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Case-control association mapping without cases

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Abstract

The case-control association study is a powerful method for identifying genetic variants that influence disease risk. However, the collection of cases can be time-consuming and expensive; in some situations it is more practical to identify family members of cases. We show that replacing cases with their first-degree relatives enables genome-wide association studies by proxy (GWAX). In randomly-ascertained cohorts, this approach enables previously infeasible studies of diseases that are rare in the cohort, and can increase power to detect association by up to 30% for diseases that are more common in the cohort. As an illustration, we performed GWAX of 12 common diseases in 116,196 individuals from the UK Biobank. By combining these results with published GWAS summary statistics in a meta-analysis, we replicated established risk loci and identified 17 newly associated risk loci: four in Alzheimer's disease, eight in coronary artery disease, and five in type 2 diabetes. In addition to informing disease biology, our results demonstrate the utility of association mapping using family history of disease as a phenotype to be mapped. We anticipate that this approach will prove useful in future genetic studies of complex traits in large population cohorts.

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Introduction

In a typical case-control genetic association study, a researcher genotypes a set of individuals that have a disease (the "cases") and a set of individuals that do not have the disease (the "controls"). For each genetic variant, the difference in allele frequency between cases and controls can be used to estimate the causal effect of the genetic variant on the disease (assuming all potential confounders have been accounted for). While powerful, this study design requires an *a priori* decision about which disease is of interest, as well as substantial effort to identify matched cases and controls. An alternative approach is a cohort study, in which individuals are sampled from the general population and many phenotypes are collected on each individual. An advantage of a cohort study is that the cohort can be subdivided to create case-control studies of many different diseases.

However, cohort studies are limited by the fact that diseases that are rare in the sampled population will be under-represented in the cohort. A disease may be rare in a sampled population for many reasons. First, the population may not include the demographic group where the disease is most prevalent. For example, the UK Biobank (a current gold standard cohort study) sampled individuals in the age range of 45-69 (at the time of recruitment) [Sudlow et al., 2015]. By definition, this cohort does not include individuals with lethal childhood diseases, and at present there are only a handful of individuals with Alzheimer's disease or other late-onset diseases. Other sampling approaches, like cohorts made from customers of consumer genomics companies (e.g. Eriksson et al. [2010], `DNA.Land`), have analogous limitations. Similarly, a disease may be rare in a sampled population because of aspects of the disease rather than the cohort: diseases that occur rarely (or kill quickly once they occur) will be rare in a randomly ascertained cohort. Further, diseases that are highly sex-biased (e.g. prostate cancer) will have considerably lower frequencies in a randomly-ascertained cohort than in a targeted one.

In this paper, we propose performing case-control studies where cases are replaced with their family members. This study design is popular in studies of longevity (where "cases" are long-lived individuals, see e.g. Barzilai et al. [2003]; Pilling et al. [2016]; Tan et al. [2010]), but has not been widely used in other situations. As a motivating example, consider Alzheimer's disease. As of March 25, 2016, there are 55 cases of Alzheimer's disease listed among the approximately 500,000 individuals in the UK Biobank. However, over 60,000 individuals note that one or both of their parents was/is affected with the disease. An individual with a single affected parent can be thought to have one chromosome sampled from a population of "cases" and one from "controls". If the allele frequency (in the standard case-control setting) of some variant that increases risk of a disease is f_A in cases and f_U in controls, then the allele frequency in individuals with a single affected parent is $\frac{f_U+f_A}{2}$. This motivates a "proxy-case"-control association study where "proxy-cases" are the (unaffected) relatives of affected individuals and "controls" are (unaffected) relatives of unaffected individuals. We refer to this approach as a Genome-Wide Association study by proXy (GWAX).

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Results

We first explored the power of this approach with simulations and analytical calculations. Specifically, we focused on the situation where we have information about the diseases of the parents of an individual (Methods). We initially considered the case where we have no phenotype information about genotyped individuals themselves, though we consider this case later on.

