Genetic Effects on Dispersion in Urinary Albumin and Creatinine in Three House Mouse (Mus musculus) Cohorts

Guy M. L. Perry
Department of Biology, University of Prince Edward Island, Charlottetown, PEI, Canada C1A 4P3

ABSTRACT Conventionally, quantitative genetics concerns the heredity of trait means, but there is growing evidence for the existence of architectures in which certain alleles cause random variance in phenotype, termed ‘phenotypic dispersion’ (PD) or ‘variance QTL’ (vQTL), including in physiological traits like disease signs. However, the structure of this phenomenon is still poorly known. PD for urinary albumin (PD_{PDUAlb}) and creatinine (PD_{PDUcrea}) was mapped using curated data from two nearly genetically identical F2 mouse (Mus musculus) cohorts (383 male F2 C57BL/6J×A/J (97 SNP) and 207 male F2 C57BL/6J×A/J ApoE knockout mice (144 SNP)) and a related mapping cohort (340 male F2 DBA/2J×C57BL/6J (83 SNP, 8 microsatellites)). PD_{PDUcrea} was associated with markers in regions of Chr 1 (5-64 megabases (MB); 141-158 MB), 3 (87-117 MB), 8 (37-68 MB), 14 (92-117 MB) and 17 (14-24 MB) with several positions and quantitative architectures in common between the two C57BL/6J×A/J cohorts, most of which had a negative dominant construction. One locus for PD_{PDUcrea} was detected on Chr 19 (57 MB) in the C57BL/6J×A/J ApoE²⁻/⁻ cohort. The large number of negative dominant loci for albuminuria dispersion relative to conventional quantitative trait loci suggests that the development of albuminuria may be largely genetically dynamic and that randomization in this development is detrimental.

KEYWORDS

phenotypic dispersion
albuminuria
creatinine
homeostasis
Mus musculus
negative dominance

Conventional quantitative genetics concerns heritable differences in mean phenotype (Roff 1997). However, there is increasing evidence that some genotypes confer significant differences in random or residual variability rather than stable mean phenotype, so that intra-individual or inter-individual randomization among genotypes or genetic groups may constitute a properly heritable genetic effect instead of sheer error (Reeve and Robertson 1953; Perry et al. 2003; Sorensen and Waagepetersen 2003; Ordas et al. 2008; Rönnegård and Valdar 2012). This effect has been described as ‘phenotypic dispersion’ (PD) (Perry et al. 2012a) and may reflect the effects of ‘variance QTL’ (vQTL) on trait variance (Rönnegård and Valdar 2012). As early as the 1950s, divergent selection experiments in Drosophila found simultaneous changes in means and variances for wing length and body size (Reeve and Robertson 1953; Clayton and Robertson 1957), suggesting the accumulation of both alternate variants and randomizing alleles via incidental inclusion of extreme individuals during selection (Hill and Zhang 2004). Since that point, genetic variation for heterogeneity has been found in plants (Hall et al. 2007; Ordas et al. 2008), fish (Perry et al. 2003), birds (Rowe et al. 2006; Wolc et al. 2009) and mammals (SanCristobal-Gaudy et al. 1998; Sorensen and Waagepetersen 2003; Rönnegård et al. 2010; Perry et al. 2012a), including rodent disease models (Ibáñez-Escriche et al. 2008) and human phenotypes and gene expression (Perry et al. 2012c; Hulse and Cai 2013; Perry et al. 2013). Theoretical investigations of residual variance suggest a genetic architecture resembling classical trait means (μ, σ) (Hill and Zhang 2004; Hill and Mulder 2010) or the general inability of inbred individuals to buffer minor environmental perturbation (Lerner 1977). Most examples of dispersion come from common environments (i.e., Perry et al. 2003; Sorensen and Waagepetersen 2003; Wolc et al. 2009; Rönnegård et al. 2010; Perry et al. 2012a; Sell-Kubiak et al. 2015; Conley et al. 2018) so that an explanation of heredity for environmental buffering (de Visser et al. 2003) seems improbable, although an assay of dispersion in airway hyperresponsiveness (AHR) found increasing genotypic differences in PD at a Chr 10 locus with increasing methacholine dosage, suggesting environmental gradients in the expression of dispersion loci.
polymorphisms (SNP) with a roughly even distribution across all autosomes and the X chromosome were genotyped in Doorenbos et al. A, and 144 in Doorenbos et al. B.

