Supplementary Material

Supplementary material for “Pleiotropic loci associated with foot disorders and common periparturient diseases in Holstein cattle” (Lai et al. 2021).

1 Supplementary Tables

Table S1. Significant and suggestive SNPs detected in the two-trait linear mixed model association analysis and the linkage disequilibrium (LD) blocks they defined for sole ulcers (SU) and digital dermatitis (DD), SU and white line disease (WLD), DD and mastitis, DD and milk fever, and SU and metritis.

Table S1 is available in the Excel workbook containing all supplemental tables.

Table S2. Genes that overlapped with linkage disequilibrium blocks defined from the genome-wide association analyses for sole ulcers (SU) and digital dermatitis (DD), SU and white line disease (WLD), DD and mastitis, DD and milk fever, and SU and metritis. Phenotypes associated with mouse knockout models of protein-coding genes and the functional relevance of the phenotype to the dataset, if applicable, are also listed. (See Table S4 for which phenotypes were considered functionally relevant for each disorder.)

Table S2 is available in the Excel workbook containing all supplemental tables.
Table S3. Previously defined quantitative trait loci (QTL) or associations overlapping with or in the linkage disequilibrium (LD) blocks defined from the two-trait genome-wide association analyses for sole ulcers (SU) and digital dermatitis (DD), SU and white line disease (WLD), DD and mastitis, DD and milk fever, and SU and metritis that were functionally relevant to at least one of the two traits.

Table S3 is also available in the Excel workbook containing all supplemental tables.

| Dataset                  | LD block location                      | Length (kb) | Overlapping QTL or association                                         | Reference                                                                 |
|--------------------------|----------------------------------------|-------------|------------------------------------------------------------------------|---------------------------------------------------------------------------|
| DD and mastitis          | 1                                      | 125550933   | 125822143                 | 271.2 Digital dermatitis                                                   | (Lai et al., 2020)                                                       |
|                          | 1                                      | 125839933   | 125852054                 | 12.1 Feet and legs conformation                                           | (Cole et al., 2011)                                                     |
|                          |                                        |             |                           | Length of productive life                                                 |                                                                          |
|                          |                                        |             |                           | No overlap with functionally relevant QTL/associations                    |                                                                          |
|                          | 28                                     | 33357088    | 33385923                 | 28.8                                                                      |                                                                          |
| SU and WLD               | 8                                      | 42926603    | 44642925                 | 1716.3 Blood cortisol level                                               | (Chen et al., 2020)                                                     |
|                          |                                        |             |                           | Bovine tuberculosis susceptibility                                       | (Richardson et al., 2016; González-Ruiz et al., 2019)                   |
|                          | 17                                     | 41328134    | 41328134                 | 0 No overlapping QTL/associations                                        |                                                                          |
|                          | 27                                     | 37518206    | 38922466                 | 1404.3                                                                    |                                                                          |
|                          |                                        |             |                           | Foot angle                                                                |                                                                          |
|                          |                                        |             |                           | Length of productive life                                                 |                                                                          |
|                          |                                        |             |                           | Net merit                                                                  |                                                                          |
|                          |                                        |             |                           | Rear leg placement - rear view                                            |                                                                          |
|                          |                                        |             |                           | Rear leg placement - side view                                            |                                                                          |
|                          |                                        |             |                           | Somatic cell score                                                        |                                                                          |
| SU and DD                | 1                                      | 125550933   | 125822143                 | 271.2 Digital dermatitis                                                   | (Lai et al., 2020)                                                       |
|                          | 8                                      | 42926603    | 44642925                 | 1716.3 Blood cortisol level                                               | (Chen et al., 2020)                                                     |
|                          |                                        |             |                           | Bovine tuberculosis susceptibility                                       | (Richardson et al., 2016; González-Ruiz et al., 2019)                   |
|                          | 14                                     | 81655298    | 81664096                 | 8.8 No overlapping QTL/associations                                      | (Lai et al., 2020)                                                       |
| DD and milk fever        | 1                                      | 125550933   | 125822143                 | 271.2 Digital dermatitis                                                   | (Lai et al., 2020)                                                       |
|                          | 18                                     | 24087895    | 24329676                 | 241.8 No overlapping QTL/associations                                    | (Chen et al., 2020)                                                     |
|                          | 28                                     | 34935232    | 35093950                 | 158.7 No overlapping QTL/associations                                    | (Richardson et al., 2016; González-Ruiz et al., 2019)                   |
|                          |                                        |             |                           |                                                                           |                                                                           |
|                          | 28                                     | 35837718    | 36740498                 | 902.8 No overlapping QTL/associations                                    | (Neupane et al., 2018)                                                  |
|                          | 28                                     | 38776483    | 42482917                 | 3706.4 No overlapping QTL/associations                                   |                                                                           |
| SU and metritis          | 8                                      | 42926603    | 44642925                 | 1716.3 Blood cortisol level                                               | (Chen et al., 2020)                                                     |
|                          |                                        |             |                           | Bovine tuberculosis susceptibility                                       | (Richardson et al., 2016; González-Ruiz et al., 2019)                   |
|                          |                                        |             |                           | Bovine respiratory disease susceptibility                                | (Neupane et al., 2018)                                                  |
|                          | 25                                     | 22127459    | 22966511                 | 839.1 No overlapping QTL/associations                                    |                                                                           |
|                          | X                                      | 75319558    | 75610976                 | 291.4 No overlapping QTL/associations                                    |                                                                           |
**Table S4.** Phenotypes that were considered functionally relevant digital dermatitis (DD), sole ulcers (SU), white line disease (WLD) and other health disorders.

| Gene function         | Infectious | Noninfectious |
|-----------------------|------------|---------------|
|                       | DD | Mastitis | Metritis | SU | WLD | Milk fever |
| Adipose/fat           | x  | x        |          |    |     |            |
| Bone                  | x  | x        | x        |    |     |            |
| Cartilage             | x  | x        |          |    |     |            |
| Chondrocyte           | x  | x        |          |    |     |            |
| Immune                | x  | x        | x        |    |     |            |
| Hair                  | x  |          |          |    |     |            |
| Skin                  | x  |          |          |    |     |            |
| Collagen              |    |          |          | x  |     |            |
| Glucose metabolism    |    |          |          |    | x   |            |
| Fibroblast proliferation |    |          |          |    |     |            |
Figure S1. Quantile-quantile plot for two-trait genome-wide association analysis of (a) sole ulcer (SU) and digital dermatitis (DD), (b) SU and white line disease (WLD), (c) DD and mastitis, (d) DD and milk fever, and (e) SU and metritis.