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Low prevalence of *CWH43* variants among Finnish and Norwegian idiopathic normal pressure hydrocephalus patients: a cohort-based observational study

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Abstract

Background Heterozygous *CWH43* loss-of-function (LOF) variants have been identified as iNPH risk factors, with 10–15% of iNPH patients carrying these variants in cohorts from the US. Mouse model harboring *CWH43* LOF variants display a hydrocephalic phenotype with ventricular cilia alterations. Our aim was to study the effect of *CWH43* variants on disease risk and clinical phenotype in Finnish and Norwegian iNPH cohorts.

Methods We analyzed *CWH43* LOF frameshift deletions (4:49032652 CA/C, Leu533Ter and 4:49061875 CA/C, Lys696AsnfsTer23) in Finnish iNPH patients from the Kuopio NPH registry (n = 630) and FinnGen (iNPH n = 1 131, controls n = 495 400), and Norwegian iNPH patients from EADB (n = 306). The Kuopio and Norwegian cohorts included possible and probable iNPH patients based on the American-European iNPH guidelines. FinnGen cohort included iNPH patients based on ICD-10 G91.2 with the exclusion of secondary etiologies, and controls having no diagnosis of hydrocephalus.

Results In the Kuopio cohort of Finnish iNPH patients, 2.9% carried *CWH43* variants (Leu533Ter 2.1%, Lys696AsnfsTer23 0.8%), with one homozygous Leu533Ter carrier. In FinnGen, 3.1% of iNPH patients carried heterozygous variants (Leu533Ter 2.6%, Lys696AsnfsTer23 0.5%) compared to 2.5% of controls (p = 0.219, OR = 1.23, 95% CI 0.85–1.72), with no effect on disease risk or onset age. Importantly in the FinnGen cohort, none of the 23 compound heterozygote or 59 homozygote individuals had hydrocephalus diagnosis. In the Norwegian iNPH cohort, 5.2% of patients were heterozygous variant carriers (Leu533Ter 3.3%, Lys696AsnfsTer23 2.0%). No differences in clinical phenotype (age, triad symptoms, shunt response, vascular comorbidities) were found between carriers and noncarriers in any cohort.

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However, 74% of variant-carrying iNPH patients in FinnGen were female, compared to 47% of noncarriers (p = 0.002). Pedigrees indicated no autosomal dominant co-inheritance of iNPH and the *CWH43* variants.

Conclusions We studied the iNPH-associated *CWH43* LOF variants for the first time on a population-scale. Contrary to previously reported findings in smaller cohorts, our study revealed a low prevalence of these variants in the population-scale Finnish iNPH cohort, with no effect on disease risk of iNPH. The prevalence in the Norwegian iNPH cohort was also low compared to previous studies.

Keywords Normal pressure hydrocephalus, CWH43, Genetics, Finnish, Norwegian, FinnGen, EADB, Risk, Onset age

Background

Idiopathic normal pressure hydrocephalus (iNPH) is a chronic neurological disease affecting the elderly population. Clinical symptoms are characterized by a symptom triad of deteriorating gait, memory problems and urinary incontinence [1, 2]. Neuroradiological findings include enlarged brain ventricles, tight high convexity sulci and often disproportionately enlarged subarachnoid-space hydrocephalus (DESH) [3, 4]. It has also been found that asymptomatic ventricular enlargement (AVE) or asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM) seems to precede the development of clinical symptoms in iNPH [5, 6]. The current treatment option to alleviate symptoms is shunt surgery for cerebrospinal fluid (CSF) drainage [7].

The pathogenesis of iNPH is not yet fully understood, but current findings support the idea that it is multifactorial, likely involving genetic predisposition and an increased burden of cardiovascular comorbidities [8–10]. Pedigrees of familial iNPH have indicated an autosomal-dominant inheritance pattern for the disease [11], and familial history of iNPH has been reported in around 5–11% of cases in the Finnish population [12]. Importantly, new genetic findings are starting to emerge, particularly with our recently published large-scale genome-wide association study (GWAS) in normal pressure hydrocephalus (NPH) [8] and the previous findings of *CWH43* variants being associated with iNPH [13, 14].

Two studies from the US previously showed that two heterozygous loss-of-function (LOF) frameshift deletions in *CWH43* [4:49032652 CA/C, Leu533Ter and 4:49061875 CA/C, Lys696AsnfsTer23 (in GRCh38)] were overrepresented in cohorts of 53 and 94 genotyped iNPH patients. The prevalence of either one of these variants among these iNPH patients was 10–15%, which was significantly higher than in the controls [13, 14].

In a mouse model harboring heterozygous or homozygous *CWH43* variants ($CWH43^{WT/M533}$, $CWH43^{M533/M533}$), which correspond to the human Leu533Ter variant, or a compound heterozygous model ($CWH43^{M533/A530}$), the mice developed features of iNPH, including communicating hydrocephalus, as well as gait and balance problems. The deletions resulted in reduced ventricular cilia and altered distribution of GPI-anchored proteins on the choroid plexus and ependymal cells in the mouse brain ventricles [13]. Additionally, the homozygous deletion ($CWH43^{M533/M533}$) in the mouse model caused downregulation of *L1CAM* in the ventricular and subventricular zones [15]. A recent CSF-proteomics study also reported *L1CAM* downregulation in iNPH [16]. Importantly, LOF variants of *L1CAM* are known to cause X-linked congenital hydrocephalus and neurodevelopmental defects [17], suggesting a potential link between congenital and late-onset chronic hydrocephalus.

So far, *CWH43* variants in iNPH have not been studied in cohorts outside of the US or on a population-wide scale. The aim of this study was to evaluate the effect of *CWH43* LOF variants Leu533Ter and Lys696AsnfsTer23 on the risk and clinical phenotype of iNPH in a population-scale Finnish iNPH cohort and in a large Norwegian iNPH cohort.

Methods

We studied the effects of two frameshift LOF deletions in the *CWH43* gene in relation to iNPH: chr 4:49032652 (CA/C, GRCh38, p.Leu533Ter) and chr 4:49061875 (CA/C, GRCh38, p.Lys696Asnfs23Ter) [NC_000004.12:g.49032653del, NM_025087.3:c.1596del, NP_079363.2:p.Leu533Ter (CA2916994, rs147750792) and NC_000004.12:g.49061878del, NM_025087.3:c.2088del, NP_079363.2:p.Lys696AsnfsTer23 (CA2917167, rs538616012)] [13]. In this study, we utilized two cohorts of Finnish iNPH patients from the Kuopio NPH registry (Kuopio cohort, n = 630) and FinnGen (FinnGen cohort, n = 1 131), and a cohort of Norwegian iNPH patients (Norwegian cohort, n = 306) from European Alzheimer's Disease DNA BioBank (EADB).

Participant selection

Kuopio cohort of Finnish iNPH patients

The Kuopio University Hospital (KUH) NPH registry was used to study the prevalence of *CWH43* variants in the Finnish iNPH cohort and to compare the clinical phenotype between the variant carriers and noncarriers. The registry also has data on family relationships, and this

was used to observe the manifestation of *CWH43* deletions in iNPH pedigrees.

The KUH NPH registry contains data on the nationwide iNPH population, as it collects patient data from all neurosurgical units in Finland. The data includes information e.g. about demographics, symptoms, treatment, comorbidities, imaging, genotypes and family history. All the patients have been clinically evaluated by a neurosurgeon and a neurologist to fulfill the clinical diagnostic criteria for possible or probable iNPH based the American-European iNPH guidelines [1]. The patients had at least one triad symptom, which included gait problems, cognitive impairment and urinary incontinence, and neuroradiological findings indicative of iNPH, which include an Evans Index > 0.3, tight high convexity and occasionally DESH. Most of the patients also underwent a prognostic test prior to shunt placement, which included a tap test, a 24-h intraventricular pressure monitoring or a lumbar infusion test. A positive shunt response in the Kuopio cohort was determined based on a clinical evaluation at 3 months. This included various measures, ranging from a liberal overall clinical assessment to objective modified 12-point Kubo scale-based grading, where a reduction of at least 1 point indicated clinically significant improvement, as well as measured gait velocity [18].

