GENETIC ANALYSIS OF Bphse: A NOVEL GENE COMPLEMENTING RESISTANCE TO Bordetella pertussis-INDUCED HISTAMINE SENSITIZATION

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**Abbreviations:** *B. pertussis*, *Bordetella pertussis*; *Bphs/Bphs*, *Bordetella pertussis* induced histamine sensitization; *Bphse*, enhancer of *Bordetella pertussis* induced histamine sensitization; *Bpss*, *Bordetella pertussis* induced serotonin sensitization; *Bpbs*, *Bordetella pertussis* induced bradykinin sensitization; HA, histamine; Histh/Histh, non-*Bordetella pertussis* induced histamine hypersensitivity; *Hrh1/HRH1*, histamine receptor H1; PTX, pertussis toxin; T1H, type 1 hypersensitivity; VP, vascular permeability; LD, linkage disequilibrium; GPCR, G-protein coupled receptor; ER, endoplasmic reticulum; EMC, endoplasmic membrane protein complex; ERAD, endoplasmic reticulum-associated degradation; MGP, mouse genomes project; MPD mouse phenome database.
ABSTRACT

Histamine is a bioactive amine associated with a plethora of normal and pathophysiological processes, with the latter being dependent on both genetic and environmental factors including infectious agents. Previously, we showed in mice that susceptibility to *Bordetella pertussis* and pertussis toxin (PTX) induced histamine sensitization (Bphs) is controlled by histamine receptor H₁ (*Hrh1/HRH1*) alleles. Bphs susceptible and resistant alleles (*Bphss*/*Bphsr*) encode for two-conserved protein haplotypes. Given the importance of HRH1 signaling in health and disease, we sequenced *Hrh1* across an extended panel of laboratory and wild-derived inbred strains and phenotyped them for Bphs. Unexpectedly, eight strains homozygous for the *Bphsr* allele phenotyped as Bphs, suggesting the existence of a modifying locus segregating among the strains capable of complementing Bphs’. Genetic analyses mapped this modifier locus to mouse chromosome 6; designated *Bphs*-enhancer (*Bphse*), within a functional linkage disequilibrium domain encoding multiple loci controlling responsiveness to histamine (*Bphs/Hrh1* and *Histh1-4*). Interval-specific single-nucleotide polymorphism (SNP) based association testing across 50 laboratory and wild-derived inbred mouse strains and functional prioritization analyses resulted in the identification of candidate genes for *Bphse* within a ∼5.5 Mb interval (Chr6:111.0-116.4 Mb), including *Atg7, Plxnd1, Tmcc1, Mkml, Il17re, Pparg, Lhfpl4, Vglir4, Rho* and *Syn2*. Taken together, these results demonstrate the power of combining network-based computational methods with the evolutionarily significant diversity of wild-derived inbred mice to identify novel genetic mechanisms controlling susceptibility and resistance to histamine shock.
INTRODUCTION

Histamine (2-[4-imidazole]-ethylamine; HA) is an endogenous biogenic monoamine that is synthesized, stored intracellularly within granules; following cellular activation HA is released by mast cells, basophils, platelets, neurons, and enterochromaffin-like cells in the stomach [1]. After release, free HA mediates its pleiotropic effects by binding to four different seven-transmembrane G-protein-coupled receptors (GPCRs): histamine receptor H₁-H₄ (HRH1, HRH2, HRH3, and HRH4), differentially expressed on target cells in various tissues [2]. HA acting through these receptors influences a diverse array of physiological processes, including brain function, neurotransmission, secretion of pituitary hormones, cell proliferation and differentiation, hematopoiesis, embryonic development, wound healing and regeneration, and the regulation of gastrointestinal, cardiovascular, and secretory functions [2]. In addition, HA plays a major role in inflammation and the regulation of innate and adaptive immune responses in both normal and pathologic states [3, 4].

Historically, HA is most well-known for its role in shock and anaphylaxis [5]. It was first isolated from the parasitic mold ergot of rye (Claviceps purpurea) and then synthesized by the decarboxylation of histidine [6-8]. HA was shown to elicit anaphylactic shock-like symptoms when injected into mammals, including bronchiolar constriction, constricted cardiac and pulmonary arteries, and stimulated cardiac contraction [9-11]. Further research firmly established HA as a natural constituent of the body and a mediator of anaphylactic shock [5]. There is significant variability in susceptibility to HA-shock among animal species, with guinea pigs and rabbits being highly susceptible, versus mice and rats which are generally remarkably tolerant to in vivo injections of HA [12].
Interestingly, prior exposure to *Bordetella pertussis* (*B. pertussis*) or purified pertussis toxin (PTX) overcomes HA resistance among a subset of laboratory derived inbred strains of mice [13]. This phenotype is designated Bphs for *B. pertussis*-induced HA sensitization [14, 15]. Bphs-susceptible (Bphs*) strains die within 30 minutes following HA injection; which is thought to result from hypotensive and hypovolemic shock while Bphs-resistant (Bphs’) strains remain healthy [16]. The sensitizing activity elicited by exposure to *B. pertussis* is a function of PTX-catalyzed adenosine diphosphate-ribosylation of the alpha subunit of heterotrimeric guanine nucleotide-binding protein (Gαi/o), specifically Gαi1/3 [17, 18]. In addition to HA sensitization, PTX-treated mice exhibit increased systemic vascular permeability and sensitization to serotonin (Bpss) and bradykinin (Bpbs) [17, 19].

Our previous genetic studies mapped the autosomal dominant Bphs locus controlling susceptibility to mouse chromosome 6 (Chr6) and identified it as histamine receptor H1 (*Hrh1/HRH1*) [15, 20]. Susceptibility segregates with two conserved *Hrh1/HRH1* haplotypes, mice with the *Hrh1s/HRH1s* allele (encoding Pro263, Val312, Pro330) phenotype as Bphs* while mice with the *Hrh1r/HRH1r* allele (encoding Leu263, Met312, Ser330) are Bphs’. These amino acid changes occur within the third intracellular loop of this G protein-coupled receptor (GPCR): a domain implicated in signal transduction, protein folding, and trafficking. Functionally, HRH1* and HRH1r alleles equally activate Gαq/11, the G protein family members that couple HRH1 signaling to second messenger signaling pathways, indicating that the genetic control of susceptibility and resistance to Bphs is not inherently due to differential activation of either Gαq or Gα11 [21]. However, the two alleles exhibit differential cell surface expression and altered intracellular trafficking, with the HRH1r allele selectively retained within the endoplasmic reticulum.
(ER). Importantly, all three amino acid residues (Leu\textsuperscript{263}, Met\textsuperscript{312}, Ser\textsuperscript{330}) comprising the HRH1\textsuperscript{r} haplotype are required for altered expression \cite{21}.

In this study, we carried out an expanded phenotype screen for Bphs susceptibility and resistance that included previously unstudied wild-derived inbred strains of mice, and identified eight Bphs\textsuperscript{S} strains, despite carrying the Bphs\textsuperscript{R} Hrh1\textsuperscript{r}/HRH1\textsuperscript{r} allele. Genetic analyses identified a dominant modifying locus linked to Bphs/Hrh1 capable of complementing Hrh1\textsuperscript{r}/HRH1\textsuperscript{r} to create a Bphs\textsuperscript{S} phenotype. We have designated this locus Bphse for Bphs-enhancer. Interval-specific single nucleotide polymorphism (SNP) based association testing and functional enrichment is used to identify candidate genes for Bphse.
RESULTS

_Hrh1/HRH1 alleles are highly conserved in mice._ We undertook a genetic approach to screen for evolutionarily selected mechanisms that may be capable of modifying the Bphs’ phenotype. Toward this end, we sequenced ~500 bp stretch of genomic DNA encompassing the third intracellular loop of _Hrh1/HRH1_ across 91 laboratory and wild-derived inbred strains of mice (Table 1). Surprisingly, other than the three amino acid changes (Pro^{263}, Val^{312}, Pro^{330} → Leu^{263}, Met^{312}, Ser^{330}) described earlier as “susceptible” (Hrh1^{s}/HRH1^{s}) and “resistant” (Hrh1^{r}/HRH1^{r}) haplotypes [15], we did not identify any additional non-synonymous amino acid changes. Of the 91 strains, 22 carry the _Hrh1^{r}/HRH1^{r}_, whereas 69 carry the _Hrh1^{s}/HRH1^{s}_ allele (Table 1). We next mapped the evolutionary distribution of the two alleles onto a mouse phylogenetic tree (Supplementary Figure 1) [22]. The _Hrh1^{r}/HRH1^{r}_ allele was primarily restricted to wild-derived group 7 strains and a select sub-branch of group 1 Bagg albino derivatives, whereas the _Hrh1^{s}/HRH1^{s}_ allele was distributed across groups 2-6, which encompasses Swiss mice, Japanese and New Zealand inbred strains, C57/58 strains, Castle mice, C.C. Little DBA and related strains.

Compared to classical inbred strains, wild-derived mice exhibit sequence variation at approximately every 100-200 base pairs and are, in general, more resistant to a variety of pathogens [23-27]. Group 7 strains exemplify this genetic diversity in that it includes representatives of _Mus musculus (M. m) domesticus_ (PERA, PERC, WSB, ZALENDE and TIRANO), _M. m. musculus_ (PWK, PWD, CZECHI, and CZECHIII), _M. m. castaneus_ (CAST), _M. m. molossinus_ (JF1, MSM, MOLF, MOLD, MOLC), _M. m. hortulanus_ (PANCEVO), _M. m. spretus_ (SPRET), _M. m. praetextus_ (IS), or hybrids of _M. m. musculus_
and *M. m. domesticus* (SKIVE), *M. m. musculus* and *M. m. poschiavinus* (RBF) and of *M. m. castaneus* and *M. m. domesticus* (CALB) [28-30]. This genetic variability represents a rich source of evolutionarily selected diversity and has the potential to lead to the identification of genes controlling novel regulatory features arising from host-pathogen co-evolutionary adaptations.

To screen for functional modifying loci capable of complementing *Hrh1r*/HRH1r, we phenotyped a panel of group 1 (Bagg albino derivatives) and 7 (wild-derived) mice that genotyped as *Hrh1r*/HRH1r for susceptibility to Bphs. While nine *Hrh1r*/HRH1r strains tested were Bphs' as expected, we found eight that were remarkably susceptible to Bphs (Table 2). Importantly, these Bphs' strains are confined primarily to group 7 wild-derived strains (Supplementary Figure 1) in contrast to *Hrh1r*/HRH1r strains from Group 1 that were mostly Bphs'. Moreover, comparison of the entire *Hrh1* gene (Chr6:114,397,936-114,483,296 bp) between several of the Group 1 and Group 7 phenotyped strains found no segregating non-synonymous structural variants (data not shown) between Bphs' and Bphs' strains suggesting that the complimenting locus/loci in Group 7 is independent of additional previously unidentified *Hrh1s*/HRH1s structural variants.

To confirm the existence of a modifying locus capable of restoring Bphs' in mice with a *Hrh1r*/HRH1r allele and to assess its heritability, we selected a subset of Bphs'-*Hrh1r*/HRH1r (MOLF, PWK) and Bphs'-*Hrh1r*/HRH1r (AKR, CBA, C3H, MRL) strains for follow-up studies. We studied *F*1 hybrids between the select strains of interest and HRH1-knockout B6 mice (HRH1KO), which lack a functional *Hrh1s*/HRH1s gene required for Bphs' [31]. These mice can, however, provide potential complementing genetic elements in trans. (*B6 × HRH1KO* *F*1 and (*C3H.Bphs*<sup>SJL</sup> × HRH1KO) *F*1 harbor the *Hrh1s*/HRH1s-
allele while (C3H × HRH1KO) F1, (CBA × HRH1KO) F1, (MRL × HRH1KO) F1 and (AKR × HRH1KO) F1 have the $Hrh1r/-/HRH1r/-$ allele. Both $Hrh1s$-by-HRH1KO F1 hybrids were Bphs$, whereas the $Hrh1r$-by-HRH1KO F1 hybrids were Bphs$ (Table 3), in agreement with our prior finding that $Hrh1s/-/HRH1s/-$ controls dominant susceptibility to Bphs [14]. In contrast, (MOLF × HRH1KO) F1 and (PWK × HRH1KO) F1 hybrids, that harbor the $Hrh1r/-/HRH1r/-$ allele, were Bphs$. This data supports the existence of one or more dominant loci in MOLF and PWK capable of complementing Bphs’ in $Hrh1r/-/HRH1r/-$ mice.

A functional linkage disequilibrium (LD) domain on Chr6 encodes multiple loci controlling HA-shock. Given the evidence from inbred strains of mice indicating that a quarter or more of the mammalian genome consists of chromosomal regions containing clusters of functionally related genes, i.e., functional linkage disequilibrium (LD) domains [32, 33], we hypothesized that the dominant locus complementing $Hrh1r/HRH1r$ may reside within such a LD domain. Support for the existence of a functional LD domain controlling responsiveness to HA is supported by our recent finding that $Histh1-4$, four QTL on Chr6:45.9-127.9 Mb controlling age- and inflammation-dependent susceptibility to HA-shock in SJL/J, FVB/NJ, NU/J, and SWR/J mice, are in strong LD with $Bphs/Hrh1$ (Chr6:114,397,936-114,483,296 bp) [34, 35].

To test this, we generated 114 (MOLF × HRH1KO) × HRH1KO backcross (BC) mice (Table 3), genotyped their $Hrh1$ alleles, and phenotyped them for Bphs. As expected, none of the 54 homozygous HRH1KO mice phenotyped as Bphs$. Of the 114 BC mice studied, 54 (47%) were Bphs$, which is consistent with genetic control by a single locus. Furthermore, of the 60 HRH1$^{MOLF}$ ($Hrh1r/HRH1r$) mice, 54 were Bphs$ and 6
were Bphs', indicating that the locus capable of complementing Bphs' is in fact linked to \textit{Bphs/Hrh1}. We have designated this locus \textit{Bphse} for Bphs-enhancer.

To further test the hypothesis that \textit{Bphse} is linked to \textit{Hrh1}, we generated a cohort of Bphs-phenotyped (AKR × PWK) × AKR BC1 mice and performed linkage analysis using informative markers across a ~70 Mb region encompassing \textit{Hrh1}. Both AKR and PWK mice carry the \textit{Hrh1}/HRH1' allele; however, unlike AKR mice, which are Bphs', PWK mice are Bphss (Table 2). Overall, 83 of 168 (49%) (AKR × PWK) × AKR BC1 mice were Bphss (Table 4). This is in agreement with the segregation of \textit{Bphse} in (MOLF × HRH1KO) × HRH1KO BC1 mice and provides further evidence that \textit{Bphse} is in LD with \textit{Bphs}.

Marker loci from rs36385580 thru \textit{D6Mit135} (Chr6: 59.3-128.8 Mb) exhibited significant linkage to Bphss with maximal linkage across the interval bounded by \textit{D6Mit102} (Chr6:93,463,949-93,464,093 bp) and rs31698248 (Chr6:120,207,213 bp) encompassing \textit{Hrh1}.

We next confirmed the existence and physical location of \textit{Bphse} by congenic mapping. Marker-assisted selection was used to introgress the \textit{Bphse}MOLF and \textit{Bphse}PWK intervals onto the Bphs' C3H and AKR backgrounds, respectively. Starting at N5 through N10, heterozygous and homozygous BC mice were phenotyped for Bphs (Figure 1). Compared to C3H (C3H and C3H.\textit{BphseC3H/C3H}) and AKR (AKR and AKR.\textit{BphseAKR/AKR}) mice, both C3H.\textit{BphseC3H/MOLF} and AKR.\textit{BphseAKR/PWK} mice were Bphs'. Overall, \textit{Bphse}C3H/MOLF and \textit{Bphse}AKR/PWK mice were significantly more susceptible to Bphs than \textit{Bphse}C3H/C3H and \textit{Bphse}AKR/AKR mice (\(\chi^2 = 60.63, df = 1, p<0.0001\)). The physical mapping results confirm the linkage of \textit{Bphse} to \textit{Bphs/Hrh1} and \textit{Histh1-4} (Chr6:45.9-127.9 Mb) [34, 35], and importantly provide strong support for the existence of a functional LD domain.
on Chr6 encoding multiple loci controlling susceptibility to HA-shock following exposure to environmental factors and infectious agents, including influenza A [35].

**Identification of candidate genes for Bphse.** Given that many laboratory and few wild-derived inbred strains have undergone deep sequencing (30–60× genome coverage) with publicly available variant datasets in Mouse Phenome Database (MPD; https://phenome.jax.org/) [36] and Mouse Genomes Project (MGP; https://www.sanger.ac.uk/data/mouse-genomes-project/) [37], we retrieved all coding and non-coding single nucleotide polymorphism (SNP) data available across the Bphse congenic interval (Chr6:59.3-128.8 Mb) among our seventeen Bphs phenotyped Hrh1r/HRH1r mouse strains (Table 2). As expected, this dataset lacked SNP coverage for several of the wild-derived inbred strains (>98% SNP missing compared with C57BL/6J) that were phenotyped for Bphs in this study. To complement our dataset, we utilized Chr6 region capture sequencing (see Materials and Methods) to sequence and identify SNPs within the Bphse interval, and integrated these SNPs with the publicly available dataset. This approach yielded a total of 1,303,072 SNPs among which 13,257 SNPs had 100% coverage (no missing genotypes) across all seventeen strains.

To identify variants that segregate with Bphs among Hrh1r/HRH1r strains, we used efficient mixed-model association (EMMA) [38] and both the larger dataset of 1,303,072 SNPs as well as the smaller dataset of 13,257 SNP with the anticipation that having complete genotypes would increase the power to detect segregating variants. However, both datasets yielded no significant or suggestive associations (data not shown) which led us to speculate that perhaps the number of mouse strains available for genetic association analysis may be a limiting factor. To test this, we asked if we could identify
genetic variants that segregate with Bphs\textsuperscript{s} independent of \textit{Hrh1}/HRH1 haplotype with the rationale that this approach will identify \textit{Bphs}/\textit{Hrh1} (positive control) as well as polymorphic gene candidates for \textit{Bphse}. Moreover, \textit{Bphse} expressivity requires \textit{Hrh1}/HRH1. This method greatly enhanced the number of mouse strains for genetic association analysis, as numerous mouse strains have been phenotyped for Bphs over the years by us and others [15, 17, 19, 39, 40].

To accomplish this, we generated SNP datasets as before but across a larger panel of 50 inbred mouse strains (\textit{Hrh1}/HRH1\textsuperscript{r} and \textit{Hrh1}/HRH1\textsuperscript{s}) (Supplementary Table 1). Using this approach, we identified 3 SNPs in \textit{Atg7} as significant with a stringent cut-off ($p<3.81E-06$) and another 163 SNPs in 27 genes with a moderate cut-off ($p<5.00E-02$) that were associated with Bphs\textsuperscript{s} (Figure 2A and Supplementary Table 2). There was no difference in predicted candidate genes using either the smaller dataset (13,257 SNPs) or the larger dataset (1,303,072 SNPs). It is important to reiterate that this approach of combining both \textit{Hrh1}/HRH1\textsuperscript{r} and \textit{Hrh1}/HRH1\textsuperscript{s} mouse strains may predict candidates for both \textit{Bphs} and \textit{Bphse}. Thus, \textit{Hrh1}, which is a positive control for this analysis and whose polymorphism has been earlier shown to underlie \textit{Bphs} among laboratory inbred strains [15], was among the candidate genes supporting the predictions from this analysis. We also know that the DNA sequence of the entire \textit{Hrh1} gene (~85 kb) among several \textit{Hrh1}/HRH1\textsuperscript{r} strains harbor no additional segregating nonsynonymous structural variants (data not shown) between Bphs\textsuperscript{s} and Bphs\textsuperscript{r} mice, excluding involvement of any previously unidentified \textit{Hrh1}/HRH1 structural alleles underlying \textit{Bphse}. 
The *Bphse* predicted candidate genes cluster in a narrow interval of ~5.5 Mb on Chr6:111.0-116.4 Mb (Figure 2A). Given that our larger dataset (1,303,072 SNPs) includes several thousand SNPs in this shortlisted region of ~5.5Mb, we asked if we could impute the missing SNPs and do a high-dimensional association run. To impute missing SNPs, we utilized the Viterbi algorithm implemented in HaploQA [41, 42] and generated a complete dataset of 78,334 SNPs across Chr6:111.0-116.4 Mb. Using this, we ran a high-resolution genetic association analysis and found *Atg7*, *Tmcc1*, *Il17re*, *Vgll4*, and several others as top hits for *Bphse* (*p*<5.00E-02) (Figure 2B-C; Supplementary Table 3).

