



Figure 2 Ranking KDGs of the CIC IBD networks. One hundred and thirty-three KDGs were identified and scored with respect to genetic association to IBD, involvement in inflammatory processes associated with IBD, and association with IBD-related clinical traits. The KDGs are listed clockwise around the disk in rank order, starting with the top ranked KDG at the top of the disc. Each of the internal rings represents either a summary statistic used in the ranking or a type of disease support used to form the summary statistics for the ranking. The first two tracks are normalized rank and rank by disease trait enrichment, respectively, and the remaining tracks 3–10 are KDG rankings per trait (**Supplementary Table 16**): track 3, IBD GWAS; track 4, original immune network; track 5, Crohn's disease versus control (CL_ileum); track 6, Crohn's disease versus CL_colon; track 7, Crohn's disease versus ulcerative colitis colon; track 8, CRP; track 9, disease duration; track 10, VEO IBD genes. The color depicted in each element signifies the degree of support provided by the trait rank for the corresponding KDG, with cooler colors reflecting weaker support and hotter colors reflecting stronger support. Black asterisks denote KDGs that have already been linked to IBD experimentally. Orange asterisks indicate prioritized KDGs for experimental validation.

KDG algorithm to determine these master regulators¹⁰, we identified 133 KDGs across all three intestinal CIC IBD networks (**Supplementary Table 15**). To prioritize these for experimental validation, we annotated them using four different categories of IBD-focused data sets: (i) genes identified in genetic studies as associated with IBD or very early onset (VEO) IBD; (ii) IBD-specific ileum and colon gene expression signatures from the MSH population; (iii) correlation signatures between clinical traits associated with IBD and gene expression data from the CERTIFI

population; and (iv) the original immune network. We projected each of these IBD gene sets onto each of the CIC IBD networks and identified the KDG signatures most enriched for the IBD gene and trait signatures (**Supplementary Tables 15 and 16**). We then rank-ordered the 133 KDGs on the basis of a composite score that considered all lines of evidence supporting the KDGs in an IBD-informative context, thus providing a quantitative measure of the importance and degree of causal association each KDG had to IBD. From the top 10% of the KDGs in this rank-ordered list (**Figs. 1d** and **2**, and **Supplementary**