Polygenic Transcriptome Risk Scores Can Translate Genetic Results Between Species

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Abstract Genome-wide association studies have demonstrated that most

traits are highly polygenic; however, translating these polygenic signals into biological insights remains difficult. A lack of satisfactory methods for translating polygenic results across species has precluded the use of model organisms to address this problem. Here we explore the use of polygenic transcriptomic risk scores (PTRS) for translating polygenic results across species. Unlike polygenic risk scores (PRS), which rely on SNPs, PTRS use imputed gene expression for prediction, which allows cross-species translation to orthologous genes. We first developed RatXcan, which is a framework for transcriptome-wide association studies (TWAS) in outbred rats. Leveraging predicted transcriptome and genotype data from UK Biobank, and the genetically trained gene expression models from RatXcan, we scored more than 3,000 rats using human-derived PTRS for height and BMI. Strikingly, we found that these human-derived PTRS significantly predicted analogous traits in rats ($r = 0.08$, $P = 8.57 \times 10^{-6}$; $r = 0.06$, $P = 8.51 \times 10^{-4}$, respectively). The genes included in the PTRS were enriched for biological pathways including skeletal growth and metabolism and were over-represented in tissues including pancreas and brain. This approach facilitates experimental studies in model organisms that examine the polygenic basis of human complex traits and provides an empirical metric by which to evaluate the suitability of specific animal models and identify their shared biological underpinnings.

Introduction

Over the last decade, genome-wide association studies (GWAS) have identified numerous genetic loci that contribute to biomedically important traits [***Visscher et al., 2017***]. However, translating these results into biologically meaningful discoveries remains extremely challenging [***Lewis and Vassos, 2020***, ***Martin et al., 2019***, ***Alliance et al., 2021***]. GWAS have demonstrated that most traits have a highly polygenic architecture, meaning that numerous genetic variants with individually small effects confer risk [***Loos, 2020***]. The cumulative results from GWAS can be used to construct polygenic risk scores (PRS), which summarize the effects of many loci on a trait [***Wray et al., 2007***].

Model organisms provide a system in which the effect of genotype, genetic manipulations and environmental exposures can be experimentally tested. Whereas the tools for using model organisms to study *individual* genes are well established, there are no satisfactory methods for studying the *polygenic* signals obtained from GWAS in model organisms. PRS are not suitable because they summarize the effects of many single-nucleotide polymorphisms (SNPs) on a trait; however, humans SNPs do not have direct homologs in other species, and even if they did, they would not be expected to have the same effects or to tag the same causal variants.

To address this problem, we sought to develop a novel method that allows translation of polygenic signals from humans to other species and vice-versa. This method focuses on gene expression, rather than SNPs, and builds on our past work with polygenic transcriptomic risk scores (PTRS) [***Liang et al., 2022***]. PTRS are premised on the regulatory nature of most GWAS loci [***Maurano et al., 2012***] and use genetically regulated gene expression (transcript abundance), instead of SNPs as features for prediction. We recently showed that PTRS are useful for translating polygenic signals between different human ancestry groups [***Liang et al., 2022***], supporting the view that the effects of genes on a phenotype are conserved across ancestry groups. In the current project we hypothesized that the relationships between genes and phenotypes are conserved not only between human ancestry groups, but also across species. Thus, we explored whether PTRS trained using human data could predict similar traits in another species by applying the PTRS to orthologous genes in the target species. We selected heterogeneous stock (HS) rats because they are a well characterized, outbred mammalian population for which dense genotype, phenotype and gene expression data data are available in thousands of subjects [***Solberg Woods and Palmer, 2019***] [***Chitre et al., 2020***].

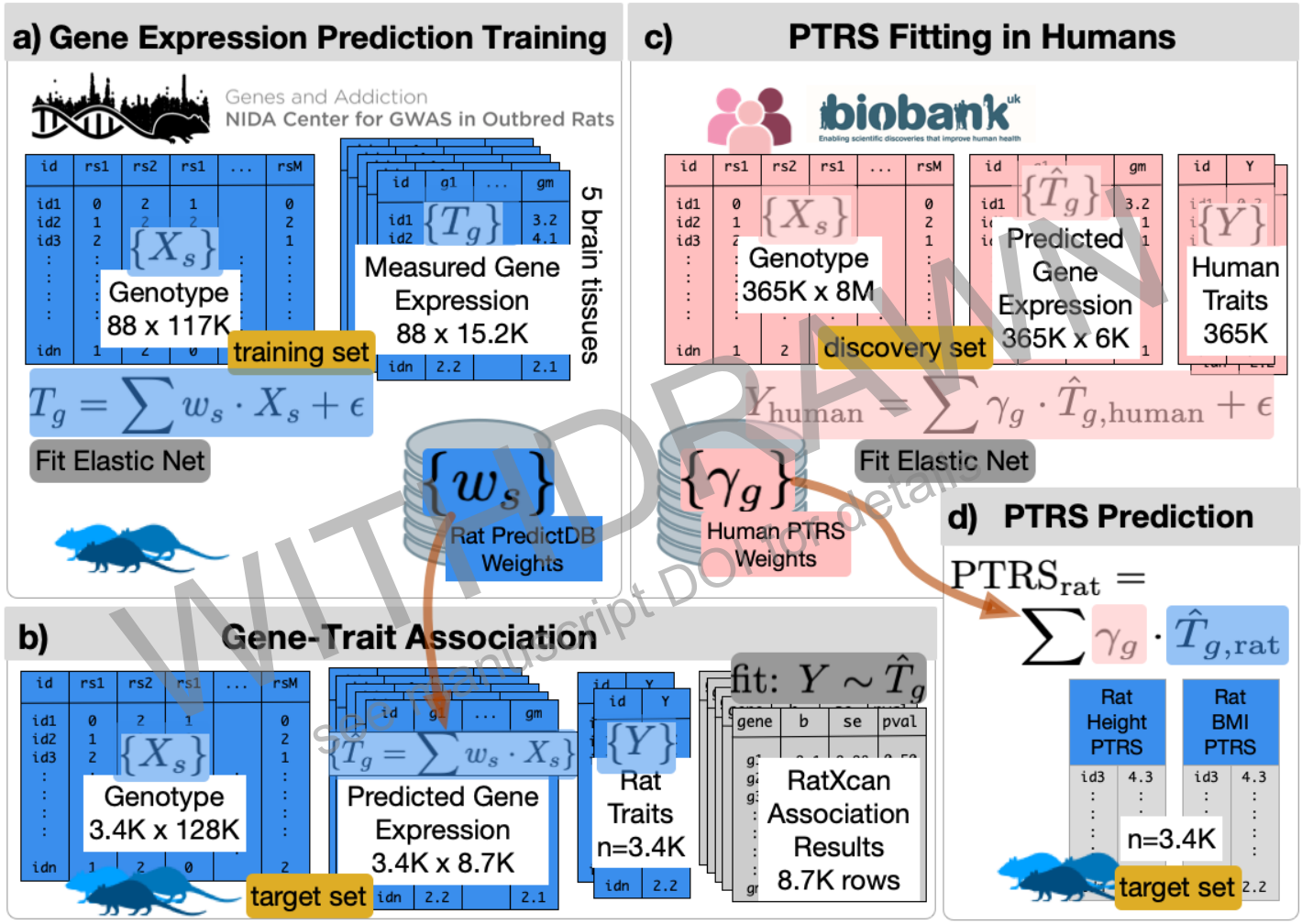

Figure 1. Schematic representation of cross-species polygenic translation framework.
The workflow was divided into 4 stages: a) gene expression prediction training, b) gene-trait association, c) PTRS fitting in humans, d) PTRS prediction. a) In the gene expression prediction training stage, we used genotype (117,155 SNPs) and gene expression data (15,216 genes) from samples derived from 5 brain regions in 88 rats. The prediction weights (rat PredictDB weights) are stored in predictdb.org. Rats used in this stage constitute the training set. b) In the gene-trait association stage, we used genotype and phenotype data from the target set of 3,407 rats (no overlap with training set rats). Predicted gene expression (8,567 genes for which prediction was possible) was calculated for all the 3,407 target set rats, and gene-trait associations were tested using RatXcan (N=1,463-3,110). We queried human gene-level associations from PhenomeXcan to estimate enrichment levels with our rat findings. c) Human PTRS weights were fitted using elastic net regression of height and BMI on predicted whole blood gene expression levels (7,002 genes) in the UK Biobank (N=356,476). d) The human PTRS weights were used for complex trait prediction in rats. PTRS trained in humans were then used to predict analogous traits in our target rat set. Prediction performance of PTRS was calculated as the correlation (and partial correlation) between the predicted scores in rats and the observed traits. Analyses in rats are shown in blue and analyses in humans are shown in pink.