**Cohort 3 (Sheehan et al. 2007)**

The third cohort (Sheehan et al. 2007; MPD:205), consisting of male $F_2$ C57BL/6J/$\{B6\} \times DBA/2j\{D2\}$ mice $F_1$ phenotyped for urinary creatinine and albumin and reported in Sheehan et al. (2007). This cohort shared only one of the source strains with the above two cohorts (DBA/2j) and was included for comparison to those more closely related groups. $F_1$ reciprocal females ($\{B6\times D2\}$ and $\{D2\times B6\}$) were bred from B6 and D2 mice from the Jackson Laboratories. An additional $F_1$ ($\{D2\times B6\}$) cohort was produced and used to breed a total of 340 $F_2$ C57BL/6J/$\{D2\} \times DBA/2j\{D2\}$ male mice from an initial cross of B6 females bred with DBA2 males. $F_2$ mice were phenotyped with spot urine collections and genotyped over all 19 autosomes and the X chromosome using 83 SNP, and at eight microsatellites on chromosome 2, for a mean intermarker spacing of 17 cM.

Marker location was assigned throughout based on the Cox et al. (2009) reference marker map build using base-pair (BP) distances to avoid possible mis-position from sex differences in recombination by region (Broman et al. 1998; Sakamoto et al. 2000; Popa et al. 2012).

**Animal usage:** Ethical animal use in the original studies was monitored and approved by the Institutional Animal Care and Use Committee (IACUC) of The Jackson Laboratory.

**Association analysis:** All analysis was performed in SAS (2011). In order to protect against distributional errors, the deviation of individuals from predicted multivariate values were estimated from externally Studentized residuals (Steel and Torrie 1980) in which ordinary Studentized residuals were estimated in a general linear model of the form

$$y_{ij} = \mu + \alpha_i + \beta_{MLH}X_{MLH} + \beta_{Ucrea}X_{Ucrea} + e_{ij}$$

where $y_{ij}$ is albuminuria or creatinine for individual $j$, $\mu$ is the mean phenotype for the cohort, $\alpha_i$ is the effect of marker locus $i$, $\beta_{MLH}$ is the partial regression effect of multilocus heterozygosity (MLH), $\beta_{Ucrea}$ is the partial regression effect for glomerular filtration rate and $e_{ij}$ is individual residual error. MLH was included at this level to account for possible inbreeding effects and calculated as $MLH = n_{het}/n_{total}$ within individuals in each group across all available genotypes. Regression effects for creatinine were only included for albuminuria. Each model was initially run without locus terms at each analytical stage order to determine covariates for the genomic models including locus terms, which were used in order to account for the effects of known and undetected conventional loci on albuminuria (see Doorenbos et al. 2008).

Individual residual error estimates ($\hat{e}_{ij}$) were absolute-transformed ($|\hat{e}_{ij}|$); as absolute divergence of any particular individual from that predicted by genotype, these were then considered to be phenotypic dispersion (PD) for that trait ($PD_{UAB}$, $PD_{Ucrea}$). Since absolute-transformed distributions are left-skewed with strong lower bounds at the abcissa, marker-dispersion associations were fit using Tobit quantitave and limited models (Tobin 1958) with a lower bound of zero with PD as the dependent variable and locus as an independent variable.
along with significant covariates. In Tobit censored distributions, the actual y of the true variable γ is only observed where γ > τ, the lower truncation value, and as y′ otherwise (i.e., y = y′ where y > τ). The truncated PDF of such a system then is expressed as f(y|y > τ) = f(y)/(P(y > τ)) and transforming by [a = μ/σ, b = 1/σ] produces P(y > τ) = 1 − Φ[−a/b, where a = τ−μ and Φ(−a/b)] is the cumulative distribution function (CDF; Steel and Torrie 1980; Greene 2002) of the original data so that the likelihood becomes

\[ L = \prod_{i=1}^{N} \frac{f(y_i)}{1 - \Phi(a)} . \]

Model terms were optimized by the default quasi-Newtonian Broyden-Fletcher-Goldfarb-Shanno algorithm (Press et al. 2007). The significance of genotypic effects in the analysis of each locus was determined via a joint nonequivalence Wald contrast against mean PD in the referential A/J homozygote (\(H = (\mu_P^{A/J} = 0, \mu_P^{A/A} = 0)\)) (see Parsaud 2008; SAS 2014), the last genotype being fit via default as the referential genotype against the rest of the population. MLH was included as a covariate where it was significantly associated with PD (P < 0.1) to account for the possible production of phenoaberrancy by the failure of increasingly inbred individuals to buffer phenotype against exogenous and endogenous stresses, termed genetic homeostasis (Lerner 1977). Additivity and dominance were estimated in SAS using contrast statements equivalent to Grifﬁng’s potency ratio \(h_p = (2\mu_{CA} - (\mu_{CC} + \mu_{AA})/)(\mu_{CC} - \mu_{AA}) = Q/L\) (Grifﬁng 1990) where Q is the quadratic dominant effect and L is the classical linear differentiation between alternate homozygotes. Additivity was tested by contrast against the midparent phenotype ((\(PD_C + PD_A)/2\)) (contrast statement +1 -1). Dominance was tested sequentially using the vectors \(Q = [+0.5CC + 0.5CA - 1.0AA]\) and \(Q = [-1.0CC + 0.5CA + 0.5AA]\) to test positive dominance and \(Q = [+1.0CC - 0.5CA - 0.5AA]\) and \(Q = [-0.5CC - 0.5CA + 1.0AA]\) to test negative dominance (Aurelio et al. 2000; Lee and Sabapathy 2008).

