

Genetic Survey of Adult-Onset Idiopathic Intracranial Hypertension

Markus H. Kuehn, PhD, Rajashree Mishra, BS, Benjamin E. Deonovic, MS, Kimberly N. Miller, BA, Shana E. McCormack, MD, Grant T. Liu, MD, Mark J. Kupersmith, MD, Michael Wall, MD, the NORDIC IIHTT Study Group

Background: Idiopathic intracranial hypertension (IIH) is a condition characterized by increased intracranial pressure of unknown cause. IIH has been shown to be associated with female sex as well as obesity. This genome-wide association study was performed to determine whether genetic variants are associated with this condition.

Methods: We analyzed the chromosomal DNA of 95 patients with IIH enrolled in the Idiopathic Intracranial Hypertension Treatment Trial and 95 controls matched on sex, body mass index, and self-reported ethnicity. The samples were genotyped using Illumina Infinium HumanCoreExome v1-0 array and analyzed using a generalized linear mixed model that accounted for population stratification using multidimensional scaling.

Results: A total of 301,908 single nucleotide polymorphisms (SNPs) were evaluated. The strongest associations observed were for rs2234671 on chromosome 2 ($P = 4.93 \times 10^{-07}$), rs79642714 on chromosome 6 ($P = 2.12 \times 10^{-07}$), and rs200288366 on chromosome 12 ($P = 6.23 \times 10^{-07}$). In addition, 3 candidate regions marked by multiple associated SNPs were identified on chromosome 5, 13, and 14.

Conclusions: This is the first study to investigate the genetics of IIH in a rigorously characterized cohort. The study was limited by its modest size and thus would have only been able to demonstrate highly significant association on a genome-wide scale for relatively common alleles exerting large effects. However, several variants and loci were identified that might be strong candidates for follow-up studies in other well-phenotyped cohorts.

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The etiology of idiopathic intracranial hypertension (IIH) and is poorly understood. Female sex and high body mass index are significantly associated with elevated risk of IIH. These data suggest that sex- and obesity-related physiologic factors may be important in the development of IIH (1,2).

Some investigators have suggested that IIH may have a familial component (3), and 5% of patients enrolled in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) stated that other family members had IIH (4). Sibling or twin pairs of IIH patients also have been reported (5–10). Most of these studies describe instances of 2 or 3 family members who had IIH (4). Sibling or twin pairs of IIH patients also have been reported (5–10). Most of these studies describe instances affecting 2 or 3 family members, but a family with 6 affected individuals also has been described (11). In a comprehensive review, 27 individuals belonging to 11 families in a cohort of 237 patients were identified (3). This degree of familial occurrence is much higher than what might be expected by chance and suggests a familial (i.e., genetic) component to the disease. However, a clear Mendelian inheritance pattern for a single gene with a strong effect has not been demonstrated. More likely, any genetic bias toward developing IIH is mediated by multiple genes, each having a modest effect. IIH may then occur

Department of Ophthalmology and Visual Sciences (MHK, KNM, MW), The University of Iowa, Iowa City, Iowa; Division of Human Genetics (RM), Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Department of Biostatistics (BED), The University of Iowa, Iowa City, Iowa; Division of Endocrinology and Diabetes (SEM), Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Department of Pediatrics (SEM), Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; Division of Ophthalmology (GTL), Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and New York Eye and Ear Infirmary (MJK), Icahn School of Medicine at Mount Sinai, New York, New York.

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Address correspondence to Markus H. Kuehn, PhD, Department of Ophthalmology and Visual Sciences, The University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242; E-mail: markus-kuehn@uiowa.edu

when environmental factors, such as weight gain, are present in individuals with a genetic background of increased susceptibility. Involvement of both environmental and genetic factors in the etiology of neurologic disease is common (12).

The IIHTT, conducted from 2009 to 2014, was the largest prospectively analyzed cohort of untreated patients with IHH (13,14). During enrollment, DNA was obtained from study participants as well as from unaffected controls. This material was used in a genome-wide association study (GWAS), a method designed to identify the presence of one or many genetic variants that are associated with a particular disease. This study is the first of its kind that has been conducted to determine whether genetic variants contribute to the pathophysiology of IHH.

MATERIALS AND METHODS

Patient Samples

All experiments conformed to the Declaration of Helsinki and were approved by the respective institutional review board of the participating institutions. Written informed consent was obtained from all study participants.