Results

Experimental setup

To build a framework for translating genetic results between species, we followed the experimental setup illustrated in Fig. 1. In the *training stage* (Fig. 1a), we investigated the genetic architecture of gene expression and built prediction models of gene expression in rats. We used genotype and transcriptome data from five brain regions sampled from 88 rats, generated by the NIDA Center for GWAS for Outbred rats (Fig. 1a). In the *association stage* (Fig. 1b), we used their genotype data to predict the transcriptome in a non-overlapping *target set* of 3,407 rats and tested for association between the genetically predicted gene expression and 7 physiological traits by adapting the PrediXcan software, which was originally developed for use in humans [***Gamazon et al., 2015***] to rats ('RatXcan'). The physiological traits were: body length, body weight, BMI (body length/body weight^2), three fat pad weights, and fasting glucose. In the *discovery stage* (Fig. 1c), we determined the human-derived PTRS weights for height and BMI using data from 356,476 individuals of European-descent from UK Biobank. In the final stage (Fig 1d), we used these human-derived weights in conjunction with genetically predicted gene expression for rats in the target set. We assessed the prediction performance by comparing the predictions from the PTRS to the true body length (which is equivalent to human height) and BMI for each rat.

Genetic Architecture of Gene Expression across Brain Tissues

To inform the optimal prediction model training, we examined the genetic architecture of gene expression by quantifying its heritability and polygenicity. Unless otherwise specified, we show the results for nucleus accumbens core in the main section and for the remaining tissues in the supplement.

We calculated the heritability of expression for each gene by estimating the proportion of variance explained (PVE) using a Bayesian Sparse Linear Mixed Model (BSLMM) [***Zhou et al., 2013***]. We restricted the feature set to variants within 1 Mb of the transcription start site of each gene since this is expected to capture most cis-eQTLs. Among the 15,216 genes considered, 3,438 genes were heritable in the nucleus accumbens core, with 95% credible sets's lower boundary greater than 1%. The mean heritability ranged from 8.86% to 10.12% for all brain tissues tested (Table 1). Fig. 2a shows the heritability estimates for gene expression in the nucleus accumbens core, while heritability estimates in other tissues are shown in Fig. S1. In humans, we identified a similar heritability distribution (Fig. 2b, Fig. S2) based on whole blood samples from GTEx.

Next, to evaluate the polygenicity of gene expression levels, we examined whether predictors with more polygenic (i.e., many variants of small effects) or more sparse (i.e., just a few larger effect variants) architecture correlated better

with observed expression. We fitted elastic net regression models using a range of mixing parameters from 0 to 1 (Fig. 2c). The leftmost value of 0 corresponds to ridge regression, which is fully polygenic and uses all cis-variants. Larger values of the mixing parameters yield more sparse predictors, with the number of variants decreasing as the mixing parameter increases. The rightmost value of 1 corresponds to lasso, which yields the most sparse predictor within the elastic net family. Similar to reports in human data [***Wheeler et al., 2016***], sparse predictors outperformed polygenic predictors (Fig. 2c).

We used the 10-fold cross-validated Pearson correlation (R) between predicted and observed values as a measure of performance (Spearman correlation yielded similar results). We observed a substantial drop in performance towards the more polygenic end of the mixing parameter spectrum (Fig. 2c). For reference, we show similar results using human gene expression data from whole blood samples in GTEx individuals (Fig. 2d). Overall, these results indicate that the genetic architecture of gene expression in rats (detectable at current sample sizes) is sparse, similar to that of humans [***Wheeler et al., 2016***].

Generation of Prediction Models of Gene Expression in Rats

Based on the relative performance across different elastic net mixing parameters, we chose a value of 0.5, which yielded slightly less sparse predictors than lasso but provided robustness to missing or low quality variants; this is the same value that we have chosen in the past for humans datasets [***Gamazon et al., 2015***].

We trained elastic net predictors for all genes in all 5 brain regions. The procedure yielded 8,244-8,856 genes across five brain tissues from the available 15,216 genes (Table 1). The 10-fold cross-validated prediction performance (R^2) ranged up to 80% with a mean of 8.51% in the nucleus accumbens core. Similarly to Fig. 1a and b, mean prediction R^2 was consistently lower than mean heritability, as is expected since genetic prediction performance is restricted by its heritability. Other brain tissues yielded similar prediction performance (Table 1). Reassuringly, prediction performance values followed the heritability curve, confirming that genes with highly heritable expression tend to be better predicted than genes with low heritability in both rats and humans (Fig. 2a-b). Interestingly, we identified better prediction performance in rats than in humans (Fig. S3), despite heritability of gene expression being similar across species (Fig. 2a-b).

In Fig. 3a-b, we show the prediction performance of two of the best predicted genes in rats (*Mgmt*, $R^2 = 0.72$) and humans (*RPS26*, $R^2 = 0.74$). Across all genes, we found that the prediction performance in rats was correlated with that of humans ($R = 0.061$, $P = 8.03 * 10^{-6}$; Fig. 3c). Furthermore, performance per gene between two tissues was similar in both rats (Fig. 3d) and humans (Fig. 3e), namely, genes that were well-predicted in one tissue were also well-predicted in another tissue. Correlation of prediction performance across tissues ranged from 58 to

84% in rats and 42 to 69% in humans.

Having established the similarity of the genetic architecture of gene expression between rats and humans, we transitioned to the *association stage*.

Brain Region	# Rats	# Genes Predicted	Average R^2	Average cis h^2
Nucleus Accumbens Core (NAcc)	78	8,567	8.51%	9.82%
Infralimbic Cortex (IL)	83	8,856	8.87%	9.77%
Lateral Habenula (LHb)	83	8,244	7.78%	8.86%
Prelimibic Cortex (PL)	81	8,315	9.33%	10.12%
Orbitofrontal Cortex (OFC)	82	8,821	9.13%	9.82%

Table 1. Summary of heritability and prediction performance in rats. The table shows the number of rats used in the prediction, number of genes predicted per model, the average predicion performance R^2, and average cis-heritability cis h^2, for all gene transcripts.

PrediXcan/TWAS Implementation in Rats (RatXcan)

To extend the PrediXcan/TWAS framework to rats, we developed RatXcan. We used the predicted weights from the *training stage* to estimate the genetically regulated expression in the *target set* of 3,407 rats. We then tested the association between predicted expression and seven physiological traits.

We identified 90 Bonferroni significant genes ($P(0.05/5388) = 9.28 \times 10^{-6}$) in 57 distinct loci separated by ± 1 MB for rat body length (Fig. 4a) and 21 significant genes in 15 loci for rat BMI (Fig. 4b; Supplementary Table 1). Among the top significant genes, *Adcy3* was associated with fat traits ($P = 7.22 \times 10^{-16}$) and body weight ($P = 2.41 \times 10^{-4}$). The human ortholog, *ADCY3*, was associated with BMI [***Speliotes et al., 2010***] and was reported to mediate energy homeostasis and is considered a promising therapeutic target for obesity [***Saeed et al., 2018***]. Similarly, *Prlhr* was associated with fat traits, body weight, BMI, and body length ($P = 5.55 \times 10^{-17}$, $P = 2.81 \times 10^{-16}$, $P = 5.12 \times 10^{-12}$, $P = 4.65 \times 10^{-04}$, respectively). The human ortholog, *PRLHR*, was associated with BMI and body fat percentage ($P = 1.76 \times 10^{-6}$, $P = 3.62 \times 10^{-6}$) [***Pividori et al., 2020***]. *PRLHR* encodes for a 7-transmembrane domain receptor for prolactin-releasing hormone [***Ozawa et al., 2002***]. *PRLHR* was found to be associated with lactation, regulation of food intake and pain-signal processing [***Atanes et al., 2021***]. Moreover, both *Adcy3* and *Prlhr* have previously been identified as candidate genes for adiposity in the HS rat population [***Chitre et al., 2020***].

