKBB Application Number 31063.

This study was conducted according to the Declaration of Helsinki. The study was approved by the Kuopio University Hospital Research Ethics Board (5/2008, 276/2016, 1041/2019).

Data Availability

Based on national and European regulations (General Data Protection Regulations), access to individual-level sensitive health data requires approval from national authorities for specific research projects and designated researchers. The health data discussed here were obtained from the national health register authorities, including the Finnish Institute of Health and Welfare, Statistics Finland, KELA, and the Digital and Population Data Services Agency, and approved for use in the FinnGen project, either by the individual authorities or the Finnish Data Authority, Findata. As authors of this study, we are unable to grant access to individual-level data to others. Researchers seeking access to health register data can apply through the Finnish Data Authority Findata (findata.fi/en/permits/) while individual-level genotype data can be requested from Finnish biobanks using the Fingenious portal (site.fingenious.fi/en/) hosted by the Finnish Biobank Cooperative FINBB (finbb.fi/en/). Finnish biobanks can provide access to research projects within the scope regulated by the Finnish Biobank Act. Summary statistics from data releases will be publicly available after a 1-year embargo period and can be accessed from finngen.fi/en/access_results.

Access to UKBB individual-level data can be applied through the UKBB portal (ukbiobank.ac.uk/enable-your-research/apply-for-access).

Results

The NPH GWAS included 1,522 patients with NPH (mean age 72.2 [SD 8.2], 52.9% women) as cases, and the primary sensitivity analysis included a subset of 1,055 patients with iNPH (mean age 72.4 [SD 7.7], 52.5% women) as cases. The number of non-hydrocephalic controls in both groups was 451,091 (mean age 60.5 [SD 18.0], 43.8% women). The genomic control lambda for the 50th percentile in the NPH GWAS was 1.0386 (QQ plot in eFigure 1) and in the iNPH GWAS 1.0119, indicating no residual population stratification. Heritability due to additive genetic effects (h^2) of NPH was 0.0059. The UKBB cohort for the meta-analysis and replication analysis included 173 NPH cases and 419,453 controls.

In the NPH GWAS, we initially identified 599 significantly associated variants in 8 loci associated with NPH with $p < 5.0e-8$. The lead variants of 6 of these loci remained statistically significant upon meta-analysis with the UKBB data (eTable 1, eFigure 2). These top associated leading variants were rs7962263 (odds ratio [OR] 0.71, minor allele frequency [MAF] 0.25, $p = 1.0e-14$) near *SLCO1A2*, rs798495 (OR 1.29, MAF 0.365, $p = 2.9e-12$) near *AMZ1/GNA12*, rs10828247 (OR 0.77, MAF 0325, $p = 1.5e-11$) near *MLLT10*, rs561699566 and rs371919113 (OR 0.76, MAF 0.319, $p = 1.5e-11$) near *CDCA2*, rs56023709 (OR 1.24, MAF 0.543, $p = 3.0e-9$) near *C16orf95*, and rs62434144 (OR 1.23, MAF 0.433, $p = 1.4e-8$) near *PLEKHG1* (Table 1, eTables 2, and 3). The loci rs11217863 (OR 1.34, MAF 0.124, $p = 1.1e-8$) near *ARHGEF12* and rs576021375 (OR 1.54, MAF 0.0419, $p = 3.4e-8$) near *CSNK1E* were significant in the FinnGen cohort, but failed to replicate in the UKBB data. The meta-analysis did not yield any additional significant loci compared with the initial analysis. Adjusting the NPH GWAS for type 2 diabetes (T2D) and hypertension had no appreciable effect on the results (eFigure 3). All the top NPH-associated variants were common variants (MAF >0.01). A Manhattan plot is presented in Figure 2.

In the sensitivity analysis of 1,055 patients with iNPH, allelic variation in 4 loci remained associated with iNPH with $p < 5.0e-8$. The top associated leading variants were rs7962263 (OR 0.70, MAF 0.25, $p = 2.1e-11$) near *SLCO1A2*, rs10828247 (OR 0.74, MAF 0.325, $p = 4.6e-10$) near *MLLT10*, rs798511 (OR 1.28, MAF 0.347, $p = 2.7e-8$) near *AMZ1* and *GNA12*, and rs56023709 (OR 1.28, MAF 0.543, $p = 1.7e-8$) near *C16orf95* (Table 2).