As a complementary approach to identify positional candidates for *Bphse*, we employed machine-learning computation, using functional genomic networks [43] to identify network-based signatures of biological association. To this end, we used prior knowledge to generate a list of Bphs-associated biological processes and retrieved gene sets functionally associated with each term. The terms and their justifications are as follows:

- **Type I hypersensitivity/anaphylaxis**: The death response following systemic HA challenge exhibits symptoms of type I hypersensitivity/anaphylaxis including respiratory distress, vasodilation, and anaphylactic shock [44].
- **Cardiac**: There is evidence suggesting that anaphylactic shock in mice is caused by decreased cardiac output, rather than systemic vasodilation [45].
- **Histamine**: Bphs is induced by a systemic HA challenge [15].
- **G-protein coupled receptor**: HRH1 signaling is required for the Bphs phenotype, and all HA receptors belong to the family of G-protein coupled receptors [46].
• *Pertussis toxin:* Bphs is induced in mouse strains by PTX [12].

• *Vascular permeability* (VP): Hypersensitivity to HA exhibits vascular leakage in skin and muscles [34, 35].

• *Endoplasmic reticulum (ER)/endoplasmic membrane protein complex (EMC), and endoplasmic reticulum-associated degradation (ERAD):* The two HRH1 alleles exhibit differential protein trafficking and cell surface expression with the HRH1\(^r\) allele primarily retained in the ER [21]. The EMC and ERAD are intimately involved in regulating GPCR translocation to the plasma membrane [47, 48].

Each of the seven gene sets define a putative Bphs-related process that forms a distinct subnetwork of the full functional genomic network. Using this approach, we identified several hundred genes within the *Bphse* congenic locus that are functionally associated with each biological process, and thus could be gene candidates (Supplementary Table 4).

Genes that are predicted to be highly functionally related to a trait may not have functional variant alleles segregating in the study population, and may therefore be unlikely to drive the observed strain differences in Bphs. Using the list of polymorphic genes identified through high-resolution genetic association testing (Figure 2), we normalized and plotted the respective genetic association score (-log\(_{10}\) *p* \(_{EMMA}\)) with functional enrichment (-log\(_{10}\) FPR) to focus on genes that overlap both approaches (Figure 3A). The final ranking was calculated by defining a final gene score (*Scg*) for each gene, which is the sum of the (normalized) -log\(_{10}\)(FPR) and the -log\(_{10}\) (*p* \(_{EMMA}\)) (Figure 3B). The top ten candidates for *Bphse* as ranked using *Scg* are: *Atg7, Plxnd1, Tmcc1, Mkrn2, Il17re, Pparg, Lhfpl4, Vgll4, Rho* and *Syn2*. It is interesting to note that the predicted
candidates for *Bphse* not only overlap *Bphs/Hrh1* but two additional QTLs, *Histh3* (Chr6:99.5-112.3 Mb) and *Histh4* (Chr6:112.3-127.9 Mb), controlling age- and inflammation-dependent susceptibility to HA shock in SJL/J, FVB/NJ, NU/J, and SWR/J mice [34, 35]. Importantly, our findings support the existence of a smaller functional LD domain on Chr6:111.0-116.4 Mb (~5.5 Mb interval) that controls susceptibility to HA-shock elicited by both PTX dependent and independent mechanisms (Supplementary Figure 2).
DISCUSSION

*B. pertussis* and PTX elicit *in vivo* a variety of immunologic and inflammatory responses, including systemic vascular hypersensitivity to serotonin (Bpss), bradykinin (Bpbs), and HA (Bphs) [17]. Utilizing classical laboratory derived inbred strains of mice, we and others showed that susceptibility to Bpss, Bpbs, and Bphs are under unique genetic control with Bpss\(^s\) and Bpbs\(^s\) being recessive traits [17, 19] and Bphs controlled by the single autosomal dominant locus *Bphs* [14, 49], which we subsequently identified at *Hrh1/HRH1* [15]. Herein, we present data from several wild-derived inbred strains of mice that harbor the *Hrh1*/\(H Rh1^\text{r}\) allele which nevertheless phenotype as Bphs\(^s\). This is suggestive of the existence of an evolutionarily selected modifying locus that can complement *Hrh1*/\(H Rh1^\text{r}\) and is supported by the unique phylogenetic distribution of such strains *(Supplementary Figure 1)*.

Our results with the genetic cross [(MOLF x C3H) x C3H BC mice] confirm the existence of a dominant modifying locus (*Bphse*) capable of complementing Bphs\(^s\) in mice with an *Hrh1*/\(H Rh1^\text{r}\) allele. We also found that *Bphse* requires *Hrh1*/\(H Rh1\), as no BC1 mice that genotype as *Hrh1\(^{-/-}\)* were Bphs\(^s\) *(Table 3)*. Among BC1 mice that genotype as *Hrh1\(^{MOLF/-}\)*, 10% of mice phenotyped as Bphs\(^r\) indicating that *Bphse* is in LD with Bphs\(^s\)/Hrh1\(^{-/-}\). Linkage scans using microsatellite markers validated significant linkages to Chr6, with maximal significance around Bphs/Hrh1 *(Table 4)*. In addition, we mapped the physical location of this locus by making congenic mice (C3H.\(Bphse^{MOLF/-}\) and AKR.\(Bphse^{PWK/-}\)) that captured the *Bphse* locus on Chr6 (59.3-128.8 Mb, *Figure 1*) and replicated the phenotype. To our knowledge, this is the first study assessing Bphs\(^s\) in
multiple wild-derived inbred strains of mice, and clearly establish their utility in identifying novel genetic mechanisms controlling HA-shock.

Aside from genetics, several factors could influence HA sensitivity after exposure to *B. pertussis* and PTX including age, sex, and route of sensitization/challenge [12]. In our phenotyping experiments, we used 8-12-week-old mice of each sex and did not find any sex differences. This agrees with earlier studies that found no sex differences in Bphs<sup>s</sup> [47]. We also tested the route of administration of PTX and HA challenge using the intraperitoneal and intravenous routes and found no difference (data not shown). We have not tested the effect of age on Bphs<sup>s</sup> amongst the various strains; however, work from Munoz and others have reported a significant effect of age [12]. It is possible that some of the strains that are Bphs<sup>r</sup> will exhibit Histh<sup>s</sup> as they age or following treatment with complete Freund’s adjuvant [34, 35].

The region encoding *Bphse* is very large and contains hundreds of genes (Chr6:59.3-128.8 Mb). Until recently, interval specific recombinant congenic mapping was the gold standard to delimit large QTLs associated with a phenotype [48]. Of the thousands of QTLs for various phenotypes and diseases, only a small fraction of genes have been identified through sub-congenic mapping, phenotyping and sequencing. The identification of candidate genes from large genomic regions has been revolutionized with the advent of advanced sequencing technologies and genome wide association studies (GWAS) [50]. For example, the Sanger Institute has sequenced 16 inbred laboratory and wild-derived mouse genomes and The Jackson Laboratory, in conjunction with the University of North Carolina, has genotyped several hundred laboratory inbred strains using the Mouse Diversity Array, that altogether provides an almost complete picture of
genetic variation among the various strains. Our approach, however, is different from other mouse GWAS studies that have been done to identify candidate loci for several diseases [51]. Instead of running a full genome scan across a large panel of Bphs phenotyped strains, we tested association of susceptibility exclusively across the Bphse locus (Chr6:59.3-128.8 Mb). This allowed us to use the information gathered from the genetic cross and congenic mapping and delimit the region to be screened for association.

Our first screen using genotype and phenotype data across seventeen Hrh1r/HRH1r mouse strains did not yield any significant hits, due to limitation in the number of strains used. To overcome this problem, we excluded Hrh1 genotype as a co-variate. Given that several dozen laboratory inbred mouse strains (Group 2, 3 and 4) have been phenotyped for Bphs [15, 17, 19, 39, 40] and also to circumvent the sample size limitation in genetic association testing, we searched for genetic polymorphism across the 50 mouse strains that could explain overall Bphs. Hrh1, which is our positive control and associated with Bphs among classical laboratory inbred strains [15], was identified as a significant hit supporting the validity of this approach. The use of imputed datasets across 50 phenotyped strains further refined the SNPs associated with Bphs (Figure 2).

Recently, a quantitative trait gene prediction tool has been described that utilizes functional genomics information (gene co-expression, protein-protein binding data, ontology annotation and other functional data) to rank candidate genes within large QTLs associated with a respective phenotype [43]. This methodology uses biological prior knowledge to predict candidate genes that could influence multiple pathways affecting the phenotype. We utilized this approach for Bphs, which is known to involve cardiac,
vascular, and anaphylactic mechanisms [44, 45]. Because the selection of phenotype-associated gene sets is critical for final gene predictions, several terms were used to incorporate sub-phenotypes equivalent to Bphs in the expectation that use of multiple terms would help identify candidate loci for Bphse. Integration of functional predictions with genetic association (Scg, Figure 3) allowed us to focus on only those candidates that reached significance in both approaches.

Given that there is differential cell surface expression of HRH1 depending on the haplotype, it is tempting to speculate that Bphse may aid in the folding, trafficking and/or surface delivery of HRH1 [51, 52]. In this regard, Tmcc1 (transmembrane and coiled-coil domain family 1) and Atg7 (autophagy related 7) are promising candidates because of their known roles in protein trafficking in cells. Tmcc1 is an ER membrane protein that regulates endosome fission and subsequent cargo trafficking to the Golgi [53]. Similarly, Atg7 is implicated in translocation of cystic fibrosis transmembrane conductance regulator (CFTR) to the surface [54]. CFTR is a multi-pass membrane GPCRs like HRH1 in that both protein classes pass several time through the cell membrane, thus it is tempting to suggest Atg7 may act in a similar fashion to translocate HRH1 to the surface thereby resulting in the Bphs\textsuperscript{s} phenotype. It will be interesting to test the surface expression of HRH1 among the Hrh1\textsuperscript{r}/HRH1\textsuperscript{r} strains that phenotype as Bphs\textsuperscript{s} (Table 2). Results using bone marrow chimeras suggest that Bphs\textsuperscript{s} is a function of the non-hematopoietic compartments [48], so several cell types (endothelial, epithelial, stromal cells) are potential candidates for this cell surface expression analysis.

In addition to Tmcc1 and Atg7, several other predicted candidates for Bphse may have potential relevance to phenotypes associated with Bphs including anaphylaxis and
mast cell degranulation, and cardiovascular effects (Supplementary Table 4). Proliferator-activated receptor-gamma (Pparg) encodes a nuclear receptor protein belonging to the peroxisome proliferator-activated receptor (Ppar) family. Activation of PPARγ suppresses mast cell maturation and is involved in allergic disease [55, 56]. Because mast cells are major drivers of pathological events in anaphylaxis [57], Pparg may be highly relevant to Bphs. In addition, increased PPARγ expression is associated with cardiac dysfunction [57]. It will be interesting to quantify the mRNA expression of some of these candidates between Bphs and Bphs’ strains and investigate whether they interact with HRH1.

Importantly, the fact that Bphse resides within a smaller functional LD that includes Histh3 and Histh4 (Supplementary Figure 2) is of potential clinical significance. Histh is an autosomal recessive genetic locus that controls susceptibility to B. pertussis and PTX-independent, age- and inflammation-dependent HA-shock in SJL/J mice [34, 35]. Four sub-QTLs (Histh1-4) define Histh, each contributing 17%, 19%, 14%, and 10%, respectively, to the overall penetrance of Histh. Importantly, Histh is syntenic to the genomic locus most strongly associated with systemic capillary leak syndrome (SCLS) in humans (3p25.3). SCLS or Clarkson disease is a rare disease of unknown etiology characterized by recurrent episodes of vascular leakage of proteins and fluids into peripheral tissues, resulting in whole-body edema and hypotensive shock. Additionally, Histh SJL/J mice recapitulate many of the cardinal features of SCLS, including susceptibility to HA- and infection-triggered vascular leak and the clinical diagnostic triad of hypotension, elevated hematocrit, and hypoalbuminemia and as such makes them a natural occurring animal model for SCLS [34, 35]. Clearly, detailed genetic analysis and
identification of the causative genes underlying *Bphse*, *Histh3*, and *Histh4* may reveal orthologous candidate genes and or pathways that contribute not only to SCLS, but also to normal and dysregulated mechanisms underlying vascular barrier function more generally.
MATERIALS AND METHODS

Animals. AKR/J (AKR), BPL/1J, C3H/HeJ (C3H), C3H/HeN, CAST/EiJ, C57BL/6J (B6), CBA/J (CBA), CBA/N, CZECHII/EiJ, I/LnJ, JF1/MsJ, MOLD/EiJ, MOLF/EiJ (MOLF), MRL/MpJ (MRL), MSM/Ms, PWD/PhJ, PWK/PhJ (PWK), RF/J, SF/CamEiJ, and SKIVE/EiJ were purchased from the Jackson Laboratory (Bar Harbor, Maine). B6.129P-\(Hrh1^{tm1Wat}\) (HRH1KO) \[31\], C3H.\(Bphs^{S/JL}\) (C3H.\(Bphs^{S}\)) \[15\], (B6 × HRH1KO) F\(_1\), (C3H × HRH1KO) F\(_1\), (AKR × HRH1KO) F\(_1\), (MRL × HRH1KO) F\(_1\), (AKR × PWK) F\(_1\), (C3H × MOLF) F\(_1\), (MOLF × HRH1KO) × HRH1KO, (AKR × PWK) × AKR, (C3H × MOLF) × C3H, C3H.\(Bphs^{MOLF+/−}\), C3H.\(Bphse^{C3H}\), AKR.\(Bphse^{PWK+/−}\) and AKR.\(Bphse^{AKR}\) were generated and maintained under specific pathogen free conditions in the vivarium of the Given Medical Building at the University of Vermont according to National Institutes of Health guidelines. All animal studies were approved by the Institutional Animal Care and Use Committee of the University of Vermont.

\textbf{Bphs Phenotyping.} Bphs phenotyping was carried out as previously described \[15\]. Briefly, mice were injected with purified PTX (List Biological Laboratories, Inc.) in 0.025 M Tris buffer containing 0.5 M NaCl and 0.017% Triton X-100, pH 7.6. Control animals received carrier. Three days later, mice were challenged by injection with histamine (milligrams per kilogram of body weight [dry weight], free base) suspended in phosphate-buffered saline (PBS). Deaths were recorded at 30 min post-challenge. The results are expressed as the number of animals dead over the number of animals studied.

\textbf{DNA sequencing of third intracellular loop of \textit{Hrh1}.} DNA for 91 inbred laboratory and wild-derived strains of mice was purchased from the Mouse DNA resource at The Jackson Laboratory (www.jax.org) and used in an \textit{Hrh1} specific PCR reaction.
using the following primer sets: forward-740F, 5’-TGCCAAGAAACCTGGGAAAG-3’, and reverse-1250R, 5’-CAACTGCTTGGCTGCCTTC-3’ that amplify the third intracellular loop of Hrh1. Thermocycling was carried out for a 15 µl reaction mix with 2 mM MgCl2, 200 µM dNTPs, 0.2 µM primers, 1 unit of Taq polymerase and ~50 ng of genomic DNA together with an initial 2-min 97°C denaturation followed by 35 cycles of 97°C for 30 sec, 58°C for 30 sec and 72°C for 30 sec. The final extension was for 5 min at 72°C. Hrh1 amplicons from each mouse strain were gel purified (Qiagen Cat# 28115) and DNA sequencing reactions were performed with the BigDye terminator cycle sequencing kit (Applied Biosystems, Foster City, CA) using 740F or 1250F reverse primers. The reaction products were resolved on an ABI Prism 3100 DNA sequencer at the DNA analysis facility at the University of Vermont. DNA sequencing data were assembled and analyzed using MultiAlign [58]. Each potential nucleotide sequence polymorphism was confirmed by comparing it with the actual chromatographic profiles using Chromas v2.6.5 (https://technelysium.com.au/wp/)

**DNA isolation and genotyping.** DNA was isolated from mouse tail clippings as previously described [13]. Briefly, individual tail clippings were incubated with cell lysis buffer (125 mg/ml proteinase K, 100 mM NaCl, 10 mM Tris-HCl (pH 8.3), 10 mM EDTA, 100 mM KCl, 0.50% SDS, 300 ml) overnight at 55°C. The next day, 6M NaCl (150 ml) was added followed by centrifugation for 10 min at 4°C. The supernatant layer was transferred to a fresh tube containing 300 µl isopropanol. After centrifuging for 2 min, the supernatant was discarded, and the pellet washed with 70% ethanol. After a final 2 min centrifugation, the supernatant was discarded, and DNA was air dried and resuspended
in TE. Genotyping was performed using microsatellite, sequence specific, and *Hrh1* primers (Supplemental Table 5).

**Microsatellite primers:** Polymorphic microsatellites were selected to have a minimum polymorphism of 8 bp for optimal identification by agarose gel electrophoresis. Briefly, primers were synthesized by IDT-DNA (Coralville, IA) and diluted to a concentration of 10 uM. PCR amplification was performed using Promega GoTaq according standard conditions and amplicons were subjected to 2% agarose gel electrophoresis and visualized by ethidium bromide and UV light.

**Sequence-specific primers:** Genotyping was performed using sequence specific primers that differ only at the 3’ nucleotide corresponding to each allele of the identified SNP [59]. Each primer set was designed using Primer3 to have a Tmelt of 58-60°C and synthesized by IDT-DNA (Coralville, IA) and used at a concentration of 100 uM. PCR reactions were subjected to cycling conditions as described and if found to be necessary, the annealing temperature at each stage was adjusted to accommodate the optimal Tmelt. Amplicons were electrophoresed with 10 ul Orange G loading buffer on a 1.5% agarose gel stained with ethidium bromide and visualized by UV light. The presence of a SNP specific allele was scored by observing an amplicon of the expected size in either reaction.

**HRH1KO mice genotyping:** Wild-type and *Hrh1*−/− alleles were genotyped as previously described [15]. Approximately 60 ng of DNA was amplified (GeneAmp PCR system 9700, Applied Biosystems, Foster City, CA). The DNA was amplified by incubation at 94°C for 3 min followed by 35 cycles of 94°C for 30 sec, 62°C for 30 sec, and 72°C for 30 sec. At the end of the 35 cycles, the DNA was incubated at 72°C for 10 min and 4°C
for 10 min. The amplified DNA was analyzed by gel electrophoresis in a 1.5% agarose gel. The DNA was visualized by staining with ethidium bromide.