All IHH samples were obtained from female patients participating in the IIHTT (clinicaltrials.gov identifier: NCT01003639). Patients (average age 28.4 years; range: 18–52 years) underwent detailed evaluation to diagnose IHH and to ensure that they met the entry criteria of the study. A detailed description of the study's inclusion and exclusion criteria has been published elsewhere (13,14). Controls (average age 38.2 years; range: 19–59 years) also were female and had a body mass index >31 kg/m². They were examined to exclude those with symptoms or signs of IHH and were matched by self-reported ethnicity to IHH subjects at each study site.

Five to 10 mL of venous blood was obtained from all participants at the respective study sites and shipped to the University of Iowa for further processing. From these samples, genomic DNA was isolated using an automated nucleic acid purification system (Autopure LS; Genra Systems, Minneapolis, MN).

Single Nucleotide Polymorphism Array Genotyping

Genome-wide single nucleotide polymorphism (SNP) genotypes were obtained for all samples using Illumina Infinium HumanCoreExome v1-0 BeadChips that interrogate 538,448 markers. These include 240,000 genome-wide tag SNPs, representing haplotype blocks, whereas the remainder was focused on SNPs located within the coding regions of the genome. Samples were processed according to the manufacturer's recommendations and genotyped using 4 chips. Data were captured using Illumina Genome Studio v2011.1 software and the genome-wide association analysis

toolset PLINK 1.07 (15) was used for data management and basic analysis.

Haplotype phasing and imputation were conducted using ShapeIt (16) and Impute2 (17) software, respectively. Finally, associations were evaluated using the Genome-wide Efficient Mixed Model Association algorithm for standard linear mixed models (18). Power calculations were performed using the Genetic Association Study Power Calculator and plotted using the qqman R module (19). The human genome built GRCh37.p13 is used as the reference genome throughout the study.

RESULTS

DNA samples were obtained from 165 patients and 123 controls. Both men and women enrolled in the IIHTT but, because men and women have somewhat different symptom profiles (20) which could be indicative of distinct genetic risk factors, only samples from female participants were evaluated in this genetic study. Ninety-five ethnically and geographically matched pairs of IHH patients and controls were chosen randomly. These were obtained from 26 research centers across the United States and Canada and included individuals of various ethnicities (Table 1).

Genotyping resulted in a call rate $>90\%$ for all samples and consequently all samples were used during the subsequent analysis. We then excluded SNPs with a genotyping rate below 90% because SNP assays that fail in a large fraction of samples are likely to result in spurious data. Finally, SNPs with a minor allele frequency (MAF) below 1% were excluded because the statistical power for rare SNPs is extremely low. In total 2,184 SNPs were excluded due to low genotyping rate and 235,252 were excluded due to low MAF. The final analysis evaluated 301,908 SNPs.

Population stratification has the potential to confound analysis of GWAS data and leads to spurious associations (21). To minimize this possibility, pairs of ethnically matched patients and controls were submitted from each participating study site. However, because ethnicity was self-reported, we verified the absence of population stratification using the genetic markers in our model in a dimension reduction approach. To do so, we calculated the leading multidimensional scaling vectors using a matrix based on identity-by-state distances to calculate pairwise distances between the subjects (22). This technique generates quantitative estimates of similarity among groups of samples. The resultant data can be plotted to test self-reported ethnicity. As shown in Figure 1, the distribution of samples along Dimension 1, which is the primary means of discrimination, indicates that samples from individuals with African ancestry cluster separately from the other sample groups. These findings largely confirm self-reported ethnicity in the samples

TABLE 1. Distribution of self-reported race among patients with IHH and controls

	Caucasian	African American	Native American	Asian	Unknown	Total
Control	61	21	3	1	9	95
Case	63	21	4	1	6	95

IHH, idiopathic intracranial hypertension.

included in the data set. However, these findings also indicate that additional data analyses were required to avoid the generation of faulty conclusions due to the use of patients from multiple ethnicities (i.e., population stratification).

During the recruitment of participants, care was taken to obtain ethnically matched patients and controls. To verify that the sample populations were indeed balanced, an estimate of the inflation factor was calculated. The result ($\lambda_{gc} = 1$) indicates the absence of population stratification. The finding that the samples were well matched can also be demonstrated by representing the data in a quantile–quantile (Q-Q) plot. This graphical technique shows the expected distribution of association for all SNPs compared with the observed values. Perfectly matched data will fall along a single diagonal. A consistent deviation from the diagonal line ($X = Y$) indicates differences between patients and controls across the whole genome, as would be expected

to occur when ethnically unmatched samples are used. Well-controlled studies, however, show a diagonal line curving sharply at the end, which represents the small number of true associations with disease variants. Here, we conducted χ^2 tests of association stratified by race (Cochran–Mantel–Haenszel test) as well as unstratified (Fig. 2). The resulting curves are highly similar, indicating the absence of population stratification.

