Supporting Information

Itan et al. 10.1073/pnas.1218167110

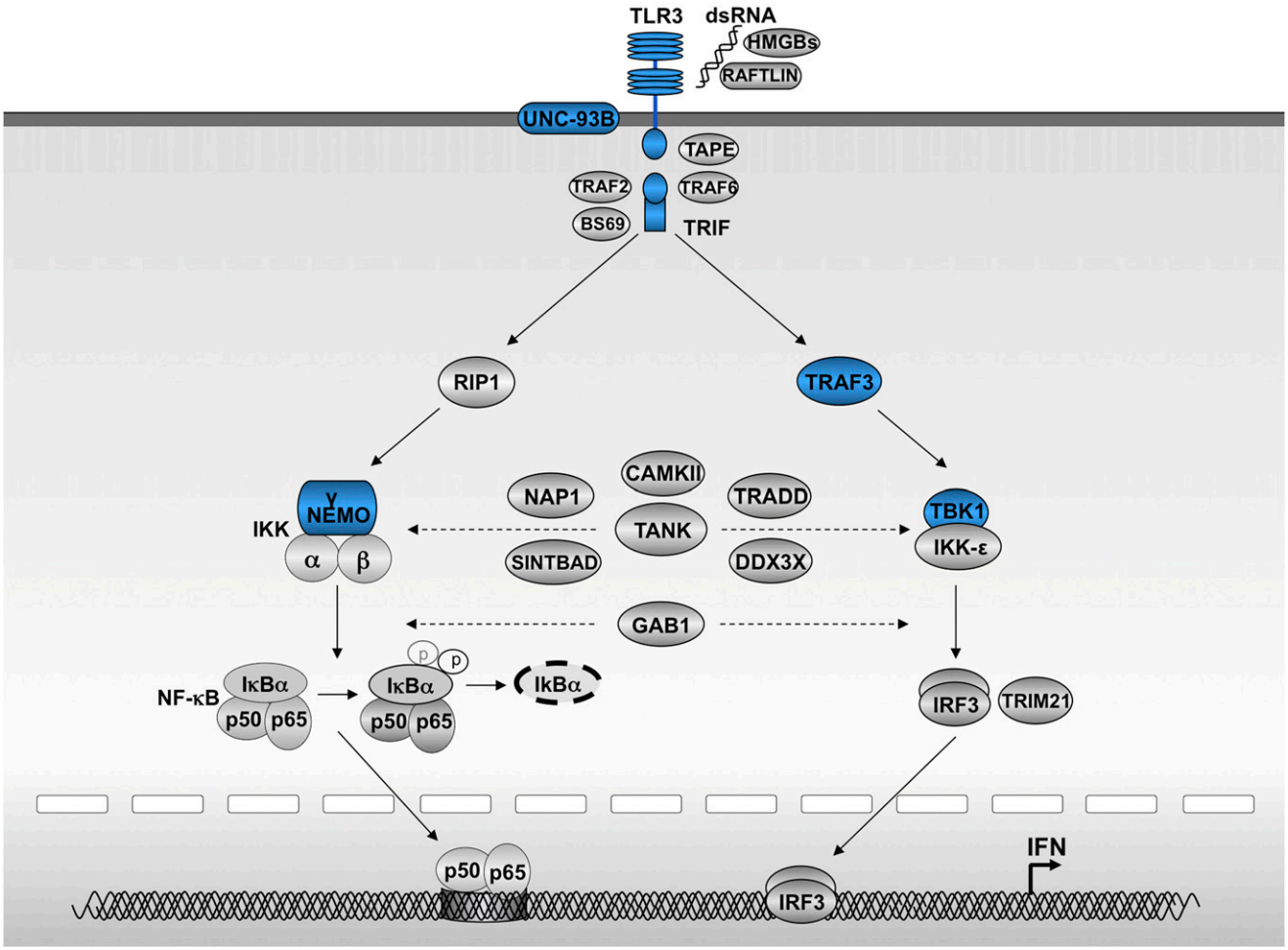

Fig. S1. The TLR3 pathway, based on available data from published studies. The pathway includes genes for which involvement in the Toll-like receptor 3 (TLR3) pathway is supported by strong experimental evidence (including the genes investigated here within the top 5% of the *TLR3* connectome) and genes known to be involved in other pathways as well.

