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Recombinant Inbred Mice as Models for Experimental Precision Medicine and Biology

David G. Ashbrook and Lu Lu

Abstract

Recombinant inbred rodents form immortal genome-types that can be resampled deeply at many stages, in both sexes, and under multiple experimental conditions to model genome-environment interactions and to test genome-phenome predictions. This allows for experimental precision medicine, for which sophisticated causal models of complex interactions among DNA variants, phenotype variants at many levels, and innumerable environmental factors are required. Large families and populations of isogenic lines of mice and rats are now available and have been used across fields of biology. We will use the BXD recombinant inbred family and their derived diallel cross population as an example for predictive, experimental precision medicine and biology.

Keywords: BXD, experimental precision medicine, genome-by-environment, systems genetics, personalized medicine, recombinant inbred strains, diallel cross, prediction

1. Introduction

One of the major objectives of modern biology and medicine is prediction: being able to take information about an individual's genome and environment and accurately predict their phenotype. This effort has taken on many forms and many names in different fields over time including population genetics [1], statistical genetics, quantitative genetics [2], genetical genomics [3], complex trait analysis [4], systems genetics [5, 6], systems medicine [7, 8], personalized medicine [9], predictive medicine and precision medicine [10, 11]. In humans, this has been greatly constrained by the *N*-of-1 problem, by which we mean that each person is a unique individual [12] – even monozygotic twins will differ in their environment. This has made it impractical, if not impossible, to accurately predict at the individual level disease risk or best treatment options for most common diseases, especially across populations [13–18], although we can, of course, make generalizations within a population. As sample sizes for genome-wide association studies have grown, it has become increasingly clear that any single commonly segregating variant is likely to have a very small impact on disease risk [19–21]. Indeed, an omnigenic model has been proposed, whereby variants in every gene are likely to affect every phenotype [22]. Even for Mendelian disorders such as Huntington's disease, there are other alleles in the genetic background which modulate age of onset [23].

How then, if there is so much complication in this one-to-one relationship (one gene variant to one phenotype), can we uncover the true many-to-many-to-many relationships that occur in biology? Phenotypes at many levels, including behavior, organ systems, cells, proteins, metabolites, and mRNAs, all interact together with sets of many gene variants, and with an individual's current and previous environmental exposures. We need to understand gene-gene (epistasis), gene-age, gene-sex, gene-treatment, and gene-environment interactions and all their combinations. One answer to this is through the use of recombinant inbred (RI) populations and their derivatives.

2. Recombinant inbred families

Recombinant inbred (RI) populations are a seemingly simple idea: two inbred strains are crossed, and their F1 progeny are then crossed again to produce an F2. Pairs of these F2 animals are mated, and new lines are established through repeated rounds of sib-mating (**Figure 1A**). By generation F20, we have a population of 99% inbred strains, each of which is a unique mosaic of homozygous genetic regions from both the parents, and for which an effectively infinite set of genetically identical individuals can be produced [24, 25]. This combination of genetic variability between strains but identical genome within strains allows the mapping of linkage between genotype and phenotype. The design has been expanded on in a variety of ways [26], such as increasing the number of parental strains (e.g. the 8 founders used for the Collaborative Cross mice [27, 28]) to increase the number

Figure 1. Production of the BXD family, transgenic crosses, and diallel crosses. Approximately half of the BXD strains are from an F₂ (A; epochs 1, 2, 4 and 6), and approximately half of the BXD strains are from advanced intercrosses (AI; B; epochs 3 and 5). Red represents regions of the genome coming from C57BL/6 J (B6), and white represents regions from the DBA/2 J (D2). Solid arrows have been used to represent a single generation of breeding. Transgenic and non-transgenic crosses for QTL mapping can be produced by crossing hemizygous transgenic mice to RI individuals, to produce litters containing both genotypes (C). The transgene is represented in yellow. A diallel cross (DAX) includes all combinations of genotypes, including the inbred ‘diagonal’, and all reciprocal crosses (D). All offspring of the DAX are isogenic, meaning that genotypes are replicable.

of variants that segregates in the population, or using multiple rounds of crossing before inbreeding, producing so-called Advanced Intercross RI strains (AI-RI) to increase the number of recombinations, and therefore the precision of mapping (**Figure 1B**; [29]). Although RI strains were first developed in mice, and it is mice that we will concentrate on in this chapter, the design has now been used for a wide variety of organisms, including *Arabidopsis* [30, 31], *Zea mays* (maize) [32], barley [33], *Drosophila melanogaster* [34], *Drosophila simulans* [35], *Caenorhabditis elegans* [36] and rat [37].

These RI families are an essential complement to data collected in humans, allowing us to build experimental platforms for what is now called precision medicine. Each isogenic RI strain within a family is effectively an immortal genome-type. This is important because it allows the same genome to be resampled using any tissue, at any age, with any method, with any environmental exposure or treatment that the researcher cares to use. This allows us to model higher-order genome-environment interactions: the many-to-many-to-many problem stated above.

Whereas in human cohorts we have to imagine a counterfactual (e.g. what would have happened had I exercised more?), in isogenic strains we can effectively run this counterfactual – almost perfectly genomically and environmentally matched individuals can be phenotyped with only a single environmental perturbation between them. Even better, we can have multiple duplicates of these identical genome-types within each arm of the study, allowing us to reduce the effect of unwanted environmental perturbations, increasing our power to detect true associations [38]. However, in some sense, this is still an *N*-of-1 study, as only a single genome-type is being used. A problem many pre-clinical studies have had is that all experiments were carried out on a single genome-type and therefore effectively a single individual. The C57BL/6 J strain is often used to represent the entire mouse species [39, 40], when in fact its phenotype can often differ from even the closely related C57BL/6 N strain [41]. This may explain some of the failures to translate effects seen in mice to effects seen in humans, as in these studies only a single (genetic) individual is being examined, and then results extrapolated to the highly genetically diverse human population. RI families overcome this problem – many genome-types can be tested and many replicates within each genome-type. Therefore, we have a high-powered system to detect and test genome-phenome associations.

The goal is accurate genome-phenome prediction. With this goal in mind, we will use the BXD family of isogenic mouse strains as our example of how this can be achieved. The BXDs are by a wide margin the largest and most deeply phenotyped mammalian family and can be used as a testbed for experimental precision medicine.

3. The BXD family

The BXD family were among the first RI strains to be produced [24, 42, 43]. This work was started by Benjamin A. Taylor who crossed female C57BL/6 J (B6 or B) and male DBA/2 J (D2 or D) strains—hence BXD (**Figure 1A**). The first sets of BXDs were intended for mapping Mendelian loci [42, 44], but the family was also used to map complex traits such as cancer and cardiovascular disease [45–48], variation in CNS structure [49–52], and behavioral and pharmacological differences [53–62]. Twenty-seven of the original 32 BXD strains are still available from The Jackson Laboratory (JAX). In the mid-1990s, Taylor began the production of a second set of BXDs [44] and added nine new strains (BXD33–BXD42). BXD1–BXD42 carry the strain suffix “/TyJ”.

We started production of another wave of BXDs at UTHSC in the late 1990s [29]. These new lines were derived from advanced intercross (AI) progeny that had accumulated chromosomal recombination events across 8 to 14 generations [63] (**Figure 1B**). These AI-derived BXDs incorporate roughly twice as many recombinations between parental genomes than do conventional F2-derived BXDs [63–67]. This improves mapping precision nearly two-fold. BXD strains BXD43 and above from UTHSC were donated to JAX once fully inbred, and carry the strain suffix “/RwwJ”.

The BXD family has been used to define specific genes and even sequence variants corresponding to 20 or more QTLs. These include two tightly linked genes, *Iigp2* and *Irgb10*, for *Chlamydia* infectivity [68, 69], *Fmn2* as a master controller of tRNA synthetases in neurons [70], *Ubp1* for blood pressure [48], *Hc* for H5N1 influenza resistance [71], *Comt* as a master controller of neuropharmacological traits [72], *Alpl* for hypophosphatasia [73], *Mrps5* for longevity [74], *Bckdhhb* for maple syrup urine disease, *Dhtkd1* for diabetes [75], *Hp1bp3* for cognitive aging [76], *Ahr* for locomotor activity [77], *Cacna2d1* for glaucoma [78] and *Gabra2* for behavioral traits [79]. Alleles discovered in the BXD have been successfully translated into medical applications in humans, such as stratified preclinical testing based on glaucoma risk alleles revealed in the BXDs [80, 81].

Two things now set the BXD family apart from all other recombinant inbred populations: the number of strains within the family, and the deep, coherent phenome that has been collected for them.

3.1 The largest mammalian recombinant inbred family

The BXD family is the largest mammalian recombinant inbred population, having expanded during its lifetime, from ~20 [42], to ~35 [44], to ~80 [29], to a total of 198 strains with data on GeneNetwork.org. There are 123 BXD strains currently distributed by The Jackson Laboratory (JAX) and an additional seventeen strains available at UTHSC, soon to be donated to JAX [82]. All 140 of these strains are available under a standard material transfer agreement. This expanded number of easily accessible strains increases the power and precision of linkage studies [82].

As the number of strains increases, there is an increase in the number of recombination junctions within the population, and consequently, quantitative trait loci (QTLs) can be narrowed down to smaller intervals. This is improved still further by the fact that approximately half of the BXD family are derived from advanced intercrosses, each of which will have a larger number of recombinations than their F2 derived cousins. We have demonstrated that when using approximately half of the family (60–80 strains), precision is close to 1 Mb for many traits [82]. This is also partially due to two other features of the family. The first, common to all RIs, is that the effective heritability of the trait can be boosted by resampling the same genome-type [38], and the second, that because there are two parents in the population, there is a well-balanced distribution of the two haplotypes across the genome (the mean minor allele frequency is ~0.44).

