bona fide risk loci for intracranial aneurysm is very strong from both Bayesian measures and conventional *P* values.

Given our power (~90%) to detect variants that confer risk of intracranial aneurysm with GRR = 1.25 and MAFs ≥ 10%, we expect that we have identified most of these variants, limited principally by potential gaps in SNP coverage. Indeed, across the rest of the genome, there was no locus with PPA >0.22 and MAF ≥10%, whereas there were 14 loci with PPAs between 0.1 and 0.22 and ORs between 1.16 and 1.25 (data not shown). We expect that a fraction of these loci are genuine intracranial aneurysm risk loci, as suggested by the excess of SNPs with $P < 1 \times 10^{-3}$ (**Fig. 1b**); exploring this possibility will require analysis of larger intracranial aneurysm cohorts and/or genotyping of alleles with lower MAFs.

Based on the results of the first GWAS of intracranial aneurysm and the role of the implicated gene products, Sox17 and $p15^{INK4b}$-$p16^{INK4a}$, we previously hypothesized[2] that the genes associated with intracranial aneurysm might play a role in determining cell cycle progression and may affect the proliferation[14] and senescence of progenitor-cell populations and/or the balance between production of progenitor cells versus cells committed to differentiation. Genes located within the newly identified regions support this idea. The protein encoded by *RBBP8*, located within the 18q11.2 region, influences progression through the cell cycle by interacting with BRCA1[15]. Similarly, of the two genes located within the 13q13.1 interval, *STARD13* contains the Rho-GAP and C-terminal STAR-related lipid transfer (START) domains and its overexpression results in suppression of cell proliferation[16]. The other gene implicated here, *KL*, encodes a transmembrane protein that modulates FGF receptor specificity[17]; mice lacking *KL* show accelerated aging in diverse organ systems[13].

On the assumption that there is a fourfold increase in the risk of intracranial aneurysm among siblings of cases[18,19] and that the SNPs combine to increase log-odds of disease in an additive fashion, the five intracranial aneurysm risk loci explain 5.2% (within the Finnish cohort), 4.0% (in the European cohort) and 3.5% (in the combined JP1 and JP2 cohort) of the familial risk of intracranial aneurysm. Under this model, the odds of developing an intracranial aneurysm varies 4.99- to 7.63-fold across the top and bottom 1% of genetic risk profiles at these loci in the populations studied here and 3.61- to 4.64-fold across the 5% extremes (**Supplementary Fig. 2**). When combined with traditional risk factors such as gender, blood pressure and smoking, these findings form the basis of future work aimed at preclinical identification of individuals who are at high risk of intracranial aneurysm formation and rupture.

URLs. eQTL browser, http://eqtl.uchicago.edu/.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Note: Supplementary information is available on the Nature Genetics website.

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AUTHOR CONTRIBUTIONS

Study Cohorts: ascertainment, characterization and DNA preparation: M.N., M.v.u.z.F., E.G., J.E.J., J.H. and A.P. (Finnish case-control); Y.M.R. and G.J.E.R. (NL cases); P.B., T.D., J. Blasco, G.Z., P.S., R.R., T.S., C.M.F., P.S., A.F.F., V.E., M.C.J.M.S., P.L., J. Byrne, J.M. and D.R. (@neurIST case series); B.K., G.A., M.S., D.K., F.W., A.O., B.S., C.S., J. Beck, F.R., C.R., D.B., C.G., E.I.S., B.M., A.R. and H.S. (DE case series); A.T., A.H., H.K. and I.I. (JP1); S.-K.L., H.Z. and Y.N. (JP2). **Control Cohorts:** A.A., L.P. and A.P. (Health2000); A.A., L.P. and A.P. (NFBC1966); C.M.v.D. and M.M.B.B. (Rotterdam Study); L.H.v.d.B. and C.W. (Utrecht); T.I. and H.E.W. (KORA-gen); S.S. (PopGen). **Genotyping:** K.B., Z.A., N.N., A.K.O., E.G., S.M., R.P.L. and M.G. (Yale); C. Perret, C. Proust and F.C. (Aneurist); S.-K.L., H.Z. and Y.N. (JP2). **Data management and informatics:** K.Y., K.B., Z.A., N.N. and M.G. (Yale); S.-K.L., H.Z. and Y.N. (JP2 cohort); **Statistical analysis:** K.Y. and M.G. **Writing team:** K.Y., K.B., M.W.S., R.P.L. and M.G. **Study design and analysis plan:** K.Y., R.P.L. and M.G.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturegenetics/.

