Phenomics: the next challenge

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Abstract | A key goal of biology is to understand phenotypic characteristics, such as health, disease and evolutionary fitness. Phenotypic variation is produced through a complex web of interactions between genotype and environment, and such a 'genotype–phenotype' map is inaccessible without the detailed phenotypic data that allow these interactions to be studied. Despite this need, our ability to characterize phenomes — the full set of phenotypes of an individual — lags behind our ability to characterize genomes. Phenomics should be recognized and pursued as an independent discipline to enable the development and adoption of high-throughput and high-dimensional phenotyping.

Pleiotropy
The ability of a single genetic change to affect more than one phenotype.

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When the debate over whether to fund a human genome project flowered in the late 1980s, one of the scientific arguments offered in opposition was that only a small part of the genome was really worth knowing — the 3–5% that was then estimated to lie in and close to protein-coding regions[1,2]. The alternative approach to a genome project was molecular genetics as usual: first identify a region of the genome that is of functional interest, then target it for sequencing. Calls to continue this traditional model for dealing with genotyping were rapidly swept aside, and the Human Genome Project was realized in a few years.

Over the past 15 years, many authors have proposed that phenomics — large-scale phenotyping — is the natural complement to genome sequencing as a route to rapid advances in biology[3–8]. The response to these propositions has mostly been silence, implying that 'phenotyping as usual'— measuring a limited set of phenotypes that seem the most relevant — is adequate. We disagree and argue that the case for phenomics is as compelling now as the case for genomics was 25 years ago and indeed shares many similarities with that case.

Phenomic-level data are necessary to understand which genomic variants affect phenotypes, to understand pleiotropy and to furnish the raw data that are needed to decipher the causes of complex phenomena, including health, crop yields, disease and evolutionary fitness. Our limited ability to understand many important biological phenomena suggests that we are not already measuring all important variables and that broadening the possibilities will pay rich dividends. Fundamentally, we can choose between focusing our efforts on what we already think is important or deciding that much of what we do not yet measure will prove useful and interesting. The question 'why not measure it all?' was fortunately affirmatively answered for genomes; it is now time to ask the same question for phenotypes.

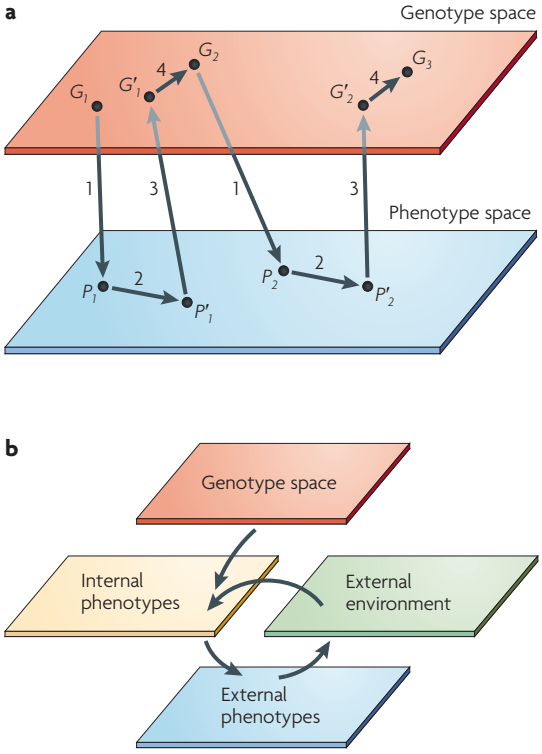
The time is ripe to consider the value of phenomic-level efforts for several reasons. First, technologies for high-throughput phenotyping are becoming increasingly available. Second, conceptual, analytical and bioinformatics approaches that enable the use of very high-dimensional data are advancing rapidly. Third, dynamic models that link phenomena across levels — from genes to cells, to organs and through to the whole organism — are in reach. Finally, in most cases, phenotypic data continue to be the most powerful predictors of important biological outcomes, such as fitness, disease and mortality. Although analyses of genomic data have been successful at uncovering biological phenomena, they are — in most cases — supplementing rather than supplanting phenotypic information.

In this Review, we identify the scientific rationales for carrying out phenomics research and outline current approaches to obtaining phenomic data. We then describe some of the conceptual challenges to taking full advantage of phenomic-level data. Finally, we consider how to establish phenomics as an independent discipline.

What is phenomics?

The current usage of the word 'phenome' to refer to the phenotype as a whole is due to the evolutionary biologist Michael Soulé[9]. We now define phenomics as the acquisition of high-dimensional phenotypic data on an organism-wide scale. Although phenomics is defined in analogy to genomics, the analogy is misleading in one respect. We can come close to completely characterizing a genome but not a phenome, because the information content of phenomes dwarves those of genomes:

Box 1 | **The genotype–phenotype map**



The concept of a genotype–phenotype (G–P) map is a widely used metaphor for the multiple ways in which genotypic information influences the phenotype of an organism. The term dates at least to 1970 when Jim Burns proposed linking population genetic and biochemical variation[116], but the importance of the relationship between genotype and phenotype has long been apparent. Two early versions of the G–P map concept are the epigenetic landscape of Conrad Hal Waddington[117] and Richard Lewontin's concept of evolution as taking place in the space of all possible genotypes (G space) and the space of all possible phenotypes (P space)[118].

This relationship is shown in part **a** of the figure, which indicates the mean position of a population in G and P spaces over two generations. There are four key parts to the evolutionary process, shown as numbered arrows: (1) the epigenetic process creates the phenotype using genotypic information; (2) natural selection acts in P space to change the average phenotype of parents away from the average phenotype of all individuals; (3) the identity of successful parents determines which genotypes are preserved; and (4) genetic processes such as mutation and recombination alter position in G space. An alternative concept of the G–P map at the level of the individual is shown in part **b** of the figure. An individual can be conceptualized as occupying a single point in G space, and this position plus the environment (including other individuals, such as parents) combine to create the internal phenotypic state of the organism throughout its life. These internal phenotypes include cellular, tissue level and physiological properties. These internal phenotypes in turn shape external phenotypes such as morphology and behaviour. Phenotypes can in turn shape the environment that an individual occupies, creating complex feedback relationships between genes, environments and phenotypes. The importance of the environment suggests that we should explicitly broaden the G–P map to the genotype–environment–phenotype (G–E–P) map.

phenotypes vary from cell to cell and from moment to moment and therefore can never be completely characterized. Phenomics will always involve prioritizing what to measure and a balance between exploratory and explanatory goals.