**Linkage analysis and generation of Bphse congenic.** Segregation of genotype frequency differences with susceptibility and resistance to Bphs in (MOLF × HRH1KO) × HRH1KO and (AKR × PWK) × AKR mice were tested by χ² in 2 × 2 contingency tables. C3H.BphseMOLF+/-, C3H.BphseC3H, AKR.BphsePWK+/- and AKR.BphseAKR congenic mice were derived by marker assisted selection. (AKR × PWK) × AKR and (C3H × MOLF) × C3H mice that were heterozygous across the Bphse interval at N2 and at each successive BC generation were selected for continued breeding. Bphse congenic mice were maintained as heterozygotes.

**Low-resolution interval-specific targeted genetic association testing.** Genotype data (SNPs in both coding and non-coding) of 50 mouse strains (Supplementary Table 1) that were phenotyped for Bphs either by us or described in the literature [12, 15, 17, 19, 40], was retrieved from public databases at the Sanger Institute (https://www.sanger.ac.uk/science/data/mouse-genomes-project) and The Jackson Laboratory (https://phenome.jax.org/). The lack of representation of several inbred strains especially wild-derived strains in these databases were compensated by genotyping using chromosome region capture sequencing [59] as follows:

**DNA Fragmentation:** For chromosome region capture sequencing, 3 µg of genomic DNA from BPN/3J, BPL/1J, CASA/RkJ, CAST/EiJ, CBA/J, C3H/HeN, CZECHII/EiJ, JF1/Ms, MOLD/EiJ, MOLF/EiJ, MRL/MpJ, MSM/Ms, NU/J, PWD/PhJ, SF/CamEiJ and SKIVE/EiJ mice was sheared into fragments of approximately 200 bp with the Covaris E220 system (Covaris, USA). The sheared DNA fragments were then
purified for each of the 16 mice strains using AMPure XP Beads (Beckman, USA), following the instructions of the reagent supplier.

**DNA Library Construction:** DNA libraries of the purified fragments were constructed with SureSelect Library Prep Kit (Agilent, USA). In brief, DNA end-repair was performed for the fragments from each muse strain using 10× End Repair Buffer, dNTP Mix, T4 DNA Polymerase, Klenow DNA Polymerase, and T4 Polynucleotide Kinase. After incubation of the mixture at 20 °C for 30 min, Addition of nucleotide A at the 3' end of the sequence was performed using 10×Klenow Polymerase Buffer, dATP and Exo(-) Klenow, at 37 °C for 30 min. Ligation reaction was then conducted using T4 DNA Ligase Buffer, SureSelect Adaptor Oligo Mix, and T4 DNA Ligase at 20 °C for 15 min. The adaptor-ligated library was finally amplified through using SureSelect Primer, SureSelect ILM Indexing Pre Capture PCR Reverse Primer, 5X Herculase II Rxn Buffer, 100 mM dNTP Mix, and Herculase II Fusion DNA Polymerase. The condition for the amplification was fixed as: initial denaturation at 98°C for 2 min, followed by 30 cycles of reactions at 98 °C for 30 Sec, 65 °C annealing for 30 Sec, 72 °C extension 30 Sec. Purification of the amplified products was performed with 1.8X Agencourt AMPure XP beads for each of the libraries. The average insert length for the adaptor-ligated libraries ranged between 225 ~ 275bps.

**Hybridization capture:** The libraries were subjected for the hybridization capture using the SureSelect Target Enrichment Kit (Agilent, USA), following the instruction of the reagent supplier. The prepared library were then reacted with SureSelect Block Mix at 95 °C for 5min, followed by holding at 65 °C, and the Hybridization Buffer plus capture library mix were added and maintained at 65 °C for 24hrs. Finally, Dynabeads
M-280 streptavidin (Life, USA) was used for the enrichment of the Captured DNA libraries [60, 61].

**Index amplification:** For each enriched captured DNA library, the index amplification was performed with 5X Herculase II Rxn Buffer, 100 mM dNTP Mix, SureSelect ILM Indexing Post Capture Forward PCR Primer, and Herculase II Fusion DNA Polymerase. The reaction procedure was: 98°C Pre-denaturation for 2 Min, 98 °C denaturation for 30 Sec, 57 °C annealing for 30 Sec, 72 °C extension for 30 Sec, amplification for 12 rounds, followed by purification using 1.8 times the volume of AMPure XP Beads. DNA libraries of 250-350 bp range were obtained for the subsequent sequencing [60].

**DNA Sequencing:** A 10 ng library was used for cluster generation in cBot with the TruSeq PE Cluster Kit (illumina, USA) followed by bidirectional sequencing in an Illumina Hiseq 2500 to obtain the data of 2x150 bp.

**Data processing and SNP calls:** To ensure the quality of subsequent information analysis, the original sequence was filtered with the software SolexaQA to get high quality Clean Reads [62]. Efficient high-quality sequencing data was mapped to the reference genome mm10 by the BWA software [63], samtools [64] was used for sorting, picard tools was used for duplicate read removal, and GATK was used for realignment around indels and base quality score recalibration [65]. Finally, GATK HaplotypeCaller was used for SNP detection.

All SNP datasets (MPD, Chromosome region capture sequencing) were collated to yield a total of 1,303,072 SNPs across the Bphse interval (Chr6: 59-129 Mb), among which 13,257 SNPs had 100% coverage (no missing genotypes) across all strains.
To calculate associations between genetic polymorphisms and Bphs, we used efficient mixed-model association (EMMA) [38]. This method treats genetic relatedness as a random variable in a linear mixed model to account for population structure, thereby reducing false associations between SNPs and the measured trait. We used the likelihood ratio test function (emma.ML.LRT) to generate \( p \)-values. Significance was assessed with Bonferroni multiple correction testing. The \(-\log\) transformed \( p \)-values were plotted using GraphPad Prism7 and genomic coordinates included for each SNP using the latest mouse genome build GRCm38.p5/mm10.

**Genotype imputation methodology.** A merged SNP dataset over the Chr6 region 111.0-116.4 Mb (GRCm38 / mm10 and dbSNP build 142) was constructed from the 11 SNP genotyping datasets available (see Supplementary Table 6) on the Mouse Phenome Database (MPD) [41, 42, 66-71]. This MPD-derived merged genotype dataset of 577 strains was then merged with the genotype data for 50 strains generated earlier for low resolution mapping (see "low resolution interval-specific targeted genetic association testing"). We leveraged the genotype data from over 577 strains to impute genotypes for missing SNP states across the region for the 50 strains of interest (see Supplementary Table 1). To impute genotypes on a target strain, we utilized the Viterbi algorithm implemented in HaploQA [41, 42] where the input was a subset of strains most phylogenetically similar to the target strain. This imputation strategy resulted in a dataset of 78,334 SNPs in the genomic region of interest. Across all 50 strains, the median number of missing SNP genotypes after imputation was 2.45% with a maximum missing of only 5.4% for one of the strains.
**Trait-related gene sets.** The positional candidate genes were ranked based on their predicted association with seven functional terms related to the Bphs phenotype: “Cardiac”, “G-protein coupled receptor”, “Histamine”, “Pertussis toxin”, “Type I hypersensitivity”, “Vascular Permeability”, and “ER/EMC/ERAD”. Gene Weaver [72] was used to identify genes annotated with each term. Each term was entered the Gene Weaver homepage (https://geneweaver.org) and search restricted to human, rat, and mouse genes, and to curated lists only. Mouse homologs for each gene were retrieved using the batch query tool in MGI (http://www.informatics.jax.org/batch_data.shtml). In addition, using the Gene Expression Omnibus (GEO) and PubMed, additional gene expression data sets were retrieved for each phenotype term. Final gene lists consisted of the unique set of genes associated with each process term.

**Functional enrichment and ranking of Bphs associated genes.** We associated genes with Bphs-related functions as described in Tyler et al. [34]. Briefly, we used the connectivity weights in the Functional Network of Tissues in Mouse (FNTM) as features for training support vector machines [73]. Each feature consisted of the connection weights from a given gene to genes in the functional module. To improve classification and reduce over-generalization we clustered each functional gene set into modules, each less than 400 genes [43]. For each of these modules, we trained 100 SVMs to classify the module genes from a balanced set of randomly chosen genes from outside the module. We used 10-fold cross validation and a linear kernel. We also trained each SVM over a series of cost parameters identified by iteratively narrowing the cost parameter window to identify a series of eight cost parameters that maximized classification accuracy. We then used the training modules to score each positional candidate gene in the Bphse locus.
To compare scores across multiple trained models, we converted SVM scores to false positive rates.

**Combined gene score.** To create the final ranked list of positional candidate genes, we combined the SNP association scores with the functional predictions derived from the SVMs. We scaled each of these scores by its maximum value across all positional candidates and summed them together to derive a combined gene score ($S_{cg}$) that incorporated both functional predictions and genetic influence:

$$
S_{cg} = \frac{-\log_{10}(pEMMA)}{-\log_{10}(FPR_{SVM})}
$$

where the denominators of the two terms on the right-hand side are the maximum values of $-\log_{10}(pEMMA)$ and $-\log_{10}(FPR_{SVM})$ over all positional candidates in $Bphse$, respectively, which normalizes the functional and positional scores to be comparable to each other. SNPs were assigned to the nearest gene within 1Mb. If more than one SNP was assigned to a gene, we used the maximum negative $\log_{10} p$ value among all SNPs assigned to the gene.
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**Table 1.** Distribution of $Hrh1^s$ and $Hrh1^r$ alleles in laboratory and wild-derived inbred mouse strains.

| Susceptible Haplotype $(Pro^{263}, \text{Val}^{312}, \text{Pro}^{330})$ | Resistant Haplotype $(\text{Leu}^{263}, \text{Met}^{312}, \text{Ser}^{330})$ |
|------------------------|------------------------|
| $Hrh1^s$               | $Hrh1^r$               |
| 129X1/SvJ              | C57BR/cdJ              | P/J                  | AKR/J                |
| 129S1/SvlmJ            | C57L/J                 | PERACEVO/EiJ         | BPL/1J               |
| 129T2/SvEmsJ           | C58/J                  | PERA/EiJ             | C3H/HeJ              |
| A/HeJ                  | CALB/RkJ               | PERC/EiJ             | C3H/HeN              |
| A/J                    | CE/E                   | PL/J                 | CASA/RkJ             |
| A/WySnJ                | DBA/1J                 | RBF/DnJ              | CAST/EiJ             |
| ALR/LtJ                | DBA/2J                 | RIIIS/J              | CBA/J                |
| ALS/LtJ                | DDY/JclSidSeyFrkJ      | SB/LeJ               | CBA/N                |
| B10.S/DvTee            | EL/SuzSeFrkJ           | SEA/GnJ              | CZECHI/EiJ           |
| B10.S/McdgJ            | FVB/NCr                | SEC/1ReJ             | CZECHII/EiJ          |
| BALB/cByJ              | IS/CamRkJ              | SENCARA/PtJ          | I/LnJ                |
| BALB/cJ                | KK/HIJ                 | SENCARB/PtJ          | JF1/Ms               |
| BDP/J                  | LEWES/EiJ              | SENCARC/PtJ          | MOLC/RkJ             |
| BPH/2J                 | LG/J                   | SJL/J                | MOLD/RkJ             |
| BPL/1J                 | LP/J                   | SJL/BmJ              | MOLF/EiJ             |
| BPN/3J                 | MA/MyJ                 | SM/J                 | MRL/MpJ              |
| BTBRT+                 | MOR/RkJ                | SPRET/EiJ            | MSM/Ms               |
| BXSB/MpJ               | NOD/LtJ                | ST/BJ                | PWD/PhJ              |
| C57BL/10J              | NON/LtJ                | SWR/J                | PWK/PhJ              |
| C57BL/10SnJ            | NOR/LtJ                | SWX-4/TyJ            | RF/J                 |
| C57BL/6ByJ             | NZB/BJIN               | TIRANO/EiJ           | SF/CamEiJ            |
| C57BL/6J               | NZO/HILtJ              | YBR/EiJ              | SKIVE/EiJ            |
| C57BLKS/J              | NZW/LacJ               | ZALENDE/EiJ          |                      |
Table 2. Bphs susceptibility of mice with the *Hrh1r*/HRH1r allele.

| Strain          | Groupa | 100 | 50 | 25 | Total | % Aff | p-valueb |
|-----------------|--------|-----|----|----|-------|-------|----------|
| C3H/HeJ         | 1      | 0/3 | 0/2| 0/2| 0/7   | 0     | 0        |
| C3H/HeN         | 1      | 0/2 | 0/2| 0/2| 0/6   | 0     | 0        |
| C3H             |        |     |    |    |       |       |          |
| C3H             | 1      | 0/5 | 0/4| 0/4| 0/13  | 0     |          |
| AKR/J           | 1      | 1/3 | 0/2| 0/2| 1/7   | 14    | 0.4      |
| CAST/EiJ        | 7      | 1/3 | 0/3| 0/3| 1/9   | 11    | 0.4      |
| CBA/J           | 1      | 0/3 | 0/2| 0/2| 0/7   | 0     |          |
| CBA/N           | 1      | 0/3 | 0/2| 0/2| 0/7   | 0     |          |
| CBA             |        |     |    |    |       |       |          |
| CBA             | 1      | 0/6 | 0/4| 0/4| 0/14  | 0     | 1.0      |
| I/LnJ           | 6      | 2/7 | 0/3|-   | 2/10  | 20    | 0.2      |
| MSM/Ms          | 7      | 0/3 | 0/3|-   | 0/6   | 0     | 1.0      |
| MRL/MpJ         | 1      | 0/3 | 0/2| 0/2| 0/7   | 0     | 1.0      |
| SF/CamEiJ       | 1      | 0/4 | 0/2|-   | 0/6   | 0     | 1.0      |
| SKIYE/EiJ       | 7      | 2/7 | 1/6| 0/2| 3/15  | 20    | 0.2      |
| BPL/1J          | 5      | 1/2 | 2/2| 2/2| 5/6   | 83    | 0.0005   |
| CZECHII/EiJ     | 7      | 4/4 | 2/4| 2/2| 8/10  | 80    | <0.0001  |
| JF1/MsJ         | 7      | 2/3 | 2/3|-   | 4/6   | 67    | 0.004    |
| MOLD/EiJ        | 7      | 2/2 | 1/2| 2/2| 5/6   | 83    | 0.0005   |
| MOLF/EiJ        | 7      | 2/2 | 5/5| 5/5| 12/12 | 100   | <0.0001  |
| PWD/PhJ         | 7      | 5/7 | -  | -   | 5/7   | 71    | 0.001    |
| PWK/PhJ         | 7      | 2/2 | 2/2| 2/2| 6/6   | 100   | <0.0001  |
| RF/J            | 1      | 2/2 | 2/2| 2/2| 6/6   | 86    | <0.0001  |

Mice were injected with 200 ng of PTX on D0. Three days later the animals were challenged with the indicated dose of HA (mg dry weight free base/kg body weight) by intraperitoneal injection and deaths recorded as number of animals dead/number of animals tested at 30 minutes post HA challenge. a according to mouse family tree (adapted from Petkov et al. [22]). b Relative to C3H mice.
Table 3. Bphs susceptibility of *Hrh1* and *Hrh1′* by HRH1KO F1 hybrid mice.

| Strain | Histamine (mg/kg) | Total | % Aff | p-value<sup>a</sup> |
|--------|------------------|-------|-------|---------------------|
|        | 100  | 50  | 25  | 12.5 | 6.25 |           |       |
| HRH1KO | 0/2  | 0/2 | 0/2 | 0/2  | 0/2  | 0/10 | 0      |
| C57BL/6J | 3/3  | 3/3 | 3/3 | 2/2  | 1/2  | 12/15 | 90     | <0.0001 |
| (B6 × HRH1KO) F<sub>1</sub> | 4/4  | 4/4 | 4/4 | 3/4  | 3/3  | 18/19 | 95     | <0.0001 |
| C3H.Bphs<sub>SJL</sub> | 3/3  | 2/2 | 2/2 | 2/2  | 2/2  | 11/11 | 100     | <0.0001 |
| (Bphs<sub>SJL</sub> × HRH1KO) F<sub>1</sub> | 2/2  | 2/2 | 2/2 | 2/2  | 2/2  | 10/10 | 100     | <0.0001 |
| C3H/HeJ | 1/3  | 0/2 | 0/2 | 0/2  | 0/2  | 1/11 | 9      |
| (C3H × HRH1KO) F<sub>1</sub> | 0/2  | 0/2 | 0/2 | 0/2  | 0/2  | 0/10 | 0      |
| CBA/J | 0/2  | 0/2 | 0/2 | 0/2  | 0/2  | 0/11 | 0      |
| (CBA × HRH1KO) F<sub>1</sub> | 0/2  | 0/3 | 0/2 | 0/2  | 0/2  | 0/11 | 0      |
| AKR/J | 1/3  | 0/2 | 0/2 | 0/2  | 0/2  | 1/11 | 9      |
| (AKR × HRH1KO) F<sub>1</sub> | 0/2  | 0/2 | 0/2 | 0/2  | 0/2  | 0/10 | 0      |
| MRL/MpJ | 0/3  | 0/2 | 0/2 | 0/2  | 0/2  | 0/11 | 0      |
| (MRL × HRH1KO) F<sub>1</sub> | 2/3  | 0/2 | 0/2 | 0/2  | 0/2  | 2/11 | 18     |
| PWK/PhJ | 3/3  | 3/3 | 2/2 | 1/2  | 0/2  | 9/12 | 75     | 0.0005  |
| (PWK × HRH1KO) F<sub>1</sub> | 3/3  | 2/2 | 2/2 | 1/2  | 1/2  | 11/13 | 85     | <0.0001 |
| MOLF/MpJ | 2/2  | 2/2 | 2/2 | 2/2  | 0/2  | 8/10 | 80     | <0.0001 |
| (MOLF × HRH1KO) F<sub>1</sub> | 2/2  | 2/2 | 2/2 | 2/2  | 0/2  | 8/10 | 80     | <0.0001 |
| (MOLF × HRH1KO) × HRH1KO | 114  | Aff | Unaff |       |       |       |       |
| HRH1<sup>−/−</sup> | 54   | 0   | 54  | 0/54 | 0%   |
| HRH1<sup>MOLF/−</sup> | 60   | 54  | 6   | 54/60 | 90%  | <0.0001 |

Mice were injected with 200 ng of PTX on D0. Three days later the animals were challenged with the indicated dose of HA (mg dry weight free base/kg body weight) by intraperitoneal injection and deaths recorded as number of animals dead/number of animals tested at 30 minutes post HA challenge. <sup>a</sup>Relative to HRH1KO mice.
Table 4. Linkage of Chr6 marker loci to Bphse.

| Marker   | bp          | χ²   | p-value | A Ho | A He | Un Ho | Un He | Total |
|----------|-------------|------|---------|------|------|-------|-------|-------|
| rs36385580 | 59,353,905  | 28.8 | 7.95E-08 | 28   | 52   | 65    | 20    | 165   |
| rs38650989 | 72,592,521  | 30.6 | 3.21E-08 | 28   | 52   | 66    | 19    | 165   |
| D6Mit186   | 73,387,511  | 29.5 | 5.49E-08 | 30   | 53   | 66    | 19    | 168   |
| D6Mit102   | 93,463,949  | 38.2 | 6.36E-10 | 25   | 58   | 66    | 19    | 168   |
| D6Mit65    | 101,387,523 | 42.3 | 7.92E-11 | 25   | 58   | 68    | 17    | 168   |
| D6Mit149   | 106,005,405 | 38.5 | 5.44E-10 | 27   | 56   | 68    | 17    | 168   |
| Hrh1       | 114,397,936 |      |         |      |      |       |       |       |
| rs31698248 | 120,207,163 | 41.6 | 1.09E-10 | 26   | 56   | 69    | 16    | 167   |
| D6Mit254   | 125,356,646 | 35.6 | 2.42E-09 | 26   | 56   | 66    | 19    | 167   |
| rs30853093 | 125,365,703 | 34.5 | 4.32E-09 | 26   | 57   | 65    | 20    | 168   |
| rs30662734 | 125,370,997 | 34.5 | 4.32E-09 | 26   | 57   | 65    | 20    | 168   |
| rs36868180 | 127,629,804 | 32.7 | 1.06E-08 | 27   | 56   | 65    | 20    | 168   |
| D6Mit135   | 128,834,894 | 29.2 | 6.53E-08 | 27   | 56   | 63    | 22    | 168   |