When carrying out QTL mapping the largest gain of power is given by increasing the number of genome-types tested [38, 73], and therefore, as the largest RI family, the BXD have the most power to detect genotype–phenotype linkage. A simple app has been produced to estimate power to detect QTL in the BXD, available at <http://power.genenetwork.org> [82]. When we examine power in the BXD family, we see a fact that might seem counter-intuitive to some: power is always increased more by increasing the number of strains compared to increasing the number of within strain biological replicates, even when heritability is low. Even

at low-to-moderate heritabilities, increasing replicates above 6 within-strain gives very little improvement in power.

We should also note that the effect sizes seen in the BXD family (and other two-parent RIs), appear to be high, but this is correct, as effect size is highly dependent upon the population being studied. Effect sizes measured in families of inbred lines are typically much higher than those measured in an otherwise matched analysis of intercrosses, heterogeneous stock, or diversity outbred stock. Two factors contribute to the higher level of explained variance of loci when using inbred panels. The first reason is due to replicability. When effect size is treated as the proportion of total genomic variance explained by the QTL, effect size will increase as environmental effects decrease due to replication. That is, resampling decreases the standard error of the mean, suppressing environmental “noise” [38]. This is in addition to the increase in heritability above (i.e. an increase in total variance explained by the total genomic variance).

The second reason is that nearly all loci in inbred panels are homozygous and the same number of sampled animals will account for twice as much genetic variance as in an F2 cross, and four times as much variance as in a backcross [38]. When phenotyping with fully homozygous strains we are only examining the extreme ends of the distribution, providing a boost in power to detect additive effects. The downside is obvious: we cannot detect non-additive effects. However, if we add in members of the diallel cross population (DAX), we can now estimate both dominance and parent-of-origin effects. This is a topic we will come to later.

3.2 The deepest phenome for any family

As well as being the largest recombinant inbred family, the BXD are also the most deeply phenotyped. Over 40 years of data is now openly and publicly available at genenetwork.org, providing an unrivaled resource. This dense and well-integrated phenome consists of over 10,000 classical phenotypes [83]. The phenome begins with Taylor’s 1973 analysis of cadmium toxicity, through to recent quantitative studies of addiction [84–86], behavior [87–90], vision [91], infectious disease [92–94], epigenetics [95, 96], and even indirect genetic effects [97–99]. The BXDs have been used to test specific developmental and evolutionary hypotheses [49, 100, 101]. They have allowed the study of gene-by-environmental interactions, with environmental exposures including alcohol and drugs of abuse [86, 102–105], infectious agents [71, 106–109], dietary modifications [110–115], and stress [116, 117]. The consequences of interventions and treatments as a function of genome, diet, age, and sex have been quantified [90, 96, 115, 118–120], and gene pleiotropy has been identified [121].

Beyond this, there is now extensive omics data for the BXD. Both parents have been fully sequenced [75, 122, 123], and deep linked-read and long-read sequencing of 152 members the BXD family is underway. Over 100 transcriptome datasets are available (e.g. [124, 125]), as well as more recent miRNA [84, 126], proteome [118, 120, 127], metabolome [75, 118, 125], epigenome [95, 128], and metagenome [93, 129] profiles. Nevertheless, much more is still to be done, as many of these measures have only been taken in the liver or in specific brain regions [118, 120]. However, as each of these new datasets is added, they will be fully coherent with previous datasets, multiplicatively increasing the usefulness of the whole phenome.

Access to this plethora of data is freely available from open-source web services, allowing users to download the data, or to make use of powerful statistical tools designed for global analyses that are integrated into websites (e.g. GeneNetwork.org, bxid.vital-it.ch, and Systems-Genetics.org) [125, 130, 131].

It cannot be overstated how important it is that those using the BXDs gain access to coherent genomes and quantitative phenomes generated under diverse laboratory and environmental conditions [83, 132]. New data can be compared to thousands of publicly available quantitative traits, and with each addition, the number of network connections grows quadratically—enabling powerful multi-systems analysis for all users [73, 111, 112, 118, 125, 133]. Causal pathways can be produced from genome variants, to gene expression, to metabolite levels, to phenotype [73]. Within minutes of finding a gene of interest, a researcher can look for correlations between its expression and thousands of other genes, across dozens of tissues. Enrichment analysis can then be carried out on these ‘gene-friends’ suggesting pathways and networks that your gene of interest may be associated with. Correlations can be found between the expression of your gene and over 10,000 phenotypes, giving suggestions of the role of the gene at the whole-organism level. Shared QTLs, where both the gene-expression and a phenotype of interest are associated with the same locus, provide strong evidence of a genetic link. Using GeneNetwork.org we can build biological networks, moving from genetic variant, to expression difference, to protein expression, to whole-system outcomes, with just a few keystrokes, and without touching a lab bench [134–136]. Entire manuscripts can be written without leaving a web browser [137]. This is a massive step forward that is under-appreciated by many.

The above demonstrates how the BXD can help us achieve our goal of predictive modeling of disease risk and the efficacy of interventions [138]. Indeed, the family has already been used to test specific functional predictions of behavior based on neuroanatomical variation [139]. The BXD family is well placed to address these questions that encompass both high levels of genetic variation and gene-environmental interactions: our many-to-many-to-many problem. This is bolstered by the family’s easy extendibility into a massive diallel cross population (DAX).

4. Diallel crosses

The diallel cross is another simple idea that has been with us for over 60 years [140–142]. We now have the major opportunity to take full advantage of this approach using large panels of fully sequenced isogenic strains. A DAX is the set of all possible matings between several genome-types (**Figure 1D**). For the C57BL/6 J and DBA/2 J there are the two reciprocal F1s, and these have been used to study parent-of-origin effects and to estimate heritability (e.g. [53]). As the number of parental strains increases, the number of potential diallel crosses increases exponentially, and tools have been developed to deal with large DAXs [143]. Although we have learnt much about the genetic architecture of traits [53, 143–147], QTL mapping has been more difficult, given the relatively small number of strains used [148]. We can now imagine the full DAX for the BXD family of 140 strains – 19,460 replicable isogenic F1s, all of which have a reproducible, entirely defined genome, and any subset of which can be generated efficiently for *in vitro* and *in vivo* predictive biology and experimental precision medicine. Just as the C57BL/6 J and DBA/2 J are the parents of the BXDs, the BXD strains are the parents of a potentially huge isogenic DAX.

At the first level, this has important consequences for power and precision. The number of strains phenotyped can be increased massively, giving power to detect loci with even the weakest of effect sizes [148]. Precision can also be enhanced, as F1s can be produced which segregate for a narrow region of the genome, producing a small QTL interval containing fewer genes. All the data collected in these F1s can

be coherently integrated into the phenome already aggregated for the BXD, meaning that every new phenotype measured adds quadratically to the phenome and that any user of this F1 has access to over 40 years of data.

At the next level up, it also allows us to detect, for example, dominance and parent-of-origin effects mentioned above. Small DAXs of mouse strains have been able to identify parent-of-origin effects, epistasis, and dominance, but have been unable to map the loci causing these effects [53, 143–146, 149, 150]. By using reciprocal crosses of inbred strains (e.g. BXD001xBXD002F1 vs. BXD002xBXD001F1), we can produce isogenic litters, the members of which are all genetically identical, and whose only differences are due to parent-of-origin effects [151] (**Figure 1C**). By building a large DAX of reciprocal crosses, the genomic loci causing these dominance, epistatic, and/or parent-of-origin effects can be identified. Mapping of these non-additive effects is a complete dark zone in fully homozygous inbred populations.

Finally, and most importantly, the DAX provides a population for the testing of predictions. Using the BXD family we have enough strains to make associations, whether gene-phenotype, environment-phenotype, or gene-environment-phenotype, with high power. However, using only the inbred BXD lines, we do not have a second population in which to test predicted associations. The BXD DAX provides a matrix of 19,600 isogenic genome-types. If only the ‘diagonal’ of inbred BXD strains are used to detect associations and make predictions, any of the 19,460 isogenic F1s are available to test these associations and predictions (**Figure 1D**).

We can expand the DAX even further using easily available isogenic strains. There are approximately 200 RI strains from other two-parent mouse populations, including AXB/BXA (29 strains), AKXD (20), BXH (11), BRX58N (7), CXB (19), ILSXISS (60), LGXSM (~18), NXSM (16) and SWXJ (12), plus approximately 55–75 strains from the Collaborative Cross 8-parent RI population [28]. From these inbred parents, there are over 152,100 isogenic F1s that can be produced and replicated. An additional expansion of this design is to cross RI families to genetically engineered disease models.

5. Diallele crosses to genetically modified strains

Genetically modified animals, including humanized, transgenic and knockout mouse models, have been a vital piece in uncovering genotype-phenotype associations, but they have often suffered from the same *N*-of-1 problem as above – for example, a knockout has been produced on a single genetic background, and then phenotyped. There is ample evidence that a genetic modification produced on one genetic background can have a different phenotypic effect compared to an identical modification on a different genetic background [152–165]. Expanding above this *N*-of-1 had been difficult, as each new isogenic strain had to be produced independently with a consequent near linear increase in effort. However, each of these genetically modified isogenic lines can be added into a DAX. Now, each of any of hundreds of F1 crosses is genetically defined, replicable and isogenic, but also contains one copy of the genetic modification (**Figure 1C and D**). Given that there are now thousands of knockout strains available (e.g. from the International Mouse Phenotyping Consortium [166, 167]), creating a DAX is a relatively cheap and quick method by which to test the effects of genetic background [158, 168–171]. By using an RI population, we can map the location of modifier loci, genes, and variants [172–174].