To interpret high-dimensional phenomic data, especially when they span multiple levels of organization, we also need a phenomic conceptual framework. Luckily, this framework can build on well-established intellectual traditions for analysis of phenotypic data, including quantitative genetics, evolutionary biology, epidemiology and physiology. These fields provide tools to account for multiple sources of variation[10,11] and to untangle causes from correlations[12–14].

Why phenomics?

Studying the genotype–phenotype map. Phenomics is most frequently justified as enabling us to trace causal links between genotypes and environmental factors and phenotypes (the G–P map; BOX 1). Studies of both the genomes and the phenomes of individuals in segregating populations can be carried out in an approach known as Mendelian randomization[15–17] (BOX 2). Indeed, phenomic projects that combine genomic data with data on quantitative variation in phenotypes have recently been initiated in many species (TABLE 1), with the aim of understanding the G–P map[6].

Phenomic data are essential for accessing the pleiotropic effects of genetic variation in the G–P map. The explicit and systematic study of the pattern of pleiotropy is just beginning[18–20]. Pleiotropy often surprises us. For example, the *foraging* gene was initially discovered because of its influence on larval behaviour in *Drosophila melanogaster*[21], but it has now been shown to integrate a wide range of phenotypes in response to variation in food availability and is a possible analogue of metabolic syndrome in humans[22]. In humans, such information about pleiotropy can predict the side effects of medical interventions.

Identifying the genetic basis of complex traits. An implicit premise of genomics is that inheritance is best studied by accumulating a list of all the genetic variants that influence a phenotype, rather than studying the phenotype in detail. The results of the recent flood of genome-wide association (GWA) studies suggest that for many traits this reasoning is backwards. The details of genetic causation are turning out to be so complex that they validate the continued use of phenotype-centred approaches to study inheritance.

Metabolic syndrome
The tendency for obesity, diabetes, increased blood pressure, triglycerides and cholesterol to co-occur.

Box 2 | **Mendelian randomization**

Mendelian randomization refers to the natural genetic experiments that are set up by genetic segregation within families and variation in environmental exposures among individuals during their lives[119]. The result is that a variety of genotypes are found in any given environment (such as a family or a geographical area) and each genotype is exposed to a wide range of environmental conditions. In many cases, the proximal effects of genotype on a potential causal factor are known. The genotype is essentially a treatment effect that allows causal hypotheses to be tested, even when the hypothesis is a purely phenotypic one. For example, it is well established that various lipid-related phenotypes in humans, such as the concentrations of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides, are associated with risk of coronary heart disease (CHD)[120]. It is important to establish which of these factors have a causal effect on CHD so that therapies can be targeted at the causal phenotype. In a multivariate observational study, the effect of triglycerides on CHD disappeared when both HDL-C and LDL-C were included as predictors[121]. Does this mean that the level of cholesterol is an important cause of CHD and triglycerides are not or that the effect of triglycerides is through cholesterol? Available drug interventions cannot answer this question, as they also affect all of the major lipid phenotypes[120], but Mendelian randomization has been informative. In the case of lipid metabolism, a regulatory variant at the apolipoprotein A5 (*APOA5*) locus has a large, well-replicated effect on triglyceride levels[122,123]. A Mendelian randomization meta-analysis using this *APOA5* polymorphism suggests a direct role for triglyceride concentration in causing CHD. Each copy of the minor *APOA5* allele raised mean triglyceride concentration by 16% and lowered HDL-C concentration by 3.5%. There was no significant effect on LDL-C. Analysis of case–control studies showed a highly significant 18% increase in CHD (odds ratio of 1.18) for every minor allele carried, strengthening the case for an effect of triglycerides on CHD that is not mediated by LDL-C or HDL-C. This exemplary study shares several features of genome-driven research that argue for additional phenomic research. First, there is no detailed model that explains the causal effect of the APOA5 protein on triglyceride levels. Second, the fact that triglycerides are changed by the largest amount does not necessarily indicate that this protein is causal — perhaps the 3.5% change in HDL-C is actually of more importance. Third, the fact that some phenotypic differences have been detected does not indicate that differences in unstudied phenotypes were not also caused by the polymorphism, and these may themselves have important effects. Clearly, phenomic studies that control for more genetic effects and include a wider range of phenotypes will enable better causal inferences.

GWA studies have revealed well-supported associations, but these generally explain only a small proportion of the phenotypic variance. A striking example is human height, for which 180 stringently validated loci collectively explain only about 10% of the genetic variation[23]. Similar results have been obtained for other complex human traits, including Crohn's disease, breast, prostate and colorectal cancers, lupus erythematosus, type 1 and type 2 diabetes, lipid metabolism and heart attacks[24–26]. The most important explanation for this 'missing heritability' (REF. 27) is likely to be that the population-wide effects of most variants are tiny because the variants are rare or their effect sizes are small[28]. Thousands of polymorphisms are therefore implicated to explain the observed genetic variation[29]. Quantitative genetic models have long assumed that the number of variants is effectively infinite as a convenient approximation[30,31], and GWA study results suggest that this assumption is closer to reality than most researchers believed possible. Quantitative genetic summaries of inheritance[32] remain more informative than lists of thousands of genomic regions with inferred effects.

Prospective studies show that traditional risk factors for human disease, such as family history, blood chemistry or weight, are more effective predictors for many diseases than SNP associations[33–38]. Models including both traditional risk factors and genetic data for predictions are, at best, only marginally better at predicting disease than models based on traditional risks alone (BOX 3). Additional phenotypic information may be more informative than lengthening the list of genetic associations.

Causal explanations at the phenotypic level. The simplest justification for phenomics is that the characteristics of organisms of greatest interest to most biologists are phenotypes rather than genotypes. Such crucial phenotypes include morbidity, mortality and reproduction of humans; yield, efficiency and resistance of plants and animals under domestication; resistance of pests to our attempts to control them; and the ability of species to adapt to human-induced changes. We need to explain why phenotypes vary in a population or between species. This cannot be done without directly studying phenotypes.