The GWAX approach using proxy-cases who have one affected first-degree relative reduces the log odds ratios by a factor of around two when compared with a traditional case/control design (assuming an additive model for the impact of a genetic variant on a disease). This reduction in effect size reduces power to detect association. However, using proxy-cases may increase the effective sample size (in a cohort study) or be more logistically feasible than collecting standard cases, thus offsetting the loss in power due to effect size. We calculated the number of proxy-cases and controls required such that the power to detect association is equivalent to using true cases and controls (Supplementary Note). Across the allele frequency and effect size spectrum, the proxy-case/control approach is more powerful when there are ~ 4 times (or more) as many proxy-cases and controls as there are true cases and controls, assuming the ratios of controls to cases and controls to proxy-cases are the same (Figure 1A). For late onset diseases such as Alzheimer's disease (1.6% in the population vs. 42% in those over the age of 84 [Hebert et al., 2003]) and Parkinson's disease (0.3% in the population vs. 4% in those over 80 [de Lau and Breteler, 2006]), the proxy-case/control design gains substantial power if cohorts are sampled randomly from the population.

When both true and proxy-cases are available in a population cohort study, there may be up to a 30% gain in power to detect association (compared with a case/control study) when proxy-cases are accounted for, either by lumping them together with true-cases or considering them separately (Figure 1B, Supplementary Note). For instance, for a disease with 5% prevalence and 50% heritability on the liability scale, we expect to observe 5,000 cases and 8,597 proxy-cases in a randomly sampled cohort of 100,000. Here, for a SNP with allele frequency 0.1 in controls, an odds ratio of 1.2, there is 60.2% power at $\alpha = 5 \times 10^8$ to detect association using a standard 2×2 chi-squared test of true cases vs. controls, 87.2% power using a 2×2 test where cases and proxy-cases are lumped together, and 89.8% power using a 3×2 test where true cases, proxy-cases and controls are treated separately (Supplementary Note). When disease prevalence is greater than around 34%, the test where cases and proxy-cases are lumped together is less powerful than a standard case/control test since there are no further gains in effective sample size. Nevertheless, the 3×2 test will always be more powerful than the case/control test across disease prevalences (see Supplementary Note for details).

We performed GWAX of 12 diseases in the UK Biobank (May 2015 Interim Release). After quality control and 1000 Genomes Phase 3 imputation (Methods), 10.5 million low-frequency and common ($MAF > 0.005$) SNPs from 116,196 individuals of European ancestry were available for analysis. All of these individuals answered questionnaires regarding the diseases of their family members (though the med-

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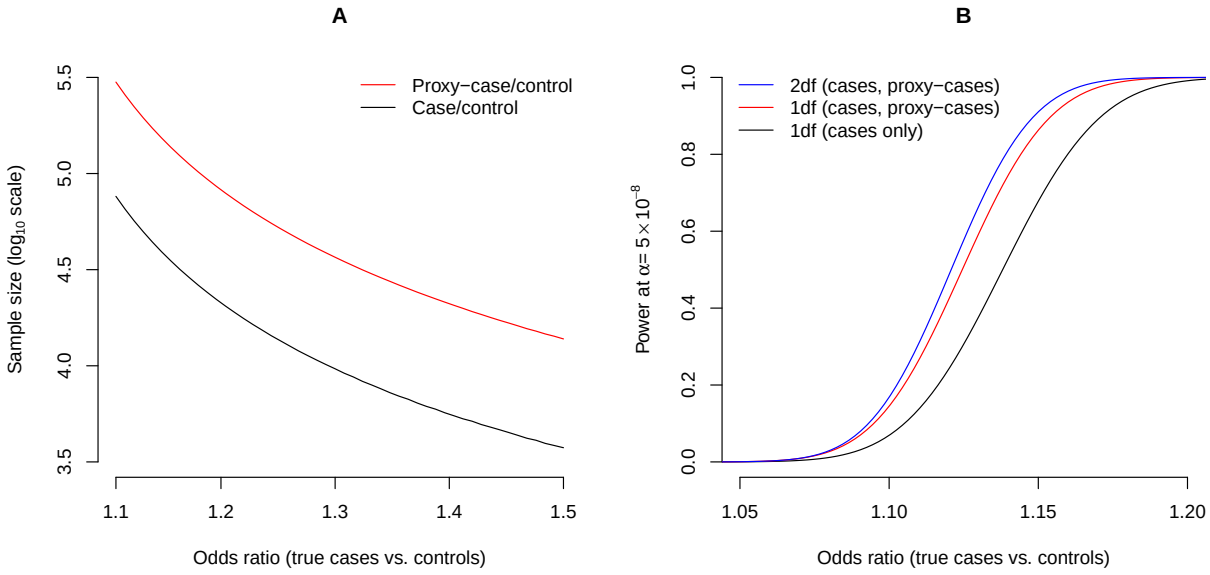