An additional sensitivity analysis was performed for a further subset of patients who had surgical operation codes for shunted iNPH (shunted iNPH n = 736, controls n = 451,091). Even with this tighter selection criteria, the main results remained similar for the 3 top loci compared with NPH and iNPH. The ORs, allele frequencies, and *p*-values are presented in Table 2.

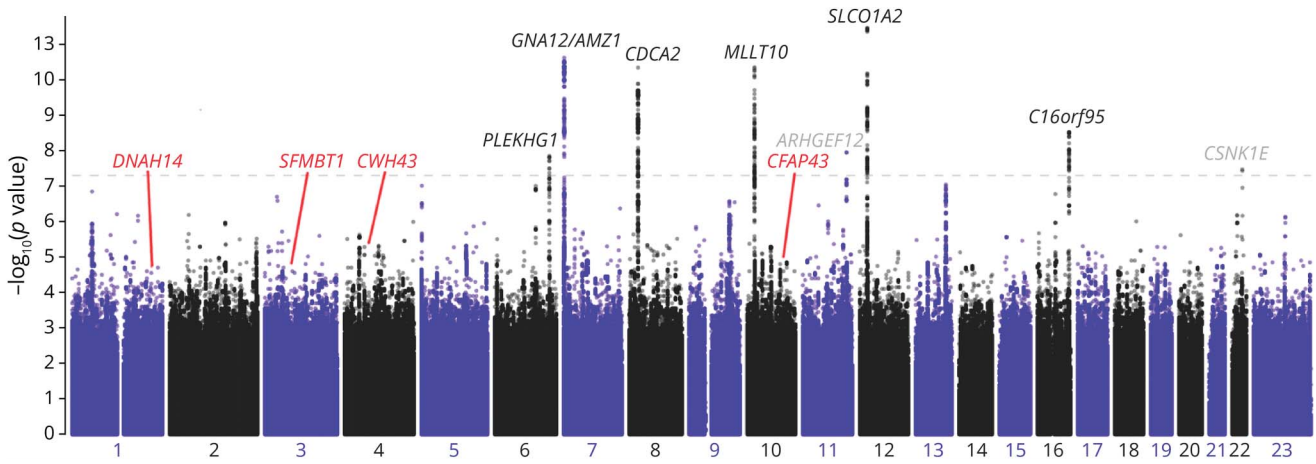
Within the loci confirmed by the meta-analysis, there were 7 fine-mapped credible sets including variants that are potentially causal for NPH. The leading variants were mainly the same as the top associated variants. Only the *SLCO1A2* gene region had 2 credible sets with the leading variants rs7962263 and rs112704675. All leading variants were common noncoding intron variants with MAF >0.01. One credible set contained coding variants but with low PIP: rs798488, a start-loss variant near *GNA12* (PIP = 0.015, $r^2 = 0.9766$) (Table 3). For iNPH, fine-mapping revealed 5 credible sets for which the leading variants near gene *SLCO1A2* were rs7962263 and rs4762816 and near *GNA12* the rs798511. The leading variants near *MLLT10* and *C16orf95* were the same as for NPH. Regional association plots for the 3 top associated loci are displayed in Figure 3 and for the other 3 loci associated with NPH at $p < 5.0e-8$ and confirmed by the meta-analysis are displayed in eFigure 4.