Rapid progress on any biological problem rests on the hope that there is at least one viewpoint to each problem that makes causation relatively simple. To express this concept, Buchanan *et al.*[39] used the metaphor of the G–P map as an hourglass (FIG. 1), in which the narrow waist of the hourglass represents a factor that can explain phenomena that seem complex at other levels. Sometimes a genetic cause is the simplest (for example, cystic fibrosis and macular degeneration), but other traits can be best explained at the phenotypic level (for example, the effect of obesity on diabetes risk) or at the environmental level (for example, the effect of asbestos on cancer risk). Access to phenomic and environmental data would enable simple explanations to be tested at these other levels of causation. It is also possible that the causation of some phenomena is inherently complex, in which case there is no hourglass shape to the causal map (FIG. 1d).

How can measuring vast numbers of variables help to uncover simple causal explanations? We do not know what the explanations are until we find them, and only by first expanding the universe of possible predictors can we hope to uncover these explanations. For example, Robson and Gwynne[40] studied male mate preference in crickets in relation to nine morphological traits. They predicted that females with large body size, legs, mandibles and spines would have the highest mating success; their results disproved all these predictions and showed that there was strong stabilizing selection for mandible length and directional selection for smaller head width. Only by including more traits in this study could the small number of traits that really matter emerge. Fitness is the phenotype crucial to understanding evolution, as variation in fitness is the cause of natural selection. Two components determine the fitness of a genetic variant. First, the pleiotropic effects of a variant on the phenotype as a whole are determined by the G–P map. Second, phenotypes interact with the environment to cause variation

Observational study
A study in which conclusions are drawn from differences between subjects that are not under the control of the investigator.

Odds ratio
The ratio of the probability that an event will occur in one group to the probability that it will occur in another, for example, diseased versus healthy groups. It is a measure of effect size for binary variables.

Heritability
The proportion of the observed phenotypic variation that is attributable to genetic variation.

Table 1 | **Example phenome projects***

Species	Description	Funding	Phenotypes	Genotyping	URLs
Plants	International Plant Phenomics Network (IPPN). Focus on development and implementation of phenotyping, rather than specific taxa	Consortium of nationally funded labs, including the Australian Plant Phenomics Centre and the German Jülich Plant Phenotyping Centre	High-throughput, robotic, non-invasive imaging across the life cycle of small, short-lived model and crop plants; metabolomes; quantitative phenotyping		• http://www.plantphenomics.com • http://www.plantphenomics.org.au • http://www.fz-juelich.de/icg/icg-3/jppc
Arabidopsis	Collaboration between groups working on *A. thaliana*, resulting in phenotyping and GWA studies on an overlapping set of 191 inbred lines	US NSF and NIH funding for initial GWA studies. Phenotyping supported by diverse grants to individual investigators	107 mostly quantitative phenotypes included in initial GWA studies[126], including resistance to pathogens, flowering traits, ionome and life history traits. No intensive phenotypes	250,000 SNPs genotyped using a chip	• http://walnut.usc.edu/2010/GWA
Drosophila	*Drosophila* Genome Reference Panel. Informal voluntary phenotyping by over 26 researchers. Lines released in 2009	Sequencing funded by the Human Genome Sequencing Center at Baylor College of Medicine. A few investigators are individually funded to phenotype, but no overall funding	Extensive variety, including physiology[127], disease resistance, gene expression, behaviour and morphology. A few phenotypes are intensively measured. No standardization	*Drosophila* Population Genomics Project: 50 lines sequenced. Human Genome Sequencing Center at Baylor College of Medicine: 192 lines sequenced	• http://flybase.org/static_pages/news/whitepapers/Drosophila_Genetic_Reference_Panel_Whitepaper.pdf • http://www.hgsc.bcm.tmc.edu/project-species-i-Drosophila_genRefPanel.hgsc • http://www.dpgp.org
Mouse	The Mouse Phenome Database (MPD) collects phenotype information for common inbred lines; 125 published and 36 unpublished phenotyping contributions	Overall funding from NIH but phenotyping efforts are funded separately	Extensive variety, no standardization. No intensive phenotyping	Assembled SNP typing of inbred lines	• http://www.jax.org/phenome
	EuroPhenome captures data from any mouse phenotyping effort, including the European Mouse Disease Clinic (EUMODIC) consortium for phenotypic screening of mutant lines and inbred lines. Favours standardized phenotyping pipelines from the European Mouse Phenotyping Resource of Standardised Screens (EMPRESS)	European Union	Extensive variety, including physiology, morphology and behaviour. Images and samples are kept for later intensive analysis. Phenotyping is largely binary or ordinal. Sample sizes are variable	European Conditional Mouse Mutagenesis (EUCOMM)	• http://www.europhenome.org • http://www.eumodic.org • http://www.empress.har.mrc.ac.uk
Rat	National BioResource Project — Rat is phenotyping ~150 established strains. Phenotyping done centrally	Japanese Ministry of Education, Culture, Sports, Science and Technology	109 phenotypes, extensive variety, favouring physiology and behaviour. Many qualitative phenotypes. Standardized phenotyping, small sample size	357 simple sequence length polymorphisms cover genomes.	• http://www.anim.med.kyoto-u.ac.jp/nbr
Dog	Canine Phenome Project. Phenotyping by volunteer scientists, veterinarians, dog owners, breeders and trainers. Online questionnaires for dog owners on pedigree, phenotype and medical history	NIH, supplemented by contributions.	Emphasis on heritable diseases relevant to human health, behaviour and breed-specific defects	SNP typing of various dog breeds. Collection of samples for future sequencing	• http://www.caninephenome.org

Table 1 (cont.) | **Example phenome projects***

Species	Description	Funding	Phenotypes	Genotyping	URLs
Human	Consortium for Neuropsychiatric Phenomics. Large (52 investigator) interdisciplinary effort. Genomic data, brain structure and function and behaviour in case–control study of three major psychiatric syndromes	NIH	Brain imaging, behaviour and cognitive phenotypes	Northern Finland Birth Cohorts, case–control genotyping	• http://www.phenomics.ucla.edu
	UK Biobank. Prospective study of 500,000 individuals, now finishing recruitment phase	MRC, Department of Health, Wellcome Trust	Baseline questionnaire and physical measurements; storage of blood and urine for eventual analysis and integration with the UK NHS health records	Samples taken for later analysis	• http://www.ukbiobank.ac.uk
	Personal Genome Project aims to recruit volunteers for genome sequencing and supplements that with phenotype data from biologically knowledgeable volunteers. Participant number is going from 10 to 100, with 100,000 as a goal	Private	Images, cell lines and medical history	Primary goal is genome sequencing. One participant fully sequenced	• http://www.personalgenomes.org

*We include projects that emphasize the characterization of the phenotypic effects of existing genetic variation rather than systematic mutagenesis projects. GWA, genome-wide association; MRC, Medical Research Council; NIH, National Institutes of Health; NHS, National Health Service; NSF, National Science Foundation.

