

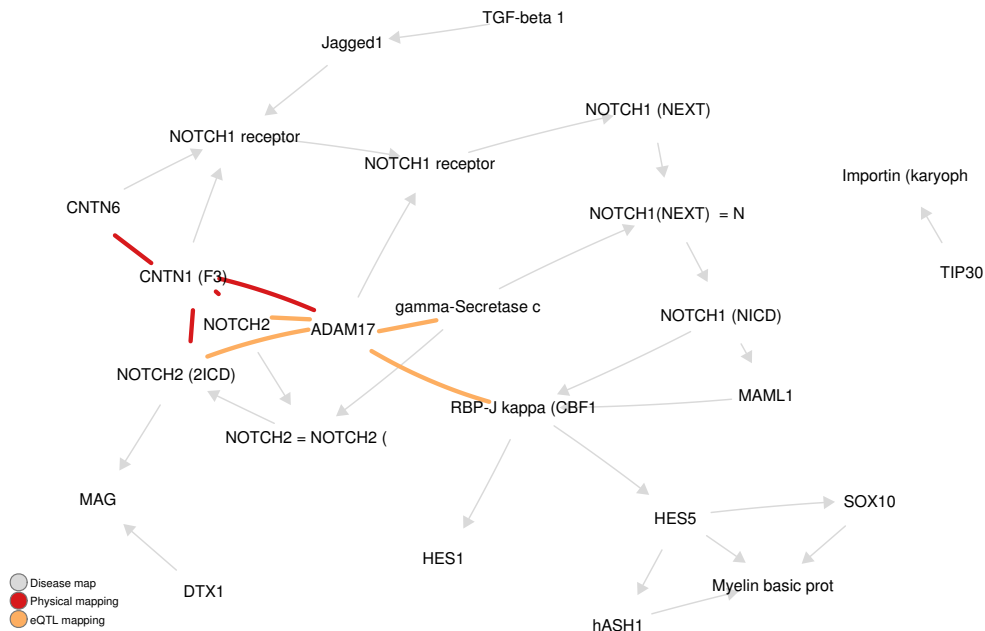
A systematic analysis of gene-gene interaction in multiple sclerosis Supplementary Materials

A Distribution of SNPs in MS disease maps

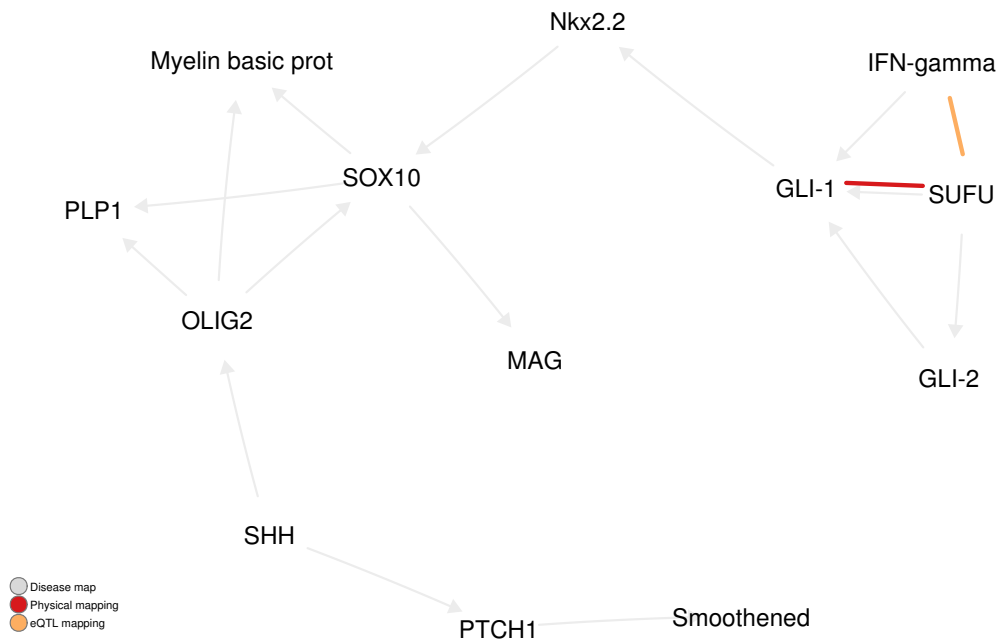
Table 1: SNP and gene distributions in each disease map for eQTL and physical mappings