To evaluate whether trait-associated genes in rats were more significantly associated with the corresponding trait in humans, we performed enrichment analysis. Specifically, we selected genes that were nominally associated with rat

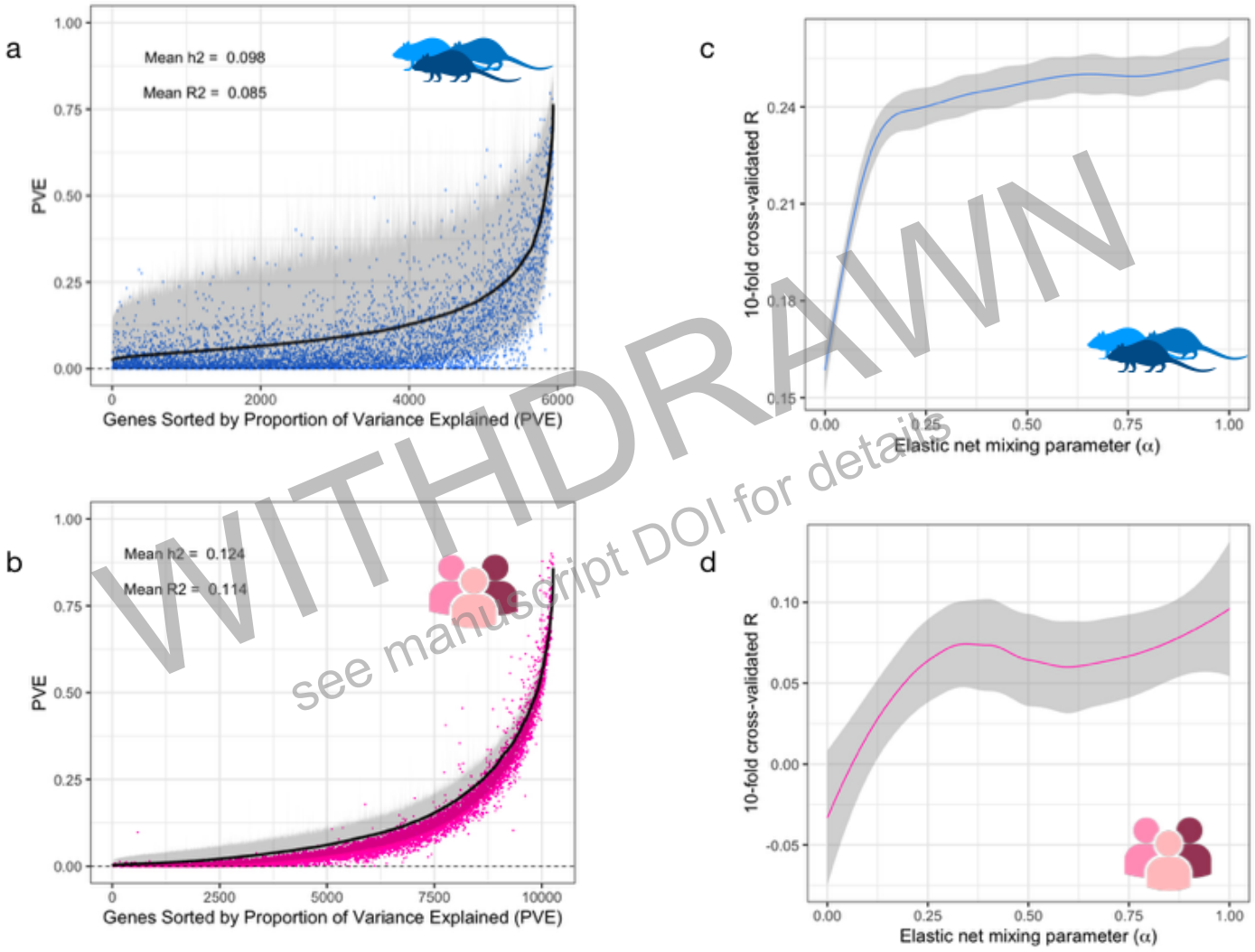

Figure 2. Heritability and sparsity of gene expression in both rats and humans. a) cis-heritability of gene expression levels in the nucleus accumbens core of rats calculated using BSLMM (black). We show only genes (N = 10,268) that have an equivalent ortholog in the GTEx population. On the x-axis, genes are ordered by their heritability estimates. 95% credible sets are shown in gray for each gene. Blue dots indicate the prediction performance (cross validated R^2 between predicted and observed expression). b) cis heritability of gene expression levels in whole blood tissue in humans from GTEx. We show only the same 10,268 orthologous genes. On the x-axis, genes are ordered by their heritability estimates. 95% credible sets are shown in gray for each gene. Pink dots indicate the prediction performance (cross validated R^2 between predicted and observed expression). c) Cross validated prediction performance in rats (Pearson correlation R) as a function of the elastic net parameter ranging from 0 to 1. d) Cross validated prediction performance in humans (Pearson correlation R) as a function of the elastic net parameter ranging from 0 to 1.

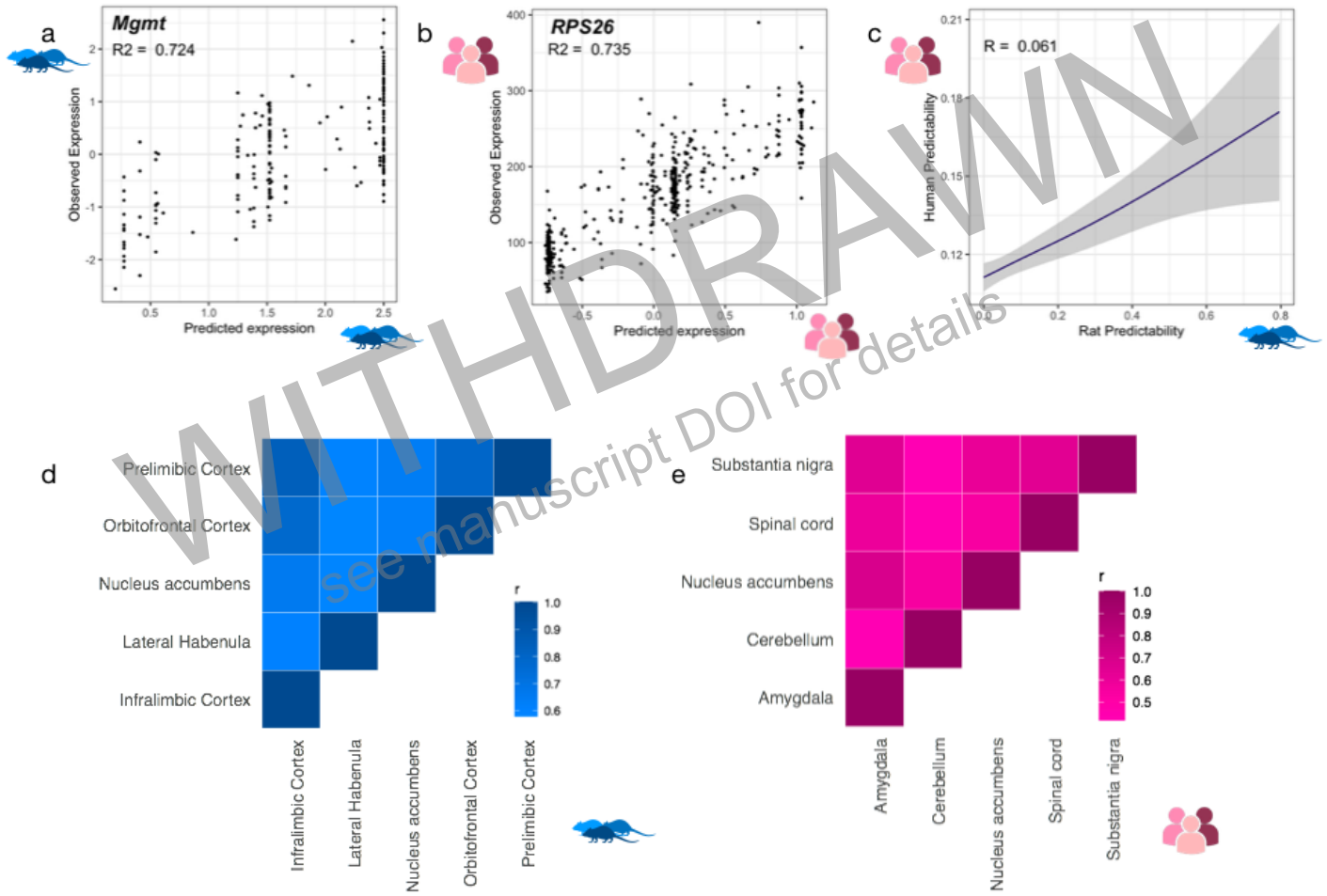

Figure 3. Shared genetic architecture of gene expression in rats and humans a) Comparison of predicted vs. observed expression for a well predicted gene in rats (*Mgmt*, $R^2 = 0.72$, $R = 0.65$, $P < 2.20 \times 10^{-16}$). b) In humans, predicted and observed expression for *RPS26* were significantly correlated ($R^2 = 0.74$, $R = 0.86$, $P < 2.20 \times 10^{-16}$). c) Prediction performance was significantly correlated across species ($R = 0.06$, $P = 8.03 \times 10^{-06}$) d-e) and across all five brain tissues tested in rats and humans. In rats, within tissue prediction performance ranged from ($R = [0.58 - 0.84]$, $P < 2.20 \times 10^{-16}$). In humans, the range was [$R = 0.42 - 0.69$, $P < 2.20 \times 10^{-16}$] .

body length ($P < 0.05$) and compared the p-value from the analogous human trait (height) against the background distribution. Given the large sample size of human height GWAS, we expected the background distribution (shown in pink, Fig. 4c) of height gene-based associated p-values to depart substantially from the identity line (in gray). The subset of genes that were associated with rat body length (in blue, Fig. 4c) showed a major departure from the background distribution, indicating that body length genes in rats were more significantly associated with human height than expected. To quantify the enrichment, we compared the p-value distribution of all the genes with the distribution of the subset of genes that were nominally significantly associated with rat body length ($P = 6.55 \times 10^{-10}$). Similar enrichment was found for BMI (Fig. 4d) ($P = 8.07 \times 10^{-07}$). This systematic enrichment across human and rat findings further encouraged us to test whether PTRS based on human studies could predict analogous traits in rats.