Table 1 Genome-Wide Significant Results in NPH

Chr:pos	RA/AA	rsid	Nearest gene	AF cases	AF controls	OR (95% CI)	*p* Value
12:21313183	C/T	rs7962263	*SLCO1A2*	0.19	0.25	0.71 (0.65–0.78)	1.0e-14
7:2757633	T/C	rs798495	*AMZ1, GNA12*	0.44	0.36	1.29 (1.20–1.39)	2.9e-12
10:21533927	A/G	rs10828247	*MLLT10*	0.27	0.33	0.77 (0.71–0.83)	1.5e-11
8:25492134	T/TG	rs561699566, rs371919113	*CDCA2*	0.26	0.32	0.76 (0.70–0.82)	1.5e-11
16:87195738	A/C	rs56023709	*C16orf95*	0.59	0.54	1.24 (1.16–1.33)	3.0e-9
11:120422429[a]	G/A	rs11217863	*ARHGEF12*	0.16	0.12	1.34 (1.21–1.48)	1.1e-8
6:150702668	C/T	rs62434144	*PLEKHG1*	0.49	0.43	1.23 (1.14–1.32)	1.4e-8
2:38354701[a]	T/C	rs576021376	*CSNK1E*	0.065	0.042	1.54 (1.32–1.80)	3.4e-8

Abbreviations: AA = alternate allele; AF = alternate allele frequency; Chr:pos = chromosome:position (in GRCh38 coordinates); NPH = normal pressure hydrocephalus; OR = odds ratio; RA = reference allele; UKBB = UK Biobank.
NPH n = 1,522, controls n = 451,091.
[a] Variant that did not retain genome-wide significance in the meta-analysis with UKBB data.

Figure 2 Manhattan Plot* of the NPH GWAS



*The nearest genes of the top associated loci (p < 5.0e-8) replicating (black) and failing to replicate (gray) with the UKBB data, and the previously iNPH associated genes (in red) are indicated in the plot. The y-axis displays −log10 p-values with the dotted line indicating the location of the untransformed limit of genome-wide significance (p = 5.0e-8). The x-axis displays the chromosome number. NPH n = 1,522 and controls n = 451,091. GWAS = genome-wide association study; NPH = normal pressure hydrocephalus; UKBB = UK Biobank.

Table 2 GWAS-Associated Variants in NPH, iNPH, and Shunted iNPH

Chr:pos	RA/AA	rsid	Nearest gene	AF controls	GWAS cases	AF cases	OR (95% CI)	*p* Value
12:21313183	C/T	rs7962263	*SLCO1A2*	0.25	*NPH*	0.19	0.71 (0.65–0.78)	**1.0e-14**
					iNPH	0.18	0.70 (0.63–0.78)	**2.1e-11**
					Shunted iNPH	0.18	0.68 (0.60–0.77)	**9.7e-10**
7:2757633	T/C	rs798495	*AMZ1, GNA12*	0.36	*NPH*	0.44	1.29 (1.20–1.39)	**2.9e-12**
					iNPH	0.44	1.28 (1.17–1.39)	**1.7e-8**
					Shunted iNPH	0.46	1.40 (1.27–1.55)	**4.5e-11**
10:21533927	A/G	rs10828247	*MLLT10*	0.33	*NPH*	0.27	0.77 (0.71–0.83)	**1.5e-11**
					iNPH	0.26	0.74 (0.68–0.82)	**4.6e-10**
					Shunted iNPH	0.26	0.72 (0.65–0.81)	**1.2e-8**
8:25492134	T/TG	rs561699566, rs371919113	*CDCA2*	0.32	*NPH*	0.26	0.76 (0.70–0.82)	**1.5e-11**
					iNPH	0.26	0.78 (0.71–0.86)	2.6e-7
					Shunted iNPH	0.26	0.79 (0.71–0.89)	7.5e-5
16:87195738	A/C	rs56023709	*C16orf95*	0.54	*NPH*	0.59	1.24 (1.16–1.33)	**3.0e-9**
					iNPH	0.60	1.28 (1.17–1.39)	**1.7e-8**
					Shunted iNPH	0.60	1.28 (1.16–1.42)	2.1e-6
6:150702668	C/T	rs62434144	*PLEKHG1*	0.43	*NPH*	0.49	1.23 (1.14–1.32)	**1.4e-8**
					iNPH	0.48	1.22 (1.12–1.32)	5.9e-6
					Shunted iNPH	0.49	1.23 (1.11–1.36)	5.0e-5

Abbreviations: AF = allele frequency; Chr:pos = chromosome:position (in GRCh38 coordinates); (i)NPH = (idiopathic) normal pressure hydrocephalus; OR = odds ratio; RA/AA = reference allele/alternate allele; UKBB = UK Biobank.
Table includes the variants that retained genome-wide significance in the meta-analysis with UKBB data. NPH n = 1,522; iNPH n = 1,055; shunted iNPH n = 736; controls n = 451,091.
Genome-wide significant p values are in bold.