internal ID	Physical mapping			eQTL mapping		
	#SNPs	#genes	average #SNPs per gene	#SNPs	#genes	average #SNPs per gene
3302	416	21	19.81	833	19	43.84
3305	70	10	7.00	238	8	29.75
3306	383	21	18.24	869	19	45.74
4455	755	38	19.87	1813	36	50.36
4593	1295	24	53.96	1647	17	96.88
4693	544	34	16.00	912	27	33.78
4703	331	28	11.82	999	27	37.00
4791	252	24	10.50	1264	23	54.96
4794	84	15	5.60	331	12	27.58
4843	984	32	30.75	1401	29	48.31
4846	1318	36	36.61	1555	32	48.59
4901	1173	35	33.51	1209	24	50.38
5199	656	28	23.43	1320	32	41.25
5288	515	27	19.07	724	22	32.91
5378	257	22	11.68	907	22	41.23
5398	141	21	6.71	1050	24	43.75
5518	392	29	13.52	1474	27	54.59
5601	348	28	12.43	742	25	29.68
5611	224	22	10.18	906	24	37.75

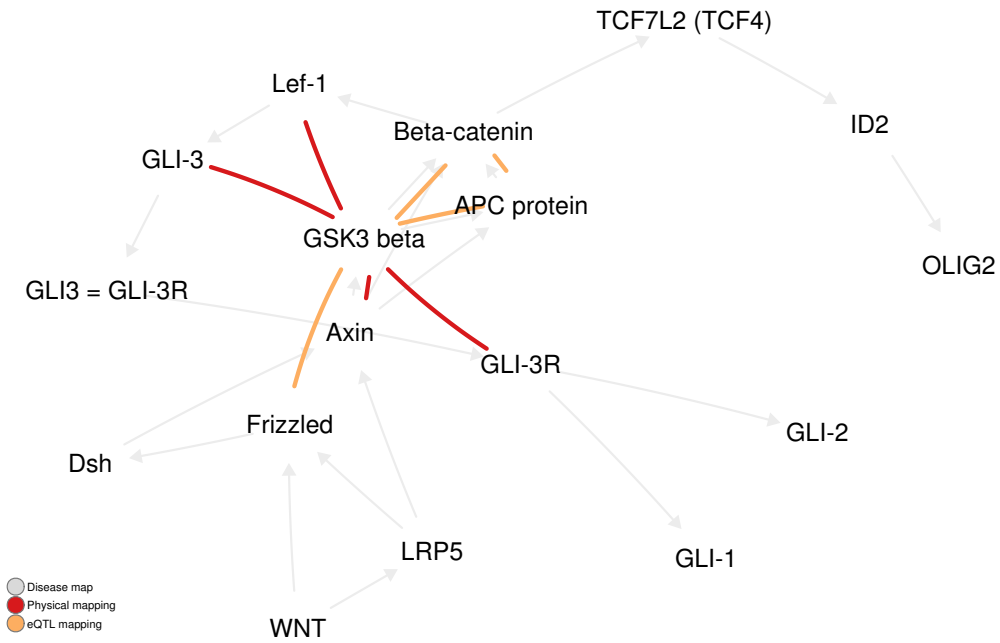
B Visualization of epiGWAS results on MetaCore disease maps