The recruitment of relatives of potentially familial iNPH patients has been done using questionnaires and phone interviews. This was part of previously published studies, where the methods were explained thoroughly [12, 19].

The Kuopio cohort of Finnish iNPH patients consisted of 630 unrelated possible or probable iNPH patients who were genotyped for the two *CWH43* variants. Additionally, five iNPH family pedigrees were observed, from which 14 asymptomatic relatives were genotyped.

FinnGen cohort of Finnish iNPH patients and controls

To study the prevalence and disease risk of *CWH43* variants in relation to iNPH on a population-wide scale, a Finnish cohort of iNPH patients (n = 1 131) and healthy controls (n = 495 400) genotyped in the FinnGen study data release 12 was used. FinnGen is a public–private research project that combines genome and digital healthcare data from over 500 000 Finns nationwide [20].

To identify the iNPH patients in FinnGen, we used the same method as in our recent NPH GWAS study [8]. Cases were selected using the International Classification of Diseases release 10 (ICD-10) diagnosis code G91.2. Cases with a potential secondary etiology for the disease, i.e. sNPH, were excluded based on diagnoses appearing prior to the first diagnosis of G91.2 (Fig. 1). This previously developed case-selection algorithm [8] was developed to align with the American-European iNPH guidelines, selecting only patients with possible or probable iNPH for the analysis, excluding those with potential sNPH [1]. All the iNPH patients had passed the genotyping quality control (QC). The age of the cases was defined as the age at the first G91.2 diagnosis, and cases were excluded if they were under 41 years old.

The controls were the remaining FinnGen participants, excluding individuals with any hydrocephalus diagnosis, as defined by inclusion as a case in the FinnGen G6_HYDROCEPH endpoint. These individuals had available diagnostic and demographic data and had passed genotyping QC. The age of the controls was defined as the age at the end of follow-up, death or moving abroad.

Many of the patients from the Kuopio iNPH cohort are known to also be included in the FinnGen data, and due to this overlap, these two Finnish cohorts cannot be considered completely independent from each other.

Norwegian cohort of iNPH patients

The Norwegian iNPH patients were a subset of the larger EADB study cohort [21, 22]. The 306 Norwegian patients were evaluated according to the same standards as the Kuopio cohort of Finnish iNPH patients, fulfilling the criteria for possible or probable iNPH based on the American-European iNPH guidelines. The Norwegian iNPH patients were additionally evaluated using the Oslo iNPH Grading Scale prior to shunt surgery [23]. A positive shunt response for the Norwegian cohort was defined as an increase of at least 2 points on the Oslo iNPH Grading Scale, based on a clinical evaluation conducted at 6–12 months [23].

Genotyping

PCR genotyping in Kuopio cohort

Quantitative real-time polymerase chain reaction (PCR) genotyping was used to genotype the *CWH43* p.Leu533Ter and p.Lys696AsnfsTer23 variants in the Kuopio cohort. Genomic DNA was extracted from venous blood samples using QIAamp DNA blood mini extraction kit (#51104, QIAGEN, Venlo, The Netherlands). TaqMan Allelic Discrimination Assay (#4351379, assay ID C_170677460_20, Thermo Fisher Scientific Inc., Waltham, MA, USA), with Applied Biosystems QuantStudio 5 Real-Time PCR System) was performed to identify the p.Leu533Ter. For p.Lys696AsnfsTer23, Custom TaqMan® assays (ID ANRWYER) was used.

Since, according to our knowledge, the homozygous variant of *CWH43* has not been detected previously, Sanger DNA sequencing was performed on one iNPH patient confirming the presence of the homozygous *CWH43* deletion of Leu533Ter (Fig. 2). Sanger sequencing was done using a BigDye Terminator v1.1 Cycle Sequencing Kit (#4337457, Applied Biosystems

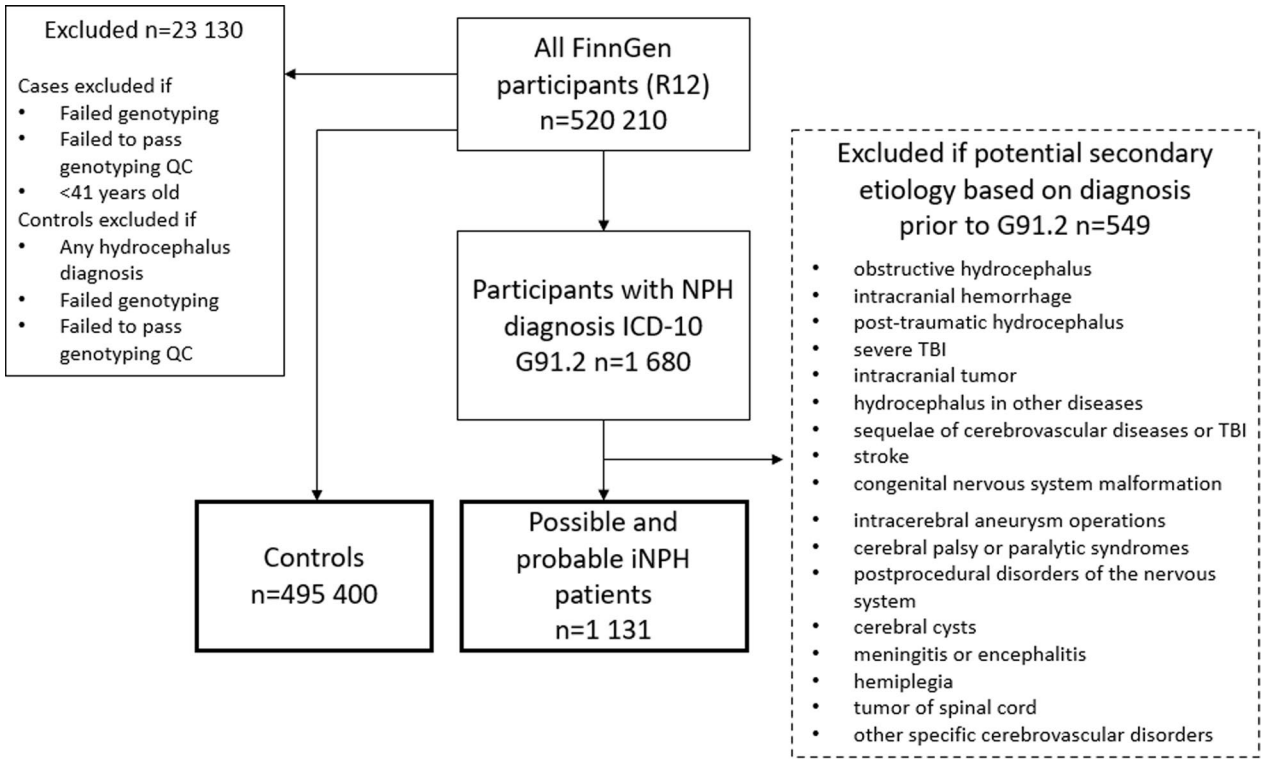

Fig. 1 Flowchart of iNPH patient and control selection in the FinnGen cohort. (i)NPH = (idiopathic) normal pressure hydrocephalus, *QC* quality control, *TBI* traumatic brain injury

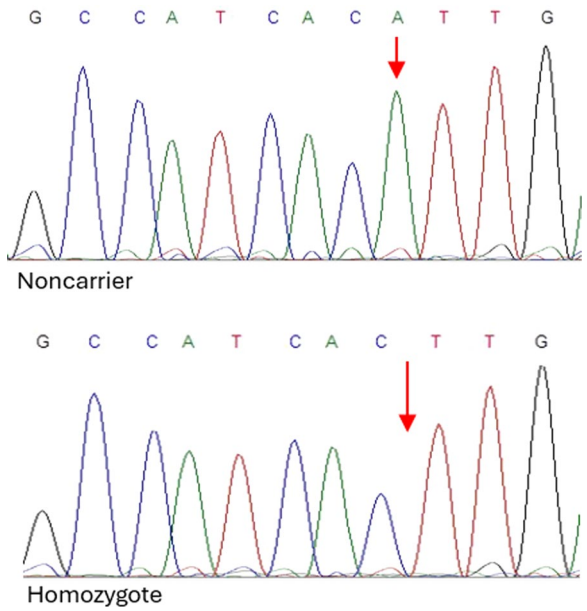

Fig. 2 Electropherogram of Sanger DNA sequencing of noncarrier and homozygous *CWH43* Leu533Ter carrier

QuantStudio 5 Real-Time PCR System), primers CWH43_EX12-M13-R(TCCTGGTTGGATGGGTTG TC) and CWH43_EX12-M13-F (GCATTTGCTTAG TCCCAGTGC) amplifying a 593 bp area according to the kits protocol and analysis using 3500XL Genetic Analyzer (Thermo Fisher Scientific Inc). These genetic analyses were performed in the Genome Centre of Eastern Finland, Kuopio.