Effect size
The magnitude of the inferred effect of one variable on another. The effect size of a SNP is the difference in phenotype between genotypes with and without one of the nucleotides.

Prospective study
An observational study in which phenotypes are measured at the beginning of the study and the fate of individuals is tracked over subsequent time intervals.

Stabilizing selection
A type of natural selection that favours intermediate phenotypes.

Directional selection
A type of natural selection in which fitness increases monotonically with increasing or decreasing phenotype.

Endophenotype
A phenotype correlated with or possibly causally related to a disease state. In psychiatric research, endophenotype is synonymous with biomarker.

Biomarker
A phenotype that is objectively measured and used as an indicator of other biological processes.

Function-valued trait
A phenotype that is a continuous function, such as a surface or a time course. It is also known as an infinite dimensional trait.

in fitness. Understanding this second important component is an entirely phenomic problem. The effects of a variant on fitness through all the phenotypes that it influences sum up to determine its fate; these effects need to be comprehensively enumerated to fully characterize the fitness effects of a variant[41]. Causation of other phenotypic states such as disease can be investigated using the same approach used for fitness[42].

Goals and technical challenges

Towards comprehensive, quantitative measurement. We distinguish two ways of being comprehensive: first, one can sample a wide variety of phenotypes, which we term extensive phenotyping; second, we define intensive phenotyping as characterizing a phenotype in great detail. For example, measuring gene expression in one tissue at one developmental stage gives data on an extensive range of genes, whereas repeated sampling of the expression of a single transcript through time would be intensive. Both approaches can be important, so phenomics will be enabled by decreasing the labour and monetary costs of phenotyping and increasing its intensity. Current phenomic efforts (TABLE 1) largely adopt extensive sampling by choosing a wide range of conventional, low-dimensional measurements. Increasing the quantitative information obtained by phenotypic measurements is another important goal for phenomics. Many human phenotype data represent qualitative judgments, for example, those relating to disease states or environmental exposures. Although phenotypes are sometimes truly categorical — such as dead or alive — in most cases, the underlying state is quantitative[43]. The continuous and multivariate nature of most phenotypes suggests that categorical phenotyping discards information (FIG. 2). The desire to obviate the use of qualitative phenotype categories is partly driving the push to find endophenotypes and biomarkers[44]. For many sets of phenotypes, such as the shape of an organism, or the change in a phenotype through time, the phenotype is best thought of as a function-valued trait, rather than as discrete measurements that can be used to capture the shape of the function[45].

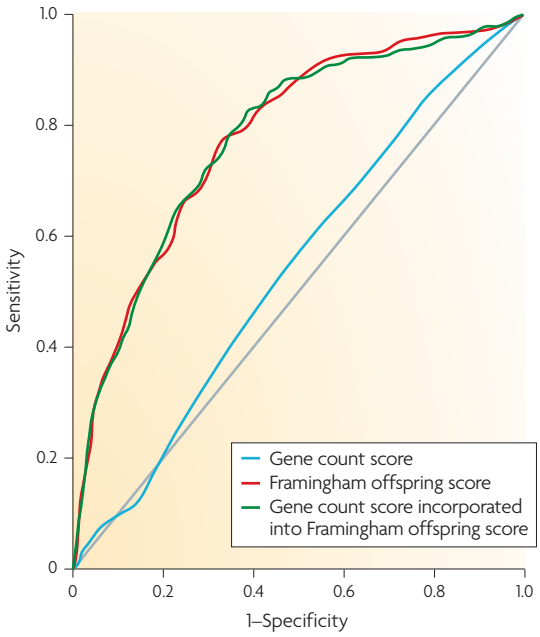
Data analytical challenges. Traditional statistics emphasize relationships between modest numbers of predictor variables and single outcome variables. Phenomic data, however, raise the possibility of addressing the 'many-to-many' relationships that are inherent in G–P maps. Techniques to deal with many-to-many data have been developed in other fields (such as econometrics and chemometrics)[46] but are less well known in biology.

Phenomics will increase both the number of phenotypes, p, that can be measured and the sample size, N. Increases in p will often outstrip increases in N, resulting in 'large p, small N' (LPSN) data sets. In LPSN situations, many models will be capable of fitting or over-fitting the data, resulting in a poor performance when the model is applied to new data. A popular but inadequate way of coping with LPSN data sets is dimension reduction — that is, decreasing the number of predictor variables before analysis — but in phenomics, we cannot make a biologically informed choice about dimension reduction, as the important features are not known *a priori*. A family of statistical techniques, including ridge and LASSO regression[47], can fit well-behaved models without dimension reduction in the LPSN case. These methods generally apply a penalty for complex models that is tuned by cross-validation.

Several lines of evidence suggest that the true dimensionality of phenotypic variation is very high and that dimension reduction will discard information, leaving us with an even more daunting prospect than LPSN — having to deal with 'high-dimension, small sample size' (HDSN) data. There is direct evidence that the dimensionality of genetic variation underlying morphometric

Box 3 | **Determining the added value of replicated genetic associations**

A useful measure of the predictive value of a model for a binary outcome, such as diseased versus healthy, is the area under the curve (AUC) statistic, which is the area under the receiver operating curve[124]. The AUC statistic gives the probability that a prediction of risk for an individual is correct. An ineffective criterion gives AUC = 0.5 and a perfect one gives AUC = 1.0.The results of a prospective study of the risk of type 2 diabetes in a sample of 5,000 middle-aged adults[37] are shown in the figure. Indices of risk based solely on the number of high-risk alleles previously identified in genome-wide association studies or on more sophisticated models that weight genotypes by their disease risk both give a modest but potentially useful AUC = 0.54. The prediction is far better using the Framingham offspring score. This simple index is based on measurements of traditional risk factors — fasting glucose, body mass index, high-density lipoprotein cholesterol, triglycerides, family history of diabetes and blood pressure — and gives AUC = 0.78. When the Framingham offspring score is combined with the high-risk allele count, the AUC remains 0.78. This suggests that, rather than detecting novel pathways, genetic information is explaining variation in the traditional risk factors that we already know about.



Over-fitting
The prediction by a statistical model of error instead of the relationship of interest. An over-fitted model has poor predictive power.

Ridge and LASSO regression
Regression techniques that choose models that both fit well and minimize the number of predictor variables (LASSO) or their total effects (Ridge).