Associations between SNPs and IHH were evaluated using a generalized linear mixed model assuming a Bernoulli response distribution and a logit link function to model the log odds of disease, given the number of minor alleles at a particular SNP. A separate model was fitted for each SNP. Figure 3 summarizes the resultant P values in a Manhattan plot format. In these plots, each SNP is represented by a dot and sorted across the human chromosomes from left to right. The Y axis corresponds to the strength of the association to disease. Several of the investigated SNPs seemed to

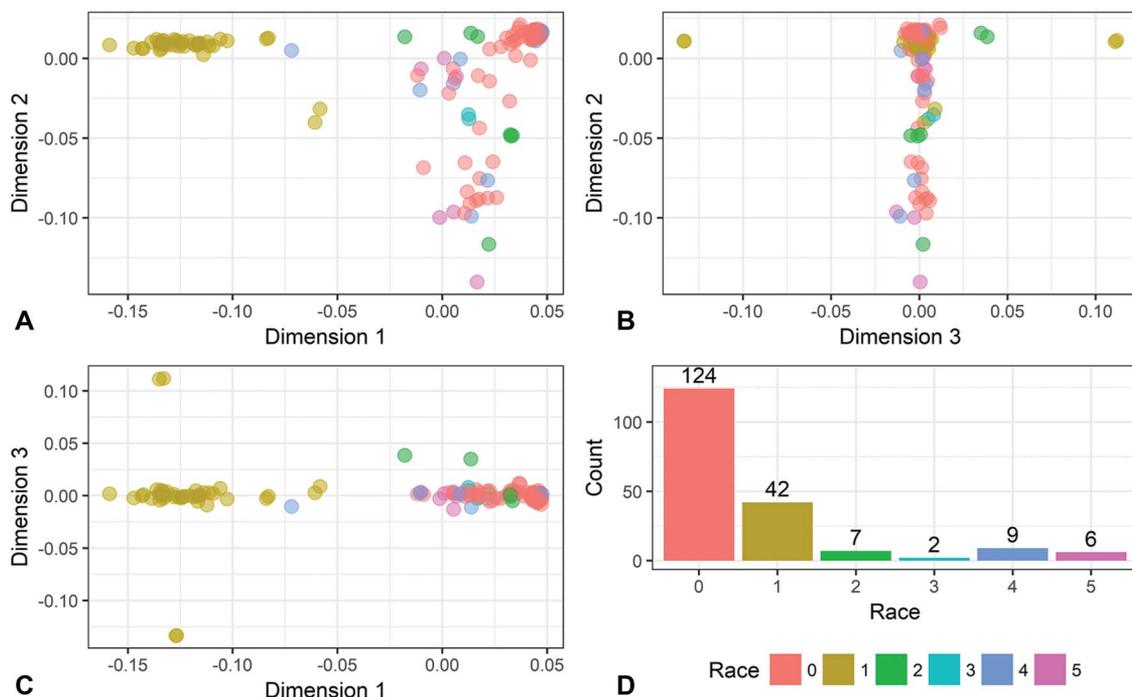


FIG. 1. Three-dimensional outcome of MDS, shown as 3 separate 2-dimensional plots (A–C). In the plots, each study sample is represented by a dot, color coded by race, and plotted according to the obtained unit-free MDS values. Shown here are (A) Dimensions 1 vs 2, (B) Dimensions 3 vs 2, and (C) Dimensions 1 vs 3. (D) Graphical representation of the distribution of self-reported ethnicity. 0 = Caucasian, 1 = African American, 2 = Native American/Alaskan, 3 = Asian, 4 = Unknown, 5 = Other. The data indicate that self-reported ethnicity was typically accurate but also stresses the need to control for data stratification. MDS, multidimensional scaling.