Figure 1. Power of proxy-case/control association designs. (A) Total sample size required to detect association at $\alpha = 5 \times 10^{-8}$ for case/control (black line) and proxy-case/control (red line) designs at a SNP with 0.1 frequency in controls. (B) Power to detect association at $\alpha = 5 \times 10^{-8}$ using two designs that account for cases and proxy-cases (in red and blue) and a standard case-only/control design (in black). The total sample size = 100,000, disease prevalence = 0.1, heritability of liability = 0.5 and allele frequency in controls = 0.1 (See Supplementary Note).

ical records of the individuals themselves are available, we did not use them in this analysis in order to illustrate the approach without using cases). The number of proxy-cases per phenotype ranged from 4,627 for Parkinson's disease to 54,714 for high blood pressure (Table S1). For each SNP, we calculated an adjusted odds ratio (OR), which is directly comparable (under a standard additive model) with ORs estimated from traditional case/control study designs (Methods) (Figure S1). The overall association results across the 12 phenotypes are shown in Manhattan plots, which show several clear peaks of association (Figure S2).

In the GWAX of these 12 diseases, 24 loci reached "genome-wide significance" ($P < 5 \times 10^{-8}$). For Alzheimer's disease, breast cancer, heart disease, high blood pressure, lung cancer, prostate cancer and type 2 diabetes, all of these represented replications of established associations (Table S3). Among the most strongly associated loci include *APOE* (rs429358, $P = 9.72 \times 10^{-195}$) for Alzheimer's disease [Corder et al., 1993], *LPA* (rs10455872, $P = 2.55 \times 10^{-25}$) and *CDKN2A/CDNKN2B* (rs4007642, $P = 7.64 \times 10^{-21}$) for heart disease/coronary artery disease [Danesh et al., 2000; The Wellcome Trust Case Control Consortium et al., 2007], *FES/FURIN* (rs8027450, $P = 6.12 \times 10^{-13}$) for high blood pressure/hypertension [The International Consortium for Blood Pressure Genome-Wide Association Studies, 2011], *FGFR2* (rs2981583, $P = 3.62 \times 10^{-12}$) for breast cancer [Hunter et al., 2007], *TCF7L2* (rs34872471, $P = 7.76 \times 10^{-45}$) for type 2 diabetes [Grant et al., 2006], and *CHRNA5/CHRNA3* (rs5813926, $P = 1.67 \times 10^{-9}$ for lung cancer [Hung et al., 2008]. We identified two genome-wide significant loci for Parkinson's disease, one of which corresponds to the established *ASH1L* locus (rs35777901, $P = 2.25 \times 10^{-8}$) [Nalls et al., 2014]. The second