Transfer PTRS from Humans to Rats

To test the portability of PTRS across species, we started by calculating the human PTRS weights, as described in ***Liang et al.*** [***2022***]. Using 356,476 UK Biobank unrelated European descent individuals, we fitted an elastic net regression with height as the outcome variable and the imputed gene expression as the predictor (height = $\sum_g \gamma_g \cdot T_g + \epsilon$ with ϵ, an error term and T_g the imputed gene expression in humans). We chose to use GTEx whole blood predictors, as it was previously reported to perform well in humans [***Liang et al., 2022***]. We applied this procedure for a range of elastic net regularization parameters to increase the flexibility of the prediction models, resulting in 37 sets of weights. The regularization parameter is a hyper-parameter that can be estimated in a validation set, which could be a subset of the target set. Here we show the prediction performance across the full range of hyper-parameters (37 models).

For each rat in the target set, we calculated 37 PTRS (one for each regularization parameter) as the weighted sum of the predicted gene expression in rats with the human-derived weights, which were already computed during the association stage ($\text{PTRS}_{\text{rat}} = \sum \gamma_g \cdot T_{g,rat}$). We used a range of 1 to 2,017 genes, after limiting the human genes that had orthologs in rats (28.72%), to discern how prediction varied as the number of genes changed. The large number of genes used for prediction is consistent with prior human literature indicating that the genetic architecture of height consists of a large number of genes [***Wood et al., 2014***].

Consistent wit prior human literature [***Yengo et al., 2018***] [***Zhao et al., 2015***], gene set enrichment analyses showed that the genes used to calculate human PTRS weights were substantially enriched for pathways and tissues that contribute to skeletal growth and metabolic processes, including myogenesis ($P = 1.18 \times 10^{-5}$), adipogenesis ($P = 7.74 \times 10^{-17}$) and fatty acid metabolism ($P = 3.97 \times 10^{-15}$) (ST. 16). Tissue analysis revealed that PTRS genes are enriched as diferentially ex-

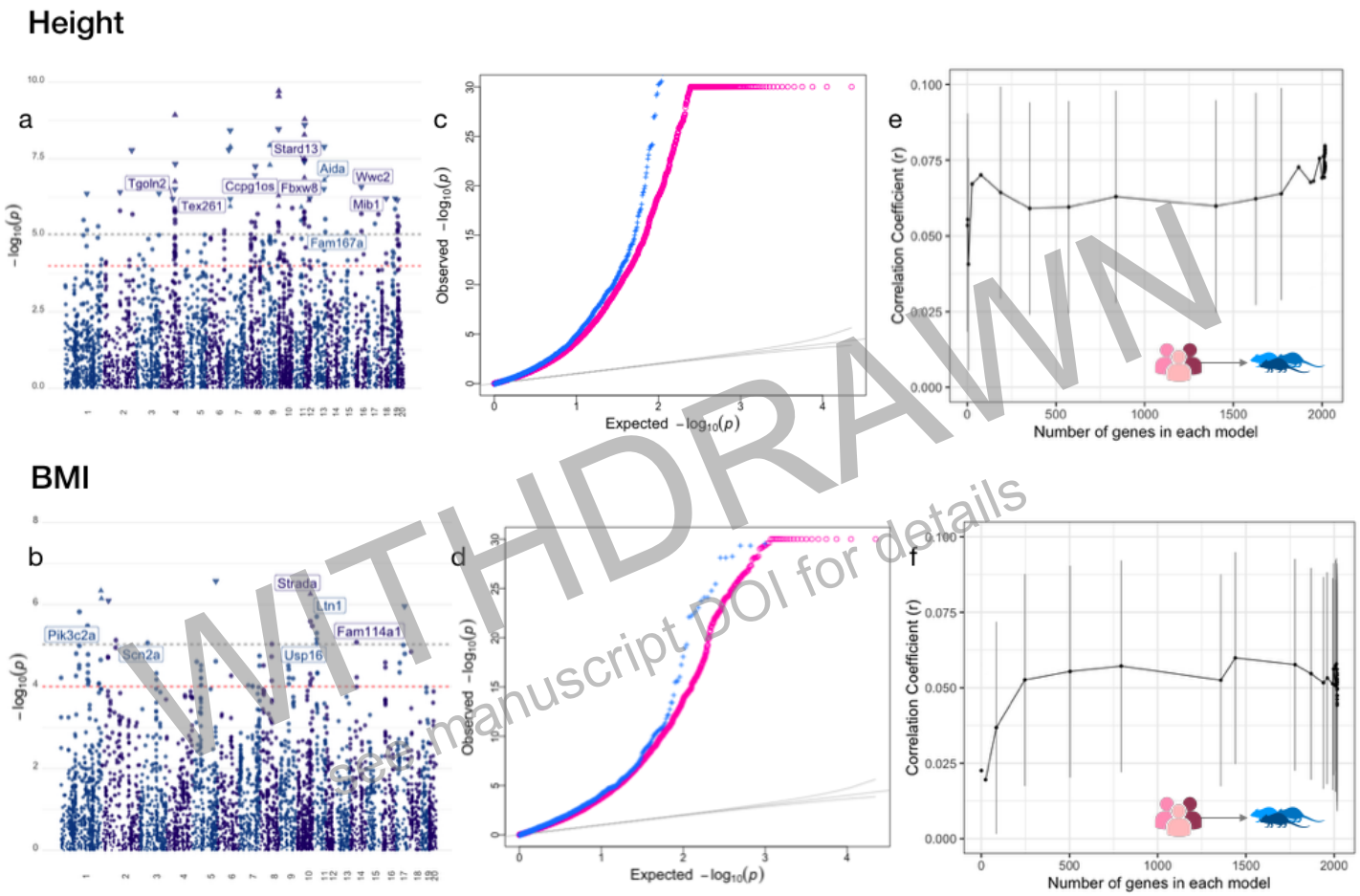

Figure 4. Polygenic Transcriptomic Risk Scores (PTRS) can translate genetic information across species. a) Manhattan plot of the association between predicted gene expression and rat body length, which is analogous to human height. b) Manhattan plot of the association between predicted gene expression and rat BMI. In both a) and b) we label the genes whose human orthologs are at least nominally associated in human data ($P < 0.01$) ; Grey dotted line corresponds to the Bonferroni correction threshold of 0.05/5,388 of tests. Red dotted line corresponds to an arbitrary threshold of 1×10^{-4}. Triangular points refer to genes that were significantly associated with body length at the Bonferroni threshold, where the direction of the triangle corresponds with the sign of the associated gene. c) Q-q plot of the p-values of the association between predicted gene expression levels in humans (phenomexcan.org). Pink dots correspond to all genes tested in humans. Blue dots correspond to the subset of genes that were nominally significantly associated with body length in rats ($P < 0.05$). d) Q-q plot of the p-values of the association between predicted gene expression levels in humans (phenomexcan.org). Pink dots corresponds to all genes in humans. Blue dots correspond to the subset of genes that were nominally significantly associated with BMI in rats ($P < 0.05$). e) Correlation between human-derived height PTRS and observed body length in rats for the 37 regularization parameters used in building the PTRS. f) Correlation between human-derived BMI PTRS and observed BMI in rats for the 37 regularization parameters used in building the PTRS. (The confidence intervals for models 1 and 2 include zero, not shown.)

pressed genes in multiple relevant tissues, including pancreas, heart, liver, and central nervous system (Fig. S4).

Strikingly, human-derived height PTRS significantly predicted body length in rats; that is, the correlation between PTRS and observed rat body length was significant for all the elastic net regularization parameters that included at least 27 genes (maximum $R = 0.08$, $P = 8.57 \times 10^{-6}$; Fig. 4e). To compare our prediction performance to that in the human population, we used the partial R^2 ($\tilde{R^2}$, the proportion of variance explained by the predictor after accounting for other covariates) reported by ***Liang et al.*** [***2022***]. The partial $\tilde{R^2}$ for body length in rats was 0.64% ($P = 8.57 \times 10^{-6}$), while in the UK Biobank European test set, the partial $\tilde{R^2}$ for height in humans was 9.40%.

We applied the same procedure to BMI and again found significant prediction; the correlation between human-derived BMI PTRS and observed BMI was significant across all regularization parameters that included at least 247 genes (maximum $R = 0.06$, $P = 8.51 \times 10^{-4}$; Fig. 4f). The maximum partial $\tilde{R^2}$ was 0.36% ($P = 8.52 \times 10^{-4}$). In UK Biobank European test set, the partial $\tilde{R^2}$ for BMI in humans was 1.45%.