An excellent example of this already exists: the Alzheimer’s disease BXD (AD-BXD) panel developed by Kaczorowski and colleagues [175, 176]. By crossing

C57BL/6J-congenic females hemizygous for the humanized 5xFAD transgene (JAX Stock No. 008730) to males from BXD strains, they produced litters, half of which had the 5xFAD transgene (the AD-BXD), and half of which did not have the 5xFAD transgene (non-transgenic-BXD). The whole litter is genetically and environmentally identical except for the presence of the transgene, giving an immediate and directly comparable control (**Figure 1C**). By crossing the humanized 5xFAD line on a single genetic background to a diverse but defined set of BXDs, they produced a population that incorporates high levels of sequence variation mirroring that of humans. They have mapped genetic and molecular causes of cognitive loss in AD-BXD mice [154, 175–179], including a broad spectrum of cognitive loss similar to that of humans with familial and late-onset AD [177]. The human transgenes in the 5XFAD line [180] sensitizes BXD hybrids to a greater or lesser degree—some begin to lose conditioned fear memory as early as 6 months; others well after a year [175], demonstrating a gene-by-gene-by-age interaction. Variation is highly heritable and mappable and gives a powerful means by which to define genetic causality and mechanisms of memory and non-cognitive loss and resilience to loss.

Neuner et al., were also able to demonstrate ‘reverse translation’ from human genomic data to mouse phenotype [175]. They generated a polygenic genetic risk score using 21 human genes which increase Alzheimer’s disease risk, and showed that the allele dosage was significantly associated with cognitive outcomes in the AD-BXD. This confirms firstly, that naturally occurring variation in these networks has overlapping effects in mice and humans, and secondly that gene-phenotype associations translate across species. This approach can be applied to many other phenotypes.

Given that phenotypes from genetically engineered mice on a single genetic background cannot be reliably generalized to other mouse genetic backgrounds [158], it is unsurprising that there are difficulties in generalizing to other species. By crossing genetically modified lines to RI strains to produce a DAX, we overcome this problem and allow the integration and translation of data to other populations and other species.

6. Integration and translation with other populations

Compared to conventional F2s and advanced intercrosses (AIs), outcrossed heterogenous stock, or diversity outbred stock, the BXD are particularly advantageous when the heritability of a trait is moderate or low because the genetic signal can be boosted greatly by resampling isogenic members of the same line many times [38]. The drawbacks of the BXDs are lower precision, and a decreased amount of variation in the population compared to e.g. multiparent families (such as the Collaborative Cross and the Diversity Outbred), and a consequent decrease in the total phenotypic variance [181]. We consider this an acceptable drawback, as we have shown that medically relevant phenotypes have variation in the family and it is possible to achieve subcentimorgan mapping precision using only half of the full set of strains [82]. Beyond this level of precision, an efficient method to transition from QTLs to causal genes, variants, and mechanisms is to take advantage of complementary resources. These include sets of other murine mapping resources, efficient *in vitro* and *in vivo* screens [74, 132, 182], and human genome-wide association study (GWAS) data.

As a specific example of combining murine populations, Taylor’s cadmium testicular toxicity mutation (BXD Phenotype 13035) that was unmappable in 1973 now maps to 3 Mb on GeneNetwork.org. When combined with SNP data for common strains, the variant can be restricted to a 400 Kb region that includes the causal *Slc39a8* gene, a heavy metal transporter expressed almost exclusively in the testes [183].

Mouse-to-human genetic translation has at least a 20-year history [184], but has taken off now that GWAS are routine [48, 78, 111, 112, 123, 125, 185, 186]. Human GWAS data can be used to refine QTL found in mice, e.g. taking advantage of the power to detect associations in the BXD to identify a homologous region in humans, and then using the precision of human GWAS to identify a candidate gene [185–187].

More importantly, mouse data can be used to determine the function and causal pathway for associations made in humans. Finding variant-phenotype associations for any phenotype with GWASs is now only limited by one's ability to collect phenotypes, but interpreting and determining the function of these variants is far more difficult, given the environmental and genetic variation in any human population. RI mice, such as the BXD, provide a method of 'reverse-translation' from human-to-mouse. Again, the work of Kaczorowski and colleagues above provides an excellent example [175] that can be applied to any other phenotypes.

7. Conclusions

Despite occasional arguments to the contrary [188, 189], mice, when used correctly, are a good model of human biology and medicine [12, 190–192]. Indeed, at least 40 Nobel Prizes have been awarded for research involving mice (<http://www.animalresearch.info/en/medical-advances/nobel-prizes>) [193], and their use has been vital in understanding the pathogenesis of many diseases. For true predictive medicine, we need to understand all gene-by-gene-by-environment-by-age-by-sex-by-treatment interactions [160], and animal models are the only way to do this at scale. The importance of using genetically diverse mice has often been overlooked, leading to difficulties with translation. RI families, such as the BXDs, and their expansions [130], including diallel crosses and reduced complexity crosses [194, 195], overcome this problem and are a vital step towards accurate, individualized, predictive medicine.

Acknowledgements

The UTHSC Center for Integrative and Translational Genomics (CITG) has supported production of the BXD colony at UTHSC and will continue to support this colony for the duration of the grant. The CITG also provides generous support for computer hardware and programming associated with GeneNetwork, and our Galaxy and UCSC Genome Browser instances. We thank the support of CITG, and funds from the UT-ORNL Governor's Chair, NIDA grant P30 DA044223, NIAAA U01 AA013499 and U01 AA016662, NHLBI R01 HL151438, and NIDDK R01 DK120567 for the work at UTHSC.

Conflict of interest

The authors have no conflicts of interest.

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References

- [1] Fisher R. Population genetics. *Proc R Soc London Ser B, Biol Sci.* 1953;141: 510-523. DOI: 10.1098/rspb.1953.0058
- [2] Green EL. Quantitative genetics of skeletal variations in the mouse. I. Crosses between three short-ear strains (P, NB, SEC/2). *J Natl Cancer Inst.* 1954;15:609-627. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/13233912>
- [3] Jansen RC, Nap JP. Genetical genomics: the added value from segregation. *Trends Genet.* 2001;17: 388-391. DOI: 10.1016/S0168-9525(01)02310-1
- [4] Threadgill DW. Meeting report for the 4th annual Complex Trait Consortium meeting: from QTLs to systems genetics. *Mamm Genome.* 2006;17:2-4. DOI: 10.1007/s00335-005-0153-5
- [5] Morahan G, Williams RW. Systems genetics: the next generation in genetics research? *Novartis Found Symp.* 2007;281:181-8; discussion 188-91, 208-9. DOI: 10.1002/9780470062128.ch15
- [6] Schughart K, Williams RW. *Systems Genetics.* Schughart K, Williams RW, editors. New York, NY: Springer New York; 2017. DOI: 10.1007/978-1-4939-6427-7
- [7] Tao Y, Liu Y, Friedman C, Lussier YA. Information visualization techniques in bioinformatics during the postgenomic era. *Drug Discov Today Biosilico.* 2004;2:237-245. DOI: 10.1016/S1741-8364(04)02423-0
- [8] Berlin R, Gruen R, Best J. Systems medicine-complexity within, simplicity without. *J Healthc informatics Res.* 2017;1:119-137. DOI: 10.1007/s41666-017-0002-9
- [9] Langreth, Waldholz. New era of personalized medicine: targeting drugs for each unique genetic profile. *Oncologist.* 1999;4:426-427. DOI: 10.1634/theoncologist.4-5-426
- [10] Wagner JB. Genomics and precision medicine to direct statin use in the young. *Prog Pediatr Cardiol.* 2009;54:101145. DOI: 10.1016/j.pppedcard.2019.101145
- [11] Lloyd KCK, Meehan T, Beaudet A, Murray S, Svenson K, McKerlie C, et al. Precision medicine: Look to the mice. *Science.* 2015;349:390. DOI: 10.1126/science.349.6246.390-a
- [12] Li H, Auwerx J. Mouse systems genetics as a prelude to precision medicine. *Trends Genet.* 2020;36:259-272. DOI: 10.1016/j.tig.2020.01.004
- [13] Fisher AJ, Medaglia JD, Jeronimus BF. Lack of group-to-individual generalizability is a threat to human subjects research. *Proc Natl Acad Sci U S A.* 2018;115:E6106-E6115. DOI: 10.1073/pnas.1711978115
- [14] Medaglia JD, Jeronimus BF, Fisher AJ. Reply to Adolf and Fried: Conditional equivalence and imperatives for person-level science. *Proc Natl Acad Sci U S A.* 2019;116:6542-6543. DOI: 10.1073/pnas.1820221116
- [15] Adolf JK, Fried EI. Ergodicity is sufficient but not necessary for group-to-individual generalizability. *Proc Natl Acad Sci U S A.* 2019;116:6540-6541. DOI: 10.1073/pnas.1818675116
- [16] Martin AR, Gignoux CR, Walters RK, Wojcik GL, Neale BM, Gravel S, et al. Human demographic history impacts genetic risk prediction across diverse populations. *Am J Hum Genet.* 2017;100:635-649. DOI: 10.1016/j.ajhg.2017.03.004