Mice were injected with 200 ng of PTX on D0. Three days later the animals were challenged with the indicated dose of HA (mg dry weight free base/kg body weight) by intraperitoneal injection and deaths recorded as number of animals dead/number of animals tested at 30 minutes post HA challenge. Segregation of genotype frequency differences with Bphs⁰ (affected = A) and Bphs¹ (unaffected = Un) in (AKR × PWK) × AKR mice were tested by χ² in 2 × 2 contingency tables. He = AKR/PWK allele, Ho = AKR allele.
**Figure 1.** Congenic mapping confirms linkage of Bphse to Bphs/Hrh1.

| Strain                  | C3H/HeJ | MOLF/MpJ | C3H.Bphse<sub>C3H/C3H</sub> | C3H.Bphse<sub>C3H/MOLF</sub> | AKR/J | PWK/J | AKR.Bphse<sub>AKR/AKR</sub> | AKR.Bphse<sub>AKR/PWK</sub> | C3H+AKR | MOLF+PWK | Bphse<sub>C3H/C3H</sub>+Bphse<sub>AKR/AKR</sub> | Bphse<sub>C3H/MOLF</sub>+Bphse<sub>AKR/PWK</sub> |
|------------------------|---------|----------|-------------------------------|-----------------------------|-------|-------|----------------------------|----------------------------|---------|----------|-----------------------------|-----------------------------|
| 4/30                   | C       | C        | C                            | C                           | C     | C     | C                           | C                           | 9/60    | 35/40    | 15/97                       | 54/72                       |
| 20/22                  | M       | M        | M                            | M                           | M     | M     | M                           | M                           | 35/40   | 35/40    | 15/97                       | 54/72                       |
| 7/50                   | C       | C        | C                            | C                           | C     | C     | C                           | C                           | 9/60    | 35/40    | 15/97                       | 54/72                       |
| 19/32                  | C       | C        | C                            | C                           | C     | C     | C                           | C                           | 9/60    | 35/40    | 15/97                       | 54/72                       |
| 5/30                   | A       | A        | A                            | A                           | A     | A     | A                           | A                           | 9/60    | 35/40    | 15/97                       | 54/72                       |
| 15/18                  | P       | P        | P                            | P                           | P     | P     | P                           | P                           | 9/60    | 35/40    | 15/97                       | 54/72                       |
| 8/47                   | A       | A        | A                            | A                           | A     | A     | A                           | A                           | 9/60    | 35/40    | 15/97                       | 54/72                       |
| 35/40                  | A       | He       | He                           | He                          | He    | He    | He                          | He                          | 9/60    | 35/40    | 15/97                       | 54/72                       |
| 19/32                  | C       | He       | He                           | He                          | He    | He    | He                          | He                          | 9/60    | 35/40    | 15/97                       | 54/72                       |
| 13                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.0001<sup>a</sup>       | <0.0001<sup)c</sup>       |
| 90                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.0001<sup>a</sup>       | <0.0001<sup>c</sup>       |
| 14                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.0002<sup>a</sup>       | <0.0001<sup>b</sup>       |
| 60                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.00001<sup>a</sup>      | <0.00001<sup>b</sup>      |
| 16                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.0001<sup>b</sup>       | <0.00001<sup>b</sup>      |
| 83                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.0001<sup>b</sup>       | <0.00001<sup>b</sup>      |
| 17                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.0001<sup>b</sup>       | <0.00001<sup>b</sup>      |
| 88                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.0001<sup>b</sup>       | <0.00001<sup>b</sup>      |
| 15                     |          |          |                               |                             |       |       |                             |                             |         |          | <0.0001<sup>b</sup>       | <0.00001<sup>b</sup>      |

Mice were injected with 200 ng of PTX on D0. Three days later the animals were challenged with the indicated dose of HA (mg dry weight free base/kg body weight) by intraperitoneal injection and deaths recorded as number of animals dead/number of animals tested at 30 minutes post HA challenge. Marker loci and their location (mm10) are listed along with the respective genotypes: C = C3H, M = MOLF, A = AKR, P = PWK and He = heterozygous. <sup>a</sup>Relative to C3H/HeJ; <sup>b</sup>Relative to AKR/J; <sup>c</sup>Relative to C3H/HeJ and AKR/J combined.
Figure 2. Genetic association with Bphs⁸ was tested using a (A) low-resolution 13,257 SNP panel across Chr6:45.0-130.0Mb followed by (B) a high-resolution 78,334 imputed SNP panel across Chr6:111.0-116.4 Mb. Both plots show negative log-transformed p-values of each SNP tested using Efficient Mixed Model Association (EMMA) on the y-axis. Each filled circle denotes a single SNP. Significance thresholds are shown with a dotted line in each panel. The x-axis denotes Mb coordinates for Chr6 (mm10). (C) Gene names are included for SNPs that crossed p-value cut-off of 5.00x10⁻³.

A
Figure 3. Integration of genetic and functional mapping approaches to predict candidates for Bphse. (A). The plot shows normalized negative log-transformed false positive rate of maximum functional enrichment (−log₁₀ FPR) on the y-axis. The x-axis denotes the corresponding normalized negative log-transformed genetic association scores. Candidates that were common across both approaches are shown. (B) The list of gene candidates as predicted by both genetic and functional approaches are ranked using a final gene score ($S_{cg}$) on x-axis and the gene names of top 20 candidates listed on y-axis. Bphs/Hrh1 association is shown in red bar.
**Supplementary Table 1.** List of 50 inbred mouse strains used in genetic association testing.

| Bphs Susceptible (41)   | Bphs Resistant (9)  |
|-------------------------|---------------------|
| 129S1/SvImJ             | C57BL/6J            |
| 129T2/SvEmsJ            | C57BLKS/J           |
| 129X1/SvJ               | C57BR/cdJ           |
| A/J                     | C57L/J              |
| A/WySnJ                 | C58/J               |
| BALB/cJ                 | CZECHII/EiJ         |
| BALB/cByJ               | DBA/1J              |
| BPL/1J                  | DBA/2J              |
| C57BL/10J               | FVB/NJ              |
| C57BL/10ScNJ            | JF1/MsJ             |
| C57BL/6ByJ              | LG/J                |
|                         |                     |
| 129S1/SvImJ             | LP/J                |
| 129T2/SvEmsJ            | MA/MyJ              |
| 129X1/SvJ               | MOLD/RkJ            |
| A/J                     | MOLF/EiJ            |
| A/WySnJ                 | NOD/ShiLtJ          |
| BALB/cJ                 | NON/ShiLtJ          |
| BALB/cByJ               | NOR/LtJ             |
| BPL/1J                  | NU/J                |
| C57BL/10J               | NZB/BINJ            |
| C57BL/10ScNJ            | NZW/LacJ            |
| C57BL/6ByJ              | P/J                 |
**Supplementary Table 2.** Genetic association analysis identifies variants on Chr6 associated with Bphs\(^6\).

| Chr | bp (mm10) | SNP       | Gene     | \(p\)-value\(_\text{EMMA}\) |
|-----|-----------|-----------|----------|----------------------------|
| 6   | 114780885 | rs31440528| I:Atg7   | 8.10E-07                   |
| 6   | 114732069 | rs31439505| I:Atg7   | 2.39E-06                   |
| 6   | 114758979 | rs31445205| I:Atg7   | 2.39E-06                   |

**Suggestive SNPs (p<0.05)**

| Chr | bp (mm10) | SNP       | Gene     | \(p\)-value\(_\text{EMMA}\) |
|-----|-----------|-----------|----------|----------------------------|
| 6   | 110966239 | rs30498521| I:Grm7   | 1.07E-03                   |
| 6   | 113466213 | rs37366170| I:Il17re | 3.14E-03                   |
| 6   | 113521759 | rs36681994| I:Emc3   | 3.14E-03                   |
| 6   | 113766702 | rs36921136| I:Atp2b2 | 3.14E-03                   |
| 6   | 114427899 | rs46432555| I:Hrh1   | 6.32E-05                   |
| 6   | 114792207 | rs31444358| I:Atg7   | 8.71E-05                   |
| 6   | 114941577 | rs6248634 | NC:LOC105242742 | 3.14E-03                |
| 6   | 114951759 | rs31456818| Vgl4     | 8.25E-06                   |
| 6   | 115008370 | rs6262329 | I:Tamm41 | 3.14E-03                   |
| 6   | 115181005 | rs31473897| I:Syn2   | 6.72E-04                   |
| 6   | 115286744 | rs31484360| NA       | 8.71E-05                   |
| 6   | 115321034 | rs31484653| NC:LOC105242744 | 1.31E-02             |
| 6   | 115464239 | rs51526492| I:Pparg  | 8.71E-05                   |
| 6   | 115565855 | rs51720018| I:Tsen2  | 3.14E-03                   |
| 6   | 115612395 | rs31487271| I:Mkm2   | 5.54E-04                   |
| 6   | 115663927 | rs31496654| I:Raf1   | 2.79E-02                   |
| 6   | 115753510 | rs6160517 | I:Tmem40 | 3.14E-03                   |
| 6   | 115782690 | rs31504457| I:Cand2  | 6.72E-04                   |
| 6   | 115853377 | rs31503770| U5:Mbd4  | 8.08E-03                   |
| 6   | 115879245 | rs31507517| I:lft122 | 1.71E-03                   |
| 6   | 115976241 | rs31518615| I:Plxnd1 | 2.11E-02                   |
| 6   | 116120070 | rs31525210| I:Tmcc1  | 3.14E-03                   |
| 6   | 116214868 | rs31533291| I:Fam21  | 6.72E-04                   |
| 6   | 116311087 | rs31535245| I:Zfand4 | 1.08E-02                   |
| 6   | 116402580 | rs31537093| I:March8 | 6.72E-04                   |
| 6   | 118643222 | rs31587804| I:Cacna1c | 1.32E-02               |
| 6   | 119353404 | rs13472337| U3:Adipor2 | 3.86E-02             |

This list was generated using a stringent cut-off \((p<3.81E-06)\) and a moderate cut-off \((p<5.00E-02)\) using Efficient Mixed Model Association (EMMA). Only the most significant SNP tagging a gene is shown. The functional location of variants is listed using the following notation: intronic (I), synonymous change (Cs), 3' untranslated region variant (U3), 5' untranslated region variant (U5), not characterized (NC) and no gene (NA).
**Supplementary Table 3.** List of genetic variants identified ($p \leq 0.05$) using imputed genotypes across Chr6:111.0-116.5 Mb.

| Chr | bp (mm10) | SNP       | Gene   | p-valueEMMA |
|-----|-----------|-----------|--------|------------|
| 6   | 111003149 | rs223699795 | I:Grm7 | 8.12E-03   |
| 6   | 112212190 | rs37480964  | NC:1700054K19Rik | 1.19E-02   |
| 6   | 112309173 | rs232269259 | I:LMCD1 | 1.19E-02   |
| 6   | 112900380 | rs39644268  | I:Srgap3 | 5.45E-05   |
| 6   | 113055745 | rs217254661 | Cn:Thumpd3 | 4.75E-04   |
| 6   | 113114553 | rs262517352 | I:Setd5 | 4.09E-02   |
| 6   | 113171903 | rs38534902  | Cs:Lhfpl4 | 4.75E-04   |
| 6   | 113244289 | rs219248113 | I:Mtmt14 | 4.75E-04   |
| 6   | 113302495 | rs24691029  | I:Capn9 | 2.99E-03   |
| 6   | 113366827 | rs236692255 | U3:Tada3 | 4.09E-02   |
| 6   | 113408719 | rs251474270 | I:Till3 | 2.61E-03   |
| 6   | 113416087 | rs37807004  | I:Rpsd3 | 7.19E-03   |
| 6   | 113422346 | rs214422450 | NA     | 1.70E-05   |
| 6   | 113434320 | rs240625517 | I:Cidec | 1.19E-02   |
| 6   | 113466530 | rs36373609  | I:Il17re | 2.39E-06   |
| 6   | 113521759 | rs36681994  | I:Emc3  | 3.14E-03   |
| 6   | 113575822 | rs22581814  | I:Fancd2 | 5.45E-05   |
| 6   | 113643111 | rs578496862 | I:Irak2 | 2.14E-04   |
| 6   | 113701102 | rs217976133 | I:Tatdn2 | 2.51E-02   |
| 6   | 113780687 | rs37734530  | I:Atp2b2 | 5.45E-05   |
| 6   | 114046481 | rs583881076 | I:Gm15083 | 8.12E-03   |
| 6   | 114134236 | rs227411521 | I:Slc6a1 | 8.12E-03   |
| 6   | 114370888 | rs579728563 | LOC105242741 | 8.12E-03   |
| 6   | 114423235 | rs46923527  | I:Hrh1  | 2.39E-06   |
| 6   | 114780885 | rs31440528  | I:Atg7  | 8.10E-07   |
| 6   | 114951759 | rs31456818  | I:Vgl4  | 8.25E-06   |
| 6   | 115008370 | rs6262329   | NC:Tamm41 | 3.14E-03   |
| 6   | 115062105 | rs58631125  | Gm36190 | 8.12E-03   |
| 6   | 115134140 | rs261281000 | I:Gm17733 | 8.12E-03   |
| 6   | 115181005 | rs31473897  | I:Syn2  | 6.72E-04   |
| 6   | 115310919 | rs31485016  | LOC105242743 | 4.03E-02   |
| 6   | 115321034 | rs31484653  | LOC105242744 | 1.31E-02   |
| 6   | 115464239 | rs51526492  | I:PPARG | 8.71E-05   |
| 6   | 115511777 | rs46370506  | Gm36301 | 1.71E-03   |
| 6   | 115533127 | rs261206240 | I:Gm36355 | 2.22E-03   |
| 6   | 115545283 | rs21272020  | I:Tsen2 | 2.22E-03   |
| 6   | 115591207 | rs586340907 | I:Mkrn2 | 1.92E-05   |
| 6   | 115638313 | rs31494668  | Cs:Raf1 | 6.70E-04   |
| 6   | 115753510 | rs6160517   | I:Temem40 | 3.14E-03   |
|   | ID       | SNP       | Location | P-value |
|---|----------|-----------|----------|---------|
| 6 | 115782690| rs31504457| I:Cand2  | 6.72E-04|
| 6 | 115808296| rs224376952| U5:Rpl32 | 1.08E-02|
| 6 | 115811422| rs249935404| I:Efcab12| 1.08E-02|
| 6 | 115853377| rs31503770| U5:Mbd4  | 8.08E-03|
| 6 | 115865708| rs582751726| I:lift122| 1.71E-03|
| 6 | 115938833| rs31509385| U3:Rho   | 1.71E-03|
| 6 | 115944960| rs31515230| U5:H1foo | 1.08E-02|
| 6 | 115988747| rs31519252| I:Plxnd1 | 4.56E-05|
| 6 | 116104121| rs235864765| I:Tmcc1  | 1.32E-06|
| 6 | 116214868| rs31533291| I:Fam21  | 6.72E-04|
| 6 | 116266396| rs31533962| I:Zfand4 | 3.14E-03|
| 6 | 116383638| rs31534014| I:March8 | 5.45E-05|

This list was generated using a moderate cut-off (p<5.00E-02) using Efficient Mixed Model Association (EMMA). Only the most significant SNP tagging a gene is listed. The functional location of variants is listed using the following notation: intronic (I), synonymous change (Cs), nonsynonymous change (Cn), 3' untranslated region variant (U3), 5' untranslated region variant (U5), not characterized (NC) and no gene (NA).
**Supplementary Table 4.** List of genes predicted to be functionally associated with Bphs physiological processes ranked by negative log of false positive rate.