Significance: Signiﬁcance thresholds were adjusted via Benjamini-Hochberg (Verhoeven et al. 2005) by trait calculated across all markers independently without reference to linkage among markers at the classic False Discovery Rate (\(P \leq k' \alpha/m\)) with a ‘hard ﬂoor’ for rejection of H’ at a nominal P = 0.01.

SNP sites for QTL for albumin excretion: The Mouse Genome Informatics (MGI) resource curated by the Jackson Laboratories (www.informatics.jax.org) was used to identify SNP between the source strains (C57BL/6 vs. A/J; DBA/2 vs. C57BL/6) at nonsynonymous coding sites (CNS), untranslated mRNA sequence (mRNA-UTR), splice sites (SS) and non-coding transcript variants (NTV) (see Ward and Kelills 2012) at genes closely linked (<10 MB) to consensus markers for PDUAlb as possible candidates for genetic effects on dispersion. Sequence information was based on the dbSNP (Mouse) Build 142 by MGI and the GRCm38 mouse genomic build. Annotation functions were obtained through databases from The Jackson Laboratories (www.informatics.jax.org), the European Bioinformatics Institute (www.ebi.ac.uk), UniProt (www.uniprot.org), GeneCards (www.genecards.org), WikiGenes (www.wikigenes.org) and homologs listed with the Rat Genome Database (www.rgd.mcw.edu).

Data availability: All data used in this work were archived and curated by the Churchill Group QTL Archive, Jackson Laboratory, Bar Harbor, MA, USA (https://phenome.jax.org/centers/QTLA) (IDs: MPD: 205, 208). Supplemental material available at Figshare: https://doi.org/10.25387/g3.6853580.

RESULTS

Multilocus heterozygosity

MLH was negatively correlated with UAlb in Doorenbos et al. A (β = −4.87 (SE 1.14), P < 0.0001) and marginally negatively correlated with UAlb in Doorenbos et al. B (β = −3.76 (SE 2.02), P = 0.0650). MLH was also negatively associated with PDUAlb in Doorenbos et al. A (β = −1.72 (SE 0.390), P < 0.0001) and B (β = −2.29 (SE 0.884), P = 0.0104). MLH was not associated with UAlb (P > 0.6) or PDUAlb (P > 0.6) in Sheehan et al.

UAlb was signiﬁcantly positively correlated with UCrea in Doorenbos et al. A (β = 0.0130 (SE 0.00593), P = 0.0287), Doorenbos et al. B (β = 0.0113 (SE 0.00603), P = 0.0630) and Sheehan et al. (β = 0.0218 (SE 0.00380), P < 0.0001). PDUAlb was positively associated with UAlb in Doorenbos et al. A (β = 0.00544 (SE 0.00203), P = 0.0077) and B (β = 0.00680 (SE 0.00264), P = 0.0110) and in Sheehan et al. (β = 0.0118 (SE 0.00203), P < 0.0001).

Association analysis

Doorenbos et al. A covered a linkage distance of 1.22 M, Doorenbos et al. B 1.18 M and Sheehan et al. 1.17 M. A total of 97 SNP markers were available for Doorenbos et al. A, 144 SNP markers for Doorenbos et al. B, and eight microsatellites and 83 SNP in Sheehan et al. (Table 1).

Several genomic regions were signiﬁcantly associated with PDUAlb in both Doorenbos et al. cohorts, with highly similar genetic architecture in these mapping groups (Table 2; Figure 1). PDUAlb was associated with SNP genotype over the approximate region of 5-64 MB on Chr 1 in Doorenbos et al. A and B, here considered to represent a locus for albuminuria dispersion (PDUAlb1) (Table 2; Figure 1). Contrast tests for dominance and additivity indicated that PDUAlb1 was partially negative dominant (Lee and Sabapathy 2008) for the C57BL/6J allele, so that C57BL/6J homozygotes and C57BL/6J homozygotes had lower PDUAlb than A/J homozygotes (PDOMR < 0.01) (Table 2; Figure 2). PDUAlb1 was signiﬁcantly associated with Chr 1 markers in the 141-158 MB range in Doorenbos et al. (Table 2; Figure 1). A post-Benjamini correction (PFDR < 0.05). Contrast tests indicated that this position was overdominant with C57BL/6J A/J heterozygotes and C57BL/6J homozygotes had lower PDUAlb than A/J homozygotes (PDOMR < 0.01) (Table 2; Figure 2). In Doorenbos et al. B, PDUAlb was only nominally (P < 0.05) associated with a marker in this range (SNP 01-153183498-M) but PDUAlb had the same structure at this locus in Doorenbos et al. B as in A. In combination, another consensus PD locus was considered to exist at this position (PDUAlb2).