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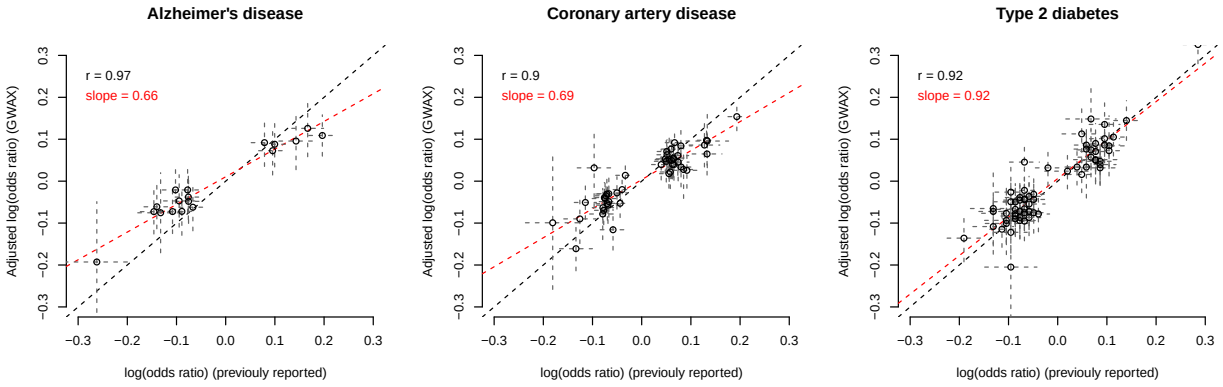

Figure 2. Comparison of adjusted ORs and previously reported case/control ORs at established risk loci for three diseases with publicly available summary statistics. Each point represents a previously reported risk variant and its corresponding effect size. The dashed gray lines are 95% confidence intervals. The dashed red line (and corresponding slope) is the fitted line from least squares regression. The dashed black line is is $y = x$. Reported effect sizes and list of established risk loci were obtained from - Alzheimer's disease: Lambert et al. [2013]; coronary artery disease: The CARDIoGRAMplusC4D Consortium [2015]; type 2 diabetes: DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium et al. [2014].

locus at *SLIT3* (rs1806840, $P = 6.39 \times 10^{-9}$) is implicated in Parkinson's disease risk at genome-wide significance for the first time, although this SNP is reported as "non-significant" ($P > 0.05$, see URLs) in Nalls et al. [2014] so we do not discuss it further.

In principle, the adjusted odds ratios obtained from a proxy-case/control design might differ from those obtained from a standard case/control design for a number of reasons. For example, dominance effects will distort these ORs in different ways in the two study designs. Likewise, errors made by children in recalling the diseases of their parents would bias our estimates, as would direct causal effects of a child's genotype on a parental phenotype (if, for example, a partially-heritable childhood behavior influences the diseases of their parents). Indeed, across 11 of the 12 phenotypes, females were significantly more likely to report a first-degree relative with the disease than males (Table S2), indicating at least some recall bias. To test the extent of these biases, we obtained summary association statistics from previously published GWAS for four phenotypes: Alzheimer's disease [Lambert et al., 2013], coronary artery disease [The CARDIoGRAMplusC4D Consortium, 2015], major depressive disorder [Ripke et al., 2013] and type 2 diabetes [DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium et al., 2014]. Across established loci for three of these diseases (no genome-wide significant loci were reported for major depressive disorder), the direction and relative size of effects were consistent between our adjusted ORs and those reported previously ($0.92 <$ Pearson's $r < 0.97$), though the adjusted ORs were slightly underestimated ($0.66 < \beta < 0.92$) (Figure 2). We observed significant ($P < 0.01$) genetic correlations between our GWAX results and the published GWAS summary statistics for coronary artery disease ($r_g = 0.93$), major depressive disorder ($r_g = 0.67$), type 2 diabetes ($r_g = 0.91$) and Alzheimer's disease ($r_g = 0.44$).

Motivated by these consistent odds ratios, and in an effort to identify additional risk loci, we per-