Cross-validation
The process of choosing a statistical model based on its ability to predict data that are not used to fit the model. It is commonly accomplished by splitting one data set into two, with one part used for training and the other for validation.

Dimensionality
The number of orthogonal directions in a space defined by multiple phenotypic measurements that have independent variation.

Partial least-squares regression
A statistical technique that identifies the combinations of variables in one set that best predict the variables in another set.

Random forest
An algorithm that classifies observations into categories using a family of hierarchical rules randomly chosen from a large family of such rules.

Support vector machine
A set of machine-learning algorithms for finding the polynomial functions of predictors that best separate a data set into two categories.

variation is very high[18,42,48], perhaps as high as the number of traits measured. For example, an index of 30 seemingly unrelated phenotypic traits of milk-producing cows predicts their longevity surprisingly well[49]. As described above, GWA studies implicate many diverse genes, supporting the idea of high dimensionality.

Such high-dimensional data can be addressed with many potential models, so choosing which models to investigate is crucial. To make intelligent choices, we should take advantage of prior knowledge[17,50], for example, by specifying that causal relationships flow from some classes of variable (such as SNPs) to others (RNA abundances)[51] or structural equation models that explore hypothetical causal models[52]. Where prior information is insufficient to choose among models, we should use information from all reasonable models[53,54]. When the prediction of an outcome is the primary goal of an analysis, there is now a rich and growing family of techniques that are well suited to HDSN data, such as partial least-squares regression[55], random forests[56] and support vector machines[57].

Current statistical approaches emphasize relationships that can be unambiguously demonstrated to a very high degree of confidence, for example, by holding the false discovery rate below some threshold. Although this is justifiable when choosing the most promising candidates for follow-up studies, it will generally result in an extremely biased view of reality. A prime example is GWA studies, in which the use of very stringent statistical tests to minimize false-positive findings creates the appearance of missing heritability[28]. The use of statistical testing to classify predictors into 'yes' or 'no' effects discards information in the same way as does classifying continuous phenotypes into discrete categories. A wide range of effect sizes occurs in nature.

Causally cohesive models. G–P maps extend across all hierarchical levels of biological organization and are highly nonlinear. Most current attempts to understand maps are based on linear approximations of local behaviour at one hierarchical level. Currently, approximate and descriptive models remain useful[58], given our relative ignorance about the basis of variation in many complex traits, but to fully use phenomic data, we need to replace such models with nonlinear systems dynamic models.

Models that have an explicit link to the genotype can be called causally cohesive genotype–phenotype (cG–P) models[59]. A cG–P model forces components of the G–P map to cohere in a logically consistent and ordered way, enforcing explicit formulations of hypotheses, thereby increasing the prediction space. Doing so can both catalyze and constrain empirical work by identifying key unsolved questions and the type of data needed to solve them. cG–P models can function as intellectual meeting places for various experimental disciplines. Such models would ideally span the life cycle of organisms, from instantaneous regulatory changes to generation-length phenomena such as development and ageing (spanning 15 orders of magnitude), and explain the behaviour of biological systems from the molecular to the whole-organism level (spanning nine orders of magnitude)[60].

Understanding hierarchical, spatial and temporal flows is the aim of several efforts to link genetic variation to phenotypes by means of dynamic modelling[61–67]. A noteworthy example is a dynamic model of tooth shape in mammals[68]: this model generates predictions of the three-dimensional surface for entire teeth by integrating intracellular gene regulation and intercellular signalling with cellular properties such as growth, adhesion and shape. It can mimic the range of variation in teeth

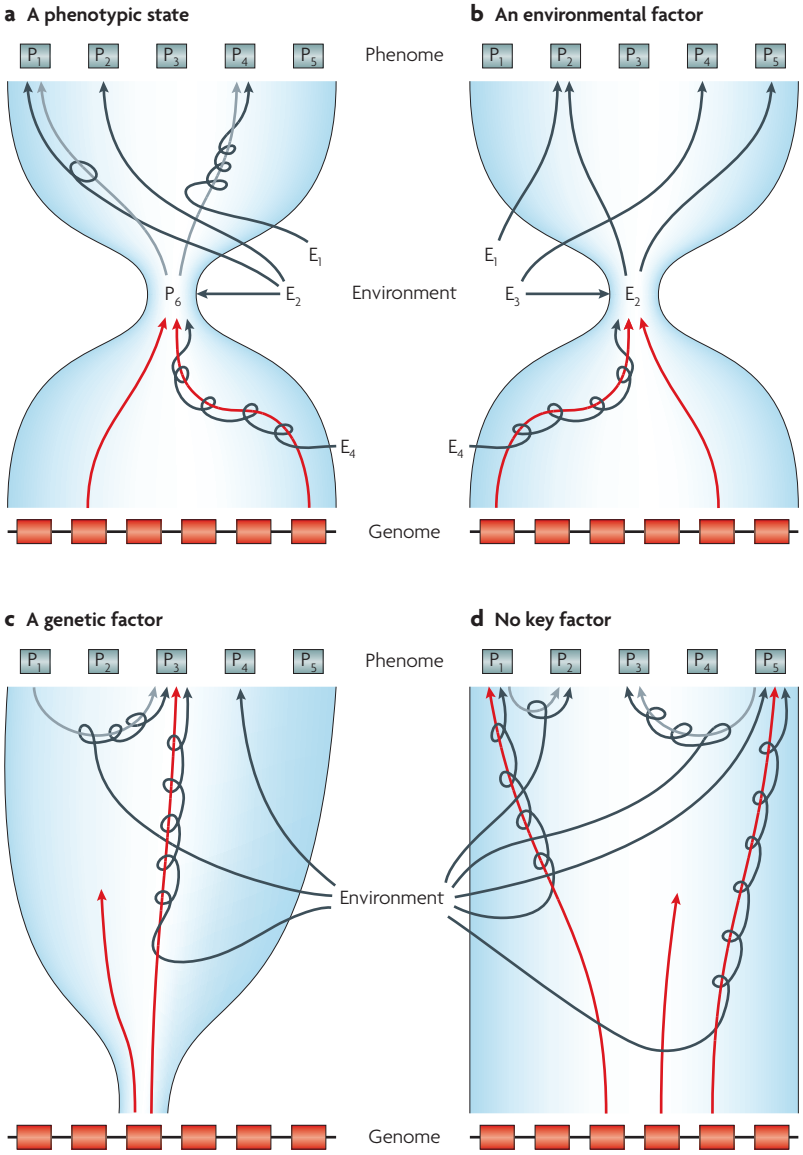


Figure 1 | **Causation scenarios.** The blue shaded areas denote the network of causation that produces the phenotypic state of an organism. Genotypes (red squares) and environmental factors interact to create phenotypes. The waist of the hourglass shows the key determinants of the phenotype. The key factor is **a** | a phenotypic state, such as obesity; **b** | an environmental factor, such as smoking (note that a genetic factor may affect whether this environment is experienced); **c** | a genetic factor, such as sickle-cell haemoglobin. **d** | There is no key factor, and the genotype–phenotype map is truly many to many.

by simple changes to the parameters of the signalling network that are hypothesized to mimic underlying genetic variation. Results from the model are suitable for comparison with intensive phenomic measurements of actual teeth.