Table 3 Fine-Mapping Credible Set Leading Variants in NPH

Top PIP variant[a]	rsid	Leading variant gene	*p* Value	Beta	AF	Finnish enrichment	PIP	No. of coding in CS[b]	No. of credible variants	Variant type
Chr12:21313183: C:T	rs7962263	*SLCO1A2*	1.0e-14	−0.34	0.25	0.833	0.15	0	9	Intron
Chr7:2757633:T:C	rs798495	*GNA12*	2.9e-12	0.24	0.37	1.256	0.066	1	66	Intron
Chr10:21533927: A:G	rs10828247	*MLLT10*	1.5e-11	−0.27	0.33	0.917	0.22	0	20	Intron
Chr8:25492134:T: TG	rs561699566, rs371919113	*CDCA2*	1.5e-11	−0.27	0.32	1.088	0.17	0	116	Intron
Chr12:21345992: C:T	rs112704675	*SLCO1A2*	1.4e-9	0.38	0.077	0.833	0.23	0	4,805	Intron
Chr16:87195738: A:C	rs56023709	*C16orf95*	3.0e-9	0.22	0.54	0.869	0.87	0	33	Intron
Chr6:150702668: C:T	rs62434144	*PLEKHG1*	1.4e-8	0.20	0.43	1.073	0.097	0	24	Intron

Abbreviations: AF = alternate allele frequency; NPH = normal pressure hydrocephalus; PIP = posterior inclusion probability; UKBB = UK Biobank.
Table includes the variants that retained genome-wide significance in the meta-analysis with UKBB data. NPH n = 1,522.
[a] Chromosome:position:reference allele:alternative allele (in GRCh38 coordinates).
[b] Number of coding variants in the credible set.

For the 4 loci that were significant in both NPH and iNPH GWASs, the association signal at 12p12.1 near *SLCO1A2* includes 2 credible sets. Allele T of rs7962263 was a protective variant against NPH with an OR of 0.71, and allele T of rs112704675 with an OR of 1.47 was a risk variant. At 10p12.31, allele G of rs10828247 was a protective variant against NPH with an OR of 0.77. The signal at 10p12.31 comprises 8 genes (*CASC10, MIR1915, SKIDA1, RNU-306P, MLLT10, HNRNPRP1, RNU6-1141P, DNAJC1*), as shown in the regional association plots (Figure 3). At 7p22.3, allele C of rs798495 was identified as a risk variant for NPH with an OR of 1.29. The signal at 7p22.3 comprises 3 genes (*AMZ1, GNA12, AC006028.1*). At 16q24.2, near *C16orf95*, allele C of rs56023709 was a risk variant for NPH with an OR of 1.24.

Notably, 3 of the top significant loci colocalized with a brain eQTL. At 12p12.1, the effect allele of rs7962263 was associated with increased expression of *SLCO1A2* in the cerebellum. Similarly, at 10p12.31, the effect allele of rs10828247 correlated with enhanced expression of *CASC10* in the cerebellum. At this locus, the leading variant and its LD partners also colocalized with non-brain eQTLs for *MLLT10* and *NEBL*. At 7p22.3, the effect allele of rs798495 was linked to decreased expression of *AMZ1* in various brain regions, while increasing the expression of *GNA12* in various tissues outside the brain.

The potential functional role of *SLCO1A2* in the etiology of NPH is supported by the specificity of its gene expression in the brain (GTEx V8 data; eFigure 5A), which increases upon aging (BrainSpan data; eFigure 5B). Moreover, according to the Allen Brain Map SEA-AD single-cell gene expression data, within the brain, *SLCO1A2* expression is specific to oligodendrocytes and endothelial cells (data not shown).

