Rare and low-frequency coding variants alter human adult height

Supplementary Information

DEPICT for ExomeChip

DEPICT was originally developed to (1) prioritize genes in associated GWAS loci, (2) identify gene sets enriched for genes in associated GWAS loci, and (3) identify tissues in which genes from associated GWAS loci are specifically expressed[1]. In this work, we adapted DEPICT to identify gene sets enriched for genes harboring significantly associated ExomeChip variants. In the following sections, we describe how the gene set enrichment analysis functionality in DEPICT was adapted to facilitate analysis of ExomeChip data. Next, we describe the input data and parameters used to perform DEPICT gene set enrichment analysis of the GWAS variants that were independent of the novel ExomeChip coding variants. Finally, we outline the steps we took to compare the results from DEPICT for ExomeChip (henceforth 'EC-DEPICT') with (1) the results from DEPICT for GWAS and (2) the results from the PASCAL method[2].

EC-DEPICT methods and analyses

ExomeChip variants and genes. We started by defining the set of variants and genes to analyze. To define a "background" set of variants with coherent annotations of their functional consequences on gene products, we used annotations from the CHARGE consortium file (see URLs, download date 2/10/16), which contained 247,037 variants in 27,196 genes. First, we limited the analysis to 220,647 variants with frameshift, non-synonymous, stopgain, stoploss, or splice-site annotations (in 17,473 unique genes). We then removed all variants that were not assessed in the height ExomeChip data, leaving 215,689 variants in 17,416 genes. For variants with different functional consequences that mapped to more than one gene, the most severe one was retained, leaving 17,415 genes. In instances where variants mapped to multiple genes with equal deleteriousness, the gene was chosen randomly. HUGO gene identifiers from the CHARGE annotation file were converted to Ensembl identifiers using Ensembl Biomart (version 84, GRCh37) gene homology mapping (see URLs, download date 4/18/2016). After removing variants that did not map to an Ensembl identifier present in DEPICT's reconstituted gene sets, we were left with 199,907 variants in 15,652 genes. Finally, to ensure valid null distributions, we also excluded all variants absent from the null ExomeChip data that was used to calculate P-values (see below). After all filtering steps, a total of 41,538 variants in 11,756 genes were included in the analysis.

Input variants to EC-DEPICT. As input to EC-DEPICT, we took variants which either (1) had P-values $<2x10^{-7}$ in the discovery or conditional analyses or (2) had P-values between $2x10^{-6}$ and $2x10^{-7}$ in the discovery analysis and a P-value of $<2x10^{-7}$ in the combined discovery and replication analysis (**Supplementary Tables 11**). Then, to discern pathways that were highlighted by coding variants independently of known GWAS signals, we filtered for ExomeChip hits for height that were either independent of known GWAS loci or were the strongest signal in known GWAS loci and removed variants where there was a common ExomeChip missense variant statistically equivalent to a GWAS variant. A total of 128 variants in 119 genes were retained and used in the analysis.

EC-DEPICT methodology overview. To assess whether the ExomeChip variants were enriched for particular reconstituted gene sets, we next developed the EC-DEPICT algorithm, which is modeled closely off that in DEPICT. First, we downloaded the reconstituted gene sets used in Pers et al. (2015)(see URLs)[1]. For each gene set, the Z-scores for pathway membership of each significant gene from the ExomeChip were retrieved and summed. Then, the summed Z-scores

were normalized relative to 2,000 null ExomeChip backgrounds (see next paragraph for details) by subtracting off the mean null Z-score for a given gene set and dividing by the null standard deviation. The resulting adjusted Z-score was then converted to a P-value using the normal distribution. The Python programming language was used to implement EC-DEPICT, and the code can be downloaded from our Github repository (see URLs).

Null ExomeChip backgrounds. To create "null" ExomeChip data, we used genotype data from the Malmö Diet and Cancer (MDC), All New Diabetics in Scania (ANDIS), and Scania Diabetes Registry (SDR) cohorts, which comprised a total of 11,899 samples of Swedish ancestry. Using the genotypes and normally-distributed simulated phenotypes with no genetic basis, we conducted 2,000 ExomeChip association studies (nulls) that included only variants present in the height ExomeChip association analysis. Each null was sorted in order of ascending P-value, and the CHARGE-based variant-to-gene mapping was used to rank-order a total of 11,756 genes. To match the number of significant genes in the height ExomeChip results, we retained the top 119 genes from each null.

False discovery rate calculations (FDR). FDRs were calculated using 50 null permutations separate from the 2,000 used for P-value calculation. For each of the 50 nulls, an EC-DEPICT P-value was calculated for each reconstituted gene set to generate a null distribution of P-values. To calculate the FDR, we divided the number of null P-values less than a given threshold by 50, and then divided that by the number of observed P-values less than the given threshold. We considered significance at an FDR of <0.01.