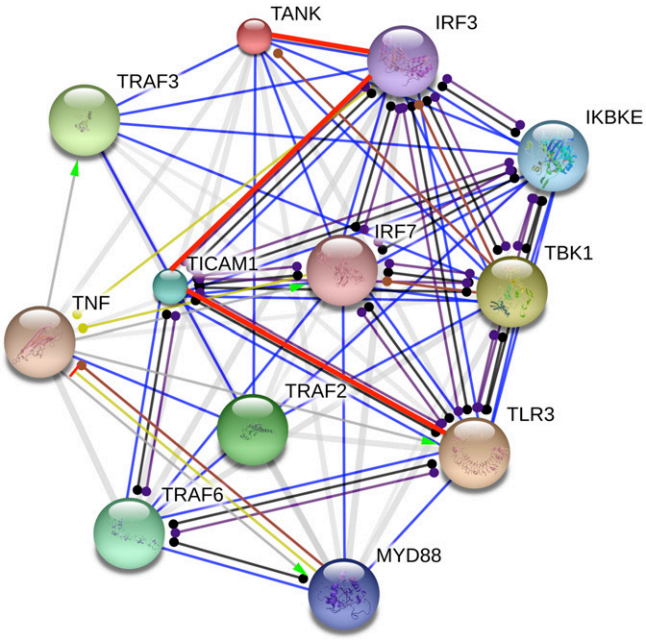

Fig. S2. String-based estimations of the route between *TLR3* and TRAF family member-associated NF-kappa-B activator (*TANK*), two closely related genes in the TLR3 pathway. This String network was generated with the minimum number of extensions required to connect *TLR3* and *TANK* via binding connections. The possible number of unique routes between *TLR3* and *TANK* on the graph shown is estimated to be in the hundreds. The whole human gene network should be taken into account to identify the true biologically plausible shortest route between the two genes. Blue connections represent binding interactions (used to generate the human gene connectome, HGC), purple indicates catalysis interactions, brown corresponds to posttranslational modifications, yellow indicates expression with inhibition, green indicates activation, black indicates reaction, and gray corresponds to the co-occurrence of the two connected genes in published studies or other databases (see http://string-db.org/ for further details). The red connections show the single biologically plausible route between *TLR3* and *TANK*, as estimated by the HGC.