As a negative control, we compared the correlation between the human-derived height PTRS and observed fasting glucose in the target set of rats. As shown in Fig. S5, the correlation was not significant (P = 0.71), confirming that a human-derived PTRS can predict a similar trait in rats, but do not predict dissimilar traits.

Discussion

Overwhelming evidence demonstrates that most complex diseases are extremely polygenic, however there are no methods for translating polygenic results in other species. Here, we present a novel analytical framework that facilitates cross-species translation of polygenic results, providing a unique and urgently needed bridge between the human and model organism disciplines. Translation of polygenic information has been challenging because, despite the utility of PRS for trait prediction in humans, SNPs do not transfer across species. Our approach circumvents this limitation by translating polygenic information to the level of genes and then relying on the mapping of orthologous genes between humans and another species, in this case rats.

A critical first step in this project was the development of RatXcan, which is the rat version of PrediXcan [***Gamazon et al., 2015***], which is a well-established statistical tool that is used in human genetics. We showed that the genetic architecture of gene expression in rats is broadly similar to humans: they are heritable, sparse, and the degree of heritablity is preserved across tissues; some of these observations are consistent with another recent publication that mapped eQTLs in HS rats [***Munro et al., 2022***]. Interestingly, despite the smaller sample sizes

used to train our prediction models, rats showed better prediction than humans. This might reflect the fact that HS rats have a preponderance of common alleles [***Chitre et al., 2020***] whereas humans have numerous rare alleles that influence gene expression but are difficult to capture in prediction models. The superior prediction may also reflect the longer haplotype blocks that are present in HS rats relative to humans [***Chitre et al., 2020***].

Using RatXcan, we tested gene-level associations of 7 physiological traits that had been previously measured in rats. Our main focus was on height and BMI because of the availability of large human GWAS that allowed us to develop robust human PTRS for those traits and because of the relatively unambiguous similarity between traits in humans and rats. We found substantial enrichment of trait-associated genes among orthologous human trait-associated genes, which encouraged us to use the human PTRS to try to predict similar traits in the HS rats.

Remarkably, we found that PTRS developed in humans significantly predicted both rat body length (which is equivalent to height) and BMI in rats. These results demonstrate that PTRS is a viable strategy for translating polygenic results between humans and rats. Even though, the proportion of body length variance explained by our PTRS was only 0.64% compared to the 9.40% in the European target set, that proportion dropped substantially as low as 1.46% when testing in non European target sets (See supplementary Table 6 in [***Liang et al., 2022***]). Closer examination of these results revealed that prediction of height improved until about 100 genes were included in the model, whereas prediction of BMI continued to improve until about 250 genes were included in the model. It is likely that larger and thus more powerful rat transcriptomic datasets would improve prediction by increasing the number of genes that contributed to prediction as well as the accuracy of prediction. In addition, of the 7,044 genes that were included in the human-derived PTRS, only 2,017 had rat orthologs; increasing our knowledge of orthologous genes or identifying other strategies to address this limitation might further improve performance.

The magnitude and significance of prediction using human PTRS for BMI to predict rat BMI was smaller than it was for human height to rat body length, which was expected given the lower heritability of human BMI. For reference, heritability estimates were more than three-fold lower for human BMI as compared to human height: 15% for BMI vs. 55% for height [***Liang et al., 2022***]. The ability to transfer polygenic signals to other species creates novel opportunities to explore the mechanisms underlying those traits. For example, genes included in the human-derived PTRS showed evidence of enrichment in relevant pathways and tissues for skeletal and metabolic processes, demonstrating that PTRS can uncover shared underlying biological mechanisms, which can be more intensively studied in model systems. It is also possible that PTRS could be used to iden-

tify which aspects (e.g. tissues, cell types, etc) of a human trait are recapitulated by analogous phenotypes in model organism, which could highlight both the strengths and limitations of a phenotype that is used to model a disease or other human trait.

For example, PTRS will provide a novel means of validating animal models of human disorders, as it will be possible to empirically test whether the genetic signature for a particular condition in humans is related to that of analogous phenotypes in rodents. Notably, PTRS captures both the magnitude and the directionality of each gene's effect on a phenotype. A potential application of PTRS could be to categorize rodents as being more or less susceptible to human traits and diseases aimed at quantifying whether non-genetic parameters (e.g., drugs, environmental stressors) alter gene expression in a way that modifies the PTRS. Another advantage of our approach is that it focuses on the role of several genes involved in a phenotype. Thus, PTRS could also serve as a toolkit for identifying components of molecular networks for drug repositioning, namely studies aimed at identifying small molecules and other interventions that can alter the global gene expression in model organisms in a way that lowers risk, as predicted by PTRS analyses.

There is a widely recognized need for methods to integrate data from genetics studies in humans and non-humans [***Palmer et al., 2021b***]. To address this need, several prior efforts combine human genetic results with sets of genes identified as differential expressed in various model organisms [***Reynolds et al., 2021***]. Two such studies examined the overlap between human GWAS results for traits related to human substance use disorder and changes in gene expression in the brain, typically following acute or chronic administration of drugs. In two of these approaches, gene sets were collected from rodent differential gene expression studies that examined the effects of alcohol and/or nicotine and then used a partitioned heritability approach, which showed enrichment of these genes in human GWAS results [***Palmer et al., 2021a***], although there was some question about the specificity of the effects [***Huggett et al., 2021***]. Another study used a broadly similar approach but also included protein-protein network information [***Mignogna et al., 2019***]. In yet another study that examined polygenicity in rodents, a cross was made to introduce genetic variability among mice that all carried the 5XFAD transgene, which recapitulates some features of Alzheimer's disease (AD). By classifying mice based on their genotype at 19 markers that were near genes implicated by human GWAS for AD, they showed evidence of epistatic modulation of the phenotypic effects of the 5XFAD allele by these 19 markers [***Neuner et al., 2019***]. While this approach shares the most commonalities with PTRS, Neuner et al [***Neuner et al., 2019***] did not extrapolate GWAS data to transcript abundance, did not preserve the weights and directionality available from TWAS and account for whether or not the mouse genes showed heritable gene expression differ-

ences.

Our studies are conceptually similar to studies that seek to examine cellular and molecular phenotypes in cultured human cells for which PRS have been calculated [***Dobrindt et al., 2020***]. In a similar manner, rats or other model organisms could be assigned PTRS such that rats with a high or low risk of a uniquely human phenotype, such as schizophrenia, could be examined to identify molecular, cellular or circuit level differences between rats with high or low scores. Similarly, just as pharmacological manipulation can be applied to cells in culture that have been sorted for PRS or PTRS scores [***So et al., 2017***], pharmacological treatments could be administered to a model species to see if the gene expression pattern changed in a manner associated with reduced risk for a disease or other condition.

There are several limitations in the current study that need be addressed in the future. The sample size of the reference transcriptome data in rats was limited. We would expect better predictability estimates in our elastic-net trained models with larger sample sizes. Second, presumably due to the lack of adequate sample size, we did not have a sufficiently robust PTRS from rats to attempt rat to human PTRS translation. Third, we suspect that in both humans and rats, some gene-level associations may be confounded by linkage disequilibrium contamination and co-regulation. This problem is likely to be more serious in model organisms where even longer range LD exists. Refining PTRS by integrating fine-mapping and co-localization approaches could improve portability across species. Finally, integration of other omic data types (e.g., protein, methylation, metabolomics) and the use of cell-specific data may improve prediction accuracy and cross-species portability. It is worth noting that while we have shown success with humans and rats, it is still not clear whether more distantly related species, such as non-mammalian vertebrates or even insects, might also lend themselves to the PTRS approach.

Despite these limitations, we have shown that PTRS, which has previously been used to address the difficulty of transferring PRS between human ancestries [***Liang et al., 2022***], can successfully transfer polygenic results between species. One important feature of this approach is its ability to preserve both magnitude and directional information about the relationship between gene expression and phenotype. This method should support new and transformative experimental designs. Most importantly, it provides a method to empirically validate traits that are studied in model systems. While the validity of these animal models has been a source of passionate debate, empirical evidence has been most based on a single example. Our polygenic approach provides a more holistic approach that is urgently needed.

Methods

Genotype and expression data in the training rat set

The rats used for this study are part of a large multi-site project focused on genetic analysis of complex traits (www.ratgenes.org). N/NIH heterogeneous stock (HS) outbred rats are the most highly recombinant rat intercross available, and are a powerful tool for genetic studies ([***Solberg Woods and Palmer, 2019***]; [***Chitre et al., 2020***]). HS rats were created by interbreeding eight inbred strains and maintained by randomized breeding strategy to minimize inbreeding and control for genetic drift.