- [17] Kim MS, Patel KP, Teng AK, Berens AJ, Lachance J. Genetic disease risks can be misestimated across global populations. *Genome Biol.* 2018;19:179. DOI: 10.1186/s13059-018-1561-7
- [18] Mostafavi H, Harpak A, Agarwal I, Conley D, Pritchard JK, Przeworski M. Variable prediction accuracy of polygenic scores within an ancestry group. *Elife.* 2020;9. DOI: 10.7554/eLife.48376
- [19] Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet.* 2014;46:1173-1186. DOI: 10.1038/ng.3097
- [20] Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature.* 2014;511:421-427. DOI: 10.1038/nature13595
- [21] Huan T, Meng Q, Saleh MA, Norlander AE, Joehanes R, Zhu J, et al. Integrative network analysis reveals molecular mechanisms of blood pressure regulation. *Mol Syst Biol.* 2015;11:799. DOI: 10.15252/msb.20145399
- [22] Boyle EA, Li YI, Pritchard JK. An expanded view of complex traits: From polygenic to omnigenic. *Cell.* 2017;169:1177-1186. DOI: 10.1016/j.cell.2017.05.038
- [23] Long JD, Lee J-M, Aylward EH, Gillis T, Mysore JS, Abu Elneel K, et al. Genetic modification of Huntington disease acts early in the prediagnosis phase. *Am J Hum Genet.* 2018;103:349-357. DOI: 10.1016/j.ajhg.2018.07.017
- [24] Crow JF. Haldane, Bailey, Taylor and recombinant-inbred lines. *Genetics.* 2007;176:729-732. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17579238>
- [25] Bailey DW. Recombinant-inbred strains. An aid to finding identity, linkage, and function of histocompatibility and other genes. *Transplantation.* 1971;11:325-327. DOI: 10.1097/00007890-197103000-00013
- [26] Teuscher F, Broman KW. Haplotype probabilities for multiple-strain recombinant inbred lines. *Genetics.* 2007;175:1267-1274. DOI: 10.1534/genetics.106.064063
- [27] Churchill G a, Airey DC, Allayee H, Angel JM, Attie AD, Beatty J, et al. The Collaborative Cross, a community resource for the genetic analysis of complex traits. *Nat Genet.* 2004;36:1133-7. DOI: 10.1038/ng1104-1133
- [28] Shorter JR, Najarian ML, Bell TA, Blanchard M, Ferris MT, Hock P, et al. Whole genome sequencing and progress toward full inbreeding of the mouse Collaborative Cross population. *G3 (Bethesda).* 2019;9:1303-1311. DOI: 10.1534/g3.119.400039
- [29] Peirce JL, Lu L, Gu J, Silver LM, Williams RW. A new set of BXD recombinant inbred lines from advanced intercross populations in mice. *BMC Genet. BioMed Central;* 2004;5:7. DOI: 10.1186/1471-2156-5-7
- [30] El-Din El-Assal S, Alonso-Blanco C, Peeters AJM, Raz V, Koornneef M. A QTL for flowering time in *Arabidopsis* reveals a novel allele of *CRY2*. *Nat Genet.* 2001;29:435-440. DOI: 10.1038/ng767
- [31] Lister C, Dean C. Recombinant inbred lines for mapping RFLP and phenotypic markers in *Arabidopsis thaliana*. *Plant J.* 1993;4:745-750. DOI: 10.1046/j.1365-3113.1993.04040745.x

- [32] Pan Q, Xu Y, Li K, Peng Y, Zhan W, Li W, et al. The genetic basis of plant architecture in 10 maize recombinant inbred line populations. *Plant Physiol.* 2017;175:858-873. DOI: 10.1104/pp.17.00709
- [33] Yin X, Struik PC, Tang J, Qi C, Liu T. Model analysis of flowering phenology in recombinant inbred lines of barley. *J Exp Bot.* 2005;56:959-965. DOI: 10.1093/jxb/eri089
- [34] Ruden DM, Chen L, Possidente D, Possidente B, Rasouli P, Wang L, et al. Genetical toxicogenomics in *Drosophila* identifies master-modulatory loci that are regulated by developmental exposure to lead. *Neurotoxicology.* 2009;30:898-914. DOI: 10.1016/j.neuro.2009.08.011
- [35] Cochrane BJ, Windelspecht M, Brandon S, Morrow M, Dryden L. Use of recombinant inbred lines for the investigation of insecticide resistance and cross resistance in *Drosophila simulans*. *Pestic Biochem Physiol.* 1998;61:95-114. DOI: 10.1006/pest.1998.2355
- [36] Snoek BL, Volkers RJM, Nijveen H, Petersen C, Dirksen P, Sterken MG, et al. A multi-parent recombinant inbred line population of *C. elegans* allows identification of novel QTLs for complex life history traits. *BMC Biol.* 2019;17:24. DOI: 10.1186/s12915-019-0642-8
- [37] Printz MP, Jirout M, Jaworski R, Alemayehu A, Kren V. Genetic models in applied physiology. HXB/BXH rat recombinant inbred strain platform: a newly enhanced tool for cardiovascular, behavioral, and developmental genetics and genomics. *J Appl Physiol.* 2003;94:2510-2522. DOI: 10.1152/jappphysiol.00064.2003
- [38] Belknap JK. Effect of within-strain sample size on QTL detection and mapping using recombinant inbred mouse strains. *Behav Genet.* 1998;28:29-38. DOI: 10.1023/A:1021404714631
- [39] Johnson M. Laboratory Mice and Rats. *Mater Methods.* 2012;2. DOI: 10.13070/mm.en.2.113
- [40] Miller RA. Not your father's, or mother's, rodent: Moving beyond B6. *Neuron.* 2016;91:1185-1186. DOI: 10.1016/j.neuron.2016.09.009
- [41] Simon MM, Greenaway S, White JK, Fuchs H, Gailus-Durner V, Sorg T, et al. A comparative phenotypic and genomic analysis of C57BL/6J and C57BL/6N mouse strains. *Genome Biol.* 2013;14:R82. DOI: 10.1186/gb-2013-14-7-r82
- [42] Taylor BA, Heiniger HJ, Meier H. Genetic analysis of resistance to cadmium-induced testicular damage in mice. *Proc Soc Exp Biol Med.* 1973;143:629-633. DOI: 10.3181/00379727-143-37380
- [43] Morse HC, Chused TM, Hartley JW, Mathieson BJ, Sharrow SO, Taylor BA. Expression of xenotropic murine leukemia viruses as cell-surface gp70 in genetic crosses between strains DBA/2 and C57BL/6. *J Exp Med.* 1979;149:1183-1196. DOI: 10.1084/jem.149.5.1183
- [44] Taylor BA, Wnek C, Kotlus BS, Roemer N, MacTaggart T, Phillips SJ. Genotyping new BXD recombinant inbred mouse strains and comparison of BXD and consensus maps. *Mamm Genome.* 1999;10:335-348. DOI: 10.1007/s003359900998
- [45] Grizzle WE, Mountz JD, Yang P-A, Xu X, Sun S, Van Zant GE, et al. BXD recombinant inbred mice represent a novel T cell-mediated immune response tumor model. *Int J cancer.* 2002;101:270-279. DOI: 10.1002/ijc.10606

- [46] Lee GH, Bennett LM, Carabeo RA, Drinkwater NR. Identification of hepatocarcinogen-resistance genes in DBA/2 mice. *Genetics*. 1995;139:387-395. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7705639>
- [47] McGinnis JF, Lerious V, Pazik J, Elliott RW. Chromosomal assignment of the recoverin gene and cancer-associated retinopathy. *Mamm Genome*. 1993;4:43-45. DOI: 10.1007/BF00364662
- [48] Koutnikova H, Laakso M, Lu L, Combe R, Paananen J, Kuulasmaa T, et al. Identification of the UBP1 locus as a critical blood pressure determinant using a combination of mouse and human genetics. *PLoS Genet*. 2009;5:e1000591. DOI: 10.1371/journal.pgen.1000591
- [49] Seecharan DJ, Kulkarni AL, Lu L, Rosen GD, Williams RW. Genetic control of interconnected neuronal populations in the mouse primary visual system. *J Neurosci*. 2003;23:11178-11188. DOI: 10.1523/JNEUROSCI.23-35-11178.2003
- [50] Rosen GD, Pung CJ, Owens CB, Caplow J, Kim H, Mozhui K, et al. Genetic modulation of striatal volume by loci on Chrs 6 and 17 in BXD recombinant inbred mice. *Genes Brain Behav*. 2009;8:296-308. DOI: 10.1111/j.1601-183X.2009.00473.x
- [51] Belknap JK, Phillips TJ, O'Toole LA. Quantitative trait loci associated with brain weight in the BXD/Ty recombinant inbred mouse strains. *Brain Res Bull*. 1992;29:337-344. DOI: 10.1016/0361-9230(92)90065-6
- [52] Zhou G, Williams RW. Eye1 and Eye2: gene loci that modulate eye size, lens weight, and retinal area in the mouse. *Invest Ophthalmol Vis Sci*. 1999;40:817-825. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10102277>
- [53] Ashbrook DG, Roy S, Clifford BG, Riede T, Scattoni ML, Heck DH, et al. Born to cry: A genetic dissection of infant vocalization. *Front Behav Neurosci*. 2018;12:250. DOI: 10.3389/fnbeh.2018.00250
- [54] Knoll AT, Jiang K, Levitt P. Quantitative trait locus mapping and analysis of heritable variation in affiliative social behavior and co-occurring traits. *Genes Brain Behav*. 2018;17:e12431. DOI: 10.1111/gbb.12431
- [55] Belknap JK, Crabbe JC, Plomin R, McClearn GE, Sampson KE, O'Toole LA, et al. Single-locus control of saccharin intake in BXD/Ty recombinant inbred (RI) mice: Some methodological implications for RI strain analysis. *Behav Genet*. 1992;22:81-100. DOI: 10.1007/BF01066794
- [56] Belknap JK, Metten P, Helms ML, O'Toole LA, Angeli-Gade S, Crabbe JC, et al. Quantitative trait loci (QTL) applications to substances of abuse: physical dependence studies with nitrous oxide and ethanol in BXD mice. *Behav Genet*. 1993;23:213-222. DOI: 10.1007/BF01067426
- [57] Grisel JE, Belknap JK, O'Toole LA, Helms ML, Wenger CD, Crabbe JC. Quantitative trait loci affecting methamphetamine responses in BXD recombinant inbred mouse strains. *J Neurosci*. 1997;17:745-754. DOI: 10.1523/JNEUROSCI.17-02-00745.1997
- [58] Weimar WR, Lane PW, Sidman RL. Vibrator (vb): a spinocerebellar system degeneration with autosomal recessive inheritance in mice. *Brain Res*. 1982;251:357-364. DOI: 10.1016/0006-8993(82)90754-5
- [59] Phillips TJ, Belknap JK, Buck KJ, Cunningham CL. Genes on mouse chromosomes 2 and 9 determine variation in ethanol consumption.