Such models can be embedded in an explicit population framework, allowing the effects of mating system, selection regime and genetic architectures to be predicted[62,69]. For example, nonlinear cG–P models have been used to show how genetic variation affecting the form of *cis*-regulatory input functions may reshape the G–P map by changing the relative importance of *cis* and *trans* variation[62], to disclose the relationships between possible statistical genetic architectures and the anatomy of regulatory networks[69], and to refine single-locus genetics by providing a direct link between classical models of gene action and gene regulatory biology[70].

Non-genetic models have been used to integrate properties of biological systems across the full hierarchy of spatial scales. The Virtual Physiological Human Initiative (VPH)–Physiome Project[71,72] has produced detailed hierarchical models of several mammalian organ systems by integrating the theoretical and experimental efforts of a large network of investigators. For example, a model ensemble of the heart links genetic variation and protein pathways to the integrative function of cardiac cells, tissues and the intact heart. To do so, it incorporates models of biochemical processes, electrical activation, mechanical contraction, fluid mechanics, energy supply and use and cell signalling[72]. Despite the enormous complexity of such models, they have demonstrated explanatory power[73]. The heart models can now be modified to correspond to the morphology and organ-level behaviour of individual patients by integrating data from magnetic resonance imaging (MRI)[72]. The heart model ensemble is now being used in a cG–P context to study how genetic variation is propagated from the ion channel level to the whole organ phenotype.

Phenomic tools

A broad categorization of phenotypes we would like to be able to characterize is shown in TABLE 2, along with the capabilities to do extensive and intensive sampling. The combined measurement of all these phenotype classes on the same individuals is particularly challenging. We highlight a few of the most promising technologies for phenomic-scale measurement and the ways in which they need to be improved.

Transriptomics and epigenomics. Nucleic acid-based measurements of transcriptomes and epigenomes are the most widely known source of extensive phenomic data. Many large data sets are available in different species. Gene expression profiling is widely used in disease settings such as the diagnosis and prediction of cancer outcomes[74,75]. The vast number of features that can be measured, however, obscures important challenges. Gene expression varies with cell type and developmental stage, and obtaining intensive data sets is challenging. It is frequently difficult to obtain homogeneous tissue, particularly when expression is rare or transient or in tissues that are difficult to access, such as brain or heart. RNA data sets have been widely used to make inferences about causal relationships[17,76], but mixed samples violate the assumptions behind such inferences[77]. Techniques suitable for intracellular or single-cell assays are being developed[78].

Proteomics and metabolomics. Proteomics and metabolomics are increasing their throughput owing to a similar set of procedures: separation to simplify the sample followed by mass spectrometry to identify the compounds present. Both approaches integrate a wide variety of

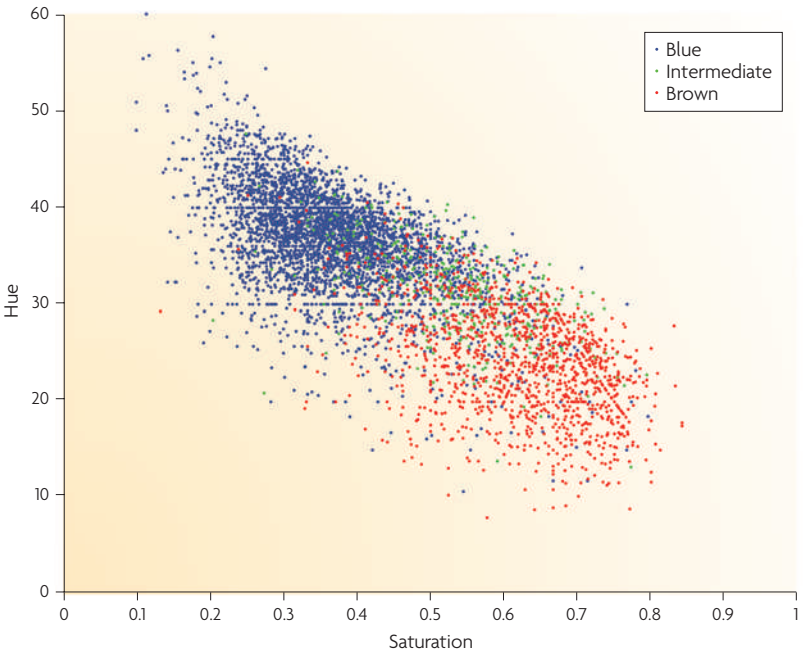


Figure 2 | **Quantitation of eye colour.** Eye colour is traditionally categorized into blue, brown or intermediate, but Liu *et al.*[125] quantitatively estimated the average hue and saturation of each iris from digital images. When the qualitative designation of eye colour is plotted in hue saturation space, there is a substantial overlap between the categorical assignments. A genome-wide association study of these data could identify ten loci influencing hue and/or saturation, three more than were detected in a study based on the three-category phenotype. A completely phenomic approach to eye colour would also capture the spatial pattern of eye colour, resulting in a potentially much higher dimensional phenotype space. Figure is reproduced, with permission, from REF. 125 © (2010) Public Library of Science.

post-transcriptional and regulatory events. In particular, metabolites provide important data on the environment that different individuals experience. Proteomic analyses can detect most peptides in a sample[79], although detection of rare molecules in complex mixtures is still problematic[80]. Metabolomes are substantially less complex than proteomes, but the universe of metabolites is not fully characterized[81,82]. Typical high-throughput metabolomic analyses resolve the abundance of <30 compounds[82]. In humans, metabolome-wide association studies have identified metabolites reliably associated with phenotypes such as blood pressure[83] and coronary heart disease[84].