PDUAlb was signiﬁcantly associated with SNP genotype in Doorenbos et al. A and B over the 50-150 MB range on Chr 3 at the Benjamini threshold (Table 2; Figure 1). Contrast tests at the peak SNPs 03-114106772-M (113.5 MB) in Doorenbos et al. A and 03-138373014-M (137.5 MB) in Doorenbos et al. B indicated partial negative dominance as for PDUAlb1 with signiﬁcantly higher PDUAlb in C57BL/6J homozygotes than either other genotype in Doorenbos et al. B (PDOMR < 0.001), and marginally higher PDUAlb than heterozygotes and signiﬁcantly higher PDUAlb than A/J homozygotes in Doorenbos et al. A (Table 2; Figure 2). This was a wider genomic range than other consensus loci with different ranges of overlap, but based on the significance of marker-PDuAlb associations in these closest markers and the similarity of PD means by genotype, it was considered that these results represented a third locus for albuminuria dispersion (PDUAlb3).
On Chr 8, $PD_{UAB}$ was associated with SNP over the 37-43 MB range on Chr 8 in both Doorenbos et al. A and B (Table 2; Figure 1). Like $PD_{UAB1}$ and $PD_{UAB3}$, contrast tests indicated that $PD_{UAB4}$ was partially negative dominant with the $PD_{UAB}$ for C57BL/6J homozygotes being higher than either of the other genotypic classes ($P_{FDR} < 0.01$) (Table 2; Figure 2). On Chr 14, $PD_{UAB}$ was significantly associated with genotype over 26.2-88.5 MB in Doorenbos et al. A and 92.4-117.4 MB in Doorenbos et al. B (Table 2; Figure 1). As most of the other consensus loci, genetic architecture at the SNP 14-079218045-M in Doorenbos et al. A and 14-108203728-M in Doorenbos et al. had significant negative dominant and additive components ($P < 0.05$) with C57BL/6J homozygotes having higher dispersion than any other genotypic class ($P_{FDR} < 0.05$) (Table 2; Figure 2).

Markers in the anterior regions of Chr 17 (peaks at 17-050794277-N (15 MB) in Doorenbos et al. A and 17-022861830-N (24 MB) in Doorenbos et al. B) were significantly associated with $PD_{UAB}$ (Table 2; Figure 1). As $PD_{UAB1}$ and $PD_{UAB3} = 3$, this locus also appeared to be partially negative dominant with A/J homozygotes having significantly lower dispersion than C57BL/6J/A/J heterozygotes or A/J homozygotes ($P_{FDR} < 0.01$) (Table 2; Figure 2).

There were a number of markers associated with $PD_{UAB}$ in only one of the two cohorts (Chr 6, 10, 11, 15 and 18 in Doorenbos et al. A; Chr 5, 10 and 11 in Doorenbos et al. B), largely negative dominant or overdominant (Table 2, Figures 1, 3). Two loci on Chr 15 and 16 were significantly associated with $PD_{UAB}$ in Doorenbos et al. A and B but with contrasting effects in each cohort so that A/J alleles had high random variance in Doorenbos et al. A while C57BL/6J alleles had high random variance in Doorenbos et al. B (Table 2). In the Sheehan et al. C57BL/6JxDBA/2J mice, a single overdominant locus on Chr 5 spanning 22-47 MB was associated with $PD_{UAB}$, with C57BL/6JxDBA/2J heterozygotes the highest dispersion of the three genotypic classes ($P < 0.01$) (Table 2; Figures 1, 3).

No genomic region was associated with $PD_{BUN}$ at the FDR ($P > 0.1$). A single marker in the anterior end of Chr 19 (SNP 19-060823449-N; 56.5 MB) was significantly associated with $PD_{UAB}$ ($r^2 = 0.183$) (Figure 2), here termed $PD_{UAB}$ and having overdominant expression for PD in C57BL/6JxDBA/2J heterozygotes in Doorenbos et al. B ($P = 0.0002$). There was no evidence of this effect in Doorenbos et al. A or Sheehan et al.; a linked SNP (19-059089086-M) was associated with $PD_{UAB}$ before FDR correction (Figure 1), appearing dominant (not shown). No locus for dispersion in albuminuria was linked to this position.