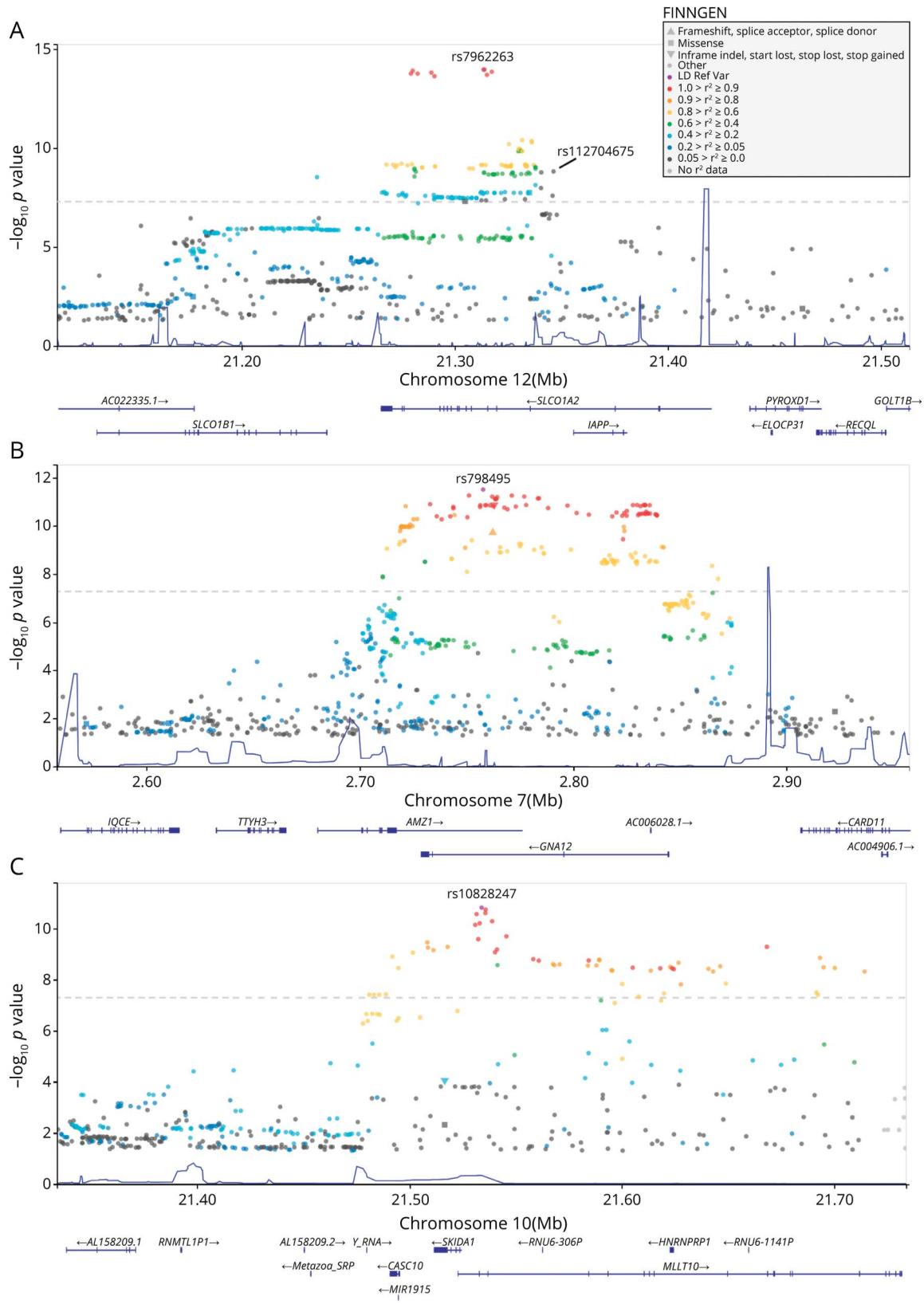
The genetics of NPH may relate to the genetics of brain ventricle size as evidenced by the increased odds of having NPH in the highest quantiles of PRS calculated for the UKBB GWAS summary statistics for "volume of ventricular CSF (normalized to head size)" (eFigure 6).