Imaging. Imaging is ideal for phenomic studies owing to the availability of many technologies that span molecular to organismal spatial scales[85], the intensive nature of the characterization and the applicability of generic segmentation techniques to data. Spatial or temporal data on many phenotype classes such as morphology, behaviour, physiological state, and locations of proteins and metabolites can be captured in intensive detail by imaging. Spectroscopic imaging of crop plants can be used to predict many properties on very large populations[86]. Imaging technologies vary widely in the rate of measurement. Two-dimensional images from photography and traditional microscopy are cheap and quick to acquire, so specimen handling time is often the limiting factor in their acquisition. The simplest three-dimensional imaging combines information from different real or virtual slices through a specimen, which are then combined to reconstruct the three-dimensional form. Volumetric imaging of live specimens can be accomplished by computerized tomography scans or MRI. Scanners, however, are expensive and scan times are long. Data can be recovered in multiple modalities simultaneously, for example, by combining optical images with positron emission tomography of metabolites[87] or recovery of multiple fluorescent features, but these approaches often require substantial time and expense to prepare samples.

Behaviour. Behaviour presents special challenges for phenomics because of its temporal nature and context dependence, which result in high variance. One trend is the intensive study of behaviour in free-living animals using increasingly miniaturized and sophisticated automated data loggers[88]. State-of-the-art technology combines such features as global positioning system locators, accelerometers, electroencephalography or neural activity recorders and video. These technologies are still expensive and rarely allow large samples of animals to be measured. More promising for high throughput is video tracking of groups of confined[89] or free-living[90] animals coupled with automated image analysis. For humans, web-based tools to recover behavioural data from volunteer subjects may prove particularly effective[6,91].

Phenome projects

Some of the most promising phenome projects are listed in TABLE 1. None of these pioneering projects comes close to realizing the full phenomic vision, largely because of the costs and shortcomings of phenotyping capabilities. For example, the mouse phenome projects address an extensive range of phenotypes and are among the best organized, but the sample of non-mutated genotypes being characterized is relatively small and the sample size of individuals is limited. Organized phenomic efforts are underway in the dog, rat and fruitfly communities, but deficiencies in coordination, funding, phenotyping or standardization are apparent to various degrees. More generally, model organisms such as yeast[92] and *Caenorhabditis elegans*[93] are hotbeds for the development of high-throughput phenotyping, but we know of no coordinated phenomic efforts other than those listed in TABLE 1.

Paradoxically, the prospects for phenomics in humans are particularly great, despite the obvious challenges of long lifespans, the inability to replicate genotypes or to perform many types of experiments. The personal and institutional interest in health already leads to repeated measurement of the phenotypes of many individuals throughout life as a result of medical care or long-term studies. The range of human phenotypes that are already being measured is extensive and research constantly expands it[94].

Several longitudinal and multi-generational epidemiological studies have already been used to study health-related phenotypes[95–97]. For instance, the Framingham

Positron emission tomography
This produces three-dimensional images through time of the concentration of a biologically interesting molecule such as glucose labelled with a radionuclide.

Table 2 | **Phenotyping across the biological hierarchy**

Level	Extensive	Intensive
DNA, RNA	Solved and costs declining rapidly. Limited by bioinformatics capabilities	Possible but costly; detailed sampling is challenging
Chromatin	Made possible by chromatin immunoprecipitation but with low precision; costly	Possible but costly; detailed sampling is challenging owing to instability
Proteins, metabolites	Mostly solved and capabilities are still improving for rare constituents	Possible but costly; detailed sampling is challenging
Cells	Huge diversity of assays is possible but most are low throughput. Image-based techniques for high throughput are promising	Many temporally continuous assays. Image-based approaches allow some combination of extensive and intensive measurement
Development	Low-throughput measures are abundant. High-throughput image-based methods are possible for small living individuals (embryos and *Caenorhabditis elegans*) and sectioned tissues	Temporal depth by repeated sampling or image-based approaches
Physiology	Huge diversity of assays is possible, but most are low throughput, unless based on proteomic or metabolomic data	Many temporally continuous assays. Spatial sampling is often possible
Morphology	Solved in principle with the use of imaging, but assays often require extensive sample preparation. Post-processing to extract and measure features requires specialized informatics capability	Intensive sampling of morphological form is possible with specialized processing. Temporal depth is limited by destructive sampling
Behaviour	Possible with continuous observation of video of confined or local populations, or for humans, self-reporting. Data extraction from video using specialized software or human labour	Extensive sampling gives intensive coverage. Specific aspects of behaviour can be intensively measured with data loggers

Heart Study investigates risk factors involved in cardiovascular disease among healthy individuals. Since 1948, investigators have collected data on hundreds of traits in over 14,000 individuals spanning three generations. The traits cover many of the phenotypic classes listed in TABLE 2, plus environmental influences, medical history and causes of mortality[95,96]. The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (please see Further information for a link to this consortium) has derived important insights into the genetic architecture of cardiovascular health and ageing using data from the Framingham Heart Study, as well as other longitudinal studies[98]. Byars *et al.*[99] recently used the Framingham data to demonstrate that natural selection has been acting in this population. There is already a huge amount of phenomic information in research results, medical records and the personal experience of each individual that could be used to enhance designed studies. Such data have been archived at many centres[100–102], and a web-based repository (the database of Genotypes and Phenotypes (dbGaP; please see Further information for a link to this database)) has been established[103].

Three of the most comprehensive phenomic efforts planned in humans are listed in TABLE 1. Although these visionary studies are tremendously exciting, examination of their details makes clear how far we still must go to obtain comprehensive phenomic data. The Consortium for Neuropsychiatric Phenomics (CNP) is a centrally funded project with a truly phenomic vision[6] but focuses on a restricted set of neural and psychological phenotypes, and sample sizes are relatively small. The prospective epidemiological UK Biobank has enrolled 500,000 subjects and is enabling phenomic-level studies by providing access to full medical records and by storing blood and urine, but the actual measurements being taken are modest in scope. George Church's Personal Genome Project envisions obtaining phenomic information and the complete genomic sequence of 100,000 volunteers. The phenomic component of this project is unrealized (please see Further information for links to these initiatives).