Mamm Genome. 1998;9:936-941. DOI: 10.1007/s003359900903

[60] Palmer AA, Lessov-Schlaggar CN, Ponder CA, McKinnon CS, Phillips TJ. Sensitivity to the locomotor-stimulant effects of ethanol and allopregnanolone: a quantitative trait locus study of common genetic influence. *Genes Brain Behav.* 2006;5:506-517. DOI: 10.1111/j.1601-183X.2005.00198.x

[61] Jones LC, McCarthy KA, Beard JL, Keen CL, Jones BC. Quantitative genetic analysis of brain copper and zinc in BXD recombinant inbred mice. *Nutr Neurosci.* 2006;9:81-92. DOI: 10.1080/00268970600691365

[62] Rodriguez LA, Plomin R, Blizard DA, Jones BC, McClearn GE. Alcohol acceptance, preference, and sensitivity in mice. I. Quantitative genetic analysis using BXD recombinant inbred strains. *Alcohol Clin Exp Res.* 1994;18:1416-1422. DOI: 10.1111/j.1530-0277.1994.tb01444.x

[63] Darvasi A. Experimental strategies for the genetic dissection of complex traits in animal models. *Nat Genet.* 1998;18:19-24. DOI: 10.1038/ng0198-19

[64] Williams RW, Gu J, Qi S, Lu L. The genetic structure of recombinant inbred mice: high-resolution consensus maps for complex trait analysis. *Genome Biol.* 2001;2:RESEARCH0046. DOI: 10.1186/gb-2001-2-11-research0046

[65] Parker CC, Sokoloff G, Cheng R, Palmer AA. Genome-wide association for fear conditioning in an advanced intercross mouse line. *Behav Genet.* 2012;42:437-448. DOI: 10.1007/s10519-011-9524-8

[66] Parker CC, Cheng R, Sokoloff G, Palmer AA. Genome-wide association for methamphetamine sensitivity in an advanced intercross mouse line. *Genes Brain Behav.* 2012;11:52-61. DOI: 10.1111/j.1601-183X.2011.00747.x

[67] Pandey AK, Williams RW. Genetics of gene expression in CNS. *Int Rev Neurobiol.* 2014;116:195-231. DOI: 10.1016/B978-0-12-801105-8.00008-4

[68] Miyairi I, Tatireddigari VRR, Mahdi OS, Rose LA, Belland RJ, Lu L, et al. The p47 GTPases Iigp2 and Irgb10 regulate innate immunity and inflammation to murine Chlamydia psittaci infection. *J Immunol.* 2007;179:1814-24. DOI: 179/3/1814 [pii]

[69] Miyairi I, Ziebarth J, Laxton JD, Wang X, van Rooijen N, Williams RW, et al. Host genetics and Chlamydia disease: prediction and validation of disease severity mechanisms. *PLoS One.* 2012;7:e33781. DOI: 10.1371/journal.pone.0033781

[70] Mozhui K, Ciobanu DC, Schikorski T, Wang X, Lu L, Williams RW. Dissection of a QTL hotspot on mouse distal chromosome 1 that modulates neurobehavioral phenotypes and gene expression. *PLoS Genet.* 2008;4:e1000260. DOI: 10.1371/journal.pgen.1000260

[71] Boon ACM, Williams RW, Sinasac DS, Webby RJ. A novel genetic locus linked to pro-inflammatory cytokines after virulent H5N1 virus infection in mice. *BMC Genomics.* 2014;15:1017. DOI: 10.1186/1471-2164-15-1017

[72] Li Z, Mulligan MK, Wang X, Miles MF, Lu L, Williams RW. A transposon in Comt generates mRNA variants and causes widespread expression and behavioral differences among mice. Hoheisel J, editor. *PLoS One.* 2010;5:e12181. DOI: 10.1371/journal.pone.0012181

[73] Andreux PA, Williams EG, Koutnikova H, Houtkooper RH, Champy M-F, Henry H, et al. Systems genetics of metabolism: the use of the BXD murine reference panel for multiscalar integration of traits. *Cell.*

2012;150:1287-1299. DOI: 10.1016/j.cell.2012.08.012

[74] Houtkooper RH, Mouchiroud L, Ryu D, Moullan N, Katsyuba E, Knott G, et al. Mitonuclear protein imbalance as a conserved longevity mechanism. *Nature*. 2013;497:451-457. DOI: 10.1038/nature12188

[75] Wu Y, Williams EG, Dubuis S, Mottis A, Jovaisaite V, Houten SM, et al. Multilayered genetic and omics dissection of mitochondrial activity in a mouse reference population. *Cell*. 2014;158:1415-1430. DOI: 10.1016/j.cell.2014.07.039

[76] Neuner SM, Garfinkel BP, Wilmott LA, Ignatowska-Jankowska BM, Citri A, Orly J, et al. Systems genetics identifies Hp1bp3 as a novel modulator of cognitive aging. *Neurobiol Aging*. 2016;46:58-67. DOI: 10.1016/j.neurobiolaging.2016.06.008

[77] Williams EG, Mouchiroud L, Frochaux M, Pandey A, Andreux P a, Deplancke B, et al. An evolutionarily conserved role for the aryl hydrocarbon receptor in the regulation of movement. *PLoS Genet*. 2014;10:e1004673. DOI: 10.1371/journal.pgen.1004673

[78] Chintalapudi SR, Maria D, Di Wang X, Bailey JNC, NEIGHBORHOOD consortium, International Glaucoma Genetics consortium, et al. Systems genetics identifies a role for Cacna2d1 regulation in elevated intraocular pressure and glaucoma susceptibility. *Nat Commun*. 2017;8:1755. DOI: 10.1038/s41467-017-00837-5

[79] Mulligan MK, Abreo T, Neuner SM, Parks C, Watkins CE, Houseal MT, et al. Identification of a functional non-coding variant in the GABAA Receptor $\alpha 2$ subunit of the C57BL/6J mouse reference genome: Major implications for neuroscience research. *Front Genet*.

2019;10:188. DOI: 10.3389/fgene.2019.00188

[80] Chen D-S, Dai J-Q, Han S-C. Identification of the pheromone biosynthesis genes from the sex pheromone gland transcriptome of the diamondback moth, *Plutella xylostella*. *Sci Rep*. 2017;7:16255. DOI: 10.1038/s41598-017-16518-8

[81] Ibrahim MM, Maria DN, Mishra SR, Guragain D, Wang X, Jablonski MM. Once daily pregabalin eye drops for management of glaucoma. *ACS Nano*. 2019;13:13728-13744. DOI: 10.1021/acsnano.9b07214

[82] Ashbrook DG, Arends D, Prins P, Mulligan MK, Roy S, Williams EG, et al. The expanded BXD family of mice: A cohort for experimental systems genetics and precision medicine. *bioRxiv*. 2019;672097. DOI: 10.1101/672097

[83] Ashbrook DG, Mulligan MK, Williams RW. Post-genomic behavioral genetics: From revolution to routine. *Genes Brain Behav*. 2018;17:e12441. DOI: 10.1111/gbb.12441

[84] Mulligan MK, Dubose C, Yue J, Miles MF, Lu L, Hamre KM. Expression, covariation, and genetic regulation of miRNA Biogenesis genes in brain supports their role in addiction, psychiatric disorders, and disease. *Front Genet*. 2013;4:126. DOI: 10.3389/fgene.2013.00126

[85] Dickson PE, Miller MM, Calton MA, Bubier JA, Cook MN, Goldowitz D, et al. Systems genetics of intravenous cocaine self-administration in the BXD recombinant inbred mouse panel. *Psychopharmacology (Berl)*. 2016;233:701-714. DOI: 10.1007/s00213-015-4147-z

[86] Dickson PE, Roy TA, McNaughton KA, Wilcox TD, Kumar P, Chesler EJ. Systems genetics of

sensation seeking. *Genes Brain Behav.* 2019;18:e12519. DOI: 10.1111/gbb.12519

[87] Graybeal C, Bachu M, Mozhui K, Saksida LM, Bussey TJ, Sagalyn E, et al. Strains and stressors: an analysis of touchscreen learning in genetically diverse mouse strains. Zhuang X, editor. *PLoS One.* 2014;9:e87745. DOI: 10.1371/journal.pone.0087745

[88] Mulligan MK, Williams RW. Systems genetics of behavior: a prelude. *Curr Opin Behav Sci.* 2015;2:108-115. DOI: 10.1016/j.cobeha.2015.01.014

[89] Carhuatanta KAK, Shea CJA, Herman JP, Jankord R. Unique genetic loci identified for emotional behavior in control and chronic stress conditions. *Front Behav Neurosci.* 2014;8:341. DOI: 10.3389/fnbeh.2014.00341