### Distribution of genetic architectures

Of all loci significantly associated with PD traits in all three cohorts (including dual additive and dominance components for partially dominant loci), 19 were additive, one was high-dominant (heterozygote equal to the high-PD homozygote), 20 were negative dominant, five overdominant and four underdominant (Table 2). For those loci with statistical analogs in both Doorenbos et al. cohorts, there were ten loci with additive effects, 11 with negative dominance, two overdominants and one underdominant (Table 2).

#### C57BL/6J-vs-A/J candidate SNP

SNP between the C57BL/6J and A/J strains linked to dispersion loci occurred in genes affecting cell growth/mitosis/platelet action (Arid5a, Egf, Fgfl, Fg20, Igals, Ipr3, Ogfr1, Pgl, Rbc1c, Rab23, Qox1), immunology (Arid5a, Lorr1f, Msr1, Mts1, Ph3f), serine/threonine physiology (Camk2d, Dicl, Dusp4, Pkmy1, Pss29, Pss30, Pss33, Pss34, Pss40, Pss41, Smok2b, Srm2), DNA repair and mitotic checkpoint maintenance (Ene2, Ecc5, Mccmd2, Tdrd5, Telo2, Tex15, Tt12), cellular construction/morphology (Actrb1, Ank2, Cap40, Col11a1, Col5a2, Dnah7b, Dst, Ogfr1, Mdg, Mts1), G-protein coupled receptors (Fdn1c, Fpr3, Fpr-rs3, Fpr-rs4, Fpr-rs6), calcium physiology (Bank, Dnasd12, Pdldh9, Pkd1, Saraf), gene expression (transcription, splicing, translation) (Err1, Purg, Rbm20, Rpb1, Tmrtb9, Tmrt11, Tmrt13). Some SNP variants occurred at genes linked to other renal diseases including autosomal dominant polycystic kidney disease (ADPKD) (Pkd1) and autosomal recessive polycystic kidney disease (ARPKD) (Pkd1) and cystic fibrosis (Ske9A3R2). Two genes (Gcnf and Tbl3) contained WD-40 domains. There were a variety of SNP in coding sites for vornomonal genes and in type C2H2 zinc fingers (Flywchi, Wzi1, Zfpf proteins) (Table S1).

#### DISCUSSION

Six syntenic consensus loci for albuminuria dispersion were detected in Doorenbos et al. A and B on Chr 1 (5-64 megabases (MB), $PD_{UAB}$; 141-158 MB, $PD_{UAB}$), Chr 3 (~113 MB, $PD_{UAB}$), Chr 4 (37-68 MB, $PD_{UAB}$), Chr 14 (92-117 MB, $PD_{UAB}$) and Chr 17 (14-24 MB, $PD_{UAB}$), all unlinked to conventional albuminuria loci. Each syntenic locus in Doorenbos et al. had the same genetic architecture in both cohorts, which strongly implies validation of these positions. A single locus for $PD_{UAB}$ was detected in Sheehan et al. on Chr 5 (22.3-46.6 MB) with no syntenic effect in either other group. There is significant variance in the onset of albuminuria and CKD (Moranne et al. 2009) and the number of independent dispersion loci in this work suggests that albuminuria distributions may be largely determined by a number of independent arrays of genes with randomizing effects on disease onset and progression. The mechanics of dispersion loci could range from ephemeral physiological ‘twitches’ to randomization in the progression of long-term biological insult ranging from the unaffected state to the disease state vs. retention of the unaffected status; dispersion in albuminuria, with attendant morphological changes (glomerular damage and inflammation with subsequent podocyte damage from infection, self-defense or complement thrombosis) (Doorenbos et al. 2008; Coto et al. 2013; Regal et al. 2018). Only a single locus was detected for dispersion in creatinine; this sole finding against the larger number of loci for albuminuria may reflect more constant creatinine expression as a baseline estimator of kidney throughput (Stevens et al. 2013). C57BL/6J
Table 2 Chromosome (Chr), approximate position in megabase-pairs (MB) and centiMorgans (cM; consensus map (Cox et al. 2009)), unadjusted nominal significance (P), proportion of total PD_{UAlb} explained by each marker (r²), and the architecture ('Form': A = additive, D+ = positive dominant, D- = negative dominant, OD = overdominant, UD = underdominant) and unadjusted significance of effects (P_{arch}) for single-nucleotide polymorphisms (SNP) associated with phenotypic dispersion in urinary albumin (PD_{UAlb}) in 383 male F2 C57BL/6J × 129S1/SvImJ and 207 male F2 C57BL/6J × 129S1/SvImJ ApoE⁻/⁻ mice (Mus musculus) (Doorenbos et al. 2008) using quantitative limited (Tobit) models. ‘Locus’ refers to positions detected in the same location in both cohorts. The high-PD allele is indicated in brackets under ‘Form’.