The future of phenomics

The basic requirements of an ideal phenomics effort are easy to state but difficult to achieve: genomic information on a large sample of genotypes, which are each exposed to a range of environments; extensive and intensive phenotyping across the full range of spatial and temporal scales; and low cost. It is clear that the cost of a phenome project using current technology would be extremely high. We see the attractiveness of a phenome project as analogous to that of the Human Genome Project in the late 1980s. When originally proposed, the genome project attracted opposition because of the lack of a basic map and the high cost of sequencing[1]. When the project was reshaped to make technology development to lower costs an initial priority and basic mapping was added to the project, it attracted substantial support from the molecular genetics community[2]. Consequently, we believe that the path to the phenome begins by building the infrastructure for phenomic projects, rather than immediate large-scale phenotyping. Three attractive targets permit progress towards these goals: technology development, statistical and analytical capabilities, and incentives to integration.

Technology. The first priority of a phenome project would be to develop technologies that maximize throughput of *p* and *N* and substantially lower the cost of doing so. Currently, such technology development is often narrowly focused on the needs of a single biological system or research programme. We should favour general solutions that can readily be modified for use in different taxa. Promising technologies for generalization include metabolomics, imaging, microfluidics and nanotechnology. Perhaps the most promising recent trend is the recruitment of engineers and materials scientists into the study of phenotypes, which has resulted, for example, in lab-on-a-chip devices that automate measurement and specimen handling[93,104]. Funding through a coordinated programme designed to further the goals of phenomics could help spur the development of such technologies. Given the magnitude of the phenomic challenge and considering the demands of multi-scale modelling, it is likely that we will need to foster entirely new measurement technologies based, for example, on nanodevices[105].

Data analysis. Navigating HDLN data sets is extremely challenging. The wider adoption of methods that deal with multiple models, prior knowledge and estimation, instead of statistical testing is needed. Although specialists can navigate these issues, most software that is widely available and easy to use is not informed by these needs. As with technology, adoption of newer analytics is limited by ignorance of state-of-the-art methods and the availability of tools. One important area for new analytics is in automating data analysis[106]. The combinatorial universe of possible models to investigate quickly outstrips human capabilities as additional data dimensions are sampled. Automated techniques that go beyond the mere description of patterns will be necessary to accelerate nonlinear systems modelling.

Integration. Most concurrent phenotypic studies use independent samples of genotypes or individuals, missing an opportunity to measure the covariances between phenotypes that are crucial to building and validating causal models of the G–P map. Fragmented scientific research is the historical norm. The undeniable successes of this entrepreneurial paradigm seem to validate a wide variety of institutional, sociological and personal factors that preserve this fragmentation. The history of genomics, however, suggests that such fragmentation can be suspended and that the potential gains for doing so are enormous. The US National Institutes of Health (NIH) supports integrative efforts in medicine through its Clinical and Translational Science Awards programme (please see Further information for a link).

If we imagine a future in which high-throughput phenomics are practical, how might this accelerate biological understanding? First, phenomics could help tighten the relationship between experimental measurement and modelling. For example, the experimental data needed to minimally characterize a single mouse heart[72] require time-consuming, expensive efforts by highly trained personnel, including detailed *in vivo* MRI measurements[107]; mounting of the heart to obtain left ventricle pressure–volume data[108]; mounting right ventricle muscle tissue to measure force and heat generation, for calcium imaging and for patch clamping[109]; and, finally, fixation and slicing of the heart to obtain structural data[110]. If a high-throughput alternative were available, modellers could have ready access to the natural range of variation in heart structure and function, enabling rapid tests of each model. Second, phenomics may open up completely new ways of using models to uncover genetic and environmental variation by identifying key parameters. Direct measurement of such parameters will improve our ability to test causal hypotheses suggested by the models, leading to rapid gains in our understanding of the G–P map. Third, high-capacity phenomics would enable a quantitative understanding of how ageing proceeds, which is crucial because age is still the best predictor of both heart function and disease[111–114], as for many other complex diseases. Ageing is manifested in so many different ways that a quantitative understanding of an ageing heart will demand dramatically more data than understanding young and non-diseased hearts[60,115].

Conclusion

The genome project has led to gains in basic research at least as great as the proponents during the 1980s foretold, although the promise for medicine is largely unfulfilled. We have discovered a wealth of important novel phenomena, including many that could not have been found in the 3–5% of the genome that was thought to be interesting in 1987. The comprehensive nature of genomic data has spawned entirely new disciplines that use the availability of genome sequence as a starting point. By identifying phenomics as a discipline in its own right, we can accelerate progress in the parts of biology and medicine that have benefited only indirectly from genomics. We can look forward to the development of technology and expertise for high-throughput phenotyping that will free most researchers from having to be technical wizards or invent novel data analyses to take advantage of these data. Phenotypes are what matters about organisms; it is difficult to imagine that comprehensive phenotyping will not pay benefits at least as great as the Human Genome Project.

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Competing interests statement
The authors declare no competing financial interests.

DATABASES
Database of Genotypes and Phenotypes (dbGaP): http://www.ncbi.nlm.nih.gov/gap
The Mouse Phenome Database (MPD): http://www.jax.org/phenome
Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/omim

FURTHER INFORMATION
Australian Plant Phenomics Facility: http://www.plantphenomics.org.au
Canine Phenome Project: http://www.caninephenome.org
Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: http://web.chargeconsortium.com/main
Consortium for Neuropsychiatric Phenomics (CNP): http://www.phenomics.ucla.edu
***Drosophila* Genetic Reference Panel (DGRP):** http://www.hgsc.bcm.tmc.edu/project-species-i-Drosophila_genRefPanel.hgsc, http://flybase.org/static_pages/news/whitepapers/Drosophila_Genetic_Reference_Panel_Whitepaper.pdf
***Drosophila* Population Genomics Project (DPGP):** http://www.dpgp.org
European Mouse Disease Clinic (EUMODIC): http://www.eumodic.org
European Mouse Phenotyping Resource of Standardised Screens (EMPRESS): http://www.empress.har.mrc.ac.uk
Europhenome Mouse Phenotyping Resource: http://www.europhenome.org
International Plant Phenomics Network (IPPN): http://www.plantphenomics.com
Jülich Plant Phenotyping Centre (JPPC): http://www.fz-juelich.de/icg/icg-3/jppc
National BioResource Project for the Rat in Japan (NBRP): http://www.anim.med.kyoto-u.ac.jp/nbr
National Institutes of Health Clinical and Translational Science Awards: http://www.ctsaweb.org
Personal Genome Project: http://www.personalgenomes.org
The Virtual Physiological Human Initiative (VPH): http://www.vph-noe.eu/home
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