[90] Philip VM, Duvvuru S, Gomero B, Ansah TA, Blaha CD, Cook MN, et al. High-throughput behavioral phenotyping in the expanded panel of BXD recombinant inbred strains. *Genes Brain Behav.* 2010;9:129-159. DOI: 10.1111/j.1601-183X.2009.00540.x

[91] Geisert EE, Williams RW. Using BXD mouse strains in vision research: A systems genetics approach. *Mol Vis.* 2020;26:173-187. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32180682>

[92] Hayes KS, Hager R, Grecis RK. Sex-dependent genetic effects on immune responses to a parasitic nematode. *BMC Genomics.* 2014;15:193. DOI: 10.1186/1471-2164-15-193

[93] McKnite AM, Perez-Munoz ME, Lu L, Williams EG, Brewer S, Andreux PA, et al. Murine gut microbiota is defined by host genetics and modulates variation of metabolic traits. White BA, editor. *PLoS One.* 2012;7:e39191. DOI: 10.1371/journal.pone.0039191

[94] Wang J, Yoon TW, Read R, Yi A-K, Williams RW, Fitzpatrick EA. Genetic variability of T cell responses in hypersensitivity pneumonitis identified using the BXD genetic reference panel. *Am J Physiol Lung Cell Mol Physiol.* 2020;318:L631-L643. DOI: 10.1152/ajplung.00120.2019

[95] Baker CL, Walker M, Arat S, Ananda G, Petkova P, Powers NR, et al. Tissue-specific trans regulation of the mouse epigenome. *Genetics.* 2019;211:831-845. DOI: 10.1534/genetics.118.301697

[96] Sandoval-Sierra JV, Helbing AHB, Williams EG, Ashbrook DG, Roy S, Williams RW, et al. Body weight and high-fat diet are associated with epigenetic aging in female members of the BXD murine family. *Aging Cell.* 2020;e13207. DOI: 10.1111/acel.13207

[97] Ashbrook DG, Sharmin N, Hager R. Offspring genes indirectly influence sibling and maternal behavioural strategies over resource share. *Proceedings Biol Sci.* 2017;284:20171059. DOI: 10.1098/rspb.2017.1059

[98] Ashbrook DG, Gini B, Hager R. Genetic variation in offspring indirectly influences the quality of maternal behaviour in mice. *Elife.* 2015;4:e11814. DOI: 10.7554/eLife.11814

[99] Baud A, Mulligan MK, Casale FP, Ingels JF, Bohl CJ, Callebort J, et al. Genetic variation in the social environment contributes to health and disease. Feldman MW, editor. *PLoS Genet.* 2017;13:e1006498. DOI: 10.1371/journal.pgen.1006498

[100] Hager R, Lu L, Rosen GD, Williams RW. Genetic architecture supports mosaic brain evolution and independent brain-body size regulation. *Nat Commun.* 2012;3:1079. DOI: 10.1038/ncomms2086

- [101] Oren Y, Nachshon A, Frishberg A, Wilentzik R, Gat-Viks I. Linking traits based on their shared molecular mechanisms. *Elife*. 2015;4. DOI: 10.7554/eLife.04346
- [102] Théberge ET, Baker JA, Dubose C, Boyle JK, Balce K, Goldowitz D, et al. Genetic influences on the amount of cell death in the neural tube of BXD mice exposed to acute ethanol at midgestation. *Alcohol Clin Exp Res*. 2019;43:439-452. DOI: 10.1111/acer.13947
- [103] Zhou D, Zhao Y, Hook M, Zhao W, Starlard-Davenport A, Cook MN, et al. Ethanol's effect on Coq7 expression in the hippocampus of mice. *Front Genet*. 2018;9:602. DOI: 10.3389/fgene.2018.00602
- [104] Mulligan MK, Zhao W, Dickerson M, Arends D, Prins P, Cavigelli SA, et al. Genetic contribution to initial and progressive alcohol intake among recombinant inbred strains of mice. *Front Genet*. 2018;9:370. DOI: 10.3389/fgene.2018.00370
- [105] Wang LS, Jiao Y, Huang Y, Liu XY, Gibson G, Bennett B, et al. Critical evaluation of transcription factor Atf2 as a candidate modulator of alcohol preference in mouse and human populations. *Genet Mol Res*. 2013;12:5992-6005. DOI: 10.4238/2013.November.26.9
- [106] Chella Krishnan K, Mukundan S, Alagarsamy J, Hur J, Nookala S, Siemens N, et al. Genetic architecture of group a streptococcal necrotizing soft tissue infections in the mouse. Bessen DE, editor. *PLoS Pathog*. 2016;12:e1005732. DOI: 10.1371/journal.ppat.1005732
- [107] Russo LM, Abdeltawab NF, O'Brien AD, Kotb M, Melton-Celsa AR. Mapping of genetic loci that modulate differential colonization by *Escherichia coli* O157:H7 TUV86-2 in advanced recombinant inbred BXD mice. *BMC Genomics*. 2015;16:947. DOI: 10.1186/s12864-015-2127-7
- [108] Nedelko T, Kollmus H, Klawonn F, Spijker S, Lu L, Heßman M, et al. Distinct gene loci control the host response to influenza H1N1 virus infection in a time-dependent manner. *BMC Genomics*. 2012;13:411. DOI: 10.1186/1471-2164-13-411
- [109] Boon ACM, DeBeauchamp J, Hollmann A, Luke J, Kotb M, Rowe S, et al. Host genetic variation affects resistance to infection with a highly pathogenic H5N1 influenza A virus in mice. *J Virol*. 2009;83:10417-10426. DOI: 10.1128/JVI.00514-09
- [110] Rodrigues B de A, Muñoz VR, Kuga GK, Gaspar RC, Nakandakari SCBR, Crisol BM, et al. Obesity increases mitogen-activated protein kinase phosphatase-3 levels in the hypothalamus of mice. *Front Cell Neurosci*. 2017;11:313. DOI: 10.3389/fncel.2017.00313
- [111] Jha P, McDevitt MT, Gupta R, Quiros PM, Williams EG, Gariani K, et al. Systems analyses reveal physiological roles and genetic regulators of liver lipid species. *Cell Syst*. 2018;6:722-733.e6. DOI: 10.1016/j.cels.2018.05.016
- [112] Jha P, McDevitt MT, Halilbasic E, Williams EG, Quiros PM, Gariani K, et al. Genetic regulation of plasma lipid species and their association with metabolic phenotypes. *Cell Syst*. 2018;6:709-721.e6. DOI: 10.1016/j.cels.2018.05.009
- [113] Jones BC, Jellen LC. Systems genetics analysis of iron and its regulation in brain and periphery. *Methods Mol Biol*. 2017;1488:467-480. DOI: 10.1007/978-1-4939-6427-7_22
- [114] Reyes Fernandez PC, Replogle RA, Wang L, Zhang M, Fleet JC. Novel genetic loci control calcium absorption

and femur bone mass as well as their response to low calcium intake in male BXD recombinant inbred mice. *J Bone Miner Res.* 2016;31:994-1002. DOI: 10.1002/jbmr.2760

[115] Fleet JC, Replogle RA, Reyes-Fernandez P, Wang L, Zhang M, Clinkenbeard EL, et al. Gene-by-Diet interactions affect serum 1,25-Dihydroxyvitamin D levels in male BXD recombinant inbred mice. *Endocrinology.* 2016;157:470-481. DOI: 10.1210/en.2015-1786

[116] Diessler S, Jan M, Emmenegger Y, Guex N, Middleton B, Skene DJ, et al. A systems genetics resource and analysis of sleep regulation in the mouse. Kramer A, editor. *PLoS Biol.* 2018;16:e2005750. DOI: 10.1371/journal.pbio.2005750

[117] Jung SH, Brownlow ML, Pellegrini M, Jankord R. Divergence in Morris Water Maze-based cognitive performance under chronic stress Is associated with the hippocampal whole transcriptomic modification in mice. *Front Mol Neurosci.* 2017;10:275. DOI: 10.3389/fnmol.2017.00275

[118] Williams EG, Wu Y, Jha P, Dubuis S, Blattmann P, Argmann CA, et al. Systems proteomics of liver mitochondria function. *Science.* 2016;352:aad0189. DOI: 10.1126/science.aad0189

[119] Roy S, Sleiman MB, Jha P, Williams EG, Ingels JF, Chapman CJ, et al. Gene-by-environmental modulation of longevity and weight gain in the murine BXD family. *bioRxiv.* 2020;776559. DOI: 10.1101/776559

[120] Williams EG, Roy S, Statzer C, Ingels J, Bohl C, Hasan M, et al. The molecular landscape of the aging mouse liver. *bioRxiv Syst Biol.* 2020;2020.08.20.222968. DOI: 10.1101/2020.08.20.222968

[121] Wang L, Jiao Y, Wang Y, Zhang M, Gu W. Self-confirmation and ascertainment of the candidate genomic regions of complex trait loci - A none-experimental solution. Kulwal PL, editor. *PLoS One.* 2016;11:e0153676. DOI: 10.1371/journal.pone.0153676

[122] Keane TM, Goodstadt L, Danecek P, White MA, Wong K, Yalcin B, et al. Mouse genomic variation and its effect on phenotypes and gene regulation. *Nature.* 2011;477:289-294. DOI: 10.1038/nature10413

[123] Wang X, Pandey AK, Mulligan MK, Williams EG, Mozhui K, Li Z, et al. Joint mouse-human phenome-wide association to test gene function and disease risk. *Nat Commun.* 2016;7:10464. DOI: 10.1038/ncomms10464

[124] King R, Lu L, Williams RW, Geisert EE. Transcriptome networks in the mouse retina: An exon level BXD RI database. *Mol Vis.* 2015;21:1235-1251. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26604663>