FinnGen genotyping

In FinnGen, genotyping was done by using Illumina and Affymetrix chip arrays (Illumina Inc., San Diego, and Thermo Fisher Scientific, Santa Clara, CA, USA) [20]. Samples were excluded if they were duplicates, or had ambiguous sex, high genotype missingness (> 5%), excess heterozygosity (± 4 SD), or non-Finnish ancestry. After the sample exclusions, the FinnGen dataset (release 12) included 520 210 individuals. Variants were excluded if they had high missingness (> 2%), low Hardy–Weinberg equilibrium ($p < 1e\text{-}6$) or low minor allele count (< 3). The samples were pre-phased with Eagle 2.4.1 using 20 000 conditioning haplotypes. Genotype imputation was conducted using Beagle 4.1 and a population-specific SISu v4.2 reference panel, which uses GRCh38 coordinates and includes 8 554 Finnish whole-genome sequenced

individuals. The imputed genotypes were phased with Eagle 2.4.1. After imputation, variants with an imputation INFO score < 0.6 or minor allele frequency < 0.0001 were excluded. For Leu533Ter imputation Info value was 0.997 and for Lys696AsnfsTer23 0.987.

EADB genotyping

The EADB genotyping methods have been previously described [21]. A standard quality control was conducted on variants and samples from each dataset. Genotypes were then imputed using the TOPMed reference panel. As the genotypes of the Leu533Ter (imputation quality 0.992) and Lys696AsnfsTer23 (imputation quality 0.790) variants were imputed in the EADB data, we validated the imputation by comparing the PCR genotypes of the Finnish iNPH patients to their imputed genotypes in the EADB data. In this comparison the genotypes matched for all 486 Finnish iNPH samples, indicating perfect accuracy between the two methods.

Statistical methods

In the Kuopio and Norwegian cohorts, statistical analysis were done using IBM SPSS Statistics 27 software for the comparison between the *CWH43* variant carriers and noncarriers, using $p < 0.05$ as the statistical significance level. Fisher's exact test (two-tailed) or χ^2-test (two-tailed) was applied for categorical variables. The Mann–Whitney U-test was used for continuous variables (non-normal data distribution).

For FinnGen data, all analysis was conducted in R 4.4.0. To test the effect of the variants on iNPH risk, three Cox Proportional-Hazards Models were generated: (1) Leu533Ter, (2) Lys696AsnfsTer23variants and (3) Leu533Ter and Lys696AsnfsTer23 heterozygous variants combined to one category, and homozygotes and compound heterozygotes to another. The relationships between noncarriers (CA/CA), heterozygotes (CA/C) and homozygotes (C/C) with patient's onset age were assessed using the coxph function of the survival R -package [24, 25]. Cox Proportional-Hazards assumption for the models was tested with Schoenfeld test by cox.zph function of the survival R-package. Kaplan–Meier survival curves were plotted by using the survfit2 function of the ggsurvfit R-package [26].

Results

CWH43 variants in the Kuopio cohort of Finnish iNPH patients

Prevalence of CWH43 variants and clinical phenotype of iNPH

Overall, 18 (2.9%) out of the 630 Finnish iNPH patients from the Kuopio cohort carried either of the studied *CWH43* LOF variants. For the Leu533Ter variant, 12 (1.9%) patients carried the heterozygous deletion, and in addition, one patient homozygous for Leu533Ter was found. Lys696AsnfsTer23 was carried as heterozygous by 5 (0.8%) patients. For Lys696AsnfsTer23 we did not find any homozygous carriers. The carriers and noncarriers of Leu533Ter and Lys696AsnfsTer23 had similar mean ages at symptom onset (67.6 years vs. 69.8 years, $p = 0.165$) and at shunt placement (70.6 years vs. 71.8 years, $p = 0.348$). For the variant carriers, 77.8% were female compared to 52.4% of the noncarriers ($p = 0.052$) (Table 1).

The *CWH43* variant carrier status had no statistically significant effect when carriers of Leu533Ter and Lys696AsnfsTer23 were combined and assessed for the presence of the triad symptoms, type 2 diabetes (T2D), arterial hypertension (HTA) and shunt response. The full triad was present in 82.4% of carriers versus 71.4% of noncarriers ($p = 0.418$). All of the 18 patients who were *CWH43* deletion carriers were shunted and had a high positive shunt response rate of 94.4%, based on clinical evaluation at 3 months, compared to 89.1% of noncarriers ($p = 0.708$). DESH features were observed in 66.7% of the *CWH43* deletion carriers for whom brain MRI or CT scans were available (Table 1).

Case of homozygote CWH43 variant carrier

In the Kuopio cohort, we identified one homozygous *CWH43* Leu533Ter carrier with iNPH. No homozygous carriers for this deletion have been previously reported with iNPH. The female patient had a symptom onset age of 60 with progressive gait difficulties. At the age of 75, her gait had deteriorated to a stride length of around 20 cm, accompanied by symptoms of freezing gait, balance problems, and the need for a mobility aid. Additionally, she had developed cognitive decline, with a Mini-Mental State Examination of 18/30 points, and paranoid symptoms. Urinary incontinence was also present. The first brain CT scans were taken only after symptom onset, with findings indicative of iNPH (ventriculomegaly, DESH and tight high convexity sulci based on the axial plane) (Fig. 3). A Spinal MRI offered no explanation for the gait problems and there was no known secondary etiology for the hydrocephalus. A CSF tap test (35 ml) was performed as a prognostic test pre-shunt, with no apparent improvement in symptoms, and intra-cranial pressure monitoring showed increased pulsatility, with the baseline in the normal range. A ventriculoperitoneal shunt (Spitz-Holter valve) was then placed, resulting in a moderate improvement of urinary and cognitive symptoms, but with no improvement in gait. A cortical biopsy taken during the shunt placement showed no diagnostic pathological findings. She lived to the age of 92.