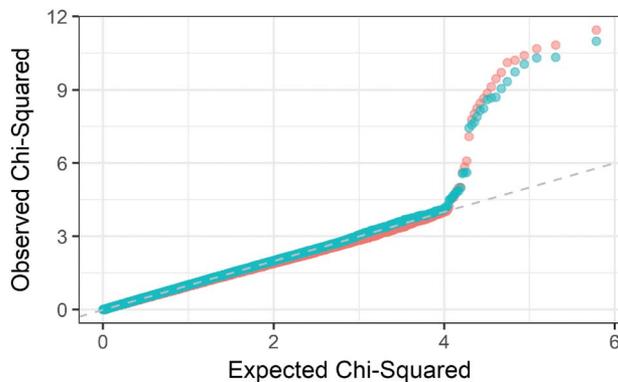


FIG. 2. Q-Q plot of χ^2 test of association stratified by race (red, Cochran-Mantel-Haenszel test) and not stratified (green). The plot depicts the expected distribution of association (x axis) for each SNP compared with the observed values (y axis). Generally, only a small number of SNPs should differ from the expected distribution, as is the case here, indicating that cases and control groups are well matched. SNP, single nucleotide polymorphism.

be associated with IIH with P values that are uncommonly high for a study of this size. However, the MAF of these SNPs in our data set differs considerably from that reported by the 1000 Genomes Project (23), suggesting that these findings may be spurious. To determine if these findings are artifacts of poorly performing genotyping probes, we used polymerase chain reaction to amplify the corresponding chromosomal regions in several samples and determined the genotypes using Sanger sequencing. The resulting sequence data did not correlate with those obtained by chip genotyping, confirming our notion that these data are incorrect. Consequently, these SNPs were excluded from subsequent analyses.

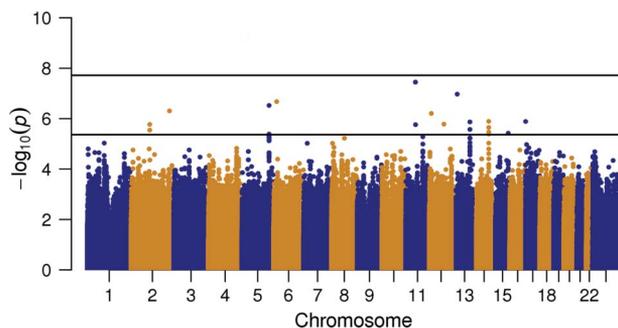


FIG. 3. Manhattan plot of IIH-GWAS. The $\log_{10} P$ values of each SNP, indicating the strength of the association, are plotted by chromosome. Loci possibly associated with the disease are designated by vertically stacked dots, resembling tall buildings in a city's skyline, and can be seen on chromosome 5, 13, and 14. Lines indicate P value of 0.05 (bottom) and genome-wide significance (5×10^{-8} , top). GWAS, genome-wide association study; IIH, idiopathic intracranial hypertension; SNP, single nucleotide polymorphism.

After removal of unreliable data, no SNPs with P values below the commonly used threshold of 5×10^{-8} for genome-wide association remained. However, we did identify several individual SNPs that are highly likely to be associated with IIH (See **Supplement Digital Content**, Table E1, <http://links.lww.com/WNO/A306>). These include rs2234671 on chromosome 2 ($P = 4.93 \times 10^{-07}$), rs79642714 on chromosome 6 ($P = 2.12 \times 10^{-07}$), rs200288366 on chromosome 12 ($P = 6.23 \times 10^{-07}$), and rs9578751 on chromosome 13 ($P = 1.07 \times 10^{-07}$).

A stronger case for an association with IIH can be made for 3 chromosomal regions identified here that each contain multiple SNPs, all at P values between 3×10^{-7} and 9×10^{-6} (See **Supplement Digital Content**, Table E1, <http://links.lww.com/WNO/A306>). Loci with a strong association are often indicated by several SNPs and the variant with the strongest association is flanked by additional SNPs with lesser, but noticeable, association. The first of these loci contains 11 SNPs and is located on chromosome 5, between nucleotides 154,836,185 and 154,898,325 (e.g., rs55652507, $P = 2.99 \times 10^{-07}$, odds ratio [OR] = 2.64). It does not seem to contain expressed genes. A second string of 5 SNPs with moderate association is located on chromosome 13 and spans from 97,606,867 to 97,615,932 (e.g., rs9300378, 5.83×10^{-06} , OR = 0.393). It includes an exon of LINC00359, a long non-coding RNA. Finally, a third potentially associated region, also indicated by 5 SNPs, is located on chromosome 14 from position 89,736,723 to 89,742,271, positioned within the FOXN3 gene (e.g., rs8018129, $P = 9.33 \times 10^{-06}$, OR = 3.94).