For training the gene expression predictors, we used RNAseq and genotype data pre-processed for ***Munro et al.*** [***2022***]. We used 88 HS male and female adult rats, for which whole genome and RNA-sequencing information was available across five brain tissues [nucleus accumbens core (NAcc), infralimbic cortex (Il), prelimbic cortex (PL), orbitofrontal cortex (OFC), and lateral habenula (Lhb); Table 1]. Mean age was 85.7 ± 2.2 for males and 87.0 ± 3.8 for females. All rats were group housed under standard laboratory conditions and had not been through any previous experimental protocols. Genotypes were determined using genotyping-by-sequencing, as described previously in [***Parker et al., 2016***], [***Chitre et al., 2020***] and [***Gileta et al., 2020***]. Bulk RNA-sequencing was performed using Illumina HiSeq 4000 with polyA libraries, 100 bp single-end reads, and mean library size of 27M. Read alignment and gene expression quantification was performed using RSEM and counts were upper-quartile normalized, followed by additional quality controlled filtering steps as described in ***Munro et al.*** [***2022***]. Gene expression levels refer to transcript abundance for reads aligned to the gene's exons using the Ensembl Rat Transcriptome.

For each gene, we inverse normalized the TPM values to account for outliers and fit a normal distribution. We then performed PEER factor analysis [***Stegle et al., 2010***]. We regressed out sex, batch number, batch center and 7 PEER factors from the gene expression and saved the residuals for all downstream analyses.

Genotype and phenotype data in the target rat set

We used genotype and phenotype data in 3,407 rats (i.e., target set) reported in ***Chitre et al.*** [***2020***]. We used phenotypic information on body length (including tail), BMI (including tail), body weight, fasting glucose levels, and fat pad traits (epididymal fat, parametrial fat, and retroperitoneal fat). To simplify interpretation, we aggregated the results of the three fat traits using the ACAT meta-analysis method [***Liu et al., 2019***]. For each trait, sex, age, batch number and site, were regressed out if they were significant and if they explained more than 2 % of the variance, as described in [***Chitre et al., 2020***].

Querying human gene-trait association results

To retrieve analogous human gene-trait association results, we queried PhenomeX-can, a web-based tool that serves gene-level association results for 4,091 traits based on predicted expression in 49 GTEx tissues [***Pividori et al., 2020***]. Orthologous genes (N = 22,777) were mapped with Ensembl annotation, using the *biomart* R package and were one to one matched.

Estimating gene expression heritability

We calculated the cis-heritability of gene expression from the training set using a Bayesian sparse linear mixed model, BSLMM [***Zhou et al., 2013***], as implemented in GEMMA. We used variants within the ±1Mb window up- and down-stream of the transcription start and end of each gene annotated by Gencode v26 [***Frankish et al., 2021***]. We used the proportion of variance explained (PVE) generated by GEMMA as the measure of cis-heritability of gene expression. We then display only the PVE estimates of 10,268 genes that were also present in the human gene expression data.

Heritability of human gene expression, which was also calculated with BSLMM, was downloaded from the database generated by ***Wheeler et al.*** [***2016***]. Genes were also limited to the same 10,268 as above.

Examining polygenicity versus sparsity of gene expression

To examine the polygenicity versus sparsity of gene expression in rats, we identified the optimal elastic net mixing parameter α, as described in ***Wheeler et al.*** [***2016***]. Briefly, we compared the prediction performance of a range of elastic net mixing parameters spanning from 0 to 1 (11 values from 0 to 1, with steps of 0.1). If the optimal mixing parameter was closer to 0, corresponding to ridge regression, we deemed gene expression trait to be polygenic. In contrast, if the optimal mixing parameter was closer to 1, corresponding to lasso, then the gene expression trait was considered to be more sparse. We also restricted the number of genes in the pipeline to the 10,268 orthologous genes.

Training gene expression prediction in rats

To train prediction models for gene expression in rats, we used the training set of 88 rats described above and followed the elastic net pipeline from predictdb.org. Briefly, for each gene, we fitted an elastic net regression using the *glmnet* package in R. We only included variants in the cis region (i.e., 1Mb up and downstream of the transcription start and end). The regression coefficient from the best penalty parameter (chosen via *glmnet*'s internal 10-fold cross validation [***Zou and Hastie, 2005***]) served as the weight for each gene. The calculated weights (w_s) are available in predictdb.org. For the comparison of number of predictable genes across species, we ran the same cross-validated elastic net pipeline in four GTEx tissues

with sample sizes similar to that of the rats: Substantia Nigra, Kidney Cortex, Uterus and Ovary. To ensure fair comparison, we used the same number of genes that were orthologous across all four human tissues and rat tissues.

Estimating overlap and enrichment of genes between rats and humans

For human transcriptome prediction used in the comparison with rats, we simply downloaded elastic net predictors trained in GTEx whole blood samples from the PredictDB portal, as previously done in humans [***Barbeira et al., 2021***]. This model was different from the ones used in the UK Biobank for calculating the PTRS weights (See Calculating PTRS in a rat target set).

We quantified the accuracy of the prediction models using a 10-fold cross validated correlation (R) and correlation squared (R^2) between predicted and observed gene expression [***Zou and Hastie, 2005***]. For the rat prediction models, we only included genes whose prediction performance was greater than 0.01 and had a non-negative correlation coefficient, as these genes were considered well predicted.

We tested the prediction performance of our elastic net model trained in nucleus accumbens core in an independent rat reference transcriptome set. We predicted expression in the reference set of 188 individuals and compared to observed genetic expression in the nucleus accumbens core.

Implementing RatXcan

We developed RatXcan, based on PrediXcan [***Gamazon et al., 2015***] [***Barbeira et al., 2018***] in humans. RatXcan uses the elastic net prediction models generated in the training set. In the prediction stage, we generated a predicted expression matrix for all genes in the rat target set, by fitting an additive genetic model:

$$Y_g = \sum_k w_{k,g} X_k + \epsilon$$

Y_g is the predicted expression of gene g, $w_{k,g}$ is the effect size of marker k for gene g, X_k is the number of reference alleles of marker k and ϵ is the contribution of other factors that determine the predicted gene expression, assumed to be independent of the genetic component.

We then tested the association between the predicted expression matrix and each trait; this was done for available phenotypes. We fitted a linear regression of the phenotype on the predicted expression of each gene, which generated gene-level association results for all gene trait pairs.

Estimating overlap and enrichment of genes between rats and humans

We queried PhenomeXcan to identify genes associated with analogous traits in humans. PhenomeXcan provides gene level associations aggregated across all

available GTEx tissues, as calculated by MultiXcan (and extension of PrediXcan) [***Barbeira et al., 2019***]. To this aim, we adapted MultiXcan to similarly aggregate our results across the 5 tested brain tissues in rats. We used a Q-Q plot to inspect the level of enrichment across rat and human findings. To quantify enrichment, we used a Mann-Whitney test as implemented in R to discern whether the distribution of the p-values for genes in humans was the same for the genes that were and were not nominally significant in rats.

Calculating PTRS weights in the UK Biobank

We calculated human-derived height and BMI PTRS weights using elastic net with a mixing parameter of 0.5, as described in ***Liang et al.*** [***2022***]. We predicted expression levels in 356,476 UK Biobank unrelated White British participants using whole blood prediction models trained in GTEx. We used the prediction models trained with UTMOST based on grouped lasso, which borrows information across tissues to improve prediction performance [***Barbeira et al., 2020***, ***Hu et al., 2019***]. The predicted expression was generated using high quality SNPs from Hapmap2 [***McCarthy et al., 2016***]. We performed elastic net regression with height and BMI as the predicted variables and the predicted expression matrix from 356,476 UK Biobank unrelated White British individuals. More specifically, for each regularization parameter λ, we selected weight parameters γ_g that miminized the mean squared difference between the predicted variable Y and prediction model $X\gamma+\gamma_0$ where $\hat{T}_g \in \mathbb{R}^{N\times 1}$ is the standardized predicted expression level of gene g across N individuals and $\hat{C}_l \in \mathbb{R}^{N\times 1}$ is the the observed value of the lth standardized covariate:

$$\gamma^{EN} = argmin_{\gamma} \overbrace{\frac{1}{N} \parallel Y - X\gamma - \gamma_0 \parallel_2^2 + \lambda\alpha \parallel \gamma \parallel_1 + \lambda_a(1-\alpha)(\parallel \gamma \parallel)_2^2}^{loss:l\gamma}$$

$$X := [\hat{T}_1, ..., \hat{T}_m, C_1, ..., C_L]$$

where γ_0 is the intercept, m the number of genes, L is the number of covariates, $||B||_2^2$ is the l_2 norm and the $||B||_1$ is the l_1 norm of the effect size vector. α denotes the elastic net mixing parameter and λ is the regularization parameter. 37 different λ's were used, generating 37 different sets of predictors. Covariates included age at recruitment (Data-Field 21022), sex (Data-Field 31), and the first 20 genetic PCs. For more details, see ***Liang et al.*** [***2022***]. The values of the regularization parameters were chosen in a region likely to cover a wide range of sparsity in the resulting models, from very sparse, containing a couple of genes, to dense, containing all genes ***Liang et al.*** [***2022***].