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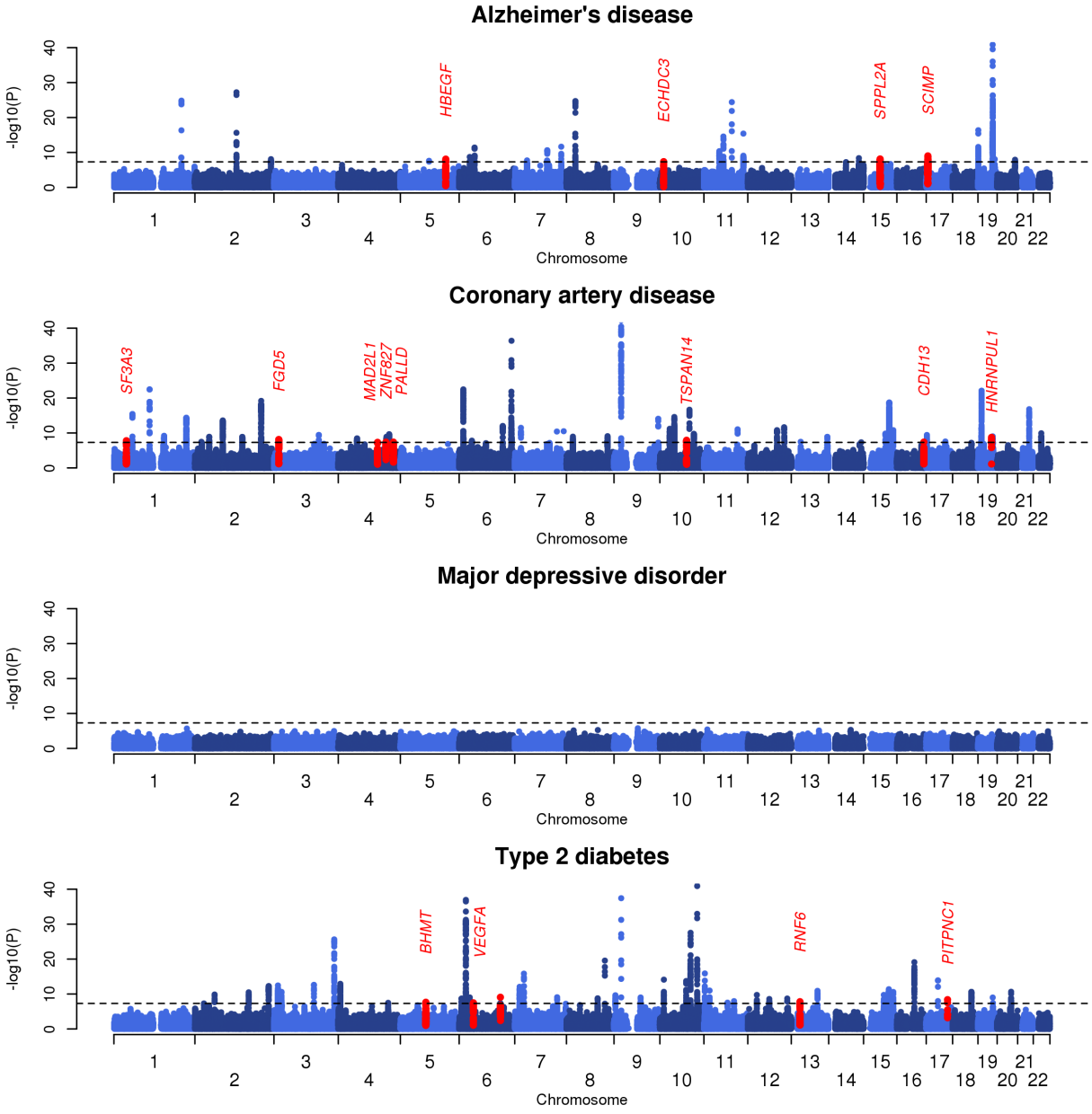

Figure 3. Manhattans plot of fixed-effects meta-analysis results for four phenotypes. Chromosome and positions are plotted on the x-axis. Strength of association is plotted on the y-axis. Novel risk loci are indicated in red. The dashed horizontal line indicates the genome-wide significant threshold of $P < 5 \times 10^{-8}$. $-\log_{10}$ P-values are truncated at 40 for illustrative purposes.