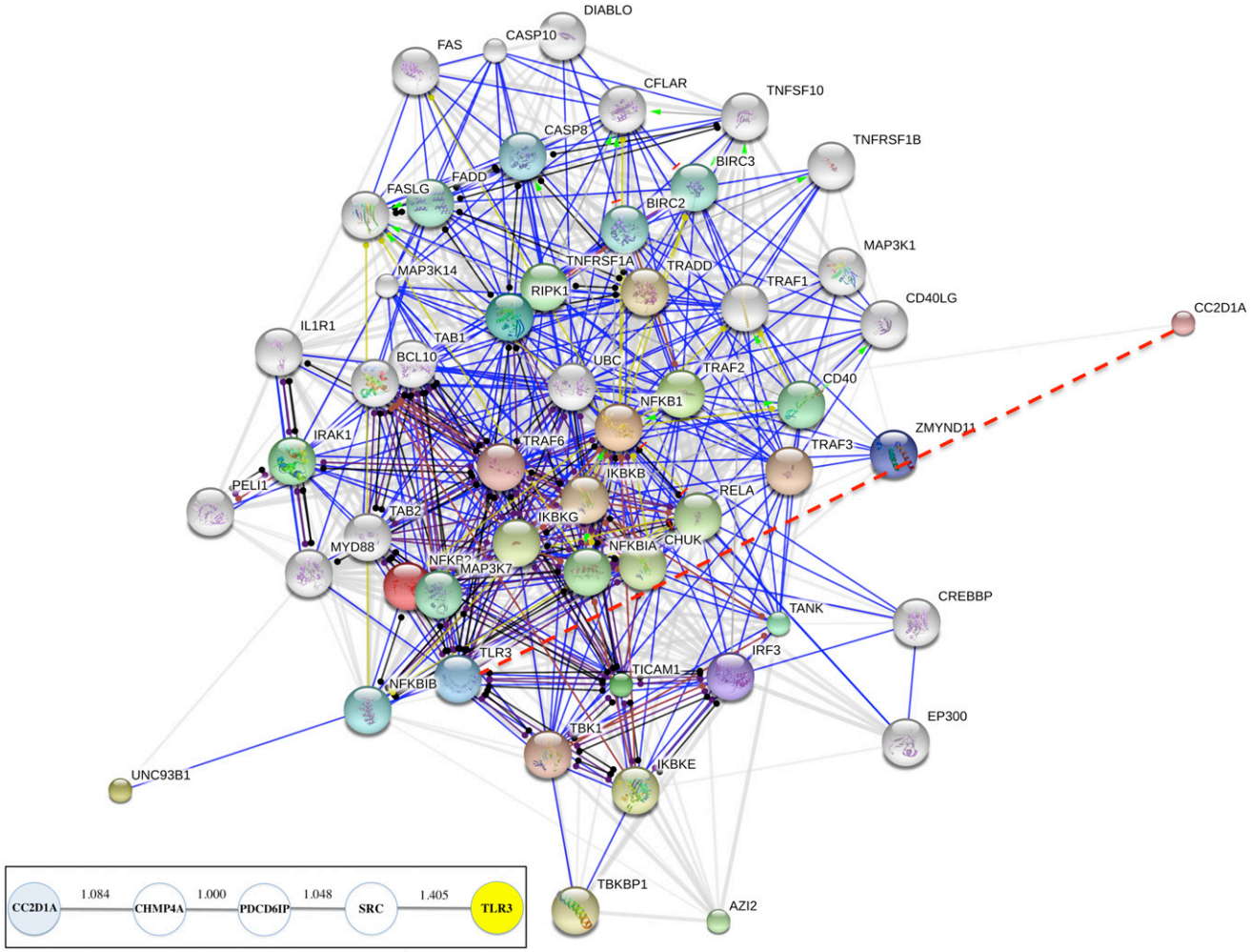

Fig. S3. An attempt to use String to estimate the shortest biological route between *TLR3* and coiled-coil and C2 domain containing 1A (*CC2D1A*/*TAPE*)—a gene of the TLR3 pathway. As in Fig. S2, generated by String interface "actions" network (http://string-db.org), *TLR3* and *CC2D1A* could not initially be connected, and they are shown within the context of all experimentally validated TLR3 pathway genes, with three attempts to extend the network to find a route connecting these two genes, using default parameters (low constraint parameters and further extensions did not generate such a connection either). Identification of the single shortest biologically plausible route is almost impossible, as the number of possible routes between the two genes is estimated to be in the millions and relevant genes along the route are missing. The colors indicating the types of connection are as in Fig. S2. The bottom left panel shows the single biologically plausible route and distance between *TLR3* and *CC2D1A*, as estimated by the HGC. See Table S1 and Table S2 for a detailed description of the predicted biological distance and route between *TLR3* and all of the genes predicted to be biologically closest to it, including its pathway genes. For a full description of the *TLR3* connectome (and any gene-specific connectome of interest), see http://lab.rockefeller.edu/casanova/HGC.

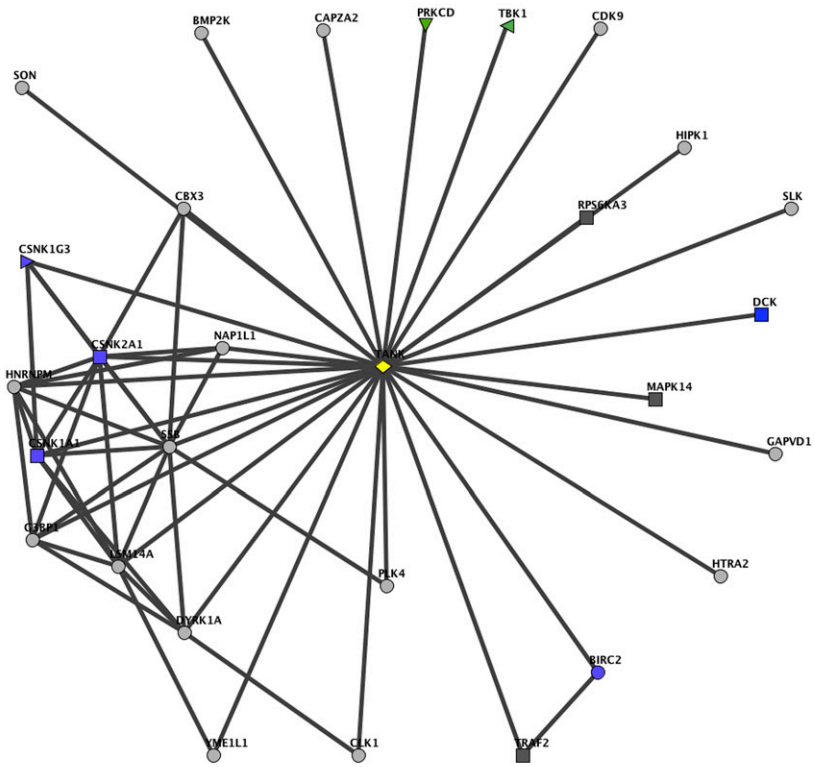

Fig. S4. FunCoup-based estimations of the route between *TLR3* and *TANK*. Details as in Fig. S2. Generated by the FunCoup physical interactions network. There is no possible predicted route between *TLR3* and *TANK* (both in yellow) when only these two genes are used as input. See http://funcoup.sbc.su.se for a detailed network description.