Calculating PTRS in a rat target set

To calculate human-derived PTRS for both height and BMI in the target rats, we used the predicted gene expression matrix calculated for the association stage.

For each rat, we multiplied the predicted expression with the corresponding weight for that gene, derived from the human PTRS. The aggregated effects of these weighted genes are summarized in a single score, PTRS:

$$\text{PTRS(rat)} = \sum \gamma_g \cdot \hat{T}_g\text{(rat)}$$

We generated 37 PTRS models for height and BMI for a range of regularization parameters (Fig. 4e-f).

To identify biologically relevant tissues, pathways and gene sets associated with the genes included in the PTRS, we applied multiple complementary analyses using FUMA v1.3.8 [***Watanabe et al., 2017***]. These included tissue enrichment using differentially expressed genes across 54 specific tissue types from GTEx V8. We included multiple gene sets (KEGG, Reactome, GO and Hallmark) from the Molecular Signature Database (MsigDB) v7.0.

Quantifying PTRS prediction performance

We calculated the Pearson correlation (R) coefficient between PTRS of height and BMI and analogous observed phenotypes in rats. To facilitate comparison with previous papers, we report partial $\tilde{R}^2$. In rats, we used traits that were already adjusted for covariates, $\tilde{R}^2$ is equivalent to R^2. We verified that using Spearman correlation did not change the substance of the results (data not shown).

Code and Data Availability

The code used for this work is available at https://github.com/hakyimlab/Rat_Genomics_Paper_Pipeline. Genotype and expression data are available through [***Munro et al., 2022***]. Prediction models for gene expression in all five brain tissues in rats are available at predictdb.org

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Author contributions

A.A.P. and H.K.I. conceived the cross species PTRS and supervised the work. N.S. and Y.L. performed a large portion of the analyses. N.S. and S.S-R. analyzed and interpreted the results and wrote the initial draft of the manuscript. S.M., D.M., A.C., D.C., L.S-W, and O.P. pre-processed and analyzed the RNAseq, genotype, and phenotype data. R.C., J.G., A.M.G., A.G., K.H., A.H., C.P.K., C.L.S-P., J.T., T.W., H.C., S.F., K.I., P.M., L.S. were involved in various aspects of the collection of the rat physiological traits. All authors read, edited and approved the final version of the manuscript.

Competing interests

The authors declare no conflict of interest.

Ethics declaration

Not applicable.

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Supplementary information

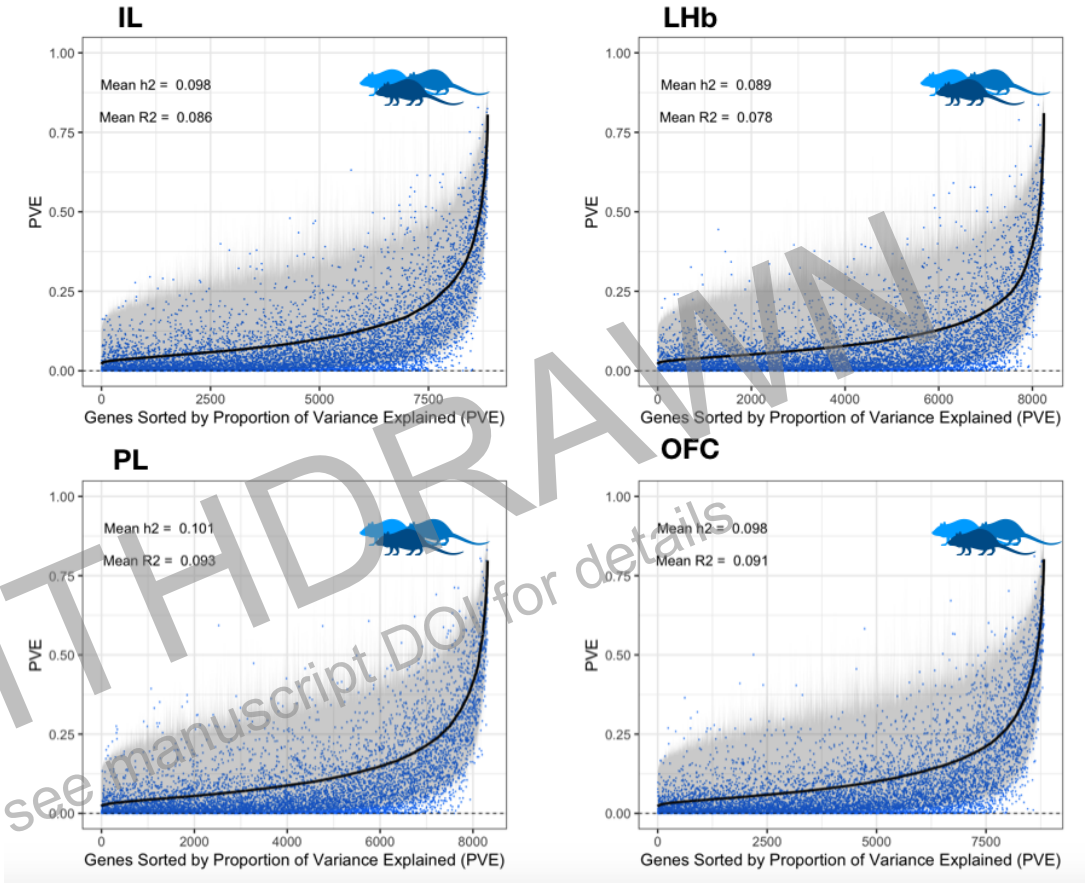

Figure S1. Gene expression was heritable [8.86-10.12%] and comparable across several brain tissues tested (Infralimbic Cortex, IL; Lateral Habenula, LHb; Prelimibic Cortex, PL; Orbitofrontal Cortex, OFC) in rats. We refer to heritability (h^2, cis-heritability within 1Mb) as the proportion of variance explained (PVE). Across all brain tissues tested, heritability estimates were significantly correlated ($R = [0.58 - 0.83]$, $P < 2.20 \times 10^{-16}$).

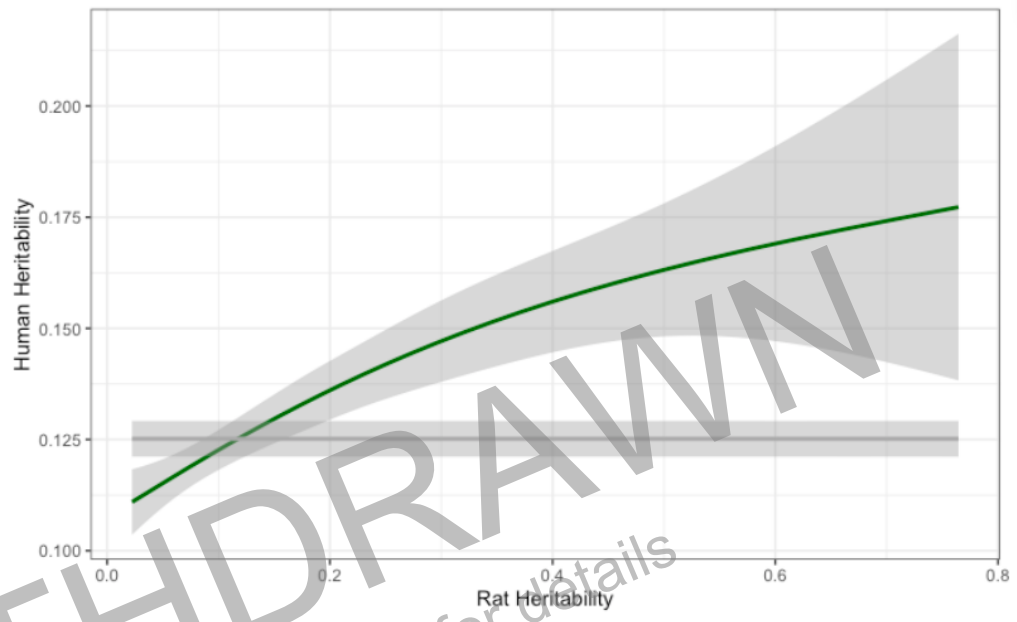

Figure S2. Heritability of gene expression was correlated between rats and humans. We found a significant correlation ($R = 0.067$, $P = 4.34 \times 10^{-12}$) between heritability estimates in rats and humans. Confidence intervals are represented as gray bars. The gray line represents the null distribution.