Table 1 Finnish iNPH patients (Kuopio cohort). Prevalence of *CWH43* variants and comparison of clinical phenotype

	***CWH43* variant carriers, n (%)**		***CWH43* variant noncarriers, n (%)**	**p-value**
	Homozygote	**Heterozygote**		
CWH43 Leu533Ter	1 (0.2%)	12 (1.9%)	617 (97.9%)	
CWH43 Lys696AsnfsTer23	0 (0.0%)	5 (0.8%)	625 (99.2%)	
CWH43 Leu533Ter or Lys696AsnfsTer23	18 (2.9%)		612 (97.1%)	
Sex, female	14 (77.8%)		298/559 (52.4%)	0.052
Mean age at onset (SD)	67.6 (6.2)		69.8 (7.6)	0.165
Mean age at shunt (SD)	70.6 (5.9)		71.8 (7.6)	0.348
Full triad symptoms	14/17 (82.4%)		305/427 (71.4%)	0.418
Gait problem	18 (100%)		452/459 (98.5%)	0.870
Memory problem	15/17 (88.2%)		382/459 (83.2%)	0.854
Urinary incontinence	16 (88.9%)		377/459 (82.1%)	0.752
Type 2 diabetes	4 (22.2%)		170/556 (30.6%)	0.605
Arterial hypertension	12 (66.7%)		346/554 (62.5%)	0.809
Shunt response[a]	17 (94.4%)		472/530 (89.1%)	0.708
DESH[b]	6/9 (66.7%)			

Finnish iNPH cohort (Kuopio cohort) n = 630, Variants in GRCh38 coordinates

iNPH Idiopathic normal pressure hydrocephalus, *SD* Standard deviation

[a] Clinical evaluation at 3 months

[b] Disproportionately enlarged subarachnoid-space hydrocephalus

CWH43 variants in iNPH families

Five pedigrees were drawn based on the genotyped patients and healthy relatives, indicating the *CWH43* deletion carrier status when available. The pedigrees show no apparent indication of an autosomal dominant inheritance pattern of iNPH that would be solely related to the LOF deletions in *CWH43* (Fig. 4). Overall, in the Kuopio cohort of Finnish iNPH patients, two (11%) out of the 18 *CWH43* variant carriers (both Leu533Ter carriers) were known to have a family member with iNPH.

In the iNPH families, two asymptomatic relatives who were *CWH43* variant carriers were identified, with available brain imaging. A 52-year-old heterozygous carrier of the Leu533Ter variant showed no signs of ventricular enlargement on CT scans at this age, despite carrying the genetic variant. In contrast, a 68-year-old heterozygous carrier of the Lys696AsnfsTer23 variant presented with AVE (Evans Index > 0.3) on MRI (Fig. 5).

CWH43 variants in the FinnGen cohort of Finnish iNPH patients and controls

Prevalence of CWH43 variants and the clinical phenotype of iNPH

The prevalence of *CWH43* variants in the population-wide FinnGen cohort of 1 131 Finnish iNPH patients was in-line with our observations in the partly overlapping Finnish Kuopio cohort. There were 29 (2.6%) heterozygous carriers of Leu533Ter among the iNPH patients, whereas 6 (0.5%) were heterozygous for Lys696AsnfsTer23. Among the 495 400 controls, 10 143 (2.0%) were heterozygous and 52 (0.01%) homozygous for Leu533Ter (Table 2). For Lys696AsnfsTer23, 2 394 (0.5%) were heterozygous and 7 (0.001%) homozygous. Overall, in the FinnGen cohort, 35 (3.1%) out of the 1 131 iNPH patients were carriers of either Leu533Ter or Lys696AsnfsTer23, compared to 12 572 (2.5%) of the 495 400 controls (p = 0.219, OR = 1.23, 95% CI 0.849–1.717). The mean age of the iNPH patients was 72.6 years (SD 7.7), and 60.7 years (SD 18.0) for the controls, while 47.7% of the patients and 56.4% of the controls were female.

Interestingly, from the phased genotype data, we also identified 23 controls who were compound heterozygous carriers for Leu533Ter and Lys696AsnfsTer23, i.e. carried biallelic LOF mutation in *CWH43.* The median age of the homozygous and compound heterozygous carriers (n = 82) was 63 years.

Among the iNPH patients in the FinnGen cohort, the clinical variables were similar between the *CWH43* variant carriers and noncarriers regarding mean age of onset [72.0 (SD 7.0) vs. 72.6 (SD 7.7), p = 0.528] or prevalence of comorbid T2D and HTA. The majority of iNPH patients that were carriers were female 74.3% compared to 46.9% of noncarriers (p = 0.002) (Table 3). Additionally, the FinnGen controls were compared for *CWH43* variants and the clinical variables (Suppl. 1).

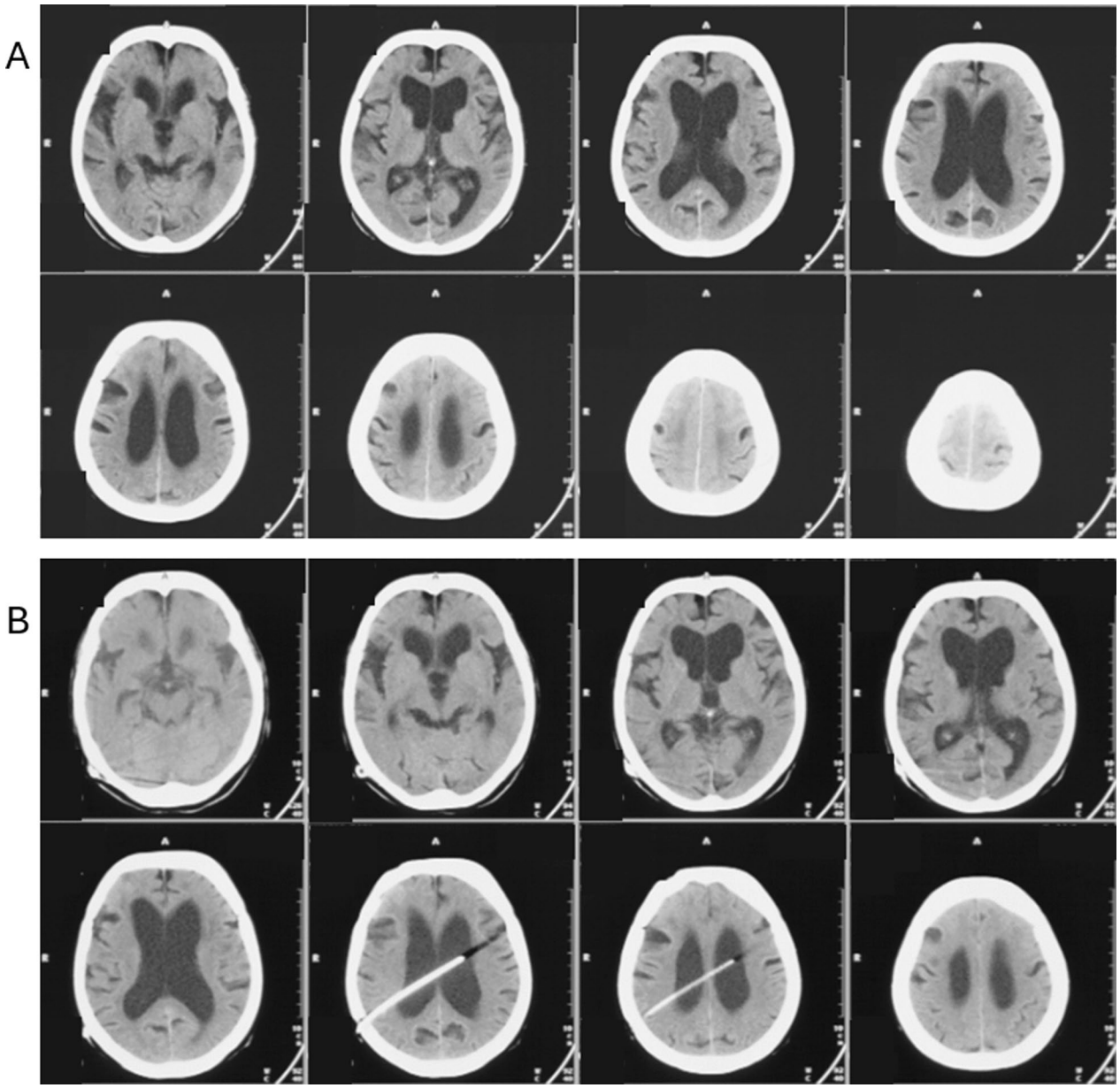

Fig. 3 Brain images of a shunted iNPH patient harboring homozygous *CWH43* Leu533Ter (4:49032652 CA/C). **A** CT scans at the time of diagnosis. **B** Post-shunt surgery CT scans. Axial plane images show features of iNPH (enlarged brain ventricles, DESH and tight high convexity sulci)

Effect of CWH43 variants on the risk of iNPH

To test the effect of Leu533Ter and Lys696AsnfsTer23 variants on the risk of iNPH, three cox hazard models were generated for the FinnGen cohort. The Schoenfeld test for all three models yielded p-values greater than 0.05, indicating that the assumptions of the models were satisfied. However, the *CWH43* variants did not affect the iNPH onset age, as the model p-values were not significant (Leu533Ter $p=0.401$, Lys696AsnfsTer23 $p=1.000$, and Leu533Ter and Lys969AsnfsTer23 combined $p=0.413$) (Fig. 6, Suppl. 2). This indicates that the Leu533Ter and Lys696AsnfsTer23 deletions do not affect the risk of iNPH in the Finnish population.