| Chr | MB (cM) | Marker         | P      | r²   | Form | P_{arch} | Chr | MB (cM) | Marker         | P      | r²   | Form | P_{arch} |
|-----|---------|----------------|--------|------|------|----------|-----|---------|----------------|--------|------|------|----------|
| 1   | 22.6 (8.7) | 01-023061064-M  | 0.0005 | 0.0401 | D- (A) | 0.0001 | 0.0006 | 35.7 (14.5) | 01-036208806-N  | 0.0072 | 0.0769 | D- (A) | 0.0027 |
| 1   | 157.9 (67.7) | 01-157000923-M  | 0.0004 | 0.077  | OD   | 0.0004 | 0.0073 | 154.1 (64.7) | 01-153183498-M¹ | 0.0351 | 0.0501 | OD   | 0.0129 |
| 2   |          |                |        |      |      |          | 68.9 (39.5) | 02-069853291-N  | < 0.0001 |        | D- (A) | 0.0001 |
| 3   | 113.5 (49.5) | 03-114106772-M  | 0.109  | 0.0249 | A (B) | 0.0034 | 0.0043 | 137.5 (63.9) | 03-138370314-M  | < 0.0001 | 0.203  | D- (B) | 0.0001 |
| 5   | 131.3 (63.4) | 06-131929438-M  | 0.0019 |        |      |          |        | 110.6 (53.4) | 05-107871207-M  | 0.0001 |        | OD   | 0.0001 |
| 8   | 43.8 (23.9) | 08-041947937-M  | 0.0011 | 0.0677 | D- (A) | 0.0004 | 0.0008 | 43.0 (23.9) | 08-041043944-M  | < 0.0001 | 0.240  | D- (A) | < 0.0001 |
| 10  | 85.9 (42.8) | 10-086567143-M  | 0.0117 |        |      |          |        | 17.9 (7.5) | 10-10733522-M  | 0.0083 |        | D- (A) | 0.0084 |
| 11  | 14.9 (8.6) | 11-014984030-M  | < 0.0001 |        | A (B) | 0.0035 | 0.0055 | 60.9 (38.0) | 11-061500282-N  | < 0.0001 | 0.203  | D- (B) | < 0.0001 |
| 12  | 88.5 (44.2) | 14-079218045-M  | 0.0027 | 0.0331 | D- (B) | 0.0007 | 0.0038 | 92.4 (45.3) | 14-083150973-M  | < 0.0001 | 0.159  | D- (B) | < 0.0001 |
| 15  | 92.1 (14.5) | 15-093195380-M  | 0.0002 |        | A (A) | < 0.0001 | < 0.0001 | 70.3 (32.2) | 15-070911071-M  | 0.0008 |        | A (A) | 0.0008 |
| 16  | 6.2 (1.8) | 16-005644892-N  | 0.0061 |        | A (A) | 0.0021 | 0.0021 | 32.1 (21.4) | 16-031026287-C  | 0.0007 |        | A (A) | 0.0033 |
| 17  | 51.8 (26.8) | 17-050794277-N  | 0.0012 | 0.0790 | D- (A) | 0.0004 | 0.0008 | 23.8 (12.0) | 17-022861830-N  | < 0.0001 | 0.129  | D- (A) | < 0.0001 |
| 18  | 11.1 (5.7) | 18-010953833-N  | 0.0050 |        | OD   | 0.0017 |        |                    |          |        |        |          |

The SNP marker 01-153183498-M was only marginally associated with PD_{UAlb} in Doorenbos et al. B (P < 0.1) but is included here to compare the similarity of its architecture with the presumably syntenic region in Doorenbos et al. A.
C57BL/6J mice (white symbols) (Sheehan et al. 2007). Significant points with maximal association with \( P_D^{U_{\text{Alb}}} \) are indicated (i.e., \( P_D^{U_{\text{Alb}}} \)).

\[ PD \]