Phenotype	SNP	Chr	Position (GRCh37)	Eff/Alt allele	Freq	OR (adj.)	P-value	Nearby genes
Alzheimer's disease	rs2074612	5	139,714,690	T/C	0.438	1.08	8.00×10^{-9}	*HBEGF*
	rs7920721	10	11,720,308	G/A	0.380	1.07	4.27×10^{-8}	*ECHDC3*
	rs59685680	15	51,001,534	G/T	0.198	0.92	7.32×10^{-9}	*SPPL2A, TRPM7, USP50*
	rs77493189	17	5,118,951	G/T	0.123	1.11	9.60×10^{-10}	*SCIMP, ZNF594, RABEP1, USP6*
Coronary artery disease	rs61776719	1	38,461,319	C/A	0.446	0.95	1.63×10^{-8}	*SF3A3, FHL3*
	rs4685219	3	14,894,188	A/G	0.376	1.05	7.33×10^{-9}	*FGD5, NR2C2*
	rs11723436	4	120,901,336	G/A	0.313	1.05	4.77×10^{-8}	*MAD2L1*
	rs13109172	4	146,759,483	C/A	0.355	0.95	4.16×10^{-8}	*ZNF827*
	rs869396	4	169,688,000	A/C	0.467	0.96	4.09×10^{-8}	*PALLD*
	rs17680741	10	82,251,514	C/T	0.288	0.95	1.22×10^{-8}	*TSPAN14, SH2D4B, FAM213A*
	rs7500448	16	83,045,790	G/A	0.252	0.95	4.09×10^{-8}	*CDH13*
	rs15052	19	41,813,375	C/T	0.176	1.08	1.82×10^{-9}	*HNRNPUL1, TGFB1, CCDC97, AXL*
Type 2 diabetes	rs1291041	5	78,443,735	T/G	0.352	0.94	2.26×10^{-8}	*BHMT*
	rs744103	6	43,805,362	T/A	0.312	1.07	3.32×10^{-8}	*VEGFA*
	rs4273712	6	126,964,510	G/A	0.266	1.08	8.38×10^{-10}	-
	rs301047	13	26,788,114	G/A	0.186	1.08	1.56×10^{-8}	*RNF6*
	rs11658220	17	65,646,092	A/G	0.103	1.14	4.13×10^{-9}	*PITPNC1*

Table 1. Novel genome-wide significant risk loci identified through proxy-case/control analysis and meta-analysis with published genome-wide association studies of Alzheimer's disease, coronary artery disease and type 2 diabetes.

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formed fixed-effects meta-analysis combining our proxy-case/control association summary statistics with those from the previously published GWAS. This approach implicated 17 novel risk loci at genome-wide significance associated with Alzheimer's disease, coronary artery disease and type 2 diabetes (Table 1, Figure 3, Figure S3).

Among the novel loci for Alzheimer's disease include genes invovled in immune surveillance (*SPPL2A*, signal peptide peptidase like 2A) and major histocompatability complex class II signal transduction (*SCIMP*, SLP adaptor and SCK interacting membrane protein) [Friedmann et al., 2004], further highlighting the role of the innate immune system in Alzheimer's disease etiology [Chan et al., 2015; Gjoneska et al., 2015]. For coronary artery disease, one novel locus resides in an intron of *FGD5* (FYVE, RohGEF and PH domain containing 5), a member of the FGD family of guanine nucleotide exchange factors. *FGD5* has been shown to regulate *VEGF* (vascular endothelial growth factor) [Kurogane et al., 2012], a key cytokine in the formation of new vessels and potential therapeutic target for heart disease [Taimeh et al., 2013]. For type 2 diabetes, we identified a novel locus in *PITPNC1* (phosphatidylinositol transfer protein, cytoplasmic 1), a member of the phosphatidylinositol transfer protein family and has been show to be involved in lipid transport between membrane compartments [Garner et al., 2012].

Discussion

This study demonstrates proof of principle that complex disease risk loci can be identified using the genotypes of unaffected individuals and the phenotypes of their affected relatives. We applied the GWAX approach to 12 common diseases in 116,196 individuals from the UK Biobank and combined our results with publicly available GWAS summary statistics for four of these diseases. We replicated known risk loci and identified 17 novel risk loci at genome-wide significance associated with Alzheimer's disease, coronary artery disease and type 2 diabetes.

Large population cohorts such as the UK Biobank and NIH Precision Medicine Initiative along with participant-driven projects [Dolgin, 2010; Eriksson et al., 2010] are emerging as valuable resources in biomedical research. By performing association mapping using the family members of affected individuals, we partly overcome the ascertainment limitations inherent in these studies. The potential for complex trait association mapping in population cohorts may be much greater than previously thought.