[125] Li H, Wang X, Rukina D, Huang Q, Lin T, Sorrentino V, et al. An integrated systems genetics and omics toolkit to probe gene function. *Cell Syst.* 2018;6:90-102.e4. DOI: 10.1016/j.cels.2017.10.016

[126] Parsons MJ, Grimm C, Paya-Cano JL, Fernandes C, Liu L, Philip VM, et al. Genetic variation in hippocampal microRNA expression differences in C57BL/6 J X DBA/2 J (BXD) recombinant inbred mouse strains. *BMC Genomics.* 2012;13:476. DOI: 10.1186/1471-2164-13-476

[127] Williams EG, Wu Y, Wolski W, Kim JY, Lan J, Hasan M, et al. Quantifying and localizing the mitochondrial proteome across five tissues in a mouse population. *Mol Cell Proteomics.* 2018;17:1766-1777. DOI: 10.1074/mcp.RA118.000554

- [128] Sandoval-Sierra JV, Helbing AHB, Williams EG, Ashbrook DG, Roy S, Williams RW, et al. Influence of body weight at young adulthood on the epigenetic clock and lifespan in the BXD murine family. *bioRxiv*. 2019;791582. DOI: 10.1101/791582
- [129] Perez-Munoz ME, McKnite AM, Williams EG, Auwerx J, Williams RW, Peterson DA, et al. Diet modulates cecum bacterial diversity and physiological phenotypes across the BXD mouse genetic reference population. Wilson BA, editor. *PLoS One*. 2019;14:e0224100. DOI: 10.1371/journal.pone.0224100
- [130] Williams RW, Williams EG. Resources for systems genetics. In: Schughart K, Williams RW, editors. *Syst Genet Methods Protoc*. New York, NY: Springer New York; 2017. p. 3-29. DOI: 10.1007/978-1-4939-6427-7_1
- [131] Sloan Z, Arends D, W. Broman K, Centeno A, Furlotte N, Nijveen H, et al. GeneNetwork: framework for web-based genetics. *J Open Source Softw*. 2016;1:25. DOI: 10.21105/joss.00025
- [132] Williams EG, Auwerx J. The convergence of systems and reductionist approaches in complex trait analysis. *Cell*. 2015;162:23-32. DOI: 10.1016/j.cell.2015.06.024
- [133] Chesler EJ, Wang J, Lu L, Qu Y, Manly KF, Williams RW. Genetic correlates of gene expression in recombinant inbred strains: a relational model system to explore neuro behavioral phenotypes. *Neuroinformatics*. 2003;1:343-357. DOI: 10.1385/NI:1:4:343
- [134] Parker CC, Dickson PE, Philip VM, Thomas M, Chesler EJ. *Systems genetic analysis in GeneNetwork.org*. Curr Protoc Neurosci. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2017;79:8.39.1-8.39.20. DOI: 10.1002/cpns.23
- [135] Mulligan MK, Mozhui K, Prins P, Williams RW. *GeneNetwork: A Toolbox for Systems Genetics*. K. S, R. W, editors. *Methods Mol Biol*. New York, NY: Humana Press; 2017;1488:75-120. DOI: 10.1007/978-1-4939-6427-7_4
- [136] Watson PM, Ashbrook DG. GeneNetwork: a continuously updated tool for systems genetics analyses. *bioRxiv*. 2020;2020.12.23.424047. DOI: 10.1101/2020.12.23.424047
- [137] Ashbrook DG, Delprato A, Grellmann C, Klein M, Wetzel R, Overall RW, et al. Transcript co-variance with Nestin in two mouse genetic reference populations identifies Lef1 as a novel candidate regulator of neural precursor cell proliferation in the adult hippocampus. *Front Neurosci*. Frontiers Research Foundation; 2014;8:418. DOI: 10.3389/fnins.2014.00418
- [138] Hood L, Flores M. A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. *N Biotechnol*. 2012;29:613-624. DOI: 10.1016/j.nbt.2012.03.004
- [139] Yang RJ, Mozhui K, Karlsson R-M, Cameron HA, Williams RW, Holmes A. Variation in mouse basolateral amygdala volume is associated with differences in stress reactivity and fear learning. *Neuropsychopharmacology*. 2008;33:2595-2604. DOI: 10.1038/sj.npp.1301665
- [140] Griffing B. Concept of general and specific combining ability in relation to diallel crossing systems. *Aust J Biol Sci*. 1956;9:463. DOI: 10.1071/BI9560463
- [141] Kempthorne O. The theory of the diallel cross. *Genetics*. 1956;41:451-459. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17247640>

- [142] Hayman BI. The theory and analysis of diallel crosses. *Genetics*. 1954;39:789-809. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17247520>
- [143] Lenarcic AB, Svenson KL, Churchill GA, Valdar W. A general Bayesian approach to analyzing diallel crosses of inbred strains. *Genetics*. 2012;190:413-435. DOI: 10.1534/genetics.111.132563
- [144] Percival CJ, Liberton DK, Pardo-Manuel de Villena F, Spritz R, Marcucio R, Hallgrímsson B. Genetics of murine craniofacial morphology: diallel analysis of the eight founders of the Collaborative Cross. *J Anat*. 2015; DOI: 10.1111/joa.12382
- [145] Crowley JJ, Kim Y, Lenarcic AB, Quackenbush CR, Barrick CJ, Adkins DE, et al. Genetics of adverse reactions to haloperidol in a mouse diallel: a drug-placebo experiment and Bayesian causal analysis. *Genetics*. 2014;196:321-347. DOI: 10.1534/genetics.113.156901
- [146] Airey DC, Lu L, Shou S, Williams RW. Genetic sources of individual differences in the cerebellum. *Cerebellum*. 2002;1:233-240. DOI: 10.1080/147342202320883542
- [147] Maurizio PL, Ferris MT, Keele GR, Miller DR, Shaw GD, Whitmore AC, et al. Bayesian diallel analysis reveals Mx1-dependent and Mx1-independent effects on response to influenza A virus in mice. *G3 (Bethesda)*. 2018;8:427-445. DOI: 10.1534/g3.117.300438
- [148] Williams RW, Threadgill DW, Airey DC, Gu J, Lu L. RIX Mapping: a demonstration using CXB RIX hybrids to map QTLs modulating brain weight in mice. *Soc Neurosci Abst*. 2001;27.
- [149] Green EL. Quantitative genetics of skeletal variations in the mouse. II. Crosses between four inbred strains (C3H, DBA, C57BL, BALB/c). *Genetics*. 1962;47:1085-1096. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/13950066>
- [150] Shorter JR, Maurizio PL, Bell TA, Shaw GD, Miller DR, Gooch TJ, et al. A diallel of the mouse Collaborative Cross founders reveals strong strain-specific maternal effects on litter size. *G3 (Bethesda)*. 2019;9:1613-1622. DOI: 10.1534/g3.118.200847
- [151] Ashbrook DG, Hager R. Empirical testing of hypotheses about the evolution of genomic imprinting in mammals. *Front Neuroanat*. 2013;7:6. DOI: 10.3389/fnana.2013.00006
- [152] Acevedo-Arozena A, Kalmar B, Essa S, Ricketts T, Joyce P, Kent R, et al. A comprehensive assessment of the SOD1G93A low-copy transgenic mouse, which models human amyotrophic lateral sclerosis. *Dis Model Mech*. 2011;4:686-700. DOI: 10.1242/dmm.007237
- [153] Heiman-Patterson TD, Sher RB, Blankenhorn EA, Alexander G, Deitch JS, Kunst CB, et al. Effect of genetic background on phenotype variability in transgenic mouse models of amyotrophic lateral sclerosis: a window of opportunity in the search for genetic modifiers. *Amyotroph Lateral Scler*. 2011;12:79-86. DOI: 10.3109/17482968.2010.550626
- [154] O'Connell KMS, Ouellette AR, Neuner SM, Dunn AR, Kaczorowski CC. Genetic background modifies CNS-mediated sensorimotor decline in the AD-BXD mouse model of genetic diversity in Alzheimer's disease. *Genes Brain Behav*. 2019;18:e12603. DOI: 10.1111/gbb.12603
- [155] Cowin R-M, Bui N, Graham D, Green JR, Yuva-Paylor LA, Weiss A, et al. Genetic background modulates behavioral impairments in R6/2 mice and suggests a role for dominant genetic

modifiers in Huntington's disease pathogenesis. *Mamm Genome*. 2012;23:367-377. DOI: 10.1007/s00335-012-9391-5

[156] Fetterman JL, Zelickson BR, Johnson LW, Moellering DR, Westbrook DG, Pompilius M, et al. Mitochondrial genetic background modulates bioenergetics and susceptibility to acute cardiac volume overload. *Biochem J*. 2013;455:157-167. DOI: 10.1042/BJ20130029

[157] Sisay S, Pryce G, Jackson SJ, Tanner C, Ross RA, Michael GJ, et al. Genetic background can result in a marked or minimal effect of gene knockout (GPR55 and CB2 receptor) in experimental autoimmune encephalomyelitis models of multiple sclerosis. Furlan R, editor. *PLoS One*. 2013;8:e76907. DOI: 10.1371/journal.pone.0076907

[158] Sittig LJ, Carbonetto P, Engel KA, Krauss KS, Barrios-Camacho CM, Palmer AA. Genetic background limits generalizability of genotype-phenotype relationships. *Neuron*. 2016;91:1253-1259. DOI: 10.1016/j.neuron.2016.08.013

[159] Buchner DA, Trudeau M, Meisler MH. SCNM1, a putative RNA splicing factor that modifies disease severity in mice. *Science*. 2003;301:967-969. DOI: 10.1126/science.1086187