Distribution of observed P-values and type I error. Theoretically, a given set of genes could be either over- or underrepresented among genes in associated GWAS loci or among associated genes from an ExomeChip study. For the height EC-DEPICT gene set enrichment, we observed that reconstituted gene set enrichment P-values indeed followed a U-shaped curve, indicating that particular reconstituted gene sets can be either enriched or depleted of the group of genes implicated by height ExomeChip variants (the complete list of reconstituted gene set results can be downloaded online, see URLs).

To assess the type I error, we calculated all reconstituted gene set enrichment P-values for 50 null ExomeChip studies and plotted them in a histogram. Their distribution was close to uniform, as indicated by the histogram.

In further exploring the DEPICT results, we noticed that in certain scenarios, extreme non-normality of pathway membership z-scores for certain gene sets could slightly increase type 1 error in DEPICT. To determine if this issue affected our results, we performed another DEPICT analysis using a version of the reconstituted gene sets where pathway membership scores were inverse normal transformed. We then compared the ranks of each gene set in the original data with their rank in the inverse normal transform. Of the 496 originally significant gene sets, only 22 were "outliers" (> 1.5 x the interquartile range). We note that all but one of these outliers still had an FDR of <0.05 in the inverse normal transformed data, and the remaining gene set had FDR <.10. These outliers are denoted in the supplementary table with an asterisk. Additionally, we note that removing these outliers leads to the loss of only one significant meta-gene set (which is still significant at FDR <0.05). We conclude that this issue only minimally impacts these results, but recommend that future users of this method should also repeat the analysis

using inverse normal transformed pathway membership scores, and look for outliers, as an additional check.

DEPICT GWAS analysis

As input to the DEPICT analysis of height GWAS results, we started with significant noncoding variants found by GWAS (using Variant Effect Predictor for annotations). We constructed loci using DEPICT as previously described (beta version 1.1, release 194, see URLs), using 1000 Genomes phase 1 data (part of the DEPICT download bundle) and default parameters to perform the analysis (20 repetitions to compute FDRs, 500 permutations to adjust for biases), and eliminated loci containing overlap with any of the novel EC genes. This left 446 loci, which were used in the subsequent DEPICT gene set enrichment step.

Correlation of reconstituted gene sets and comparisons of results

Many of the reconstituted gene sets are correlated with each other; it is therefore logical to group together substantially similar gene sets to facilitate interpretation and analysis of the data. We therefore generated a list of "meta-gene sets" in which each meta-gene set contained a group of highly related gene sets. To do this, we calculated the Pearson correlation matrix for all pairs of the 14,462 gene sets (based on gene set membership) and subsequently clustered the reconstituted gene sets based on their similarity (i.e. Pearson's correlation coefficients). A Python implementation of the Affinity Propagation algorithm[3] was used for clustering (SciKit-Learn.clustering.AffinityPropagation version 0.17)[4]. Due to the relatively large number of reconstituted gene sets, we used a maximum iteration of 10,000 and a convergence iteration of 1,000.

We then used the meta-gene sets to compare the results from EC-DEPICT with (1) the results from DEPICT on the GWAS data and (2) the results from Pascal. In tables and figures, we used the "representative" gene set (as determined by the Affinity Propagation algorithm) as the gene set label for each meta-gene set. The P-value for each "meta-gene set" was chosen as the best P-value of any member gene set.

Similarly, we also used the meta-gene sets as labels for the heat maps in **Fig. 2** and **Supplementary Fig. 11**; each Z-score for gene set membership in the heat maps represents the Z-score for the gene set with the best P-value. Heat maps were generated using the ComplexHeatmap package in R[5]. For OMIM annotations, we supplemented a previously annotated list of OMIM genes (from Wood et *al*.[6]) with the results of a more recent search in OMIM for the terms "short stature," "overgrowth," "skeletal dysplasia," or "brachydactyly," and manually curated the combined list to include genes where mutations cause clinical abnormalities of skeletal growth. The manual curation was performed prior to obtaining the ExomeChip results.

URLs

CHARGE Consortium ExomeChip annotation file:
http://www.chargeconsortium.com/main/exomechip/
Ensembl Biomart: http://grch37.ensembl.org/biomart/
DEPICT: www.broadinstitute.org/mpg/depict
EC-DEPICT: https://github.com/RebeccaFine/height-ec-depict

EC-DEPICT height reconstituted gene set enrichment results: https://github.com/RebeccaFine/height-ec-depict/tree/master/analyses
EC-DEPICT meta-gene sets: https://github.com/RebeccaFine/height-ec-depict/blob/master/data/metacluster_labels.txt

Additional references

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