| Gene      | Cardiac | ER/EMC/ERAD | GPCR | Histamine | PTX | TrH | VP | -log max FPR |
|-----------|---------|-------------|------|-----------|-----|-----|----|--------------|
| C3ar1     | 1.38    | 1.22        | 1.32 | 1.71      | 1.56| 2.89| 2.36| 2.89         |
| Plxna1    | 1.10    | 2.24        | 0.64 | 0.43      | 0.60| 1.03| 0.53| 2.24         |
| Tnfrsf1a  | 1.35    | 1.35        | 1.22 | 1.07      | 1.33| 2.08| 1.18| 2.08         |
| Ret       | 1.81    | 2.03        | 1.04 | 1.06      | 1.17| 0.88| 1.20| 2.03         |
| Tgfa      | 1.25    | 2.03        | 0.88 | 0.90      | 0.87| 1.01| 1.09| 2.03         |
| Aqp1      | 1.89    | 1.43        | 0.90 | 0.85      | 0.81| 1.21| 1.11| 1.89         |
| Hrh1      | 1.01    | 1.83        | 0.72 | 0.70      | 0.92| 0.67| 0.69| 1.83         |
| Kcna1     | 1.65    | 1.81        | 1.70 | 0.94      | 1.06| 0.86| 0.93| 1.81         |
| Wnt7a     | 0.93    | 1.81        | 0.68 | 0.69      | 0.78| 1.20| 0.49| 1.81         |
| Emx1      | 1.17    | 1.79        | 1.37 | 1.06      | 1.51| 0.98| 0.94| 1.79         |
| Pex5      | 1.40    | 1.73        | 0.71 | 0.69      | 0.91| 0.97| 1.00| 1.73         |
| Npy       | 1.11    | 1.70        | 0.70 | 0.53      | 0.87| 0.77| 0.49| 1.70         |
| Ptpn6     | 0.93    | 1.24        | 1.24 | 1.02      | 1.28| 1.67| 1.24| 1.67         |
| Ogg1      | 0.85    | 1.66        | 0.41 | 0.45      | 0.53| 0.75| 0.45| 1.66         |
| Clec4e    | 0.62    | 0.84        | 0.85 | 0.67      | 0.81| 1.64| 0.67| 1.64         |
| Fgf23     | 0.88    | 1.12        | 1.40 | 1.43      | 1.03| 1.07| 1.63| 1.63         |
| Atp2b2    | 0.97    | 1.58        | 0.90 | 0.57      | 0.64| 0.38| 0.50| 1.58         |
| Ghrhr     | 1.07    | 1.52        | 1.58 | 0.94      | 1.13| 0.94| 0.94| 1.58         |
| Apobec1   | 0.59    | 1.49        | 0.56 | 0.67      | 0.85| 1.57| 0.82| 1.57         |
| Hoxa3     | 0.95    | 1.42        | 1.08 | 0.96      | 1.13| 1.18| 1.57| 1.57         |
| Ccl12     | 1.57    | 1.26        | 0.70 | 0.61      | 0.91| 0.90| 0.80| 1.57         |
| Nr2c2     | 1.33    | 1.56        | 0.76 | 1.39      | 0.87| 0.86| 0.74| 1.56         |
| Gata2     | 1.13    | 1.55        | 0.84 | 0.69      | 0.93| 0.95| 0.75| 1.55         |
| Snca      | 1.41    | 1.54        | 1.49 | 1.24      | 1.23| 0.79| 1.20| 1.54         |
| Cacna1c   | 1.43    | 1.27        | 1.54 | 1.12      | 0.71| 0.65| 0.77| 1.54         |
| Mitf      | 1.20    | 1.53        | 1.48 | 1.00      | 1.00| 1.23| 1.07| 1.53         |
| Cd4       | 1.14    | 1.13        | 1.19 | 1.53      | 1.40| 1.37| 0.96| 1.53         |
| Hoxa13    | 1.33    | 1.53        | 1.27 | 0.99      | 1.09| 1.22| 1.00| 1.53         |
| Slc2a3    | 0.81    | 1.52        | 0.68 | 0.46      | 0.79| 1.09| 0.54| 1.52         |
| Dok1      | 0.70    | 1.52        | 0.58 | 0.75      | 0.74| 1.28| 0.71| 1.52         |
| Vhl       | 1.30    | 1.50        | 1.13 | 0.94      | 1.19| 1.38| 1.13| 1.50         |
| Il17ra    | 0.59    | 1.50        | 0.58 | 0.73      | 0.83| 1.34| 0.52| 1.50         |
| Kcna5     | 1.49    | 1.00        | 0.65 | 0.71      | 0.70| 0.72| 0.61| 1.49         |
| Clec4d    | 0.43    | 0.85        | 0.55 | 0.74      | 0.82| 1.49| 0.60| 1.49         |
| Gene   | Adcyap1r1 | Hoxa1 | Cidec | Aicda | Bid | Il12rb2 | Hoxa2 | Mbd4 | Tlx2 | Ntf3 | Cav3 | Sftpb | Plxnd1 | Rho | Hoxa9 | Kcmf1 | Ptms | Lhfpl4 | Tacr1 | Hoxa4 | Hoxa11 | Cd8a | Mgll | Abtb | Crhr2 | Add2 | Mxd1 | Iqsec1 | Reg3g | Adams9 | Grid2 | Asprv1 | Tspan9 | Oxtr | Cntn4 | Pparg | Ltrb | Trh | Atoh1 | Lrg1 | Gdf3 | Smyd1 | Reg2 |
|--------|-----------|-------|-------|-------|-----|---------|-------|------|------|------|------|-------|--------|-----|-------|-------|------|--------|-------|------|-------|------|------|------|-------|------|-------|-------|------|------|------|-------|------|-------|------|------|------|------|------|------|------|
| Gene     | Slc6a1 | 0.74 | 1.17 | 0.70 | 0.42 | 0.69 | 0.31 | 0.42 | 1.17 |
|----------|--------|------|------|------|------|------|------|------|------|
| Ctnna2   | 0.74   | 1.17 | 0.90 | 0.61 | 0.69 | 0.51 | 0.46 | 1.17 |
| Syn2     | 0.77   | 1.16 | 0.87 | 0.49 | 0.53 | 0.68 | 0.31 | 1.16 |
| Sspo     | 0.76   | 0.74 | 0.64 | 0.59 | 0.73 | 1.16 | 0.44 | 1.16 |
| Ccnd2    | 0.96   | 1.15 | 0.59 | 0.76 | 0.85 | 1.07 | 0.63 | 1.15 |
| C1s1     | 0.44   | 1.14 | 0.51 | 0.32 | 0.35 | 0.64 | 0.37 | 1.14 |
| Rad52    | 0.51   | 1.14 | 0.46 | 0.46 | 0.53 | 0.42 | 0.46 | 1.14 |
| Gp9      | 0.59   | 0.72 | 1.02 | 0.59 | 0.73 | 1.14 | 0.47 | 1.14 |
| Dctn1    | 0.44   | 1.14 | 0.40 | 0.24 | 0.48 | 0.41 | 0.31 | 1.14 |
| Atn1     | 0.83   | 1.13 | 0.64 | 0.46 | 0.47 | 0.54 | 0.43 | 1.13 |
| H1fx     | 0.61   | 1.13 | 0.23 | 0.28 | 0.43 | 0.35 | 0.22 | 1.13 |
| Vax2     | 1.11   | 1.00 | 0.78 | 0.90 | 0.72 | 0.93 | 0.49 | 1.11 |
| Rmnd5a   | 0.29   | 1.11 | 0.18 | 0.15 | 0.44 | 0.25 | 0.09 | 1.11 |
| Gpr27    | 0.96   | 1.09 | 0.71 | 0.42 | 0.59 | 0.60 | 0.41 | 1.09 |
| Hoxa5    | 0.94   | 0.83 | 0.82 | 0.85 | 0.98 | 0.61 | 1.09 | 1.09 |
| A2m      | 0.53   | 0.47 | 0.62 | 0.44 | 0.54 | 1.08 | 0.40 | 1.08 |
| Cecr2    | 0.43   | 1.07 | 0.36 | 0.32 | 0.41 | 0.41 | 0.41 | 1.07 |
| Prokr1   | 0.91   | 0.94 | 1.07 | 0.82 | 0.80 | 0.83 | 0.80 | 1.07 |
| Zfp777   | 0.51   | 1.07 | 0.26 | 0.22 | 0.27 | 0.50 | 0.19 | 1.07 |
| Ggcx     | 0.78   | 1.07 | 0.37 | 0.50 | 0.38 | 0.53 | 0.42 | 1.07 |
| Tspan11  | 0.38   | 1.06 | 0.38 | 0.36 | 0.28 | 0.44 | 0.29 | 1.06 |
| Rybp     | 0.73   | 1.06 | 0.45 | 0.34 | 0.41 | 0.72 | 0.37 | 1.06 |
| Ift122   | 0.46   | 1.05 | 0.45 | 0.38 | 0.55 | 0.45 | 0.50 | 1.05 |
| Usp18    | 0.93   | 0.67 | 0.48 | 0.59 | 0.88 | 1.05 | 0.51 | 1.05 |
| Hpgds    | 0.84   | 0.65 | 1.05 | 0.90 | 1.01 | 0.83 | 0.80 | 1.05 |
| Hoxa10   | 0.90   | 0.91 | 0.61 | 0.63 | 0.56 | 1.05 | 0.61 | 1.05 |
| Foxp1    | 0.58   | 1.04 | 0.53 | 0.70 | 0.61 | 0.74 | 0.70 | 1.04 |
| Slc6a6   | 0.84   | 1.03 | 0.45 | 0.40 | 0.55 | 0.58 | 0.53 | 1.03 |
| Grm7     | 0.40   | 1.03 | 0.28 | 0.33 | 0.32 | 0.44 | 0.26 | 1.03 |
| Figla    | 0.65   | 1.02 | 0.60 | 0.47 | 0.55 | 0.67 | 0.36 | 1.02 |
| Fgf6     | 1.02   | 1.02 | 0.67 | 0.61 | 0.62 | 0.62 | 0.54 | 1.02 |
| Podxl2   | 0.40   | 1.01 | 0.27 | 0.31 | 0.30 | 0.39 | 0.31 | 1.01 |
| Cd163    | 0.19   | 0.31 | 1.01 | 0.31 | 0.37 | 0.34 | 0.29 | 1.01 |
| Antx1    | 0.59   | 0.79 | 1.01 | 0.56 | 0.84 | 0.68 | 0.77 | 1.01 |
| Sema4f   | 0.57   | 1.01 | 0.81 | 0.40 | 0.56 | 0.37 | 0.37 | 1.01 |
| Hoxa7    | 0.55   | 1.01 | 0.54 | 0.54 | 0.62 | 0.52 | 0.50 | 1.01 |
| Cyp26b1  | 0.68   | 1.01 | 0.70 | 0.67 | 0.58 | 0.56 | 0.63 | 1.01 |
| Ghrl     | 1.01   | 0.89 | 0.85 | 0.81 | 0.67 | 0.39 | 0.65 | 1.01 |
| Mkrn2    | 0.59   | 1.00 | 0.28 | 0.39 | 0.29 | 0.35 | 0.27 | 1.00 |
| Tuba8    | 0.82   | 1.00 | 0.32 | 0.34 | 0.42 | 0.51 | 0.32 | 1.00 |
| Mfap5    | 0.78   | 0.56 | 0.43 | 0.42 | 0.40 | 0.99 | 0.42 | 0.99 |
| Rtkn     | 0.36   | 0.98 | 0.24 | 0.30 | 0.42 | 0.35 | 0.38 | 0.98 |
| Alms1    | 0.62   | 0.80 | 0.69 | 0.89 | 0.97 | 0.37 | 0.85 | 0.97 |
| Gene       | 0.35 | 0.97 | 0.37 | 0.24 | 0.32 | 0.45 | 0.26 | 0.97 |
|------------|------|------|------|------|------|------|------|------|
| Hoxa6      | 0.57 | 0.96 | 0.33 | 0.41 | 0.39 | 0.64 | 0.43 | 0.96 |
| Wnk1       | 0.18 | 0.96 | 0.23 | 0.21 | 0.28 | 0.25 | 0.15 | 0.96 |
| Mpp6       | 0.48 | 0.57 | 0.30 | 0.45 | 0.41 | 0.96 | 0.33 | 0.96 |
| Actg2      | 0.35 | 0.96 | 0.31 | 0.28 | 0.24 | 0.38 | 0.30 | 0.96 |
| Gmcl1      | 0.54 | 0.96 | 0.29 | 0.30 | 0.24 | 0.29 | 0.38 | 0.96 |
| Clstn3     | 0.78 | 0.95 | 0.93 | 0.50 | 0.64 | 0.50 | 0.50 | 0.95 |
| Kcna6      | 0.41 | 0.95 | 0.42 | 0.31 | 0.39 | 0.25 | 0.25 | 0.95 |
| Cntnap2    | 0.36 | 0.95 | 0.35 | 0.16 | 0.08 | 0.31 | 0.20 | 0.95 |
| Bola3      | 0.25 | 0.35 | 0.36 | 0.25 | 0.27 | 0.95 | 0.31 | 0.95 |
| Edem1      | 0.18 | 0.94 | 0.22 | 0.19 | 0.19 | 0.24 | 0.20 | 0.94 |
| Pcgf1      | 0.56 | 0.94 | 0.57 | 0.53 | 0.55 | 0.65 | 0.62 | 0.94 |
| Gimap5     | 0.34 | 0.47 | 0.42 | 0.53 | 0.68 | 0.94 | 0.81 | 0.94 |
| Rnf103     | 0.49 | 0.93 | 0.34 | 0.50 | 0.52 | 0.53 | 0.47 | 0.93 |
| Kdm5a      | 0.58 | 0.41 | 0.93 | 0.64 | 0.57 | 0.55 | 0.44 | 0.93 |
| Slc6a11    | 0.58 | 0.92 | 0.44 | 0.34 | 0.34 | 0.46 | 0.40 | 0.92 |
| Klf15      | 0.68 | 0.62 | 0.92 | 0.53 | 0.63 | 0.62 | 0.55 | 0.92 |
| Dnajb8     | 0.48 | 0.92 | 0.53 | 0.73 | 0.73 | 0.65 | 0.64 | 0.92 |
| Raf1       | 0.74 | 0.82 | 0.34 | 0.31 | 0.45 | 0.91 | 0.36 | 0.91 |
| Itpr1      | 0.47 | 0.60 | 0.26 | 0.27 | 0.46 | 0.45 | 0.81 | 0.91 |
| Tmem176a   | 0.91 | 0.42 | 0.45 | 0.60 | 0.64 | 0.91 | 0.44 | 0.91 |
| Creb5      | 0.63 | 0.84 | 0.55 | 0.42 | 0.72 | 0.91 | 0.46 | 0.91 |
| Aoc1       | 0.57 | 0.90 | 0.29 | 0.32 | 0.21 | 0.51 | 0.29 | 0.90 |
| Aldh1l1    | 0.45 | 0.90 | 0.56 | 0.38 | 0.45 | 0.61 | 0.36 | 0.90 |
| Loxl3      | 0.83 | 0.60 | 0.42 | 0.44 | 0.47 | 0.89 | 0.47 | 0.89 |
| Atp6v1b1   | 0.71 | 0.88 | 0.49 | 0.34 | 0.31 | 0.53 | 0.39 | 0.88 |
| Fbn2       | 0.69 | 0.43 | 0.44 | 0.36 | 0.44 | 0.88 | 0.47 | 0.88 |
| Gpr162     | 0.58 | 0.88 | 0.56 | 0.38 | 0.48 | 0.64 | 0.34 | 0.88 |
| Skap2      | 0.36 | 0.54 | 0.42 | 0.32 | 0.45 | 0.88 | 0.24 | 0.88 |
| Il5ra      | 0.47 | 0.55 | 0.87 | 0.55 | 0.53 | 0.52 | 0.56 | 0.87 |
| Reg3a      | 0.51 | 0.87 | 0.55 | 0.39 | 0.47 | 0.24 | 0.32 | 0.87 |
| Aak1       | 0.60 | 0.55 | 0.37 | 0.38 | 0.60 | 0.87 | 0.40 | 0.87 |
| C1ra       | 0.51 | 0.55 | 0.86 | 0.65 | 0.54 | 0.60 | 0.43 | 0.86 |
| Reg1       | 0.50 | 0.69 | 0.86 | 0.32 | 0.35 | 0.48 | 0.40 | 0.86 |
| Magi1      | 0.85 | 0.84 | 0.68 | 0.58 | 0.61 | 0.86 | 0.49 | 0.86 |
| Bmp10      | 0.25 | 0.33 | 0.30 | 0.30 | 0.16 | 0.86 | 0.29 | 0.86 |
| Gene   | 0.41  | 0.86  | 0.48  | 0.31  | 0.42  | 0.56  | 0.25  | 0.86  |
|--------|-------|-------|-------|-------|-------|-------|-------|-------|
| P3h3   | 0.39  | 0.44  | 0.65  | 0.42  | 0.86  | 0.48  | 0.56  | 0.86  |
| Mcm2   | 0.41  | 0.57  | 0.47  | 0.69  | 0.60  | 0.86  | 0.46  | 0.86  |
| Clec4a2| 0.40  | 0.46  | 0.85  | 0.44  | 0.46  | 0.48  | 0.42  | 0.85  |
| Akap3  | 0.15  | 0.16  | 0.85  | 0.24  | 0.19  | 0.27  | 0.18  | 0.85  |
| Vmn1r12| 0.47  | 0.85  | 0.23  | 0.10  | 0.11  | 0.39  | 0.08  | 0.85  |
| Wbp1   | 0.54  | 0.85  | 0.34  | 0.42  | 0.43  | 0.38  | 0.85  |
| Stambp | 0.59  | 0.85  | 0.60  | 0.56  | 0.76  | 0.66  | 0.57  | 0.85  |
| Lag3   | 0.38  | 0.85  | 0.46  | 0.40  | 0.35  | 0.41  | 0.42  | 0.85  |
| Rab43  | 0.64  | 0.84  | 0.53  | 0.32  | 0.31  | 0.58  | 0.39  | 0.84  |
| Capg   | 0.35  | 0.76  | 0.43  | 0.61  | 0.52  | 0.84  | 0.53  | 0.84  |
| Zfp384 | 0.39  | 0.83  | 0.42  | 0.33  | 0.17  | 0.41  | 0.33  | 0.83  |
| Rimkib | 0.46  | 0.83  | 0.40  | 0.36  | 0.28  | 0.43  | 0.19  | 0.83  |
| Nfe2i3 | 0.67  | 0.83  | 0.49  | 0.52  | 0.46  | 0.70  | 0.42  | 0.83  |
| Eif2ak3| 0.56  | 0.78  | 0.83  | 0.68  | 0.83  | 0.77  | 0.71  | 0.83  |
| Cntn3  | 0.55  | 0.42  | 0.83  | 0.44  | 0.50  | 0.32  | 0.36  | 0.83  |
| Atg7   | 0.58  | 0.82  | 0.64  | 0.46  | 0.56  | 0.62  | 0.56  | 0.82  |
| Klg1   | 0.55  | 0.82  | 0.71  | 0.55  | 0.55  | 0.64  | 0.39  | 0.82  |
| Rasgefi1a| 0.42  | 0.80  | 0.76  | 0.28  | 0.28  | 0.48  | 0.15  | 0.80  |
| Aup1   | 0.51  | 0.80  | 0.23  | 0.18  | 0.18  | 0.40  | 0.32  | 0.80  |
| Nop2   | 0.27  | 0.39  | 0.18  | 0.27  | 0.16  | 0.80  | 0.19  | 0.80  |
| Vwf    | 0.58  | 0.80  | 0.65  | 0.43  | 0.57  | 0.60  | 0.72  | 0.80  |
| Dysf   | 0.67  | 0.67  | 0.43  | 0.38  | 0.40  | 0.80  | 0.44  | 0.80  |
| Nat8f1 | 0.51  | 0.80  | 0.33  | 0.29  | 0.49  | 0.46  | 0.19  | 0.80  |
| Prr15  | 0.44  | 0.79  | 0.61  | 0.36  | 0.50  | 0.64  | 0.33  | 0.79  |
| Nanog  | 0.41  | 0.54  | 0.50  | 0.47  | 0.32  | 0.79  | 0.40  | 0.79  |
| Reg3b  | 0.40  | 0.32  | 0.78  | 0.47  | 0.65  | 0.56  | 0.40  | 0.78  |
| Gt(ROSA)26Sor| 0.34  | 0.37  | 0.60  | 0.78  | 0.75  | 0.37  | 0.63  | 0.78  |
| 1700003E16Rik| 0.36  | 0.78  | 0.27  | 0.25  | 0.13  | 0.40  | 0.25  | 0.78  |
| Necap1 | 0.26  | 0.77  | 0.26  | 0.20  | 0.27  | 0.29  | 0.19  | 0.77  |
| Tacstd2| 0.42  | 0.37  | 0.44  | 0.39  | 0.55  | 0.77  | 0.34  | 0.77  |
| Wipf3  | 0.39  | 0.77  | 0.32  | 0.32  | 0.44  | 0.40  | 0.21  | 0.77  |
| Gadd45a| 0.70  | 0.70  | 0.50  | 0.64  | 0.70  | 0.77  | 0.66  | 0.77  |
| Neurod6| 0.65  | 0.77  | 0.71  | 0.45  | 0.55  | 0.57  | 0.49  | 0.77  |
| Mtum   | 0.56  | 0.77  | 0.49  | 0.34  | 0.43  | 0.65  | 0.34  | 0.77  |
| Slc41a3| 0.48  | 0.77  | 0.39  | 0.32  | 0.38  | 0.23  | 0.34  | 0.77  |
| Gimap4 | 0.44  | 0.76  | 0.51  | 0.46  | 0.61  | 0.50  | 0.45  | 0.76  |
| Gnb3   | 0.55  | 0.46  | 0.76  | 0.37  | 0.44  | 0.43  | 0.28  | 0.76  |
| Repin1 | 0.42  | 0.76  | 0.30  | 0.25  | 0.30  | 0.42  | 0.15  | 0.76  |
| Prok2  | 0.47  | 0.76  | 0.53  | 0.38  | 0.32  | 0.46  | 0.35  | 0.76  |
| Erc1   | 0.40  | 0.76  | 0.38  | 0.33  | 0.18  | 0.41  | 0.26  | 0.76  |
| Ano2   | 0.33  | 0.75  | 0.32  | 0.19  | 0.37  | 0.31  | 0.39  | 0.75  |
| Arpc4  | 0.46  | 0.41  | 0.22  | 0.16  | 0.53  | 0.75  | 0.17  | 0.75  |
| Gene       | 0.44 | 0.74 | 0.63 | 0.45 | 0.44 | 0.15 | 0.41 | 0.74 |
|------------|------|------|------|------|------|------|------|------|
| Hdh5       | 0.40 | 0.74 | 0.34 | 0.30 | 0.36 | 0.28 | 0.34 | 0.74 |
| Chn2       | 0.42 | 0.74 | 0.16 | 0.31 | 0.50 | 0.57 | 0.24 | 0.74 |
| Zfp467     | 0.54 | 0.73 | 0.31 | 0.29 | 0.17 | 0.41 | 0.26 | 0.73 |
| Retsat     | 0.39 | 0.73 | 0.49 | 0.40 | 0.50 | 0.21 | 0.50 | 0.73 |
| Phc1       | 0.71 | 0.57 | 0.57 | 0.67 | 0.73 | 0.67 | 0.50 | 0.73 |
| Dppa3      | 0.73 | 0.59 | 0.33 | 0.28 | 0.43 | 0.37 | 0.39 | 0.73 |
| Gapdh      | 0.43 | 0.73 | 0.25 | 0.19 | 0.42 | 0.41 | 0.18 | 0.73 |
| Mif2       | 0.52 | 0.73 | 0.43 | 0.62 | 0.71 | 0.62 | 0.47 | 0.73 |
| Mug1       | 0.31 | 0.59 | 0.23 | 0.36 | 0.72 | 0.32 | 0.36 | 0.72 |
| Ezh2       | 0.64 | 0.72 | 0.47 | 0.48 | 0.47 | 0.58 | 0.58 | 0.72 |
| Fxyd4      | 0.65 | 0.72 | 0.66 | 0.57 | 0.47 | 0.51 | 0.57 | 0.72 |
| Scnn1a     | 0.19 | 0.35 | 0.25 | 0.20 | 0.72 | 0.22 | 0.21 | 0.72 |
| Hnrnpa2b1  | 0.25 | 0.21 | 0.72 | 0.30 | 0.24 | 0.30 | 0.30 | 0.72 |
| Vmn1r45    | 0.46 | 0.65 | 0.43 | 0.43 | 0.59 | 0.72 | 0.49 | 0.72 |
| Cd8b1      | 0.43 | 0.71 | 0.29 | 0.40 | 0.61 | 0.42 | 0.44 | 0.71 |
| Htra2      | 0.33 | 0.60 | 0.28 | 0.34 | 0.24 | 0.71 | 0.45 | 0.71 |
| C9orf10    | 0.40 | 0.71 | 0.33 | 0.42 | 0.43 | 0.37 | 0.30 | 0.71 |
| Noto       | 0.48 | 0.70 | 0.40 | 0.36 | 0.53 | 0.57 | 0.44 | 0.70 |
| Cycs       | 0.43 | 0.70 | 0.26 | 0.64 | 0.70 | 0.25 | 0.41 | 0.70 |
| Txnrd3     | 0.37 | 0.70 | 0.26 | 0.26 | 0.40 | 0.29 | 0.22 | 0.70 |
| Pcblp1     | 0.18 | 0.21 | 0.18 | 0.22 | 0.69 | 0.20 | 0.19 | 0.69 |
| C1r1       | 0.26 | 0.34 | 0.69 | 0.23 | 0.26 | 0.27 | 0.24 | 0.69 |
| Mad2l1     | 0.24 | 0.46 | 0.19 | 0.32 | 0.69 | 0.28 | 0.31 | 0.69 |
| Vmn2r26    | 0.47 | 0.69 | 0.51 | 0.46 | 0.46 | 0.48 | 0.36 | 0.69 |