Future expansions of these approaches may take into account more distant relatives in a formal way, allowing for the phenotypes of all known relatives to be accounted for and analyzed in conjunction with directly genotyped individuals. Genetic studies of complex disorders may progress beyond simple "case" and "control" phenotypes, and instead leverage multiple layers of information into a direct estimate of disease liability. Large crowd-sourced family trees [Ledford, 2013] along with reported phenotypes, demographics, lifestyle surveys, medical records and epidemiological information can be combined to provide robust estimates of both the genetic and environmental components of disease liability [Campbell et al., 2010]. Using

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liability as a phenotype can also account for ascertainment biases of case/control studies [Hayeck et al., 2015; Weissbrod et al., 2015], and allow for much greater power to identify disease susceptibility variants.

Methods

Power calculations

We performed power calculations comparing a study design using true cases and controls to one with proxy-cases and controls, and estimated the sample sizes of each such that power to detect association is equivalent. We also considered the situation where both cases and proxy-cases are available in the context of a population cohort study, where the expected number of cases and proxy-cases depends on disease prevalence and heritability on the liability scale. Details of the power calculations are described in the Supplementary Note.

UK Biobank data collection

The UK (United Kingdom) Biobank is a large population-based study of over 500,000 subjects aged 45-69 years recruited from 2006-2010 [Sudlow et al., 2015]. Participants entered information about their family history of disease by answering three questions: 1) "Has/did your father ever suffer from?", 2) "Has/did your mother ever suffer from?", and 3) "Have any of your brothers or sisters suffered from any of the following diseases?". Participants were asked to choose among 12 conditions (heart disease, stroke, high blood pressure, chronic bronchitis/emphysema, Alzheimer's disease/dementia, diabetes, Parkinson's disease, severe depression, lung cancer, bowel cancer, prostate cancer and breast cancer) and were allowed to select more than one condition. Participants were also given the choice of entering "Do not know", "Prefer not to answer" or "None of the above". Throughout this manuscript, we denote heart disease, severe depression and diabetes to refer specifically to coronary artery disease, major depressive disorder and type 2 diabetes, respectively. The UK Biobank received ethics approval from the National Health Service National Research Ethics Service (Ref 11/NW/0382).

Genotyping, imputation and quality control

The UK Biobank May 2015 Interim Data Release included directly genotyped and imputed data for 152,529 individuals. Around 90% of individuals were genotyped on the Affymetrix UK Biobank Axiom array, while the remainder were genotyped on the Affymetrix UK BiLEVE array. The two platforms are similar with $> 95\%$ common marker content (847,441 markers in total). Markers were selected on the basis of known associations with phenotypes, coding variants across a range of minor allele frequencies, and content to provide good genome-wide imputation coverage in European populations for variants with minor allele frequencies $> 1\%$. Genotyped individuals were phased using SHAPEIT2 and then imputed with the IMPUTE2 algorithm using a reference panel consisting of 12,570 haplotypes from a combined UK10K and

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1000 Genomes Phase 3 dataset. In total, 73,355,667 polymorphic variants were successfully imputed. Additional information on the genotyping array, sample preparation and quality control can be found in the documents the URLs section. After QC, We took forward 116,196 unrelated individuals of European descent for analysis.

Genome-wide association by proxy

For each of the 12 common diseases, subjects were considered proxy-cases if they have at least one affected mother, father or sibling. Subjects who answered "Do not know", or "Prefer not to answer" were removed from the analysis. All other subjects were considered controls. The total number of proxy-cases and controls for each phenotype are listed in Table S1.

Association between genotype and phenotype was performed on best-guess imputed genotypes (allelic likelihood > 0.9, missingness $< 10\%$, minor allele frequency > 0.005) using logistic regression. For all analyses, we included the subjects' reported sex, age at recruitment and the first four principal components (estimated directly from the post-QC set of UK Biobank individuals) as covariates. We observed modest genomic inflation across the 12 diseases ($1.05 < \lambda < 1.07$; Figure S4).