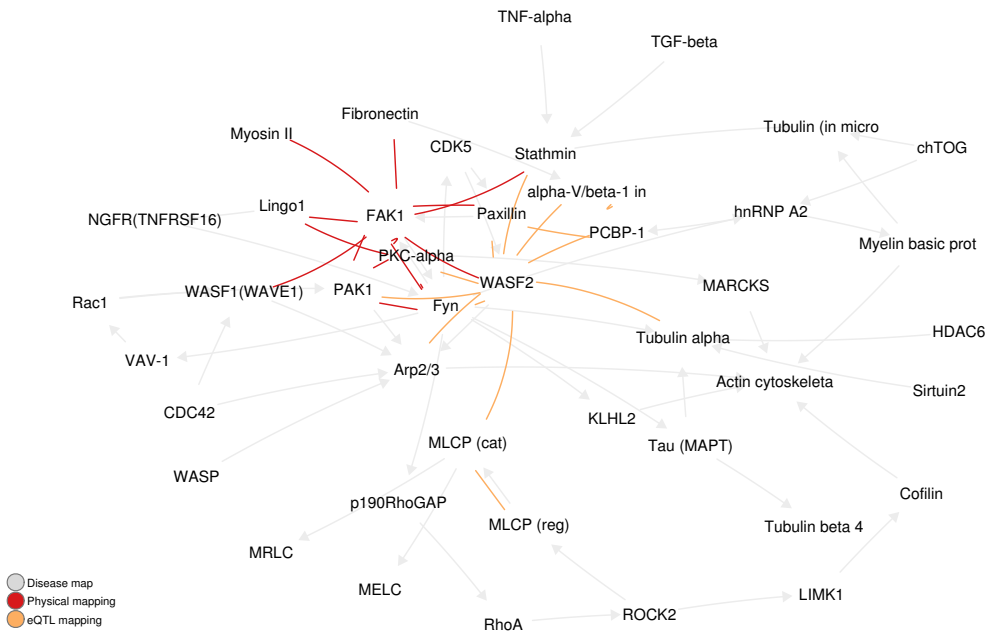
(a) DM 3302: Notch signaling in oligodendrocyte precursor cell differentiation in multiple sclerosis



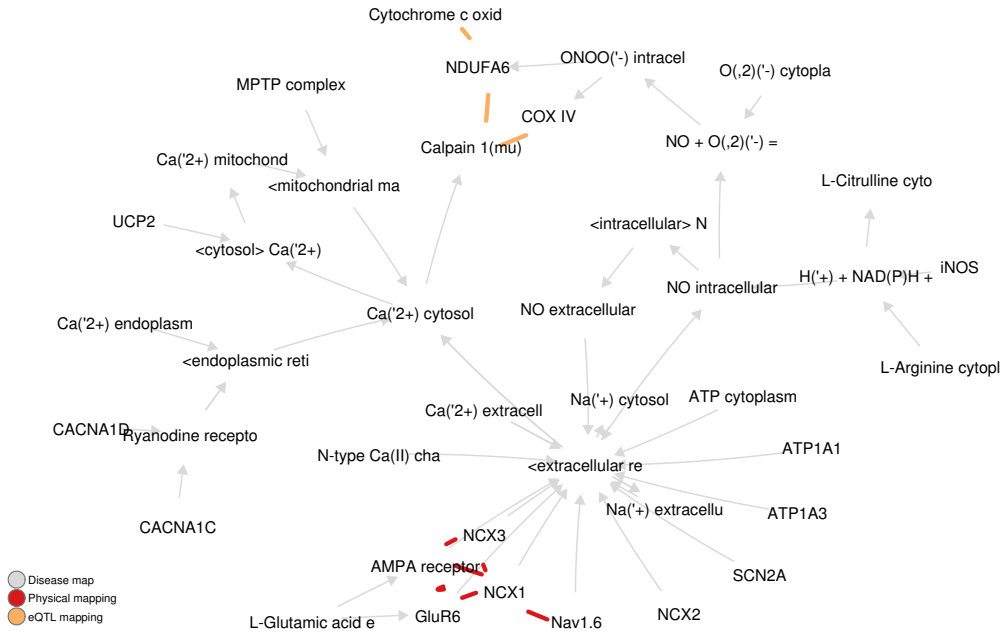
(b) DM 3305: SHH signaling in oligodendrocyte precursor cells differentiation in multiple sclerosis