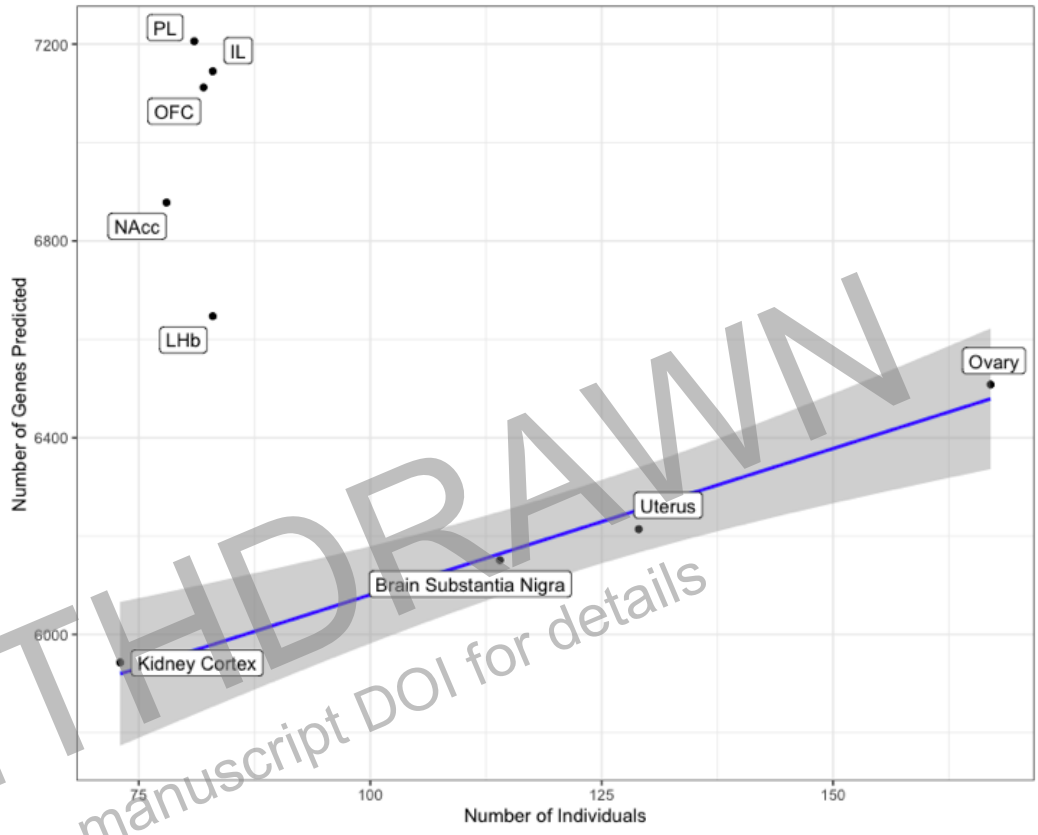

Figure S3. Prediction was greater in rat tissues than that in human GTEx tissues. The number of predicted genes across all five rat tissues was greater than those in GTEx human tissues with similar sample size. To ensure fair comparison, we included the same subset of genes that were orthologous across all tested tissues.

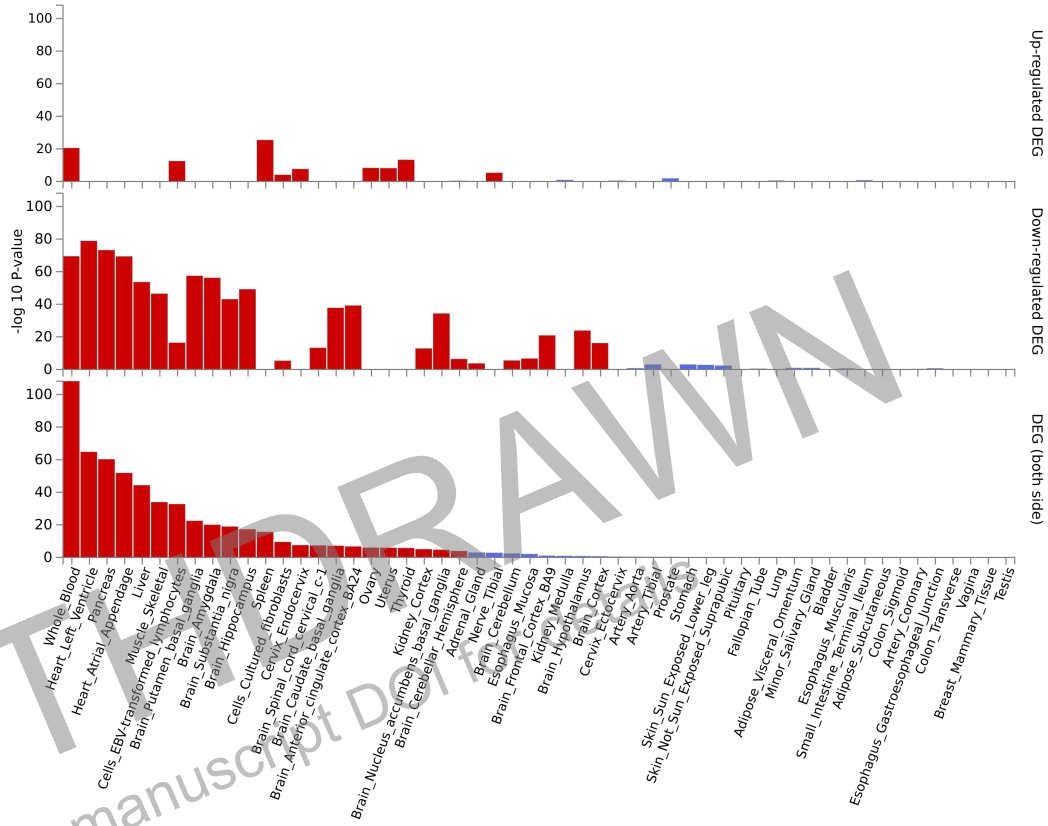

Figure S4. Tissue analysis revealed substantial enrichment in multiple relevant tissues, including heart, pancreas, muscle, liver, and central nervous system. Significantly enriched sets ($P < 0.05$) are highlighted in red.

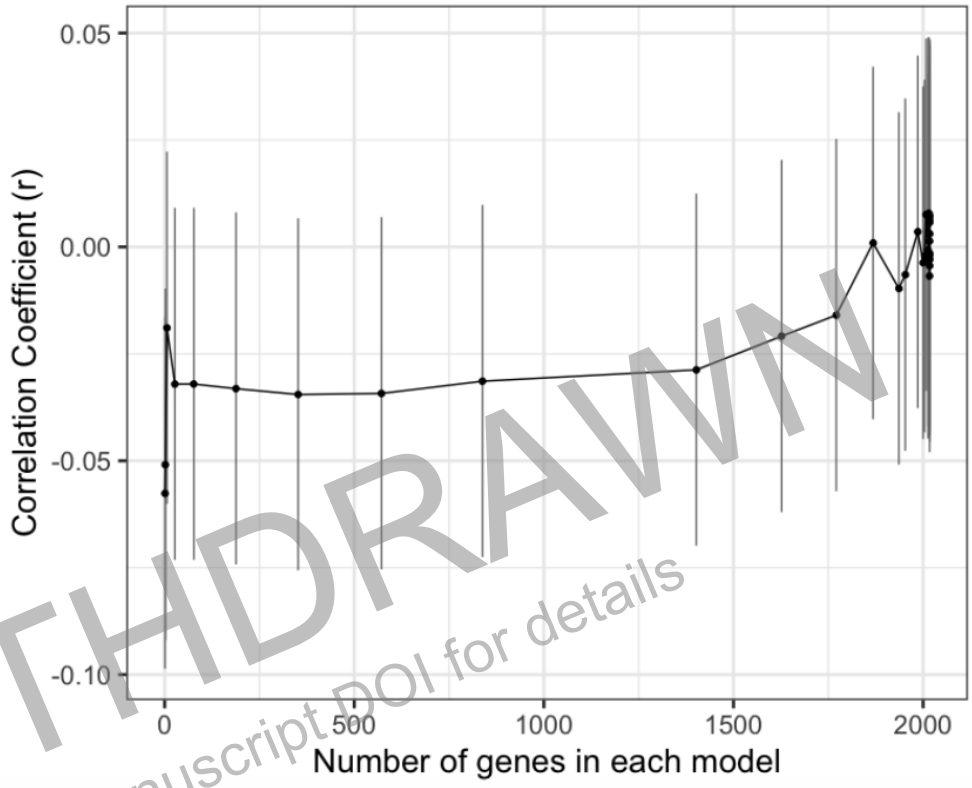

Figure S5. Human derived PTRS weights did not predict observed fasting glucose levels in rats. Human-dervied height PTRS in rats was not correlated with observed fasting glucose levels in the target rat set ($R = 0.008$, $P = 7.09 \times 10^{-1}$), which served as a negative control.