To enable direct comparison of our effect sizes to those from traditional case/control designs (as well as enabling fixed-effect meta-analysis), we calculate odds ratios using the following approximation. For each SNP, let f_A and f_U be the allele frequencies in true-cases and controls respectively, and

$$OR = \frac{f_A(1-f_U)}{f_U(1-f_A)} \tag{1}$$

be the true case/control odds ratio. If f_P is the allele frequency in proxy-cases (the vast majority of whom have only one first-degree relative affected with disease), then

$$f_P = \frac{f_U + f_A}{2}. \tag{2}$$

In order to estimate the adjusted odds ratio as a function of the observed allele frequencies in pseudo-cases and controls, we substitute f_A into (1):

$$\hat{OR} = \frac{(2f_P - f_U)(1-f_U)}{f_U(1-2f_P+f_U)}. \tag{3}$$

For the range of ORs (< 1.4) typically reported in a GWAS, the log of the adjusted odds ratio derived here is approximately double that of the log odds ratio directly estimated from logistic regression using proxy-cases and controls (Figure S1). As the odds ratios and standard errors from logistic regression take into account covariates, we report adjusted log odds ratios using this doubling approximation rather than directly estimating them from allele frequencies using equation (3). The corresponding adjusted standard error is also double the standard error of the log odds ratio from logistic regression, since $se^2 = Var(2\beta) = 2^2 Var(\beta)$.

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Genetic correlation and meta analysis

Publicly available GWAS summary association statistics were obtained for Alzheimer's disease (17,008 cases and 37,154 controls for stage 1 SNPs; plus 8,572 cases and 11,312 controls for 11,632 stage 2 SNPs) [Lambert et al., 2013], coronary artery disease (60,801 cases and 123,504 controls) [The CARDIoGRAMplusC4D Consortium, 2015], major depressive disorder (9,249 cases and 9,519 controls) [Ripke et al., 2013] and type 2 diabetes (26,488 cases and 83,964 controls) [DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium et al., 2014].

For each of the four phenotypes, we estimated the genetic correlation between our GWAX summary statistics and the published GWAS summary statistics using LD score regression with a set of ~ 1.2 million common SNPs from HapMap3 [Bulik-Sullivan et al., 2015].

Fixed-effects meta-analysis was performed using inverse variance-weighted method for all SNPs that overlap between the publicly available summary statistics and our adjusted odds ratio GWAX results. That is, for each SNP with estimated log odds ratios and standard errors, $\hat{\beta}_i$ and $\hat{se}_i$ respectively, where $i = 1$ or 2 correponding to the GWAX (adjusted log odds ratio) or GWAS results, the combined effect size is:

$$\hat{\beta}_{meta} = \frac{\sum_i \hat{\beta}_i w_i}{\sum_i w_i} \tag{4}$$

with corresponding standard error and P-value:

$$\hat{se}_{meta} = \sqrt{1/\sum_i w_i} \tag{5}$$

$$P_{meta} = 2\Phi(|\hat{\beta}_{meta}|/\hat{se}_{meta}) \tag{6}$$

where $w_i = 1/\hat{se}_i^2$ and Φ is the cumulative standard normal distribution.

Identification of independent risk loci

A locus was considered genome-wide significant if association $P < 5 \times 10^{-8}$. For both the primary proxy-case/control analysis in UK Biobank individuals and meta analyses, independent risk loci were identified using the approximate conditional and joint association method implemented in GCTA with settings $r^2 > 0.9$ and $P < 5 \times 10^{-8}$, and a reference panel consisting of 2,500 randomly selected individuals from the UK Biobank cohort [Yang et al., 2012].

URLs

UK Biobank - `http://www.ukbiobank.ac.uk`

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Genotyping and quality control of UK Biobank, a large-scale, extensively phenotyped prospective resource - `http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web.pdf`

Genotype imputation and genetic association studies of UK Biobank - `http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/imputation_documentation_May2015.pdf`

GeneticsDesign - `https://bioconductor.org/packages/release/bioc/html/GeneticsDesign.html`

Parkinson's disease GWAS summary statistics from Nalls et al. [2014] - `http://pdgene.org/view?study=1`

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