CWH43 variants in Norwegian iNPH patients

Finally, we studied the *CWH43* variants in Norwegian iNPH cohort. Overall, 16 (5.2%) out of the 306 Norwegian iNPH patients were carriers for the studied *CWH43* LOF variants. For Leu533Ter, 10 (3.3%) patients were heterozygous, and 6 (2.0%) were heterozygous for

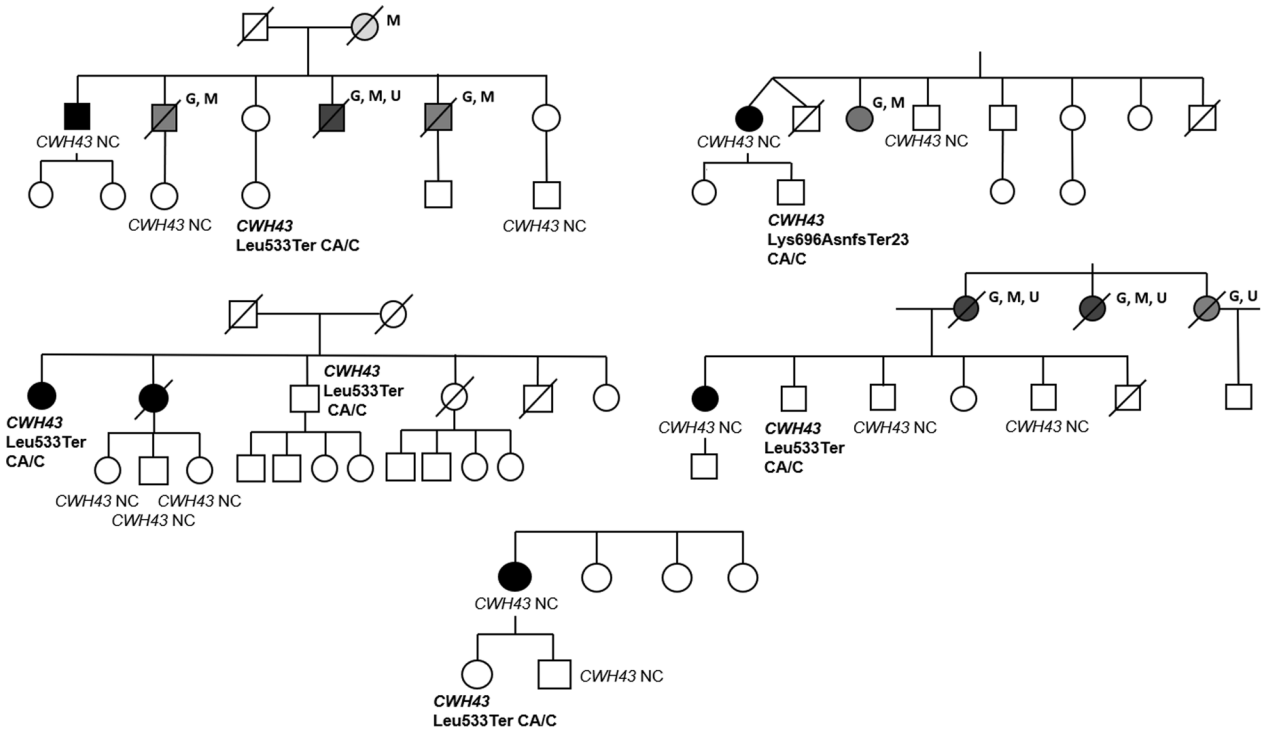

Fig. 4 Pedigrees of five Finnish iNPH families indicating the *CWH43* variant carrier status when available. Black symbol indicates an individual with iNPH. G (= gait), M (= memory), U (= urinary) indicate an individual with triad symptoms with no diagnosis of iNPH. Gray shading indicates the presence of one, two, or three triad symptoms. NC = noncarrier. None of the pedigrees show apparent signs of an autosomal dominant inheritance pattern of iNPH that would be solely linked to the *CWH43* variants, based on the family members with available genotypes. Many family members in the youngest generation of these pedigrees are still under 60 years old, making it uncertain whether they will develop iNPH later in life

Lys696AsnfsTer23. No homozygotes were identified either for Leu533Ter or Lys696AsnfsTer23 in this cohort (Table 4).

When comparing *CWH43* variant carriers (Leu533Ter and Lys696AsnfsTer23 combined) and noncarriers, 37.5% of the carriers were female, compared to 49.7% of the noncarriers (p = 0.444). The mean age of symptom onset for carriers was 70.1 years, compared to 65.2 years among noncarriers (p = 0.074). Prevalence of vascular comorbidities T2D and HTA or positive shunt response rate did not differ between variant carriers and noncarriers (Table 4).

Discussion

CWH43 variants in Finnish population and Norwegian iNPH cohort

As the Leu533Ter and Lys696AsnfsTer23 variants of the *CWH43* gene have been identified as risk factors for iNPH in cohorts from the US, and in a mouse model [13, 14], we investigated the prevalence of these variants for the first time on a population-scale in a Finnish cohort consisting of over 1000 iNPH patients and nearly half a million controls, as well as in a Norwegian cohort of over 300 iNPH patients. We found that the prevalence of *CWH43* Leu533Ter and Lys696AsnfsTer23 variants in the Finnish population and the Norwegian cohort were lower than the 10–15% in previously reported cohorts [13, 14]: approximately 3% of Finnish iNPH patients, 2.5% of Finnish controls, and 5.2% of Norwegian iNPH patients were variant carriers. We also identified the first reported case of a Finnish iNPH patient carrying a homozygous *CWH43* Leu533Ter variant. On the other hand, 59 controls who were homozygous carriers of either variant and 23 controls carrying compound heterozygous Leu533Ter and Lys696AsnfsTer23 variants causing biallelic LOF, did not have a diagnosis of hydrocephalus.

Our results indicate that, in the Finnish population, *CWH43* LOF variants do not affect the disease risk of iNPH, contradicting previous findings from smaller iNPH cohorts [13, 14]. Initially, Yang et al. found that in a cohort of 53 shunt-responsive iNPH patients, 15% carried heterozygous *CWH43* variants (Leu533Ter 7.5% and Lys696AsnfsTer23 7.5%) [13]. In another US cohort of 84 genotyped iNPH patients who shared the same ethnicity (white, non-Hispanic), 12% carried these variants (Leu533Ter 9.5% and Lys696AsnfsTer23 2.4%) compared to 5.5% in 532 healthy controls, with variant carriers having OR of 2.60 for iNPH [14].