[160] Nair RR, Corrochano S, Gasco S, Tibbit C, Thompson D, Maduro C, et al. Uses for humanised mouse models in precision medicine for neurodegenerative disease. *Mamm Genome*. 2019;30:173-191. DOI: 10.1007/s00335-019-09807-2

[161] Hahn H, Nitzki F, Schorban T, Hemmerlein B, Threadgill D, Rosemann M. Genetic mapping of a Ptch1-associated rhabdomyosarcoma susceptibility locus on mouse chromosome 2. *Genomics*. 2004;84:853-858. DOI: 10.1016/j.ygeno.2004.07.002

[162] Doetschman T. Influence of genetic background on genetically engineered mouse phenotypes. *Methods Mol Biol*. 2009;530:423-433. DOI: 10.1007/978-1-59745-471-1_23

[163] Phillips TJ, Hen R, Crabbe JC. Complications associated with genetic background effects in research using knockout mice. *Psychopharmacology (Berl)*. 1999;147:5-7. DOI: 10.1007/s002130051128

[164] Threadgill DW, Dlugosz AA, Hansen LA, Tennenbaum T, Lichti U, Yee D, et al. Targeted disruption of mouse EGF receptor: effect of genetic background on mutant phenotype. *Science*. 1995;269:230-234. DOI: 10.1126/science.7618084

[165] Sanford LP, Kallapur S, Ormsby I, Doetschman T. Influence of genetic background on knockout mouse phenotypes. *Methods Mol Biol. New Jersey: Humana Press*; 2001;158:217-225. DOI: 10.1385/1-59259-220-1:217

[166] Cacheiro P, Haendel MA, Smedley D, International Mouse Phenotyping Consortium and the Monarch Initiative. New models for human disease from the International Mouse Phenotyping Consortium. *Mamm Genome*. 2019;30:143-150. DOI: 10.1007/s00335-019-09804-5

[167] Lloyd KCK, Adams DJ, Baynam G, Beaudet AL, Bosch F, Boycott KM, et al. The Deep Genome Project. *Genome Biol*. 2020;21:18. DOI: 10.1186/s13059-020-1931-9

[168] Lifsted T, Le Voyer T, Williams M, Muller W, Klein-Szanto A, Buetow KH, et al. Identification of inbred mouse strains harboring genetic modifiers of mammary tumor age of onset and metastatic progression. *Int J cancer*. 1998;77:640-644. DOI: 10.1002/(sici)1097-0215(19980812)77:4<640::aid-ijc26>3.0.co;2-8

- [169] Dorman A, Baer D, Tomlinson I, Mott R, Iraqi FA. Genetic analysis of intestinal polyp development in Collaborative Cross mice carrying the *Apc* (Min/+) mutation. *BMC Genet.* 2016;17:46. DOI: 10.1186/s12863-016-0349-6
- [170] Nnadi SC, Watson R, Innocent J, Gonye GE, Buchberg AM, Siracusa LD. Identification of five novel modifier loci of *Apc*(Min) harbored in the BXH14 recombinant inbred strain. *Carcinogenesis.* 2012;33:1589-1597. DOI: 10.1093/carcin/bgs185
- [171] Bennett BJ, Davis RC, Civelek M, Orozco L, Wu J, Qi H, et al. Genetic architecture of atherosclerosis in mice: A systems genetics analysis of common inbred strains. Barsh GS, editor. *PLoS Genet.* 2015;11:e1005711. DOI: 10.1371/journal.pgen.1005711
- [172] Crawford NPS, Hunter KW. Germline variation and other host determinants of metastatic potential. In: Lyden D, Welch DR, Psaila B, editors. *Cancer Metastasis.* Cambridge: Cambridge University Press; 2011. p. 96-104. DOI: 10.1017/CBO9780511976117.011
- [173] Yang H, Crawford N, Lukes L, Finney R, Lancaster M, Hunter KW. Metastasis predictive signature profiles pre-exist in normal tissues. *Clin Exp Metastasis.* 2005;22:593-603. DOI: 10.1007/s10585-005-6244-6
- [174] Hunter KW, Broman KW, Voyer TL, Lukes L, Cozma D, Debies MT, et al. Predisposition to efficient mammary tumor metastatic progression is linked to the breast cancer metastasis suppressor gene *Brms1*. *Cancer Res.* 2001;61:8866-8872. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11751410>
- [175] Neuner SM, Heuer SE, Huentelman MJ, O'Connell KMS, Kaczorowski CC. Harnessing genetic complexity to enhance translatability of Alzheimer's disease mouse models: A path toward precision medicine. *Neuron.* 2019;101:399-411.e5. DOI: 10.1016/j.neuron.2018.11.040
- [176] Neuner SM, Heuer SE, Zhang J-G, Philip VM, Kaczorowski CC. Identification of pre-symptomatic gene signatures that predict resilience to cognitive decline in the genetically diverse AD-BXD model. *Front Genet.* 2019;10:35. DOI: 10.3389/fgene.2019.00035
- [177] Neuner SM, Wilmott LA, Hope KA, Hoffmann B, Chong JA, Abramowitz J, et al. TRPC3 channels critically regulate hippocampal excitability and contextual fear memory. *Behav Brain Res.* 2015;281:69-77. DOI: 10.1016/j.bbr.2014.12.018
- [178] Neuner SM, Wilmott LA, Hoffmann BR, Mozhui K, Kaczorowski CC. Hippocampal proteomics defines pathways associated with memory decline and resilience in normal aging and Alzheimer's disease mouse models. *Behav Brain Res.* 2017;322:288-298. DOI: 10.1016/j.bbr.2016.06.002
- [179] Hyman B, Tanzi RE. Effects of species-specific genetics on Alzheimer's mouse models. *Neuron.* 2019;101:351-352. DOI: 10.1016/j.neuron.2019.01.021
- [180] Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, et al. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. *J Neurosci.* 2006;26:10129-10140. DOI: 10.1523/JNEUROSCI.1202-06.2006
- [181] Abu-Toamih Atamni HJ, Iraqi FA. Efficient protocols and methods for high-throughput utilization of the Collaborative Cross mouse model for dissecting the genetic basis of complex

- traits. *Anim Model Exp Med*. 2019;2:137-149. DOI: 10.1002/ame2.12074
- [182] Smemo S, Tena JJ, Kim K-H, Gamazon ER, Sakabe NJ, Gómez-Marín C, et al. Obesity-associated variants within FTO form long-range functional connections with IRX3. *Nature*. 2014;507:371-375. DOI: 10.1038/nature13138
- [183] Dalton TP, He L, Wang B, Miller ML, Jin L, Stringer KF, et al. Identification of mouse SLC39A8 as the transporter responsible for cadmium-induced toxicity in the testis. *Proc Natl Acad Sci U S A*. 2005;102:3401-3406. DOI: 10.1073/pnas.0406085102
- [184] Stoll M, Kwitek-Black AE, Cowley AW, Harris EL, Harrap SB, Krieger JE, et al. New target regions for human hypertension via comparative genomics. *Genome Res*. 2000;10:473-482. DOI: 10.1101/gr.10.4.473
- [185] Ashbrook DG, Williams RW, Lu L, Stein JL, Hibar DP, Nichols TE, et al. Joint genetic analysis of hippocampal size in mouse and human identifies a novel gene linked to neurodegenerative disease. *BMC Genomics*. 2014;15:850. DOI: 10.1186/1471-2164-15-850
- [186] Ashbrook DG, Williams RW, Lu L, Hager R. A cross-species genetic analysis identifies candidate genes for mouse anxiety and human bipolar disorder. *Front Behav Neurosci*. 2015;9:171. DOI: 10.3389/fnbeh.2015.00171
- [187] Ashbrook DG, Cahill S, Hager R. A cross-species systems genetics analysis links APBB1IP as a candidate for schizophrenia and prepulse inhibition. *Front Behav Neurosci*. 2019;13:266. DOI: 10.3389/fnbeh.2019.00266
- [188] Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker H V, Xu W, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci U S A*. 2013;110:3507-3512. DOI: 10.1073/pnas.1222878110
- [189] Pound P, Bracken MB. Is animal research sufficiently evidence based to be a cornerstone of biomedical research? *BMJ*. 2014;348:g3387. DOI: 10.1136/bmj.g3387
- [190] Conejero L, Potempa K, Graham CM, Spink N, Blankley S, Salguero FJ, et al. The blood transcriptome of experimental melioidosis reflects disease severity and shows considerable similarity with the human disease. *J Immunol*. 2015;195:3248-3261. DOI: 10.4049/jimmunol.1500641
- [191] Takao K, Miyakawa T. Genomic responses in mouse models greatly mimic human inflammatory diseases. *Proc Natl Acad Sci U S A*. 2015;112:1167-1172. DOI: 10.1073/pnas.1401965111
- [192] Nadeau JH, Auwerx J. The virtuous cycle of human genetics and mouse models in drug discovery. *Nat Rev Drug Discov*. 2019;18:255-272. DOI: 10.1038/s41573-018-0009-9
- [193] Festing MFW, Fisher EMC. Mighty mice. *Nature*. 2000;404:815. DOI: 10.1038/35009167
- [194] Bryant CD, Smith DJ, Kantak KM, Nowak TS, Williams RW, Damaj MI, et al. Facilitating complex trait analysis via reduced complexity crosses. *Trends Genet*. 2020;36:549-562. DOI: 10.1016/j.tig.2020.05.003
- [195] Bryant CD, Ferris MT, De Villena FPM, Damaj MI, Kumar V, Mulligan MK. Reduced complexity cross design for behavioral genetics. In: Gerlai RT, editor. *Mol Stat Tech Behav Neural Res*. Elsevier; 2018. p. 165-190. DOI: 10.1016/B978-0-12-804078-2.00008-8