DISCUSSION

In this genetic survey, we examined whether an association exists between IIH and chromosomal variants that could explain the predisposition of some patients to develop this condition. One of the main strengths of this study is that all samples were obtained as part of a rigorous clinical trial, the IIHTT. Both patients and controls were examined and classified by experienced neuro-ophthalmologists following defined diagnostic criteria. This set of patient DNA likely represents the largest and best characterized collection of IIH samples to date.

In this study, we did not identify genetic loci that are highly likely to be associated with IIH. This is, at least partly, the result of limited statistical power due to the modest size of the patient cohort. Our study did have 80% power to detect disease alleles that occur at a frequency of >0.07 and confer a genotype relative risk >3 (24). Typically, GWAS requires many hundred samples before results with genome-wide significance can be achieved. However, there have been reports which successfully demonstrated genetic association using small cohorts. For example, both

the variants in the complement factor H gene associated with age-related macular degeneration (25) and the mutations in the lysyl-oxidase like 1 gene associated with exfoliation syndrome (26,27) were detectable in a cohort of the size used here.

Although we did not demonstrate strongly associated genetic variants, it is important to stress that the conclusion that there is no genetic contribution to IIH also cannot be made. Rather, a larger cohort may be required to demonstrate association. It also is conceivable that the disease is caused by mutations in numerous distinct genes each affecting a small fraction of patients. Alternatively, it is possible that numerous alleles of the same gene each contribute to the development of IIH. In any of these cases, it would be difficult to associate these changes with the disease using this particular study design. Finally, a technical limitation of this study was the use of a relatively low-density genotyping chip; it is possible that more comprehensive analyses using either high-density SNP chips or genomic sequencing could discover IIH-associated genetic variants that we did not identify.

However, we did detect loci on chromosomes 5, 13, and 14 that are highly suggestive of association with IIH. Each of these loci contains multiple SNPs, which strengthens support for true association of these regions despite the fact that genome-wide statistical significance was not reached. The locus on chromosome 5 is not located in the vicinity of known genes, but those on chromosomes 13 and 14 are located within the genes for LINC00359 and FOXP3, respectively. To the best of our knowledge, these loci do not overlap with those previously identified in other GWAS studies examining genetic contributions to conditions comorbid with IIH, such as headache or obesity. LINC00359 is a species of long noncoding RNA. Although its precise function is unknown, long noncoding RNAs are often involved in pretranslational and posttranslational regulation of gene expression and may affect the activity of multiple genes (28). FOXP3 is a forkhead family transcription factor with a role in craniofacial development (29) and it is expressed in a variety of tissues including the brain. Variants in this gene also have been associated with altered fasting blood glucose and the regulation of glucose utilization by hepatocytes (30,31). Interestingly, recent studies indicate that FOXP3 also forms a complex with an estrogen-inducible long noncoding RNA (NEAT1) to regulate the synthesis of estrogen receptor alpha as a feedback mechanism (32). As such, we believe that LINC00359 or FOXP3 are strong candidate genes for follow-up studies. Functional studies may be designed to elucidate whether variants of LINC00359 or FOXP3 alter transcriptional activity providing insight into the etiology of IIH. In addition, genetic association studies using independent cohorts of patients and, specifically

targeting the loci identified here, may be able to confirm our findings.

STATEMENT OF AUTHORSHIP

Category 1: a. Conception and design: Markus H. Kuehn, Mark J. Kupersmith, Michael Wall; b. Acquisition of data: Markus H. Kuehn, Benjamin E. Deonovic, Kimberly N. Miller, Michael Wall; c. Analysis and interpretation of data: Markus H. Kuehn, Rajashree Mishra, Benjamin E. Deonovic, Shana E. McCormack, Grant T. Liu. Category 2: a. Drafting the manuscript: Markus H. Kuehn, Rajashree Mishra, Benjamin E. Deonovic, Shana E. McCormack; b. Revising it for intellectual content: Markus H. Kuehn, Shana E. McCormack, Grant T. Liu, Mark J. Kupersmith, Michael Wall. Category 3: a. Final approval of the completed manuscript: Markus H. Kuehn, Rajashree Mishra, Benjamin E. Deonovic, Kimberly N. Miller, Shana E. McCormack, Grant T. Liu, Mark J. Kupersmith, Michael Wall.

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