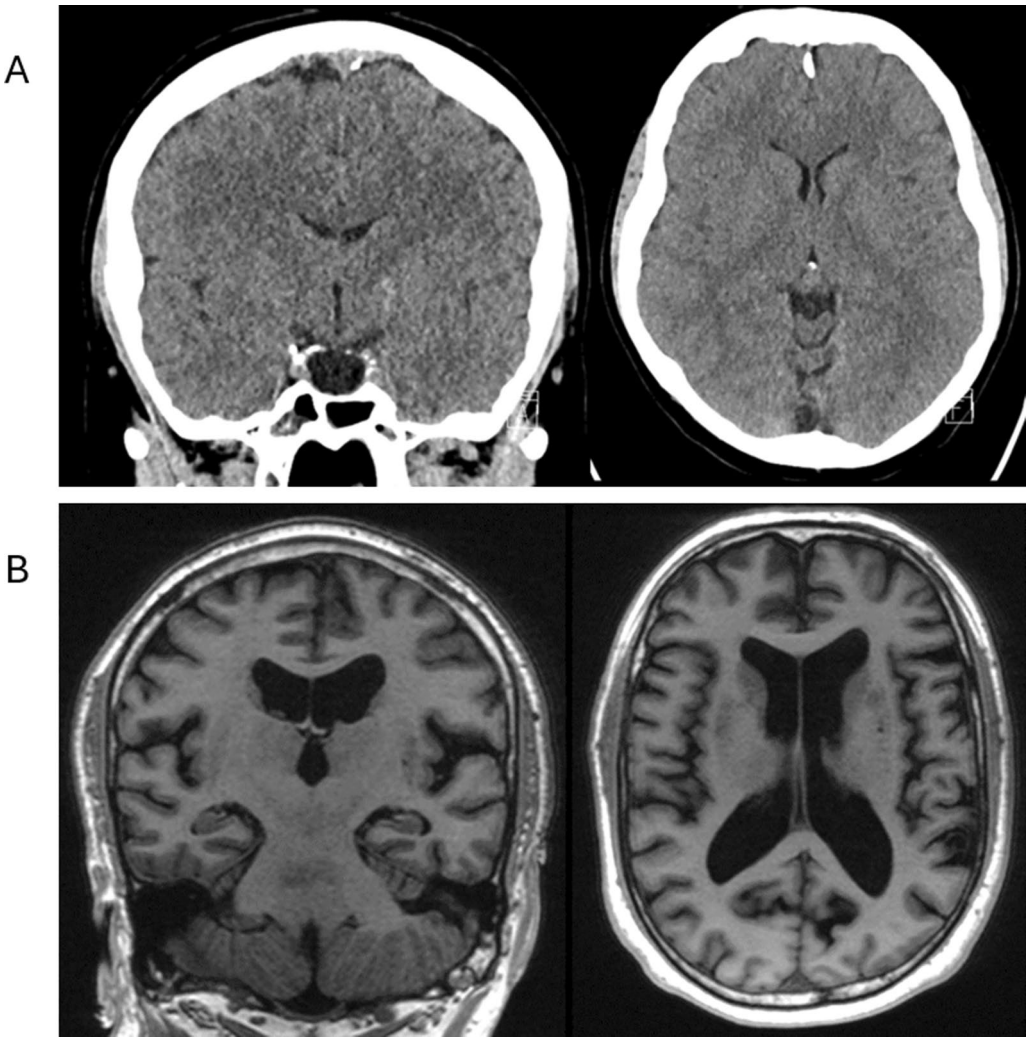

Fig. 5 Brain imaging of asymptomatic relatives carrying heterozygous *CWH43* variants. **A** CT images of a 52-year-old Leu533Ter carrier, showing no ventricular enlargement. **B** MRI images (T1-weighted) of a 68-year-old Lys696AsnfsTer23 carrier, revealing asymptomatic ventriculomegaly (Evans Index 0.34) with no DESH

Table 2 *CWH43* variant prevalence in the FinnGen cohort

	iNPH patients (n = 1 131)			Controls (n = 495 400)		
	Homozygote	**Heterozygote**	**Noncarriers**	**Homozygote**	**Heterozygote**	**Noncarriers**
CWH43 Leu533Ter	0 (0%)	29 (2.6%)	1 102 (97.4%)	52 (0.01%)	10 143 (2.0%)	485 205 (97.9%)
CWH43 Lys696AsnfsTer23	0 (0%)	6 (0.5%)	1 125 (99.5%)	7 (0.001%)	2 394 (0.5%)	492 999 (99.5%)
CWH43 Leu533Ter or Lys696AsnfsTer23	0 (0%)	35 (3.1%)	1 096 (96.9%)	59 (0.01%)[#]	12 513 (2.5%)[+#]	482 804 (97.5%)

[+] 23 controls were compound heterozygote carriers of Leu533Ter and Lys696AsnfsTer23

[#] Median age of homozygous and compound heterozygote carriers of Leu533Ter and Lys696AsnfsTer23 in controls (n = 82) was 63 years

Our current results align with our recent FinnGen GWAS study on NPH and iNPH, which used the same criteria to identify patients and controls as in this study, and where no iNPH-associated variants were identified in the *CWH43* locus [8]. In the Norwegian iNPH cohort, the prevalence of *CWH43* variants was similarly low, as in the Finnish cohorts. Unfortunately, no Norwegian control cohort was available for comparison in this study.

Table 3 Comparison of *CWH43* variant carrier and noncarrier iNPH patients in FinnGen cohort

	CWH43 **variant carriers (Leu533Ter or Lys696AsnfsTer23) (n = 35)**	***CWH43*** **variant noncarriers (n = 1 096)**	**p-value**
Median age at onset (SD)	72.0 (7.0)	72.6 (7.7)	0.528
Sex, female %	74.3%	46.9%	0.002
Type 2 diabetes %	25.7%	26.4%	1.000
Arterial hypertension %	65.7%	60.9%	0.602

iNPH n = 1 131

CWH43 variants and the clinical phenotype of iNPH

The *CWH43* variant carrier status did not impact the clinical phenotype of iNPH in either the Finnish or Norwegian cohorts, based on the variables studied. An exception was the higher proportion of female variant carriers in the FinnGen iNPH cohort, suggesting a potential for sex-linked differences, but even in this cohort the overall number of cases with variants was small. The findings are in-line with previous reports regarding triad symptoms, shunt improvement and age distribution [14]. Notably, in this study and the previous studies, the positive shunt response rate among *CWH43* variant carriers has been excellent [13, 14]. The prevalence of T2D and HTA did not differ between *CWH43* deletion carriers and noncarriers, which is an important finding considering the role of *CWH43* variants and the potential for disease-modifying interactions with vascular diseases in iNPH. Overall, T2D and HTA are overrepresented comorbidities in iNPH [9, 10] and are known risk factors for white matter disease, which is also frequently observed in iNPH [27–29]. On average, the cardiovascular disease profile and obesity rates in Americans and Finns are similar, supporting the comparability of our findings to previous *CWH43* iNPH studies [30, 31].

A previous study found that only 21% of iNPH *CWH43* carriers had DESH on imaging, compared to 57% of noncarriers, and that carriers tended to have a larger head circumference, which was suggested as a possible congenital hydrocephalus etiology with late-onset clinical presentation [14]. However, in our study DESH was more frequent, observed in 6 out of the 9 (67%) *CWH43* variant carriers with available brain scans, a frequency similar to that previously reported in a Finnish iNPH cohort [32]. However, due to the small imaging sample sizes in these studies, drawing definitive conclusions requires further research.

CWH43 genotypes and asymptomatic carriers

The novel iNPH case harboring a homozygous *CWH43* variant followed a natural clinical course of iNPH, with initial symptoms of slowly worsening gait problems that eventually evolved into the full symptom triad. Symptom onset at age 60 is on the early side of the iNPH age spectrum, but the overall clinical presentation of iNPH was typical [1, 4]. The patient remained undiagnosed for 15 years, and the shunt response was only moderate, possibly hampered due to the long delay between symptom onset and treatment [33].

In the FinnGen cohort, a further 59 individuals were identified as homozygous for deletions in Leu533Ter or Lys696AsnfsTer23 but without a diagnosis of any hydrocephalus. Additionally, 23 controls were compound heterozygous, causing biallelic LOF of *CWH43.* The median age of the Finnish homozygous and compound heterozygous controls was 63 years, placing many within the typical onset age range for iNPH [1, 4]. In a mouse model of *CWH43* variants, heterozygous, compound heterozygous and homozygous deletions all resulted in pathogenic findings [13]. Despite the expectation that homozygous or compound heterozygous carriers would be at higher risk for iNPH, our data did not support this, as none of the iNPH patients in our cohorts were compound heterozygous carriers, and only one homozygous iNPH patient was found in the Kuopio cohort. This finding further highlights the low impact of these variants on iNPH. There is also the possibility of a protective genetic or environmental factor that counteracts the pathogenic effects of *CWH43* variants, or some of these asymptomatic carriers could have undiagnosed cases of iNPH.