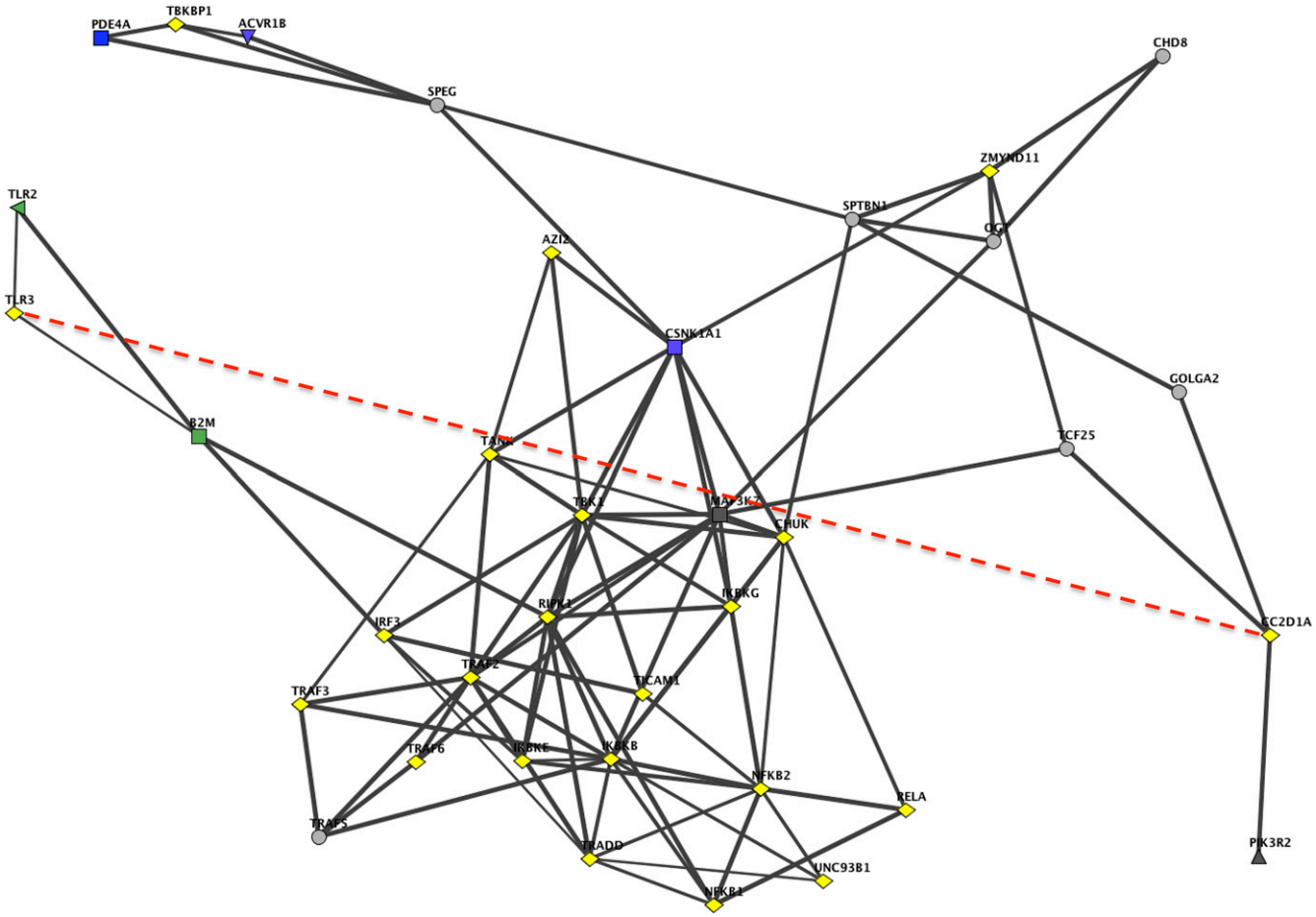

Fig. S5. An attempt to use FunCoup to estimate the shortest biological route between *TLR3* and *CC2D1A (TAPE)*. Details as in Fig. S3, generated by the FunCoup physical interactions network. *TLR3* and *CC2D1A* could not initially be connected, and they are shown within the context of all experimentally validated TLR3 pathway genes, colored in yellow. See http://funcoup.sbc.su.se for a detailed network description.