Association of phenotypic dispersion in urinary albumin (\( P_D^{U_{\text{Alb}}} \); circles) and urinary creatinine (\( P_D^{U_{\text{Crea}}} \); triangles) with marker genotype by chromosome in a) a cohort of 383 male F2 C57BL/6J × A/J house mice (Mus musculus (Doorenbos et al. A)) (solid symbols), b) a cohort of 207 male F2 C57BL/6J ApoE\(^{-/-}\) × A/J mice (gray symbols) (Doorenbos et al. B) (Doorenbos et al. 2008) and c) a cohort of 340 male F2 DBA/2J × C57BL/6J mice (white symbols) (Sheehan et al. 2007). Various SNP occurred in serine/threonine-enriched proteins, which have mediating factors like \( \text{Apoe} \) to sample size, the Beavis effect (Beavis 1998) and/or liberating effects to increasing dispersion, although the mechanics of such an effect might result in increasingly unstable physiological architecture so that downstream systems might also be subject to increasing dispersion, although the mechanics of such an effect would depend on the nature of the physiological pathway. ApoE\(^{-/-}\) mice have a wide range in nephropathic outcome (Wen et al. 2002; Buzello et al. 2004). Loci detected in only a single cohort might be related to this dispersive mediation. The genetic architecture in \( P_D^{U_{\text{Alb}}} \) appeared to be inverted between Doorenbos et al. A and B for loci on Chr 15 and 16, so that Apoe might alter the tendency to dispersion within genotypes.

A strong majority of dispersive loci were partially negative dominant, with contrasts including additive and negative dominant components. This is similar to a recent survey of \( PD \) for diabetes-related serum traits (high- and low-density lipoproteins, general cholesterol, triglycerides) in eight intercross and backcross mouse cohorts in which most \( PD \) loci were also negative dominant (Brown 2018). Not all dispersive genetic variance has this expression (Perry et al. 2013; G. M. L. Perry, unpublished results) but negative dominance—essentially recessivity for high dispersion where genetic physiological randomization is suppressed by single normalizing alleles which promote constant or stable gene activity—might be a frequent feature of this phenomenon. This propensity to suppression of randomizing variance might thus mean that ‘recessive’ high-\( PD \) genotypes are essentially detrimental as in other recessive systems (Charlesworth 2009), although the ecological implications of the phenomenon have not been extensively explored. A primarily recessive architecture for randomizing phenotype could also create additional complications in genetic analysis (Hildebrandt et al. 2009) similar to limited recessive penetrance (see Boone et al. 2013; Gao et al. 2015). This might include dispersive loci that influence the detection of normal genes (i.e., Perry et al. 2011). New model builds might need to be created in order to specifically address such systems.

**Creatinine**

One locus for \( PD^{U_{\text{Crea}}} \) was detected on Chr 19 (57 MB) in the C57BL/6J × A/J ApoE\(^{-/-}\) group. As a product of lean muscle mass, creatinine should be relatively stable, but intradividual CVs for creatinine approximate 9% (Bingham and Cummings 1985) and the heritability of individual CV in urinary creatinine was significant (\( h^2 = 8.7\% \)) in a three-generation cohort of 949 kidney stone probands and first-degree relatives (Perry et al. 2012b). Dispersion effects in fitness or survivorship from creatinine might operate through physiological related to

**vs. A/J SNP variants linked to these loci included polymorphisms at various transposable element regulators, respiratory electron chain genes, G-protein coupled N-formyl peptide receptors, vomeronasal genes, serum calcium regulators, complement receptors, signal transducers, and candidates of autosomal dominant (\( Pkd1 \)) and recessive (\( Pkhd1 \)) polycystic kidney disease (Bergmann 2015; Ghta and Cowley 2017) and cystic fibrosis (\( Slc9A3R2 \)) simultaneously mitigates the effects of the cystic fibrosis transmembrane conductance (CFTR) reducing renal cyst growth via proteostasis and reduces resting intracellular Ca\(^{2+}\) (Yanda et al. 2018). Various SNP occurred in serine/threonine-enriched proteins, which have been associated with loci linked to the coefficient of variation (CV) in total RNA production (Perry, unpublished results), diabetes severity/ onset (G. M. L. Perry, unpublished results) and diabetic plasma traits (Brown 2018; G. M. L. Perry, unpublished results). Two genes (\( Ccnf, Tbl3 \)) had WD-40 domains (Schapira et al. 2017); SNP in WD-40 domains were also associated with random variation in urinary calcium in a human cohort (\( n = 1210 \)) (Perry et al. 2013).

\( PD \) loci accounted for smaller proportions of randomized variance in Doorenbos et al. A (3–8%) than B (5–24%); this may have been due to sample size, the Beavis effect (Beavis 1998) and/or liberating effects of the \( \text{ApoE} \) KO on residual variance in the latter. The removal of mediating factors like \( \text{ApoE} \) might result in increasingly unstable physiological architecture so that downstream systems might also be subject to increasing dispersion, although the mechanics of such an effect would depend on the nature of the physiological pathway. ApoE\(^{-/-}\) mice have a wide range in nephropathic outcome (Wen et al. 2002; Buzello et al. 2004). Loci detected in only a single cohort might be related to this dispersive mediation. The genetic architecture in \( PD^{U_{\text{Alb}}} \) appeared to be inverted between Doorenbos et al. A and B for loci on Chr 15 and 16, so that Apoe might alter the tendency to dispersion within genotypes.
disease state: Gibb et al. (1989) found higher between-individual variance in creatinine clearance in diabetic children than non-diabetics.