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ONLINE METHODS

Genotyping. Whole-genome genotyping for the discovery cohort was performed on the Illumina platform according to the manufacturer's protocol (Illumina). Beadchips used for individual cohorts are presented in **Supplementary Table 2**. Replication genotyping in the JP1 cohort was performed using either Taqman (Applied Biosystems) or MassARRAY (Sequenom) assays. For the JP2 cohort, genotyping for cases was performed using the multiplex PCR-based Invader assay (Third Wave Technologies Inc.); genotyping for controls was performed on an Illumina platform as described previously[20].

Ethics. The study protocol was approved by the Yale Human Investigation Committee (HIC protocol #7680). Institutional review board approval for genetic studies, along with written consent from all study participants, was obtained at all participating institutions.

Data storage and analysis tools. We used PLINK[21] v1.06 and R statistical environment v2.9.0 (in particular, the snpMatrix package[22]) for storage of genotype data and data analysis.

Preprocessing. Prior to the analysis of genotyping data, we excluded SNPs that were located either on mitochondrial DNA or sex chromosomes, SNPs with A/T or C/G alleles, those for which all subjects were assigned as 'no call', and those that were assayed on Hap300v1 or 550v1 but were dropped from newer versions.

Sample quality control. We excluded subjects in the discovery cohort who did not conform to our study design on the basis of genotyping and information quality, cryptic relatedness and population outliers. We summarize the sample exclusion steps in **Supplementary Table 2**. This filtering process resulted in the inclusion of 835 cases and 6,529 controls in the Finnish cohort and 2,000 cases and 8,722 controls in the rest of the combined European cohort.

Imputation. We performed imputation analysis with the HapMap phase II CEU reference panel (release 24) using the IMPUTE v1 software[6]. The analysis was performed separately for the Finnish and European cohorts. We converted posterior probabilities of three possible genotypes to fractional allele dosage scores (between 0 and 2) and used these scores for association tests in order to take into account the imputation uncertainty[23]. For the quality assessment of imputed SNPs, we also converted the posterior probabilities to the most likely genotypes with the threshold at 0.9.

Case-control matching. Population stratification and independent genotyping of cases and controls are major causes of confounding in GWAS[24]. Because our study consisted of multiple independently ascertained cohorts that were genotyped separately, we performed a stringent analysis to control for these biases by inferring the genetic ancestries of subjects[25,26]. We used the Laplacian eigenmaps[27] to infer population structure. Following the determination of the number of dimensions ($K + 1$) using the threshold given in Lee *et al.*[28], we used the K-dimensional nontrivial generalized eigenvectors[29] to calculate the Euclidean distance between any two subjects.

In the course of this analysis, we excluded 'isolated' subjects who were identified by using the nearest-neighbor distance distributions in any of the two-dimensional sections. After excluding these subjects, we observed 13 dimensions in the Finnish cohort and 5 dimensions in the European cohort. The larger dimensions observed in the Finnish sample could be attributable to the presence of many isolated populations in Finland[5].

Before matching, we stratified data into males and females because female gender is a known risk factor of intracranial aneurysm[1,3]. We also set the maximum distance between cases and controls to match to be less than 0.028 in the Finnish cohort and 0.009 in the European cohort. These values were determined by examining the distribution of the nearest-neighbor distances in K dimensions (data not shown). We matched cases and controls using the fullmatch function in the R-package optmatch[30,31].

SNP quality control. For both genotyped and imputed SNPs in the discovery cohort, we applied quality-control filters to individual cohorts and to cases and controls separately on the basis of the missing rate, MAF and the P value of the exact test of Hardy-Weinberg equilibrium[32]. For imputed SNPs, we also assessed imputation quality using the average posterior probability, MAF and allelic R^2 metric[33]. Finally, we assessed differential missingness between cases and controls (**Supplementary Table 2**).

Any genotyped SNP that passed the quality-control filters both in the European and Finnish cohorts was referred to as a 'genotyped SNP', and any one for which we used the quality control–passed imputation data either in one or both of the cohorts was classified as an 'imputed SNP'.

For genotyping data of the replication cohorts, we excluded SNPs if any of the following three conditions were met in either cases or controls: (i) missing rate >0.05; (ii) P value of the exact test of Hardy-Weinberg equilibrium <0.001; or (iii) MAF <0.01.

Statistical analysis. *Cohort-wise association analysis.* We tested for association between each quality control–passed SNP and intracranial aneurysm using conditional and unconditional logistic regression for the discovery and replication cohorts, respectively[34]. For the discovery cohort, we used the matched strata to correct for potential confounding due to population stratification and gender, and for the replication cohorts we adjusted for gender. We assumed the log-additive effect of allele dosage on disease risk. We obtained P values from the score test (two-sided) and estimated the logarithm of per-allele ORs with standard errors by maximizing the conditional or unconditional likelihood. Both the test statistic and the standard error of the log of the OR were corrected using genomic control[7]. We performed the association analysis for the Finnish and European cohorts, as well as subcohorts of the European group that consisted of NL cases, DE cases or @neurIST cases and their matched controls (**Table 1** and **Supplementary Table 3**). We used the following R functions to perform the association analysis: clogit, glm and snp.rhs.tests[22].