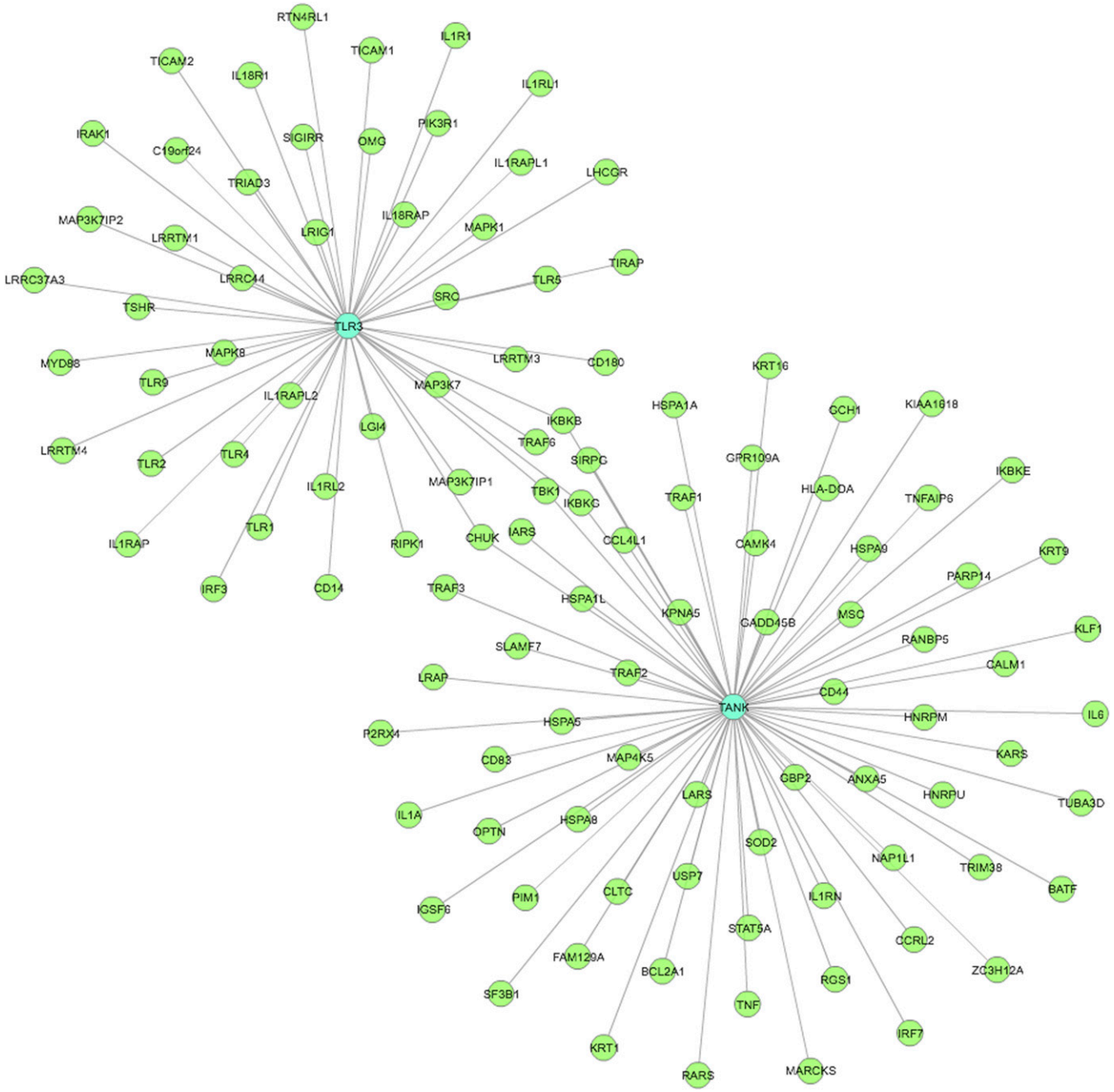

Fig. S6. HumanNet-based estimations of the route between *TLR3* and *TANK*. As in Figs. S2 and S4. *TLR3* and *TANK* are shown in cyan. See www.functionalnet.org/humannet/about.html for a detailed network description.