| Pde1c      | 0.38 | 0.68 | 0.52 | 0.29 | 0.37 | 0.17 | 0.30 | 0.68 |
| Tmem121b   | 0.42 | 0.68 | 0.50 | 0.37 | 0.38 | 0.17 | 0.29 | 0.68 |
| Adipor2    | 0.60 | 0.68 | 0.45 | 0.45 | 0.36 | 0.38 | 0.38 | 0.68 |
| Atoh8      | 0.40 | 0.57 | 0.67 | 0.35 | 0.22 | 0.41 | 0.41 | 0.67 |
| Tmem40     | 0.41 | 0.60 | 0.50 | 0.37 | 0.47 | 0.67 | 0.33 | 0.67 |
| Vmn1r41    | 0.42 | 0.32 | 0.67 | 0.53 | 0.49 | 0.44 | 0.42 | 0.67 |
| Elmod3     | 0.54 | 0.66 | 0.26 | 0.18 | 0.31 | 0.24 | 0.05 | 0.66 |
| Tgoln1     | 0.38 | 0.66 | 0.27 | 0.32 | 0.36 | 0.55 | 0.21 | 0.66 |
| Ifio1      | 0.33 | 0.66 | 0.34 | 0.33 | 0.07 | 0.28 | 0.21 | 0.66 |
| Plekhd6    | 0.49 | 0.66 | 0.38 | 0.40 | 0.36 | 0.58 | 0.41 | 0.66 |
| Sfxn5      | 0.37 | 0.66 | 0.32 | 0.32 | 0.21 | 0.32 | 0.19 | 0.66 |
| Cd207      | 0.39 | 0.51 | 0.61 | 0.47 | 0.65 | 0.48 | 0.45 | 0.65 |
| Emg1       | 0.18 | 0.65 | 0.18 | 0.24 | 0.50 | 0.22 | 0.19 | 0.65 |
| Chd4       | 0.26 | 0.65 | 0.38 | 0.29 | 0.43 | 0.40 | 0.45 | 0.65 |
| Rab11fip5  | 0.41 | 0.65 | 0.29 | 0.22 | 0.23 | 0.54 | 0.33 | 0.65 |
| Lbx2       | 0.41 | 0.65 | 0.45 | 0.41 | 0.43 | 0.43 | 0.45 | 0.65 |
| Fkbp9      | 0.29 | 0.18 | 0.28 | 0.15 | 0.45 | 0.65 | 0.25 | 0.65 |
| 1700063H04Rik | 0.40 | 0.36 | 0.65 | 0.30 | 0.24 | 0.20 | 0.36 | 0.65 |
| Gene  | 0.33    | 0.24    | 0.25    | 0.29    | 0.46    | 0.65    | 0.26    | 0.65    |
|-------|---------|---------|---------|---------|---------|---------|---------|---------|
| Gpnmb | 0.38    | 0.62    | 0.51    | 0.36    | 0.50    | 0.64    | 0.39    | 0.64    |
| Tpra1 | 0.31    | 0.64    | 0.27    | 0.14    | 0.41    | 0.39    | 0.16    | 0.64    |
| Wnt5b | 0.46    | 0.64    | 0.38    | 0.36    | 0.30    | 0.57    | 0.28    | 0.64    |
| Ccdc142 | 0.29  | 0.64    | 0.31    | 0.21    | 0.21    | 0.36    | 0.12    | 0.64    |
| Rab7  | 0.26    | 0.37    | 0.32    | 0.21    | 0.45    | 0.64    | 0.19    | 0.64    |
| Cd27  | 0.46    | 0.49    | 0.61    | 0.55    | 0.64    | 0.53    | 0.49    | 0.64    |
| Usp5  | 0.47    | 0.63    | 0.32    | 0.25    | 0.09    | 0.41    | 0.14    | 0.63    |
| Nod1  | 0.30    | 0.63    | 0.38    | 0.30    | 0.39    | 0.36    | 0.33    | 0.63    |
| Fgd5  | 0.48    | 0.63    | 0.40    | 0.29    | 0.25    | 0.41    | 0.39    | 0.63    |
| Mob1a | 0.46    | 0.63    | 0.29    | 0.33    | 0.34    | 0.51    | 0.25    | 0.63    |
| Fbxo41 | 0.44   | 0.63    | 0.30    | 0.24    | 0.42    | 0.41    | 0.25    | 0.63    |
| Mrpl53 | 0.19   | 0.63    | 0.26    | 0.17    | 0.22    | 0.24    | 0.15    | 0.63    |
| Uroc1 | 0.48    | 0.63    | 0.46    | 0.36    | 0.33    | 0.46    | 0.36    | 0.63    |
| Copg1 | 0.23    | 0.30    | 0.18    | 0.23    | 0.33    | 0.62    | 0.23    | 0.62    |
| Zfp9  | 0.30    | 0.62    | 0.40    | 0.26    | 0.29    | 0.34    | 0.21    | 0.62    |
| Nap1l5 | 0.38   | 0.62    | 0.43    | 0.27    | 0.27    | 0.27    | 0.29    | 0.62    |
| Chl1  | 0.39    | 0.45    | 0.48    | 0.41    | 0.62    | 0.43    | 0.38    | 0.62    |
| Slc6a12 | 0.62  | 0.51    | 0.58    | 0.41    | 0.42    | 0.41    | 0.39    | 0.62    |
| Igsec3 | 0.22   | 0.40    | 0.62    | 0.32    | 0.34    | 0.18    | 0.15    | 0.62    |
| Fancd2 | 0.53   | 0.56    | 0.43    | 0.50    | 0.62    | 0.29    | 0.45    | 0.62    |
| Hdac11 | 0.31   | 0.62    | 0.27    | 0.15    | 0.26    | 0.18    | 0.29    | 0.62    |
| Rassf4 | 0.38   | 0.62    | 0.40    | 0.28    | 0.28    | 0.60    | 0.29    | 0.62    |
| Vmn1r47 | 0.36  | 0.35    | 0.62    | 0.40    | 0.52    | 0.44    | 0.42    | 0.62    |
| Ninj2  | 0.54    | 0.52    | 0.45    | 0.36    | 0.43    | 0.62    | 0.32    | 0.62    |
| Washc2 | 0.25    | 0.61    | 0.28    | 0.18    | 0.25    | 0.40    | 0.16    | 0.61    |
| Parp11 | 0.30    | 0.61    | 0.37    | 0.25    | 0.28    | 0.31    | 0.30    | 0.61    |
| Tmem176b | 0.40 | 0.48    | 0.29    | 0.54    | 0.35    | 0.61    | 0.33    | 0.61    |
| Lrcc23 | 0.55    | 0.43    | 0.43    | 0.41    | 0.46    | 0.61    | 0.44    | 0.61    |
| Vopp1  | 0.22    | 0.61    | 0.50    | 0.35    | 0.20    | 0.37    | 0.36    | 0.61    |
| Tex261 | 0.30    | 0.61    | 0.24    | 0.21    | 0.13    | 0.35    | 0.28    | 0.61    |
| Tuba3a | 0.29    | 0.60    | 0.24    | 0.27    | 0.26    | 0.49    | 0.23    | 0.60    |
| Vmn1r42 | 0.35  | 0.29    | 0.60    | 0.43    | 0.36    | 0.35    | 0.35    | 0.60    |
| Tril   | 0.41    | 0.60    | 0.42    | 0.28    | 0.41    | 0.48    | 0.33    | 0.60    |
| Eno2   | 0.35    | 0.60    | 0.33    | 0.29    | 0.42    | 0.38    | 0.40    | 0.60    |
| Ino80b | 0.32    | 0.60    | 0.33    | 0.23    | 0.08    | 0.35    | 0.17    | 0.60    |
| Immt   | 0.32    | 0.60    | 0.18    | 0.28    | 0.28    | 0.35    | 0.15    | 0.60    |
| Smyd5  | 0.21    | 0.60    | 0.50    | 0.14    | 0.30    | 0.35    | 0.18    | 0.60    |
| Fbxl14 | 0.24    | 0.29    | 0.18    | 0.33    | 0.23    | 0.59    | 0.17    | 0.59    |
| Alox5  | 0.41    | 0.47    | 0.51    | 0.48    | 0.59    | 0.58    | 0.49    | 0.59    |
| Tapbp1 | 0.44    | 0.59    | 0.51    | 0.32    | 0.45    | 0.51    | 0.28    | 0.59    |
| Gkn1   | 0.24    | 0.57    | 0.59    | 0.34    | 0.43    | 0.34    | 0.23    | 0.59    |
| Prickle2 | 0.37 | 0.59    | 0.35    | 0.28    | 0.37    | 0.30    | 0.25    | 0.59    |
| Gene          | 0.26 | 0.58 | 0.35 | 0.24 | 0.22 | 0.25 | 0.35 | 0.58 |
|--------------|------|------|------|------|------|------|------|------|
| Cacna2d4     | 0.30 | 0.58 | 0.30 | 0.20 | 0.36 | 0.22 | 0.21 | 0.58 |
| Atp6v0e2     | 0.47 | 0.48 | 0.56 | 0.58 | 0.54 | 0.35 | 0.51 | 0.58 |
| Ankrd26      | 0.18 | 0.39 | 0.58 | 0.15 | 0.12 | 0.18 | 0.20 | 0.58 |
| Fam221a      | 0.33 | 0.58 | 0.29 | 0.14 | 0.26 | 0.33 | 0.16 | 0.58 |
| Creld1       | 0.38 | 0.58 | 0.37 | 0.35 | 0.41 | 0.55 | 0.34 | 0.58 |
| Vamp1        | 0.37 | 0.58 | 0.52 | 0.43 | 0.33 | 0.32 | 0.33 | 0.58 |
| Ctnn6        | 0.40 | 0.58 | 0.25 | 0.25 | 0.09 | 0.43 | 0.30 | 0.58 |
| 4921507P07Rik | 0.22 | 0.57 | 0.19 | 0.20 | 0.17 | 0.29 | 0.09 | 0.57 |
| Krc1         | 0.36 | 0.53 | 0.57 | 0.27 | 0.36 | 0.35 | 0.29 | 0.57 |
| Dqx1         | 0.28 | 0.57 | 0.48 | 0.30 | 0.46 | 0.31 | 0.25 | 0.57 |
| Acrbp        | 0.15 | 0.25 | 0.24 | 0.24 | 0.57 | 0.17 | 0.20 | 0.57 |
| Pole4        | 0.36 | 0.57 | 0.31 | 0.33 | 0.22 | 0.28 | 0.22 | 0.57 |
| St3gal5      | 0.30 | 0.57 | 0.36 | 0.31 | 0.19 | 0.38 | 0.14 | 0.57 |
| Tet3         | 0.55 | 0.39 | 0.38 | 0.39 | 0.56 | 0.44 | 0.39 | 0.56 |
| Vmn1r20      | 0.01 | 0.23 | 0.57 | 0.20 | 0.14 | 0.21 | 0.21 | 0.57 |
| Vmn1r25      | 0.42 | 0.24 | 0.57 | 0.38 | 0.42 | 0.46 | 0.34 | 0.57 |
| Lng4         | 0.41 | 0.57 | 0.39 | 0.31 | 0.44 | 0.44 | 0.29 | 0.57 |
| Gkn2         | 0.46 | 0.56 | 0.39 | 0.33 | 0.29 | 0.42 | 0.43 | 0.56 |
| Hoxa11os     | 0.43 | 0.37 | 0.54 | 0.39 | 0.56 | 0.37 | 0.35 | 0.56 |
| Vmn1r27      | 0.21 | 0.25 | 0.56 | 0.26 | 0.14 | 0.15 | 0.28 | 0.56 |
| Tcf711       | 0.31 | 0.35 | 0.32 | 0.26 | 0.19 | 0.56 | 0.32 | 0.56 |
| Il17re       | 0.42 | 0.55 | 0.55 | 0.36 | 0.43 | 0.47 | 0.31 | 0.55 |
| Gfpt1        | 0.44 | 0.44 | 0.48 | 0.35 | 0.17 | 0.55 | 0.33 | 0.55 |
| Arl8b        | 0.24 | 0.34 | 0.55 | 0.21 | 0.18 | 0.41 | 0.29 | 0.55 |
| Zxdc         | 0.43 | 0.55 | 0.49 | 0.27 | 0.21 | 0.44 | 0.23 | 0.55 |
| Fabp1        | 0.55 | 0.46 | 0.44 | 0.43 | 0.51 | 0.52 | 0.40 | 0.55 |
| Reg3d        | 0.23 | 0.32 | 0.55 | 0.44 | 0.45 | 0.49 | 0.42 | 0.55 |
| Vmn1r46      | 0.34 | 0.50 | 0.46 | 0.25 | 0.23 | 0.55 | 0.35 | 0.55 |
| Fam136a      | 0.13 | 0.25 | 0.22 | 0.30 | 0.54 | 0.20 | 0.19 | 0.54 |
| Irak2        | 0.27 | 0.54 | 0.35 | 0.21 | 0.31 | 0.39 | 0.24 | 0.54 |
| H1foo        | 0.45 | 0.54 | 0.39 | 0.36 | 0.40 | 0.47 | 0.23 | 0.54 |
| Zfp239       | 0.31 | 0.32 | 0.54 | 0.32 | 0.40 | 0.16 | 0.33 | 0.54 |
| Mmmr1        | 0.27 | 0.26 | 0.54 | 0.32 | 0.38 | 0.37 | 0.43 | 0.54 |
| Efcc1        | 0.38 | 0.36 | 0.54 | 0.36 | 0.19 | 0.41 | 0.31 | 0.54 |
| Mthfd2       | 0.26 | 0.47 | 0.26 | 0.46 | 0.45 | 0.54 | 0.30 | 0.54 |
| Ndnf         | 0.25 | 0.35 | 0.53 | 0.26 | 0.40 | 0.30 | 0.29 | 0.53 |
| Gene     | Value1 | Value2 | Value3 | Value4 | Value5 | Value6 | Value7 | Value8 |
|----------|--------|--------|--------|--------|--------|--------|--------|--------|
| Npvf     | 0.28   | 0.30   | 0.53   | 0.43   | 0.44   | 0.24   | 0.35   | 0.53   |
| Olfr215  | 0.26   | 0.53   | 0.32   | 0.31   | 0.20   | 0.32   | 0.23   | 0.53   |
| Krba1    | 0.24   | 0.53   | 0.16   | 0.20   | 0.27   | 0.14   | 0.24   | 0.53   |
| Tmem150a | 0.48   | 0.53   | 0.27   | 0.28   | 0.40   | 0.35   | 0.26   | 0.53   |
| Cbx3     | 0.30   | 0.53   | 0.24   | 0.31   | 0.27   | 0.45   | 0.33   | 0.53   |
| Fam13a   | 0.52   | 0.38   | 0.37   | 0.23   | 0.20   | 0.45   | 0.35   | 0.52   |
| Prmt8    | 0.40   | 0.52   | 0.36   | 0.29   | 0.29   | 0.42   | 0.17   | 0.52   |
| Planp    | 0.26   | 0.40   | 0.52   | 0.32   | 0.30   | 0.22   | 0.25   | 0.52   |
| Clec4f   | 0.50   | 0.49   | 0.41   | 0.44   | 0.43   | 0.52   | 0.33   | 0.52   |
| Kbtbd12  | 0.37   | 0.35   | 0.52   | 0.38   | 0.45   | 0.24   | 0.37   | 0.52   |
| Clec4a3  | 0.32   | 0.43   | 0.52   | 0.34   | 0.37   | 0.33   | 0.32   | 0.52   |
| Abcg2    | 0.25   | 0.31   | 0.36   | 0.52   | 0.38   | 0.32   | 0.32   | 0.52   |
| Spr      | 0.47   | 0.51   | 0.29   | 0.16   | 0.24   | 0.29   | 0.18   | 0.51   |
| Foxj2    | 0.37   | 0.51   | 0.40   | 0.26   | 0.44   | 0.39   | 0.41   | 0.51   |
| Ppp1r17  | 0.43   | 0.40   | 0.51   | 0.32   | 0.42   | 0.34   | 0.34   | 0.51   |
| Vmn1r40  | 0.32   | 0.30   | 0.51   | 0.38   | 0.45   | 0.45   | 0.33   | 0.51   |
| Ptcd3    | 0.19   | 0.34   | 0.46   | 0.51   | 0.51   | 0.17   | 0.08   | 0.51   |
| Il17rc   | 0.51   | 0.50   | 0.32   | 0.27   | 0.45   | 0.36   | 0.36   | 0.51   |
| M1ap     | 0.36   | 0.51   | 0.39   | 0.37   | 0.36   | 0.38   | 0.44   | 0.51   |
| Gimap9   | 0.30   | 0.43   | 0.51   | 0.31   | 0.34   | 0.37   | 0.27   | 0.51   |
| BC048671 | 0.22   | 0.38   | 0.51   | 0.35   | 0.38   | 0.22   | 0.42   | 0.51   |
| Inmt     | 0.49   | 0.50   | 0.49   | 0.41   | 0.42   | 0.51   | 0.38   | 0.51   |
| Gm5111   | 0.36   | 0.49   | 0.32   | 0.26   | 0.42   | 0.51   | 0.23   | 0.51   |
| Tmcc1    | 0.30   | 0.51   | 0.27   | 0.15   | 0.35   | 0.36   | 0.22   | 0.51   |
| Chst13   | 0.33   | 0.35   | 0.51   | 0.33   | 0.27   | 0.41   | 0.14   | 0.51   |
| Arhgap25 | 0.27   | 0.29   | 0.51   | 0.35   | 0.43   | 0.28   | 0.42   | 0.51   |
| Sec61a1  | 0.35   | 0.51   | 0.27   | 0.36   | 0.33   | 0.50   | 0.43   | 0.51   |
| Cnbp     | 0.18   | 0.23   | 0.18   | 0.22   | 0.51   | 0.20   | 0.23   | 0.51   |
| Cul1     | 0.23   | 0.37   | 0.18   | 0.21   | 0.50   | 0.21   | 0.28   | 0.50   |
| Cpne9    | 0.33   | 0.50   | 0.42   | 0.28   | 0.40   | 0.46   | 0.32   | 0.50   |
| Srgap3   | 0.40   | 0.50   | 0.40   | 0.34   | 0.34   | 0.33   | 0.27   | 0.50   |
| Vamp8    | 0.37   | 0.44   | 0.31   | 0.29   | 0.34   | 0.50   | 0.38   | 0.50   |
| Zfp956   | 0.21   | 0.50   | 0.43   | 0.23   | 0.15   | 0.34   | 0.22   | 0.50   |
| Eva1a    | 0.45   | 0.50   | 0.36   | 0.33   | 0.20   | 0.45   | 0.14   | 0.50   |
| Cflap100 | 0.39   | 0.50   | 0.38   | 0.07   | 0.23   | 0.43   | 0.26   | 0.50   |
| Tpi1     | 0.43   | 0.50   | 0.18   | 0.13   | 0.27   | 0.31   | 0.21   | 0.50   |
| Ankrd53  | 0.23   | 0.50   | 0.41   | 0.19   | 0.28   | 0.32   | 0.25   | 0.50   |
| Smarcd1  | 0.50   | 0.43   | 0.47   | 0.46   | 0.41   | 0.21   | 0.48   | 0.50   |
| Kdm3a    | 0.33   | 0.39   | 0.38   | 0.50   | 0.28   | 0.32   | 0.40   | 0.50   |
| Csgainact2 | 0.23  | 0.49   | 0.22   | 0.20   | 0.22   | 0.24   | 0.21   | 0.49   |
| Gimap7   | 0.35   | 0.43   | 0.49   | 0.38   | 0.47   | 0.42   | 0.38   | 0.49   |
| Cops7a   | 0.20   | 0.49   | 0.22   | 0.21   | 0.29   | 0.29   | 0.14   | 0.49   |
| Tmem43   | 0.44   | 0.39   | 0.31   | 0.28   | 0.49   | 0.20   | 0.49   | 0.50   |
| Gene    | 0.23 | 0.49 | 0.27 | 0.22 | 0.19 | 0.25 | 0.15 | 0.49 |
|---------|------|------|------|------|------|------|------|------|
| Pdia4   | 0.27 | 0.49 | 0.21 | 0.16 | 0.23 | 0.27 | 0.35 | 0.49 |
| Tra2a   | 0.36 | 0.49 | 0.35 | 0.31 | 0.39 | 0.37 | 0.36 | 0.49 |
| Gsdme   | 0.18 | 0.48 | 0.18 | 0.24 | 0.34 | 0.49 | 0.26 | 0.49 |
| Serbp1  | 0.33 | 0.38 | 0.49 | 0.35 | 0.09 | 0.37 | 0.35 | 0.49 |
| Lmcd1   | 0.31 | 0.48 | 0.26 | 0.20 | 0.13 | 0.25 | 0.28 | 0.48 |
| Vmn1r29 | 0.26 | 0.36 | 0.43 | 0.33 | 0.48 | 0.21 | 0.36 | 0.48 |
| Mical3  | 0.34 | 0.48 | 0.43 | 0.17 | 0.21 | 0.42 | 0.31 | 0.48 |
| Vmn1r49 | 0.29 | 0.48 | 0.40 | 0.35 | 0.36 | 0.39 | 0.33 | 0.48 |
| M6pr    | 0.37 | 0.38 | 0.27 | 0.48 | 0.48 | 0.41 | 0.43 | 0.48 |
| Tada3   | 0.30 | 0.48 | 0.34 | 0.29 | 0.14 | 0.45 | 0.14 | 0.48 |
| Exoc6b  | 0.22 | 0.48 | 0.31 | 0.28 | 0.28 | 0.43 | 0.35 | 0.48 |
| Gars    | 0.18 | 0.23 | 0.20 | 0.19 | 0.48 | 0.30 | 0.19 | 0.48 |
| Vmn1r13 | 0.26 | 0.31 | 0.47 | 0.43 | 0.48 | 0.33 | 0.46 | 0.48 |
| Brk1    | 0.18 | 0.22 | 0.26 | 0.18 | 0.48 | 0.24 | 0.21 | 0.48 |
| Lsm3    | 0.15 | 0.48 | 0.24 | 0.17 | 0.17 | 0.18 | 0.25 | 0.48 |
| Vmn1r44 | 0.37 | 0.35 | 0.48 | 0.42 | 0.45 | 0.46 | 0.40 | 0.48 |
| Depp1   | 0.35 | 0.39 | 0.48 | 0.28 | 0.26 | 0.27 | 0.32 | 0.48 |
| Atp6v1e1| 0.29 | 0.34 | 0.48 | 0.23 | 0.32 | 0.33 | 0.20 | 0.48 |
| Scrm1   | 0.42 | 0.47 | 0.25 | 0.26 | 0.34 | 0.38 | 0.21 | 0.47 |
| Eif4e3  | 0.47 | 0.44 | 0.36 | 0.19 | 0.38 | 0.40 | 0.22 | 0.47 |
| Vamp5   | 0.39 | 0.44 | 0.47 | 0.22 | 0.33 | 0.16 | 0.20 | 0.47 |
| Vmn1r14 | 0.24 | 0.27 | 0.47 | 0.38 | 0.42 | 0.14 | 0.43 | 0.47 |
| Nup210  | 0.32 | 0.39 | 0.47 | 0.24 | 0.14 | 0.33 | 0.25 | 0.47 |
| Nat8f2  | 0.22 | 0.31 | 0.47 | 0.36 | 0.39 | 0.34 | 0.32 | 0.47 |
| Vmn1r7  | 0.25 | 0.47 | 0.30 | 0.28 | 0.28 | 0.29 | 0.15 | 0.47 |
| Setd5   | 0.36 | 0.47 | 0.42 | 0.16 | 0.26 | 0.42 | 0.15 | 0.47 |
| Igf2bp3 | 0.37 | 0.35 | 0.47 | 0.34 | 0.41 | 0.44 | 0.30 | 0.47 |
| Ppp4r2  | 0.33 | 0.39 | 0.30 | 0.26 | 0.19 | 0.47 | 0.28 | 0.47 |
| Mrps25  | 0.14 | 0.19 | 0.21 | 0.24 | 0.47 | 0.11 | 0.11 | 0.47 |
| Vgll4   | 0.44 | 0.46 | 0.40 | 0.35 | 0.28 | 0.07 | 0.40 | 0.46 |
| Tax1bp1 | 0.25 | 0.46 | 0.45 | 0.38 | 0.39 | 0.32 | 0.41 | 0.46 |
| 4931417E11Rik | 0.34 | 0.39 | 0.46 | 0.36 | 0.37 | 0.24 | 0.44 | 0.46 |
| Lrttm1  | 0.37 | 0.46 | 0.44 | 0.40 | 0.29 | 0.23 | 0.37 | 0.46 |
| Olfr212 | 0.16 | 0.23 | 0.46 | 0.26 | 0.25 | 0.38 | 0.26 | 0.46 |
| Cct7    | 0.18 | 0.20 | 0.18 | 0.18 | 0.46 | 0.20 | 0.19 | 0.46 |
| Avl9    | 0.25 | 0.46 | 0.28 | 0.32 | 0.15 | 0.20 | 0.19 | 0.46 |
| Vmn1r10 | 0.21 | 0.35 | 0.46 | 0.39 | 0.43 | 0.09 | 0.41 | 0.46 |
| Sumf1   | 0.29 | 0.35 | 0.29 | 0.46 | 0.43 | 0.38 | 0.42 | 0.46 |
| Osbp13  | 0.36 | 0.42 | 0.17 | 0.19 | 0.27 | 0.46 | 0.11 | 0.46 |
| Slc4a5  | 0.35 | 0.43 | 0.36 | 0.31 | 0.39 | 0.45 | 0.19 | 0.45 |
| Brpf1   | 0.16 | 0.43 | 0.19 | 0.11 | 0.14 | 0.45 | 0.12 | 0.45 |
| Chchd6  | 0.14 | 0.38 | 0.45 | 0.24 | 0.28 | 0.23 | 0.08 | 0.45 |