Multilocus heterozygosity
Heterozygosity-trait correlations (HTCs) are linked with fitness or other traits in many systems (Willoughby et al. 2017; Brambilla et al. 2018; Kardos et al. 2018) but support for Lernerian genetic homeostasis (1977) in trait randomization has been mixed (Perry et al. 2012a; G. M. L. Perry et al., unpublished results). MLH was negatively correlated with dispersion in albuminuria in the Doorenbos et al. cohorts but not in Sheehan et al. There is evidence for variation in heterozygosity-trait correlations over subpopulations (Brock et al. 2015) and across ontogeny (Gillingham et al. 2013; Annavi et al. 2014), due to contextual variance in selection gradients. This implies some tractable, functional variability in HTCs, but the cohorts used here were lab-reared under no known selective pressure, suggesting that differences in MLH

Figure 2 Differences in mean genotypic effects on phenotypic dispersion in urinary albumin (PDUAib) by single nucleotide polymorphism (SNP) genotype for genomic regions syntenically associated with PDUAib in 383 male F2 C57BL/6J × A/J mice (’Doorenbos et al. A’) and 207 male F2 C57BL/6J ApoE<−/−> × A/J mice (’Doorenbos et al. B’) (Doorenbos, 2008 #25451) (syntenic regions by figure column). SNP marker names are indicated above each graph with the first two digits being chromosomal designation. Significant differences among genotypes for mean PD are indicated as P Bonf < 0.10*, < 0.05**, < 0.01***, < 0.001****.

Figure 3 Mean dispersion in urinary albumin (PDUAib) and creatinine (PDUCrea) by single nucleotide polymorphism (SNP) genotype for markers detected only in 383 male F2 C57BL/6J × A/J mice (’Doorenbos et al. A’) or 207 male F2 C57BL/6J ApoE<−/−> × A/J mice (’Doorenbos et al. B’) (Doorenbos, 2008 #25451). SNP markers are indicated above each graph. Significant differences among genotypes for mean PD are indicated as P Bonf < 0.10*, < 0.05**, < 0.01***, < 0.001****.
correlation were endogenous in origin. Some work indicates that HTCs at specific regions are more important than total individual heterozygosity (Rodriguez-Quilón et al. 2015) so that genetic differences between strains might be expected to generate differences in both HTCs and MLH-PD correlations. Differences in heterozygosity for specific regions enriched for immunological or other functional groups (i.e., the MHC complex on human Chr 6 and mouse Chr 17 (cytoband B-C)) might, for example, be key to variation in this effect.

Conclusions
The incidence of heritable dispersion appears to be growing (SanCristobal-Gaudy et al. 1998; Perry et al. 2003; Sorensen and Waagepetersen 2003; Hill and Zhang 2004; Ordas et al. 2008; Hill and Mulder 2010; Perry et al. 2012a; Rönnegård and Valdar 2012; Wang et al. 2014). Analytically, this represents an enormous potential area of genetic interest: dispersive systems, themselves a series of random risk factors invisible to conventional analysis, could render critical elements of genetic control conventionally undetectable (Perry et al. 2011) or mask major elements of trait distributions from genetic decomposition of architecture. High similarity of position and effect for albuminuria dispersion markers across the two cohorts strongly supports the existence of dispersion loci underlying the effect, but there was little evidence that the basis of the effect was in general physiological systems like transcription regulation or splicing. A genetic architecture ranging from negative dominance to additivity (Brown 2018) indicates that high heritable randomization values tend to be recessive so that stable expression is ‘rescued’ by a single normalizing allele. Randomization in signs or elements of disease physiology such as albuminuria might be particularly unifit, generally.

Additionally, the evolutionary consequences of such systems could be profound: dispersion loci could create ‘fuzzy’ surfaces on fitness landscapes, permitting individuals or subpopulations to transit between local adaptive peaks without the risk of intervening saddles, or mitigate competition among siblings by dispersing phenotype in close relatives, or allow single parents to produce an array of heterogenous progeny to exploit new niche space or variable environments. Albuminuria (Syme et al. 2006) and creatininuria (Gibb et al. 1989) are linked to survivorship so that dispersion in proteinuria may indeed have direct fitness relevance. The elaboration of dispersion in this system and others may provide a powerful insight into the construction of phenotype, elucidating unseen spandrels of distribution in medicine, evolution and agriculture.

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