Colocalization of the 7 credible set leading variants with existing FinnGen disease and trait end point GWAS results demonstrate the uniqueness for NPH of the 2 independent signals at 12p12.1 near *SLCO1A2* (colocalization volcano plots in eFigure 7) and those at 16q24.2 near *C16orf95* and 6q25.1 near *PLEKHG1*. Collectively, the other leading variants may suggest common genetic risks between NPH and end points related to hernia or body dimensions.

Discussion

We have performed a large-scale biobank-based GWAS on late-onset chronic hydrocephalus. Upon replication in UKBB data, we identified 6 potential risk loci for NPH. The 4 top allelic variants associated with NPH remained statistically significant also in the secondary analysis, which included only iNPH cases with the exclusion of potential secondary etiologies, and despite the reduced statistical power of the smaller iNPH subset. Our results suggest that chronic hydrocephalus may share a similar genetic risk profile regardless of potential environmental triggers. The effect sizes and ORs were also similar in both NPH and iNPH with the loci that did not reach genome-wide significance in iNPH. This indicates that the identified loci are risk loci for iNPH and likely not explained by associations with other etiologies. Our findings highlight a range of novel risk genes for iNPH, further supporting the

Figure 3 Regional Association Plots of the 3 Top NPH-Associated Loci* at (A) 12p12.1, (B) 7p22.3, and (C) 10p12.31



*Fine-mapped leading variants are indicated in their respective loci with rsid. The purple dot represents the leading variant of each credible set, and the surrounding variants are colored according to pairwise genotype correlation R2 with the leading variant. The y-axis displays the −log10 *p*-values and x-axis the chromosome position and gene annotations in GRCh38 coordinates. NPH = normal pressure hydrocephalus.

assumption that pathogenesis in iNPH is primarily multifactorial. For the leading variants, our sensitivity analysis controlling for confounding from T2D and hypertension, colocalization analysis, nor the review of the literature show any major associations with frequent comorbidities of iNPH, such as Alzheimer disease (AD), T2D, or hypertension. This strengthens the assumption that the pathogenesis of iNPH is independent of AD and reduces the probability of potential confounding biases in our results.

The strongest association between NPH and iNPH was found at the locus in 12p12.1. This locus encompasses the solute carrier organic anion transporter family member 1A2 gene (*SLCO1A2*), and our credible set variants also showed eQTL effects in its expression in the brain. Therefore, *SLCO1A2* could be a potential target gene in this locus. *SLCO1A2* encodes an organic anion transporting polypeptide 1A2 (OATP1A2), a sodium-independent transporter responsible for the cellular uptake of organic anions mainly in the liver, but in the brain, it also localizes apically in the microvascular endothelium, playing an important role in the transcellular pathway of the blood-brain barrier (BBB) and mediating the uptake of a broad spectrum of substrates.[28,29] Genetic variation of *SLCO1A2* and *SLCO1A/1B* knockout mouse models have been associated with altered drug transport function and hepatic reuptake of bilirubin and bile acids.[30]

In addition to the BBB functions, OATP1A2 has been shown to localize to the apical membrane of the choroid plexus, with enriched expression in the choroid plexus compared with the surrounding ventricular ependyma.[31] In humans, OATP1A2 is the only type of OATP1A transporter, while OATP1A1, OATP1A4, OATP1A5, and OATP1A6 are found in rodents, and OATP1A4 is generally regarded as the closest rodent ortholog to OATP1A2 in humans.[28,32] However, in the choroid plexus epithelial cells, OATP1A5 and OATP1A2 in mouse and human samples, respectively, showed similar apical localization and transport function for clearing large organic anions from CSF to the subepithelial space of choroid plexus as part of the blood-CSF border (BCSFB).[31] This OATP-mediated transepithelial transport in the choroid plexus was severely impaired in the *SLCO1A/1B* knockout mouse model.[31] Furthermore in a rat model, OATP1A4 has been identified as an important transporter for clearing organic anions from CSF at the blood-arachnoid barrier (BAB).[33] The expression of OATP1A4 is upregulated by inhibition of the TGF-β/ALK1/ALK5 pathway.[34] This pathway has been associated especially with posthemorrhagic communicating hydrocephalus, and transgenic mice overexpressing TGF-β developed hydrocephalus.[35,36] An elevated CSF biomarker level of leucine-rich alpha-2 glycoprotein, a modulator of TGF-β signaling, has been reported in iNPH.[37,38]