Meta-analysis. We combined the cohort-wise per-allele ORs in the Finnish and European cohorts using a fixed-effects model of meta-analysis for 831,534 quality control–passed SNPs to obtain the discovery results. For SNPs analyzed both in the discovery and replication cohorts, we combined JP1 and JP2 to obtain replication results and all four cohorts to obtain combined results. Our primary analysis was based on the fixed-effects model[23]. To assess the heterogeneity of the effect size between cohorts, we first divided the European cohort into three groups as described above, aiming to analyze the data without averaging effect sizes over the combined European cohorts and then combined our six cohorts using the random-effects model. We employed the restricted maximum likelihood procedure to estimate the between-cohort heterogeneity variance (τ^2) using the R function MiMa[35] (see URLs). From this estimate, we calculated the Cochran's Q statistic and the I^2 statistic (the percentage of variation across studies that is due to heterogeneity rather than chance)[36].

Bayesian evaluation of the strength of association. To evaluate the strength of association with intracranial aneurysm, we used a Bayesian approach[9,37]. A limitation of the use of P values alone is that variability in factors such as effect size, MAF and sample size can result in identical statistics that might correspond to markedly different levels of evidence regarding the strength of association[10]. The Bayes factor provides an alternative that compares the probabilities of the data under the alternative hypothesis of association versus the null hypothesis of no association. For computational simplicity, we approximated the Bayes factor as described by Wakefield[8]. For all SNPs, we assumed the same prior distribution for the log-OR: a normal distribution with a mean of 0 and a standard deviation of $\log(1.5)/\Phi^{-1}(0.975)$, where Φ is the normal distribution function[9].

The PPA[10] provides a simple probabilistic measure of evidence by introducing the prior probability of association, π_1. We assumed a uniform prior, $\pi_1 = 1/10{,}000$, for all the SNPs[11]. For Bayes factor $>10^6$, changing π_1 to a more conservative value of 1/100,000 would result in little change in the PPA.

To combine the results from multiple cohorts, we extended the formula[38] to be applicable to multiple (>2) cohorts.

Conditional analysis. For each region that contained a SNP with PPA >0.5, we examined the number of independent association signals by testing for association of every genotyped SNP with intracranial aneurysm by adjusting for the effect of a specified SNP (**Supplementary Fig. 1**).

Two-locus interaction analysis. We tested for deviation from a linear model, which assumes that two SNPs combine to increase the log-odds of disease in

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an additive fashion, using conditional (in the Finnish and European cohorts) or unconditional (in JP1 plus JP2, stratified by cohorts and gender) logistic regression. There was no significant deviation from the linear model (data not shown).

Cumulative effect. We evaluated potential clinical implications of the genetic profiles of the five intracranial aneurysm risk loci following the approach described by Clayton[39]. We fitted a five-locus conditional (Finnish and European cohorts) or unconditional (Japanese cohorts) logistic regression model including the additive and dominance-deviation terms for each locus. Using the estimated effect sizes and each individual's genotype, we calculated the risk scores for every individual. The receiver-operating characteristic curve for each ethnic cohort (Finnish, European and Japanese) was depicted using the risk score.

We also calculated the ratio of the exponential of the mean of the risk scores for control subjects within the top versus bottom 5% or 1% tails of distribution of risk scores in each cohort to obtain approximated odds ratios of disease between these classes.

The sibling recurrence risk was estimated by assuming the polygenic model that fits well to our data[39]. A fraction of the sibling recurrence risk attributable to all of the five loci was calculated by taking the ratio of the logarithm of this value and epidemiologically estimated value of 4 (refs. 18,19).

URLs. The R function MiMa, http://www.wvbauer.com/.

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小児科を受診の患者様へ

川崎病研究へのご協力のお願い

当院では、川崎病に関する研究へのご協力をお願いしています。

ご協力いただきたい方

川崎病にかかったことのある患者様と、その血縁者の方。

ご協力いただきたい内容

①血液、または、だ液を採取させていただく。
②診療記録を使用させていただく。

研究の目的

この研究は、川崎病の発症や病気の重さ、薬の効き方が、生まれながらの体質（遺伝的素因）と関連するかどうか、調べるものです。

研究成果が、将来多くの患者様に役立ちます

①患者様ごとの最適な治療法の選択
②新しい治療法の開発
③川崎病の予防

※余分に診察の費用がかかることはありません。
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ご協力いただける方は、当院小児科の担当医師までお気軽におたずねください。

研究班名：厚生労働省科学研究費
「川崎病の疾患関連遺伝子の探索と遺伝子型に基づくテーラーメイド治療法の確立」