It is also unknown whether deletions in *CWH43* lead to radiological features of AVE or AVIM without clinical symptoms of iNPH or if such changes appear earlier in life. For instance, the brain scans of a 52-year-old asymptomatic Leu533Ter carrier showed no ventricular enlargement (Fig. 5), suggesting that *CWH43* variants might not cause gross anatomical changes early in life, which would be consistent with findings in the *CWH43* mouse model [13]. However, a 68-year-old Lys696AsnfsTer23 carrier presented with AVE (Fig. 5). It should be noted that these individuals were relatives of iNPH patients, which may predispose them to a higher risk of developing iNPH regardless of the *CWH43* variants. Thus, the observed asymptomatic ventriculomegaly could be influenced by other factors besides the deletion in *CWH43*, particularly given our findings that on

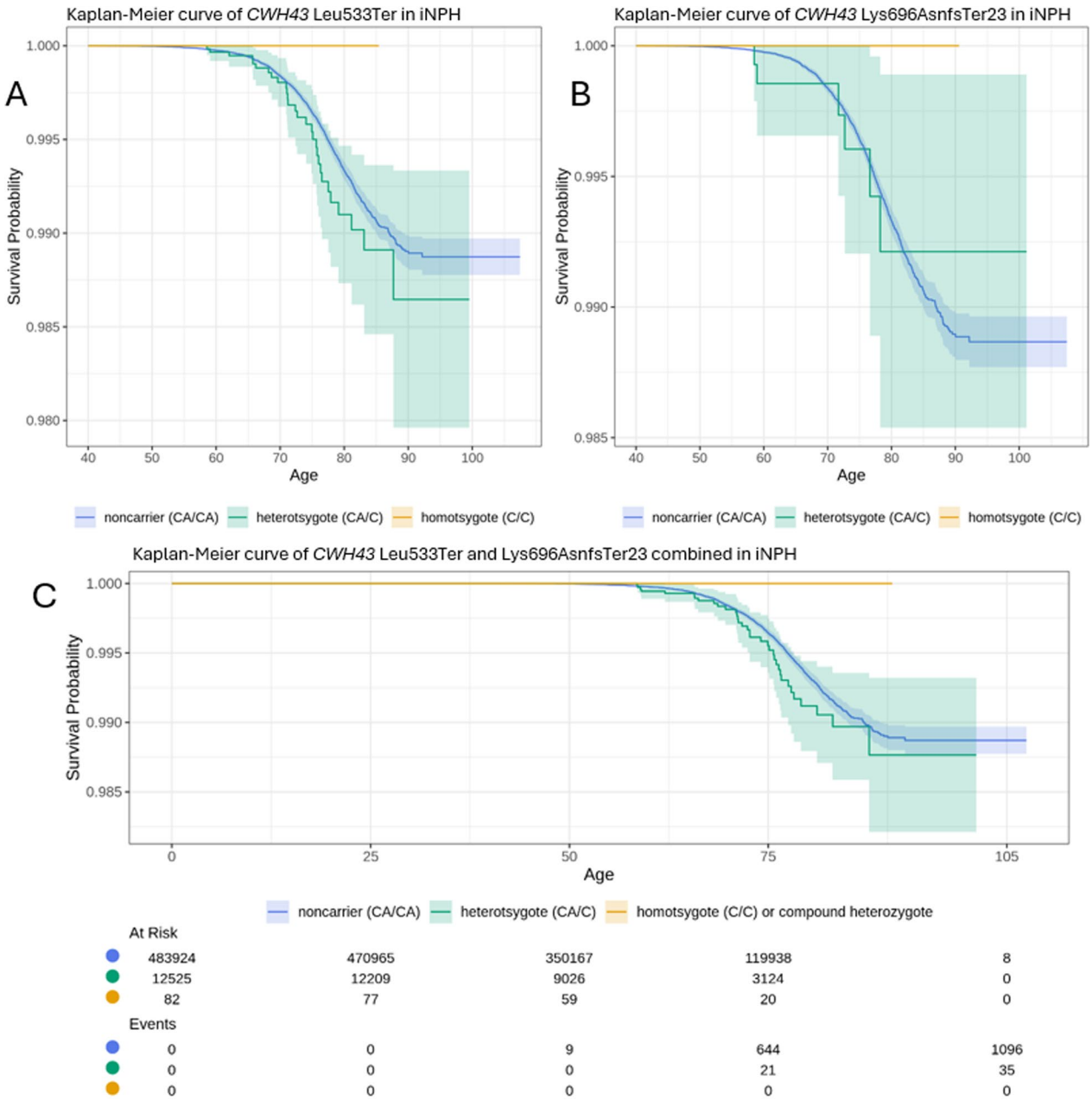

Fig. 6 Kaplan–Meier survival curves of the *CWH43* variants in the FinnGen cohort. **A** *CWH43* Leu533Ter, **B** *CWH43* Lys696AsnfsTer23, **C** *CWH43* Leu533Ter and Lys696AsnfsTer23 combined. The green shaded area indicates confidence intervals. iNPH = idiopathic normal pressure hydrocephalus. Kaplan–Meier survival curves indicate no significant effect of *CWH43* variants on the onset age or disease risk of iNPH in FinnGen cohort

a population-scale these variants have no impact on the disease risk of iNPH.

Familial iNPH and *CWH43* variants

It is unknown whether iNPH associated with *CWH43* deletions follows a Mendelian inheritance pattern. In the Kuopio cohort of Finnish iNPH patients, 11% of *CWH43* variant carriers reported a family member with iNPH, indicating no significantly higher familial clustering of this genetic variant in iNPH compared to previous reports of familial iNPH in this population [12]. However, a previous study reported that 38% of iNPH patients carrying the *CWH43* deletion had a familial history of iNPH or symptomatology [13]. Even heterozygous

Table 4 Norwegian iNPH cohort. Prevalence of *CWH43* variants and comparison of clinical phenotype

	***CWH43* variant carriers, n (%)**		***CWH43* variant noncarriers, n (%)**	**p-value**
	Homozygote	**Heterozygote**		
CWH43 Leu533Ter	0 (0.0%)	10 (3.3%)	296 (96.7%)	
CWH43 Lys696AsnfsTer23	0 (0.0%)	6 (2.0%)	300 (98.0%)	
CWH43 Leu533Ter or Lys696AsnfsTer23	16 (5.2%)		290 (94.8%)	
Sex, female	6 (37.5%)		144 (49.7%)	0.444
Mean age at onset (SD)	70.1 (10.1)		65.2 (11.5)	0.074
Type 2 diabetes	2/15 (13.3%)		46/272 (16.9%)	1.000
Arterial hypertension	6/15 (40.0%)		120/272 (44.1%)	0.796
Shunt response[a]	13/13 (100%)		189/214 (88.3%)	0.370

Norwegian iNPH cohort n = 306

iNPH Idiopathic normal pressure hydrocephalus, *SD* Standard deviation

[a] Clinical evaluation at 6–12 months

deletions in *CWH43* in mouse models have resulted in a hydrocephalic phenotype, suggesting that *CWH43* deletions could potentially predispose to autosomal dominant inheritance [13].

The pedigrees of Finnish iNPH families did not show clear evidence of an autosomal dominant or other inheritance pattern linked solely to the LOF deletions in *CWH43* (Fig. 4), but the number of genotyped relatives in these pedigrees was limited to draw definite conclusions. Also, it must be noted that many family members in the youngest generation of these pedigrees have not yet reached elderly age and may yet develop iNPH in the future.