The significant role of *SLCO1A2* in the cerebral microvascular system and BBB is intriguing, given the heavy burden of vascular comorbidities often seen in iNPH.[39] The impact of potential alterations in BBB function on the pathogenesis of iNPH remains unclear. Around 10%–20% of CSF secretion is attributed to fluid transport across the BBB.[40] Protein leakage and fibrinogen extravasation and breach of BBB integrity has been previously reported in iNPH.[41] Fibrin deposition in the brain parenchyma has been shown to correlate with astrogliosis, and both fibrin extravasation and astrogliosis have been shown to correlate with the reduction in the expression of aquaporin 4. These factors have also been linked to the glymphatic system, the function of which in iNPH could be hampered.[41,42] Of interest, the allelic variation of *SLCO1A2* has also been previously linked with progressive supranuclear palsy (PSP), with the leading variant being 12:21304500:T/G[43] (in our results p = 4.63e-8, r^2 = 0.0225 for our fine-mapped top variants 12:21313183:C/T and r^2 = 0.4808 for 12:21345992:C/T). Clinical symptoms and radiologic findings of PSP and iNPH do overlap to some extent as hydrocephalic radiologic findings have been reported to be over-represented in PSP as compared with other neurodegenerative parkinsonisms.[44] The potential association of *SLCO1A2* in both iNPH and PSP is intriguing, emphasizing the similarities and, therefore, the potential link between the 2 diseases.

According to eQTL analysis, the T allele of rs7962263 was associated with the increased expression of *SLCO1A2* in the cerebellum and it was also identified as a protective allele against NPH in our GWAS. Therefore, it is possible that loss of function in *SLCO1A2* could increase the risk of NPH. However, further studies are still needed to show that this GWAS locus really affects the function of *SLCO1A2*. Given that the expression of *SLCO1A2* was shown to be increased with age in the brain (eFigure 5B), it can be hypothesized that genetic variants in *SLCO1A2* are unlikely to affect hydrocephalus congenitally. In other words, increased expression could be a response to aging, and impaired function of this gene owing to certain genetic variants in *SLCO1A2* could make elderly individuals more prone to develop NPH, potentially by impaired transport and clearing function across the important fluid barriers in the CNS, such as BBB, BCSFB, and BAB.

The 7p22.3 locus comprises genes including *AMZ1* and *GNA12*. The credible set variants had eQTLs for *AMZ1* in the brain and for *GNA12* outside the CNS. *AMZ1* and *GNA12* are both expressed in a wide variety of tissues, but their predominant expression occurs in the brain. The *GNA12* gene encodes for the G protein alpha subunit 12. The active GTP-bound G12 alpha subunit activates RhoA by activating RhoGEF12, which is encoded by *ARHGEF12*.[45] Of interest, the *ARHGEF12* locus at 11q23.3 was an initial genome-wide significant hit, although this result failed to replicate in the meta-analysis with the UKBB data. *GNA12* is also involved in the sphingosine 1-phosphate pathway, which is intriguing because of its involvement in the angiogenesis of the periventricular fetal germinal matrix. Disruption in this pathway in a mouse model led to vascular alterations in the area, resulting in nearly a 4 times larger lateral brain ventricle size.[46] G protein–coupled receptor signaling, which is mediated by G

proteins, such as *GNA12*, has been found to have associations with hydrocephalus in mouse models.[47]