| Gene          | 1810044D09Rik | 4930544G11Rik | 4930590J08Rik | 5430402O13Rik |
|--------------|--------------|--------------|--------------|--------------|
| Dguok        | 0.21         | 0.33         | 0.33         | 0.19         |
| Lrtm2        | 0.32         | 0.33         | 0.33         | 0.33         |
| Nat8         | 0.44         | 0.33         | 0.36         | 0.36         |
| Lrrc61       | 0.37         | 0.42         | 0.27         | 0.27         |
| Lancl2       | 0.27         | 0.32         | 0.24         | 0.24         |
| Mtmr14       | 0.30         | 0.30         | 0.29         | 0.29         |
| Arl6ip5      | 0.18         | 0.32         | 0.18         | 0.18         |
| Tmsb10       | 0.26         | 0.33         | 0.33         | 0.30         |
| Nat8f4       | 0.25         | 0.34         | 0.22         | 0.20         |
| Gprin3       | 0.33         | 0.35         | 0.25         | 0.25         |
| Gm10319      | 0.11         | 0.44         | 0.16         | 0.16         |
| Hk2          | 0.36         | 0.39         | 0.27         | 0.24         |
| Jagn1        | 0.18         | 0.23         | 0.18         | 0.21         |
| march8       | 0.25         | 0.27         | 0.21         | 0.22         |
| Lpar5        | 0.27         | 0.37         | 0.25         | 0.33         |
| Ggct         | 0.30         | 0.28         | 0.26         | 0.43         |
| Gimap1       | 0.28         | 0.37         | 0.27         | 0.30         |
| Lmod3        | 0.42         | 0.41         | 0.32         | 0.14         |
| Foxi3        | 0.26         | 0.24         | 0.28         | 0.38         |
| Nat8f3       | 0.42         | 0.33         | 0.40         | 0.33         |
| Dcp1b        | 0.36         | 0.43         | 0.29         | 0.25         |
| Vmn1r53      | 0.27         | 0.43         | 0.36         | 0.36         |
| Fkbp14       | 0.37         | 0.42         | 0.33         | 0.43         |
| Pradc1       | 0.18         | 0.34         | 0.18         | 0.36         |
| Gimap3       | 0.33         | 0.38         | 0.39         | 0.42         |
| Setmar       | 0.28         | 0.42         | 0.18         | 0.36         |
| Reep1        | 0.38         | 0.42         | 0.39         | 0.28         |
| Vmn4r9       | 0.23         | 0.20         | 0.35         | 0.32         |
| Vmn1r50      | 0.30         | 0.36         | 0.42         | 0.35         |
| Zfp746       | 0.21         | 0.42         | 0.23         | 0.21         |
| Crbn         | 0.19         | 0.42         | 0.20         | 0.15         |
| Xpc          | 0.29         | 0.42         | 0.26         | 0.39         |
| Gxylt2       | 0.34         | 0.37         | 0.27         | 0.27         |
| Tmt1         | 0.15         | 0.18         | 0.16         | 0.15         |
| Herc6        | 0.33         | 0.41         | 0.33         | 0.29         |
| Vmn2r25      | 0.24         | 0.25         | 0.35         | 0.26         |
| Itprid1      | 0.20         | 0.31         | 0.28         | 0.27         |
| Tia1         | 0.20         | 0.29         | 0.35         | 0.29         |
| Gene        | 0.34 | 0.41 | 0.35 | 0.28 | 0.34 | 0.24 | 0.28 | 0.41 |
|------------|------|------|------|------|------|------|------|------|
| Nat8f5     | 0.24 | 0.30 | 0.41 | 0.40 | 0.40 | 0.32 | 0.40 | 0.41 |
| Clec4b1    | 0.22 | 0.24 | 0.35 | 0.19 | 0.41 | 0.27 | 0.16 | 0.41 |
| Kbbd8      | 0.32 | 0.41 | 0.30 | 0.33 | 0.25 | 0.32 | 0.27 | 0.41 |
| Mug2       | 0.34 | 0.41 | 0.25 | 0.16 | 0.32 | 0.27 | 0.29 | 0.41 |
| Znr2       | 0.28 | 0.41 | 0.33 | 0.29 | 0.25 | 0.21 | 0.33 | 0.41 |
| Cpvl       | 0.41 | 0.34 | 0.29 | 0.30 | 0.32 | 0.40 | 0.13 | 0.41 |
| Thnsl2     | 0.18 | 0.27 | 0.24 | 0.17 | 0.41 | 0.21 | 0.19 | 0.41 |
| Bms1       | 0.27 | 0.35 | 0.39 | 0.32 | 0.32 | 0.41 | 0.16 | 0.41 |
| C1rb       | 0.32 | 0.38 | 0.41 | 0.29 | 0.36 | 0.30 | 0.35 | 0.41 |
| Gimap6     | 0.37 | 0.30 | 0.26 | 0.41 | 0.24 | 0.34 | 0.19 | 0.41 |
| Hibadh     | 0.17 | 0.41 | 0.26 | 0.18 | 0.38 | 0.18 | 0.17 | 0.41 |
| Usp39      | 0.35 | 0.41 | 0.27 | 0.25 | 0.22 | 0.27 | 0.18 | 0.41 |
| Ccser1     | 0.41 | 0.31 | 0.24 | 0.29 | 0.38 | 0.29 | 0.38 | 0.41 |
| Eogt       | 0.34 | 0.39 | 0.41 | 0.30 | 0.30 | 0.34 | 0.22 | 0.41 |
| Prrt3      | 0.22 | 0.33 | 0.41 | 0.32 | 0.33 | 0.17 | 0.37 | 0.41 |
| Tll3       | 0.40 | 0.35 | 0.40 | 0.29 | 0.36 | 0.30 | 0.25 | 0.40 |
| Sec13      | 0.13 | 0.21 | 0.16 | 0.22 | 0.40 | 0.20 | 0.12 | 0.40 |
| Cracr2a    | 0.34 | 0.26 | 0.37 | 0.30 | 0.29 | 0.21 | 0.40 | 0.40 |
| Chchd4     | 0.31 | 0.40 | 0.23 | 0.30 | 0.15 | 0.21 | 0.17 | 0.40 |
| Ppm1k      | 0.36 | 0.40 | 0.28 | 0.25 | 0.32 | 0.18 | 0.22 | 0.40 |
| Eefsec     | 0.15 | 0.40 | 0.20 | 0.16 | 0.15 | 0.34 | 0.14 | 0.40 |
| Jazf1      | 0.27 | 0.40 | 0.25 | 0.22 | 0.33 | 0.30 | 0.12 | 0.40 |
| Camk1      | 0.31 | 0.33 | 0.35 | 0.18 | 0.13 | 0.40 | 0.25 | 0.40 |
| Zfand4     | 0.25 | 0.35 | 0.40 | 0.27 | 0.25 | 0.18 | 0.17 | 0.40 |
| 2310069B03Rik | 0.24 | 0.24 | 0.40 | 0.33 | 0.30 | 0.13 | 0.36 | 0.40 |
| Shq1       | 0.12 | 0.28 | 0.29 | 0.27 | 0.40 | 0.19 | 0.21 | 0.40 |
| V1ra8      | 0.23 | 0.25 | 0.30 | 0.20 | 0.18 | 0.40 | 0.23 | 0.40 |
| Rad18      | 0.21 | 0.37 | 0.40 | 0.29 | 0.29 | 0.21 | 0.31 | 0.40 |
| Gm765      | 0.19 | 0.33 | 0.36 | 0.32 | 0.27 | 0.34 | 0.40 | 0.40 |
| Lsm5       | 0.11 | 0.21 | 0.28 | 0.19 | 0.40 | 0.19 | 0.20 | 0.40 |
| Pdzrn3     | 0.32 | 0.36 | 0.17 | 0.10 | 0.39 | 0.25 | 0.33 | 0.39 |
| Tafa4      | 0.24 | 0.34 | 0.39 | 0.32 | 0.25 | 0.18 | 0.31 | 0.39 |
| Polr1a     | 0.33 | 0.39 | 0.23 | 0.24 | 0.16 | 0.38 | 0.11 | 0.39 |
| Vmn1r33    | 0.27 | 0.22 | 0.30 | 0.30 | 0.35 | 0.28 | 0.39 | 0.39 |
| Paij2b     | 0.19 | 0.39 | 0.18 | 0.21 | 0.39 | 0.27 | 0.25 | 0.39 |
| Mindy4     | 0.28 | 0.39 | 0.29 | 0.25 | 0.13 | 0.21 | 0.23 | 0.39 |
| C130060K24Rik | 0.25 | 0.26 | 0.39 | 0.24 | 0.14 | 0.27 | 0.38 | 0.39 |
| Gcfc2      | 0.22 | 0.32 | 0.39 | 0.21 | 0.15 | 0.26 | 0.26 | 0.39 |
| Doxl2      | 0.29 | 0.29 | 0.33 | 0.26 | 0.25 | 0.39 | 0.20 | 0.39 |
| Vmn1r48    | 0.18 | 0.24 | 0.27 | 0.27 | 0.20 | 0.39 | 0.26 | 0.39 |
| Dnah6      | 0.39 | 0.37 | 0.33 | 0.30 | 0.12 | 0.34 | 0.24 | 0.39 |
| Slc25a26   | 0.28 | 0.39 | 0.29 | 0.28 | 0.24 | 0.20 | 0.27 | 0.39 |
| Gene       | 0.32 | 0.39 | 0.27 | 0.28 | 0.20 | 0.31 | 0.24 | 0.39 |
|------------|------|------|------|------|------|------|------|------|
| Sh2d6      | 0.13 | 0.20 | 0.13 | 0.28 | 0.38 | 0.28 | 0.19 | 0.38 |
| Mrpl35     | 0.24 | 0.35 | 0.19 | 0.31 | 0.38 | 0.22 | 0.33 | 0.38 |
| Uba3       | 0.18 | 0.38 | 0.23 | 0.20 | 0.24 | 0.23 | 0.20 | 0.38 |
| Rpn1       | 0.29 | 0.29 | 0.27 | 0.31 | 0.35 | 0.27 | 0.38 | 0.38 |
| C1s2       | 0.23 | 0.38 | 0.33 | 0.22 | 0.35 | 0.20 | 0.32 | 0.38 |
| Gimap8     | 0.15 | 0.34 | 0.38 | 0.20 | 0.22 | 0.26 | 0.25 | 0.38 |
| Wdr54      | 0.25 | 0.38 | 0.22 | 0.19 | 0.14 | 0.19 | 0.10 | 0.38 |
| Isy1       | 0.28 | 0.38 | 0.27 | 0.24 | 0.24 | 0.25 | 0.28 | 0.38 |
| Duspl1     | 0.10 | 0.38 | 0.18 | 0.32 | 0.18 | 0.34 | 0.18 | 0.38 |
| Zfp786     | 0.23 | 0.34 | 0.33 | 0.34 | 0.38 | 0.14 | 0.33 | 0.38 |
| Vmn1r11    | 0.37 | 0.30 | 0.38 | 0.22 | 0.18 | 0.26 | 0.15 | 0.38 |
| Zfcp26     | 0.25 | 0.38 | 0.20 | 0.28 | 0.21 | 0.37 | 0.18 | 0.38 |
| Tafa1      | 0.22 | 0.38 | 0.35 | 0.26 | 0.19 | 0.28 | 0.21 | 0.38 |
| Vmn1r30    | 0.17 | 0.38 | 0.27 | 0.21 | 0.30 | 0.17 | 0.23 | 0.38 |
| Prdm5      | 0.37 | 0.37 | 0.28 | 0.31 | 0.35 | 0.25 | 0.31 | 0.37 |
| Zfp398     | 0.29 | 0.37 | 0.34 | 0.35 | 0.34 | 0.21 | 0.30 | 0.37 |
| Tigar      | 0.35 | 0.37 | 0.27 | 0.20 | 0.09 | 0.26 | 0.24 | 0.37 |
| Bcl2l13    | 0.36 | 0.37 | 0.35 | 0.21 | 0.26 | 0.33 | 0.29 | 0.37 |
| Vmn1r30    | 0.24 | 0.36 | 0.37 | 0.34 | 0.33 | 0.24 | 0.32 | 0.37 |
| Rpl32      | 0.29 | 0.29 | 0.37 | 0.18 | 0.12 | 0.29 | 0.33 | 0.37 |
| Vmn1r39    | 0.30 | 0.33 | 0.22 | 0.24 | 0.37 | 0.23 | 0.26 | 0.37 |
| Dusp11     | 0.22 | 0.23 | 0.22 | 0.19 | 0.17 | 0.37 | 0.25 | 0.37 |
| Nat8f6     | 0.28 | 0.37 | 0.25 | 0.20 | 0.26 | 0.34 | 0.20 | 0.37 |
| Scl25a18   | 0.27 | 0.37 | 0.33 | 0.26 | 0.28 | 0.30 | 0.32 | 0.37 |
| Il23r      | 0.26 | 0.37 | 0.33 | 0.31 | 0.16 | 0.34 | 0.28 | 0.37 |
| Fancd2os   | 0.33 | 0.37 | 0.22 | 0.23 | 0.21 | 0.19 | 0.34 | 0.37 |
| Gkn3       | 0.26 | 0.31 | 0.36 | 0.20 | 0.20 | 0.26 | 0.23 | 0.36 |
| Hoxaas3    | 0.13 | 0.18 | 0.14 | 0.21 | 0.20 | 0.17 | 0.36 | 0.36 |
| Lpcat3     | 0.25 | 0.29 | 0.24 | 0.28 | 0.21 | 0.36 | 0.12 | 0.36 |
| 1600015i10Rik | 0.33 | 0.29 | 0.32 | 0.29 | 0.21 | 0.36 | 0.32 | 0.36 |
| Vmn1r43    | 0.29 | 0.24 | 0.27 | 0.27 | 0.36 | 0.16 | 0.30 | 0.36 |
| Pcyox1     | 0.31 | 0.36 | 0.34 | 0.17 | 0.35 | 0.15 | 0.22 | 0.36 |
| Zfp248     | 0.31 | 0.36 | 0.33 | 0.28 | 0.19 | 0.34 | 0.29 | 0.36 |
| Vmn1r5     | 0.22 | 0.21 | 0.31 | 0.32 | 0.20 | 0.10 | 0.36 | 0.36 |
| Kbtbd2     | 0.21 | 0.36 | 0.24 | 0.22 | 0.17 | 0.23 | 0.19 | 0.36 |
| Vmn1r8     | 0.24 | 0.22 | 0.29 | 0.29 | 0.36 | 0.14 | 0.25 | 0.36 |
| Hmces      | 0.25 | 0.36 | 0.18 | 0.21 | 0.18 | 0.26 | 0.19 | 0.36 |
| Clec4a1    | 0.27 | 0.30 | 0.36 | 0.32 | 0.30 | 0.31 | 0.22 | 0.36 |
| Herc3      | 0.25 | 0.31 | 0.23 | 0.26 | 0.26 | 0.36 | 0.17 | 0.36 |
| Gene       | 0610030E20Rik | Tprkb   | Zfp282  | Mat2a   | Cdca3   | Stk31   | C87436  | Nagk    | Olfr214  | Vmn1r38  | Phb2    | Vmn1r23  | Rnu7    | Rpi     | Vmn1r54  | Mkm2os  | Malsu1   | Vmn2r27  | Tatdn2   | Rny3    | Ssu2    | Vmn2r20  | Vmn1r21  | Vmn1r32  | Zfp638  | Ccdc77  | Vmn1r37  | Olfr213  | Vmn2r23  | Vmn2r19  | Snmp27  | Tamm41  | Vmn2r21  | Ruvbl1   | 4933431G14Rik | Vmn1r28  | Rad51ap1 | 1700054K19Rik |
|------------|---------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Gene      | 0.24  | 0.21  | 0.12  | 0.16  | 0.28  | 0.33  | 0.13  | 0.33  |
|-----------|-------|-------|-------|-------|-------|-------|-------|-------|
| Rny1      | 0.26  | 0.32  | 0.26  | 0.25  | 0.22  | 0.23  | 0.30  | 0.32  |
| Dyrk4     | 0.23  | 0.32  | 0.24  | 0.17  | 0.23  | 0.16  | 0.20  | 0.32  |
| Nt5c3     | 0.17  | 0.16  | 0.32  | 0.28  | 0.30  | 0.06  | 0.19  | 0.32  |
| Gm9871    | 0.18  | 0.32  | 0.21  | 0.18  | 0.27  | 0.28  | 0.19  | 0.32  |
| Hnrmpf    | 0.14  | 0.22  | 0.32  | 0.24  | 0.29  | 0.18  | 0.18  | 0.32  |
| Mrpl19    | 0.30  | 0.29  | 0.32  | 0.21  | 0.13  | 0.09  | 0.21  | 0.32  |
| Efcab12   | 0.23  | 0.32  | 0.28  | 0.15  | 0.18  | 0.20  | 0.21  | 0.32  |
| Rbsn      | 0.17  | 0.32  | 0.17  | 0.26  | 0.22  | 0.22  | 0.14  | 0.32  |
| Thumpd3   | 0.30  | 0.31  | 0.27  | 0.21  | 0.22  | 0.20  | 0.24  | 0.31  |
| Grc10     | 0.28  | 0.27  | 0.18  | 0.28  | 0.25  | 0.24  | 0.31  | 0.31  |
| Clec4b2   | 0.17  | 0.24  | 0.20  | 0.26  | 0.31  | 0.19  | 0.15  | 0.31  |
| Zfp422    | 0.22  | 0.31  | 0.28  | 0.27  | 0.13  | 0.25  | 0.28  | 0.31  |
| Vmn1r22   | 0.15  | 0.31  | 0.26  | 0.19  | 0.12  | 0.27  | 0.20  | 0.31  |
| Chmp3     | 0.24  | 0.15  | 0.15  | 0.28  | 0.07  | 0.31  | 0.19  | 0.31  |
| 4930417O13Rik | 0.18  | 0.30  | 0.18  | 0.18  | 0.17  | 0.31  | 0.16  | 0.31  |
| Zfp637    | 0.25  | 0.25  | 0.31  | 0.30  | 0.13  | 0.22  | 0.14  | 0.31  |
| Vmn1r35   | 0.22  | 0.23  | 0.17  | 0.31  | 0.18  | 0.09  | 0.19  | 0.31  |
| Suclg1    | 0.23  | 0.21  | 0.28  | 0.26  | 0.18  | 0.23  | 0.31  | 0.31  |
| Vmn1r6    | 0.11  | 0.24  | 0.30  | 0.19  | 0.21  | 0.11  | 0.19  | 0.30  |
| 2610300M13Rik | 0.25  | 0.30  | 0.24  | 0.23  | 0.19  | 0.30  | 0.19  | 0.30  |
| Plekha8   | 0.22  | 0.30  | 0.12  | 0.21  | 0.25  | 0.13  | 0.16  | 0.30  |
| Zfp862-ps | 0.24  | 0.30  | 0.25  | 0.25  | 0.22  | 0.23  | 0.22  | 0.30  |
| Svs1      | 0.17  | 0.23  | 0.25  | 0.28  | 0.30  | 0.16  | 0.25  | 0.30  |
| 1700069P05Rik | 0.30  | 0.27  | 0.22  | 0.23  | 0.14  | 0.27  | 0.24  | 0.30  |
| Vmn1r51   | 0.24  | 0.24  | 0.24  | 0.28  | 0.24  | 0.21  | 0.30  | 0.30  |
| D6Wsu163e | 0.19  | 0.24  | 0.30  | 0.19  | 0.19  | 0.19  | 0.26  | 0.30  |
| 6330415B21Rik | 0.25  | 0.30  | 0.20  | 0.23  | 0.17  | 0.23  | 0.18  | 0.30  |
| Vmn1r4    | 0.29  | 0.24  | 0.24  | 0.14  | 0.17  | 0.28  | 0.09  | 0.29  |
| Zfp775    | 0.19  | 0.29  | 0.26  | 0.28  | 0.19  | 0.22  | 0.23  | 0.29  |
| Tsen2     | 0.21  | 0.29  | 0.26  | 0.29  | 0.26  | 0.22  | 0.23  | 0.29  |
| Mogs      | 0.19  | 0.24  | 0.26  | 0.29  | 0.26  | 0.17  | 0.22  | 0.23  | 0.29  |
| Vmn1r34   | 0.19  | 0.24  | 0.28  | 0.22  | 0.26  | 0.26  | 0.14  | 0.28  |
| Vmn1r16   | 0.19  | 0.15  | 0.23  | 0.26  | 0.22  | 0.21  | 0.28  | 0.28  |
| 9530062K07Rik | 0.24  | 0.22  | 0.28  | 0.12  | 0.19  | 0.21  | 0.23  | 0.28  |
| Vmn1r36   | 0.24  | 0.25  | 0.28  | 0.22  | 0.18  | 0.18  | 0.24  | 0.28  |
| Ndufa9    | 0.16  | 0.20  | 0.19  | 0.13  | 0.15  | 0.28  | 0.20  | 0.28  |
| 1700026J14Rik | 0.18  | 0.21  | 0.17  | 0.25  | 0.28  | 0.16  | 0.15  | 0.28  |
| Snrpg     | 0.17  | 0.14  | 0.28  | 0.20  | 0.22  | 0.23  | 0.25  | 0.28  |
| Vmn1r24   | 0.28  | 0.26  | 0.26  | 0.21  | 0.18  | 0.15  | 0.24  | 0.28  |
| 1700030F04Rik | 0.13  | 0.20  | 0.27  | 0.16  | 0.10  | 0.25  | 0.27  | 0.27  |
| Gene          | Score 1 | Score 2 | Score 3 | Score 4 | Score 5 | Score 6 | Score 7 | Score 8 |
|--------------|---------|---------|---------|---------|---------|---------|---------|---------|
| Vmn1r52      | 0.23    | 0.27    | 0.16    | 0.25    | 0.19    | 0.26    | 0.26    | 0.27    |
| 2610306M01Rik| 0.16    | 0.27    | 0.26    | 0.23    | 0.26    | 0.10    | 0.15    | 0.27    |
| Zfp212       | 0.19    | 0.25    | 0.27    | 0.25    | 0.16    | 0.18    | 0.22    | 0.27    |
| Vmn2r22      | 0.16    | 0.22    | 0.22    | 0.27    | 0.18    | 0.14    | 0.25    | 0.27    |
| Ccd126       | 0.20    | 0.27    | 0.25    | 0.21    | 0.18    | 0.20    | 0.21    | 0.27    |
| Vmn1r17      | 0.16    | 0.24    | 0.25    | 0.24    | 0.17    | 0.24    | 0.26    | 0.26    |
| Rnf181       | 0.21    | 0.24    | 0.21    | 0.21    | 0.14    | 0.26    | 0.19    | 0.26    |
| Vmn1r31      | 0.18    | 0.26    | 0.26    | 0.23    | 0.15    | 0.21    | 0.22    | 0.26    |
| 1700065L07Rik| 0.10    | 0.25    | 0.17    | 0.21    | 0.11    | 0.16    | 0.19    | 0.25    |
| Vmn1r18      | 0.19    | 0.16    | 0.23    | 0.22    | 0.20    | 0.24    | 0.15    | 0.24    |
| Tigd2        | 0.22    | 0.22    | 0.17    | 0.21    | 0.18    | 0.24    | 0.20    | 0.24    |
| Nfu1         | 0.17    | 0.22    | 0.16    | 0.19    | 0.23    | 0.12    | 0.20    | 0.23    |
| Rprl1        | 0.22    | 0.12    | 0.18    | 0.14    | 0.23    | 0.14    | 0.12    | 0.23    |
| 1700049E22Rik| 0.16    | 0.22    | 0.17    | 0.14    | 0.10    | 0.17    | 0.10    | 0.22    |
| 1700094M24Rik| 0.20    | 0.17    | 0.22    | 0.13    | 0.11    | 0.11    | 0.09    | 0.22    |
| Emc3         | 0.18    | 0.21    | 0.16    | 0.16    | 0.18    | 0.20    | 0.17    | 0.21    |
| 1700124L16Rik| 0.13    | 0.13    | 0.15    | 0.20    | 0.05    | 0.08    | 0.19    | 0.20    |
| Rpl34-ps1    | 0.14    | 0.15    | 0.07    | 0.14    | 0.16    | 0.09    | 0.13    | 0.16    |