Conclusions

We studied the iNPH-associated *CWH43* risk variants for the first time on a population-scale and in cohorts outside of the US. In the Finnish population, the prevalence of *CWH43* LOF variants in iNPH was low, and with no effect on the disease risk of iNPH. In the Norwegian iNPH cohort, the prevalence of *CWH43* variants was also low compared to previous studies. *CWH43* variant carrier status did not affect the clinical phenotype of iNPH based on the studied variables, apart from a higher proportion of female variant carriers in the FinnGen iNPH cohort. Additionally, we identified the first reported case of a homozygous *CWH43* variant carrier with a natural disease course of iNPH, but also multiple homozygous and compound heterozygous carriers without a diagnosis of any hydrocephalus. The brain scans of asymptomatic relatives carrying *CWH43* variants failed to consistently show ventricular enlargement. Pedigrees from Finnish iNPH families did not show a clear autosomal dominant inheritance pattern linked solely to *CWH43* variants. However, more extensive genotyping and long-term follow-up within the families would be necessary to reach a definitive conclusion about heritability. Overall, our results contradict previously reported findings in smaller cohorts, showing that in a population-scale Finnish cohort these *CWH43* variants do not affect the disease risk of iNPH.

Abbreviations

AVE	Asymptomatic ventricular enlargement
AVIM	Asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI
CSF	Cerebrospinal fluid
DESH	Disproportionately enlarged subarachnoid-space hydrocephalus
EADB	European Alzheimer's Disease DNA BioBank
GWAS	Genome-wide association study
HTA	Arterial hypertension
ICD-10	International Classification of Diseases release 10
iNPH	Idiopathic normal pressure hydrocephalus
KUH	Kuopio University Hospital
LOF	Loss-of-function
NPH	Normal pressure hydrocephalus
PCR	Polymerase chain reaction
QC	Quality control
sNPH	Secondary normal pressure hydrocephalus
T2D	Type 2 diabetes

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12987-025-00625-0.

Additional file 1

Additional file 2

Additional file 3

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Author contributions

Joel Räsänen and Seppo Helisalmi, shared first authorship. J.Rä, Se.H, Sa.H, M.H, V.L and A.L study concept or design; J.Rä, Se.H, Sa.H, J.Ra, V.E.K, A.J, B.GB, C.B, M.O, C.A, J.F, A.K, J.Ri, A.R, M.K, M.F, K.L, J.S, M.P, A.M.K, V.J, A.M.P, A.M, H.S, J.E.J, JC.L, P.K.E, A.P, M.I.K, M.H, V.L and A.L major role in the acquisition of data; J.Rä, Se.H, Sa.H, J.Ra, H.M, M.H, V.L and A.L analysis or interpretation of data; J.Rä, Se.H, Sa.H, J.Ra, H.M, M.H, V.L and A.L drafting/revision of the manuscript for content, including medical writing for content. All authors offered comments and suggestions to the initial version of the manuscript and endorsed the submitted version. All authors, upon request, had full access to all the data reported in the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study. For FinnGen, based on National and European regulations (GDPR), access to sensitive individual-level health data requires approval by national authorities for specific research projects and researchers. Health data is provided by the National Health Register Authorities, such as the Finnish Institute of Health and Welfare and Statistics Finland, and is approved by the Finnish Data Authority, Findata, or relevant agencies. Due to these regulations, FinnGen cannot grant access to individual-level data to others. Researchers seeking access to health register data can apply through the Finnish Data Authority Findata (https://findata.fi/en/permits/), while individual-level genotype data can be requested from Finnish biobanks via the Fingenious portal (https://site.fingenious.fi/en/) hosted by the Finnish Biobank Cooperative FINBB (https://finbb.fi/en/). Finnish biobanks can provide access to research projects within the scope regulated by the Finnish Biobank Act.

Declarations

Ethics approval and consent to participate

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). For Norwegians, the study was approved by the Regional Committee for Medical and Health Research Ethics (REK) of Health Region South-East, Norway (2015/1313), and the Institutional Review Board of Oslo University Hospital (2015/8128). All patients provided informed consent. Subjects in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, separate research cohorts, collected prior to 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 FinnGen study is approved by Finnish Institute for Health and Welfare (permit numbers: THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019 and THL/1524/5.05.00/2020), Digital and population data service agency (permit numbers: VRK43431/2017–3, VRK/6909/2018–3, VRK/4415/2019–3), the Social Insurance Institution (permit numbers: KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 134/522/2019, KELA 138/522/2019, KELA 2/522/2020, KELA 16/522/2020), Findata permit numbers THL/2364/14.02/2020, THL/4055/14.06.00/2020, THL/3433/14.06.00/2020, THL/4432/14.06/2020, THL/5189/14.06/2020, THL/5894/14.06.00/2020, THL/6619/14.06.00/2020, THL/209/14.06.00/2021, THL/688/14.06.00/2021, THL/1284/14.06.00/2021, THL/1965/14.06.00/2021, THL/5546/14.02.00/2020, THL/2658/14.06.00/2021, THL/4235/14.06.00/2021, Statistics Finland (permit numbers: TK-53–1041-17 and TK/143/07.03.00/2020 (earlier TK-53–90-20) TK/1735/07.03.00/2021, TK/3112/07.03.00/2021) and Finnish Registry for Kidney Diseases permission/extract from the meeting minutes on 4th July 2019. The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, BB2021_65, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, HUS/248/2020, HUS/430/2021 §28, §29, HUS/150/2022 §12, §13, §14, §15, §16, §17, §18, §23, §58, §59, HUS/128/2023 §18, Auria Biobank AB17-5154 and amendment #1 (August 17 2020) and amendments BB_2021-0140, BB_2021-0156 (August 26 2021, Feb 2 2022), BB_2021-0169, BB_2021-0179, BB_2021-0161, AB20-5926 and amendment #1 (April 23 2020) and it´s modifications (Sep 22 2021), BB_2022-0262, BB_2022-0256, Biobank Borealis of Northern Finland_2017_1013, 2021_5010, 2021_5010 Amendment, 2021_5018, 2021_5018 Amendment, 2021_5015, 2021_5015 Amendment, 2021_5015 Amendment_2, 2021_5023, 2021_5023 Amendment, 2021_5023 Amendment_2, 2021_5017, 2021_5017 Amendment, 2022_6001, 2022_6001 Amendment, 2022_6006 Amendment, 2022_6006 Amendment, 2022_6006 Amendment_2, BB22-0067, 2022_0262, 2022_0262 Amendment, Biobank of Eastern Finland 1186/2018 and amendment 22§/2020, 53§/2021, 13§/2022, 14§/2022, 15§/2022, 27§/2022, 28§/2022, 29§/2022, 33§/2022, 35§/2022, 36§/2022, 37§/2022, 39§/2022, 7§/2023, 32§/2023, 33§/2023, 34§/2023, 35§/2023, 36§/2023, 37§/2023, 38§/2023, 39§/2023, 40§/2023, 41§/2023, Finnish Clinical Biobank Tampere MH0004 and amendments (21.02.2020 & 06.10.2020), BB2021-0140 8§/2021, 9§/2021, §9/2022, §10/2022, §12/2022, 13§/2022, §20/2022, §21/2022, §22/2022, §23/2022, 28§/2022, 29§/2022, 30§/2022, 31§/2022, 32§/2022, 38§/2022, 40§/2022, 42§/2022, 1§/2023, Central Finland Biobank 1–2017, BB_2021-0161, BB_2021-0169, BB_2021-0179, BB_2021-0170, BB_2022-0256, BB_2022-0262, BB22-0067, Decision allowing to continue data processing until 31st Aug 2024 for projects: BB_2021-0179, BB22-0067,BB_2022-0262, BB_2021-0170, BB_2021-0164, BB_2021-0161, and BB_2021-0169, and Terveystalo Biobank STB 2018001 and amendment 25th Aug 2020, Finnish Hematological Registry and Clinical Biobank decision 18th June 2021, Arctic biobank P0844: ARC_2021_1001.

Consent for publication

All individual data shown has a written informed consent for publication.

Competing interests

The authors declare no competing interests.

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