Intriguingly, a GWAS meta-analysis of increased lateral brain ventricular volume in the general population reported associations with loci at 7p22.3, 10p12.31, and 16q24.2.[48] Our results indicate genome-wide significant associations of these loci also in NPH, a disease characterized by enlarged brain ventricles. The top hits in these loci 7:2760334:C/CT, 10:21589215:T/A (in our credible set with PIP < 0.01, $r^2 = 0.90$), and 16:87191495:G/A (in our credible set with PIP = 0.059, $r^2 = 0.98$) closely align with our top hits in the corresponding loci (7:2757633:T/C, 10:21533927:A/G, and 16:87195738:A/C). These associations with enlarged lateral ventricular volume in the brain with the previously mentioned genes are also supported by data from the UKBB-based Oxford Brain Imaging Genetics Server-BIG40.[49] In addition, the locus 16q24.2 encompassing the *C16orf95* has been identified as being associated with CSF phosphorylated tau levels and lateral ventricular volume in a GWAS meta-analysis studying CSF biomarkers in AD, with the leading variant being 16:87191825:G/A,[50] and it is also included in our credible set (PIP = 0.049 and $r^2 = 0.98$).

Previously, certain genetic variants have been associated with iNPH, and knockout mouse models have shown hydrocephalic findings. These include frameshift deletions causing loss of function in *CWH43* (4:49063892:CAAA/CAA; Lys696AsnfsTer23 and 4:49034669:CA/C;Leu533Ter),[13] copy number loss in intron 2 of *SFMBT1* (3:53035556),[11] and a nonsense variant in *CFAP43* (10:105893468:C/T).[12] In addition, a deletion in *DNAH14* (1:225190746–225510076) has been reported in a family with panventriculomegaly.[10] However, our GWAS did not find any significant variants in these 4 loci (eFigure 8). Based on our review of the literature, so far there seems to be no reported relevant association between these previously found genes and the top hits in our GWAS regarding neurologic conditions.

The criteria for the iNPH selection algorithm that was used to perform the sensitivity analyses were based on the standardized international diagnostic guidelines of iNPH and the Relkin criteria.[1,6] The algorithm had strict exclusion criteria to reliably exclude the sNPH cases from the analysis. A potential problem with the algorithm may be that, because of the strict exclusion criteria, some of the patients with true iNPH could become excluded from the analysis causing false negatives and loss of statistical power. On the other hand, the algorithm might fail to exclude sNPH cases if the diagnostic code for the underlying condition predisposing to sNPH was unrecorded, but we consider the risk of this to be very low. In addition, the algorithm cannot differentiate between the possible and probable iNPH diagnoses or the shunt responsiveness of the patients with iNPH.

The results of our NPH GWAS in the FinnGen cohort were replicated with the meta-analysis conducted by including an independent cohort of 173 NPH cases from UKBB data. Currently, no other large-scale NPH cohorts with appropriate controls were available. The replication cohort was not large enough to have any of its own genome-wide significant hits or yield additional new significant loci in the meta-analysis. The loci near genes *ARHGEF12* and *CSNK1E* did not retain significance in the meta-analysis, but with the *CSNK1E* loci, it must be noted that it had a MAF of only 0.5% in the UKBB data, which could cause its failure to replicate. Further studies in additional cohorts and with potentially different genetic ancestry are required to validate our results. Regardless, this study opens novel avenues for further mechanistic studies on the pathobiology of chronic hydrocephalus and CSF circulation.

We show the thus far largest GWAS in chronic hydrocephalus conducted in the FinnGen cohort. Consequently, we identified novel genetic variation associated with NPH in 6 genome-wide significant loci that also replicated in the UKBB data. These loci were near genes that have roles in the function of important fluid barriers in the CNS, such as BBB and BCSFB, and were previously found to be associated with increased lateral brain ventricle volume, a distinct feature in NPH. Our results highlight the similar effect sizes and allele frequencies in both the NPH and more specific iNPH cohorts, indicating that the identified loci are risk loci for iNPH and not explained by associations with other etiologies. The exact biological mechanisms underlying these genetic variations in the pathophysiology of NPH are still unknown, warranting further studies.

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Continued

Appendix *(continued)*

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