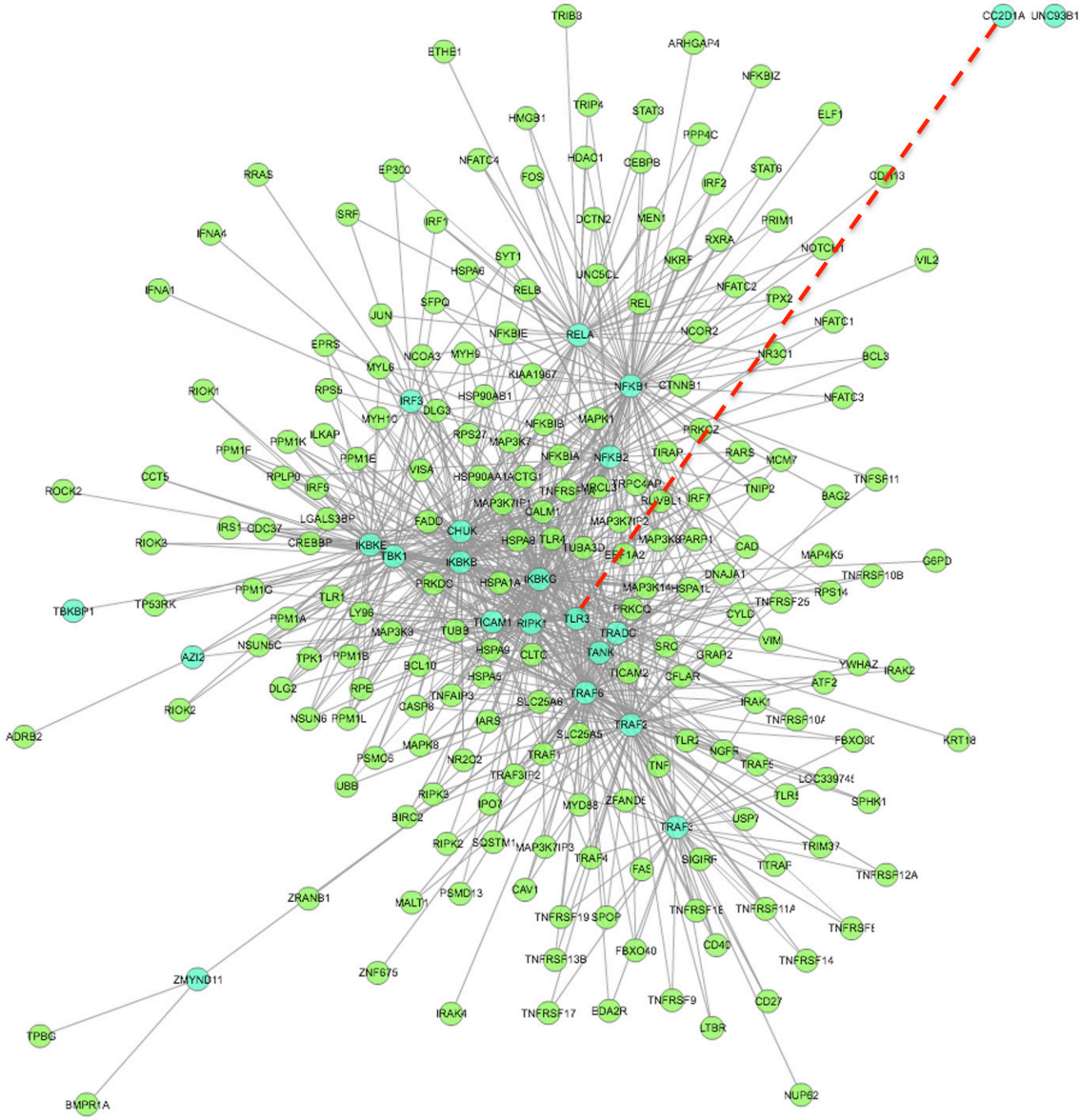

Fig. S7. An attempt to use HumanNet to estimate the shortest biological route between *TLR3* and *CC2D1A (TAPE)*. Details as in Figs. S3 and S5. *TLR3* and *CC2D1A* could not initially be connected, and they are shown within the context of all experimentally validated TLR3 pathway genes, colored in cyan. See www.functionalnet.org/humannet/about.html for a detailed network description.

Other Supporting Information Files

Table S1 (DOCX)
Table S2 (DOCX)