Genes are ranked according to the maximum individual score from any phenotype module. PTX, pertussis toxin; T1H, Type 1 hypersensitivity; VP, vascular permeability; GPCR, G-protein coupled receptor, ER, endoplasmic reticulum. EMC, endoplasmic membrane protein complex; ERAD, endoplasmic reticulum-associated degradation.
**Supplementary Table 5. Details of primers used in this study.**

### Microsatellite primers

| Name   | Mbp  | Forward          | Reverse                  |
|--------|------|------------------|--------------------------|
| D6Mit17| 71.06| 5'-ggcttgccaacaaacctgat-3' | 5'-gggtttccccctcaaatgt-3' |
| D6Mit8 | 83.66| 5'-tgcacagcagctcatctct-3' | 5'-ggaaggaaggagtggtatg-3' |
| D6Mit65| 101.33| 5'-ctcgcacaacatgtatatgt-3' | 5'-ggactcaaaactgctactgg-3' |
| D6Mit149| 105.95| 5'-acatgcagcacaactccat-3' | 5'-tttggctgctgtatgta-3' |
| D6Mit105| 107.74| 5'-ctgctcactactctattctgg-3' | 5'-caagccctatatattacacctacc-3' |
| D6Mit115| 116.61| 5'-cctttaataaagtgtctctcctg-3' | 5'-tgtcacaccaacactggc-3' |
| D6Mit254| 125.30| 5'-agtgctccctaggggtg-3' | 5'-ggggcccttagaggtgcaac-3' |

### Sequence-specific primers

| Name           | Mbp  | Forward1          | Forward2                  | Reverse                  |
|----------------|------|-------------------|---------------------------|--------------------------|
| rs36743061     | 81.89| 5'-ctgcagagagataactacctccac-3' | 5'-ctgcagagagataactctccac-3' | 5'-gacgccccagcaaatttat-3' |
| rs30936839     | 89.22| 5'-ttatatggagagcagcagcatggag-3' | 5'-ttatatggagagcagcagcatggag-3' | 5'-tactgcttggtggacgccaac-3' |
| rs29868697     | 108.45| 5'-ccacactgtgctcagggcctc-3' | 5'-ccacactgtgctcagggct-3' | 5'-aatgaaagctcctcaggcaac-3' |
| rs6257334      | 119.91| 5'-agtgcctctctgctctagctgt-3' | 5'-agtgcctctctgctctagctgt-3' | 5'-tctagcttggtgatcattacc-3' |

### Hrh1 primers

| Name    | Mbp  | Forward          | Reverse                  |
|---------|------|------------------|--------------------------|
| Hrh1 WT | 114.30| 5'-tgaagtactgtgcctgagtg-3' | 5'-ccatccgatggtctcctcctgcctgag-3' |
| Hrh1 KO | 114.30| 5'-tgaagtactgtgcctgagtg-3' | 5'-tctatcgcctccttgaccgag-3' |
Supplementary Table 6: List of datasets retrieved from mouse phenome database (www.phenome.jax.org) to collate SNP information across all studied mouse strains [41, 42, 66-71].

| Data set     | Procedure | What's in this data set                                                                 | Panel     | Sex | Year |
|--------------|-----------|----------------------------------------------------------------------------------------|-----------|-----|------|
| Broad2       | genotyping| SNP profiling, 131,000+ genomic locations, 1-19,X.                                    | inbred    |     | 2009 |
| CGD-MDA1     | genotyping| SNP profiling, 470,000+ genomic locations, 1-19,X,Y,MT.                               | inbred    | m   | 2014 |
| CGD-MDA2     | genotyping| SNP profiling, 470,000+ genomic locations, 1-19,X,Y,MT.                               | BXD w/par | m   | 2014 |
| CGD-MDA3     | genotyping| SNP profiling, 470,000+ genomic locations, 1-19,X,Y,MT.                               | ILSXISS w/par | m | 2014 |
| CGD-MDA4     | genotyping| SNP profiling, 470,000+ genomic locations, 1-19,X,Y,MT.                               | AXB, BXA, BXH, CXB, AKXL w/par | m | 2014 |
| CGD-MDA5     | genotyping| SNP profiling, 470,000+ genomic locations, 1-19,X,Y,MT.                               | B6.A, B6.PWD consomic panels | m | 2014 |
| Perlegen2    | genotyping| SNP profiling, 8,100,000+ genomic locations, 1-19,X,Y,MT.                             | inbred    | m   | 2005 |
| Sanger4      | genotyping| SNP profiling, 80,000,000+ genomic locations. SNPs and indels. 1-19,X.               | inbred    | both | 2017 |
| UCLA1        | genotyping| SNP profiling, 132,000+ genomic locations, 1-19,X.                                    | HMDP      | both| 2018 |
| UNC-GMUGA1   | genotyping| SNP profiling, 130,000+ genomic locations, 1-19,X,Y,MT.                               | CC w/par  | m   | 2020 |
| UNC-MMUGA2   | genotyping| SNP profiling, 76,000+ genomic locations, 1-19,X,Y,MT.                               | CC w/par  | both| 2017 |
**Supplementary Figure 1.** Mouse family tree (adapted from Petkov et al. [22]) showing the phylogenetic relationships among 102 inbred and wild-derived inbred strains. Group 1, Bagg albino derivatives; Group 2, Swiss mice; Group 3, Japanese and New Zealand inbred strains; Group 4, C57/Bl strains; Group 5, Castle mice; Group 6, C.C. Little DBA and related strains; Group 7, wild-derived strains. Strains with \( Hrh1^r \) allele are highlighted and their Bphs susceptibility color coded. Red = Bphs\(^a\), Green = Bphs\(^b\), and Black = Bphs unknown (Bphs\(^?\)).
Supplementary Figure 2. The predicted candidates for Bphse overlaps with Bphs/Hrh1, Histh3, and Histh4 in agreement with the genetic data that a functional LD on Chr6 encodes genes that control both *B. pertussis*/PTX-dependent and age- and inflammation-dependent susceptibility to HA-shock.