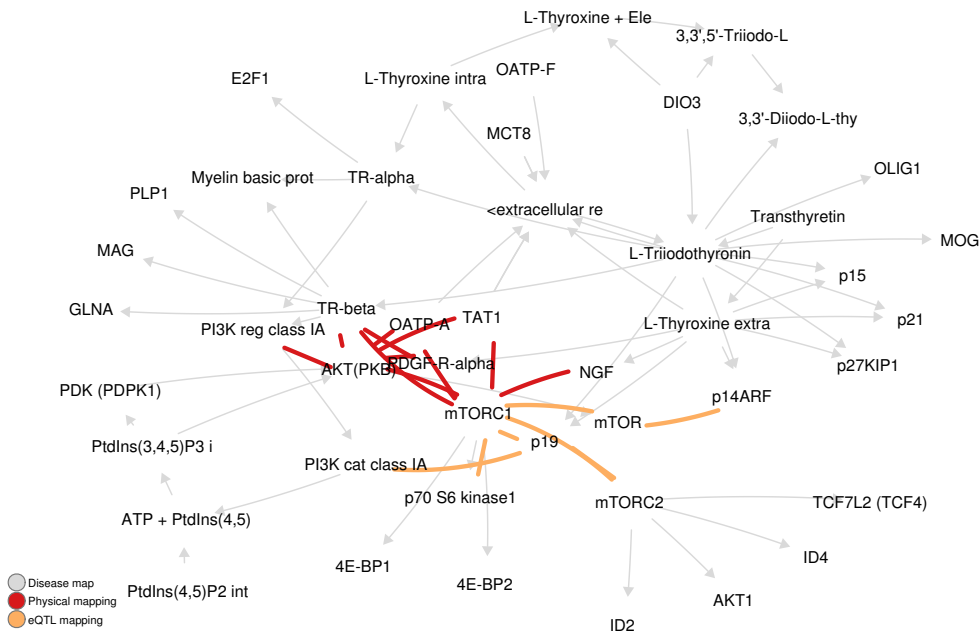
(c) DM 3306: Inhibition of oligodendrocyte precursor cells differentiation by Wnt signaling in multiple sclerosis



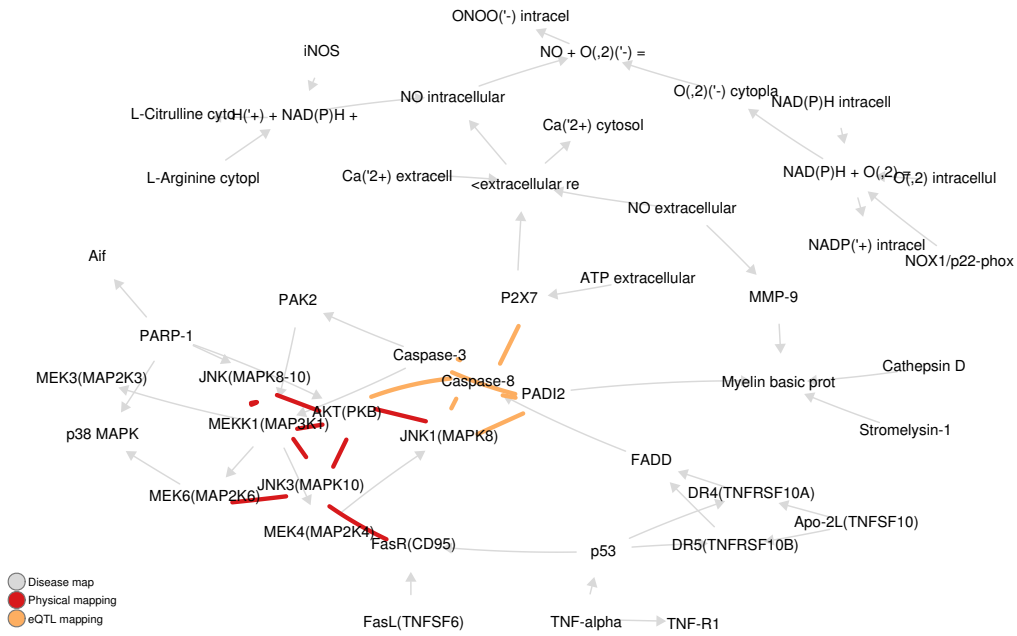
(d) DM 4455: Inhibition of remyelination in multiple sclerosis: regulation of cytoskeleton proteins



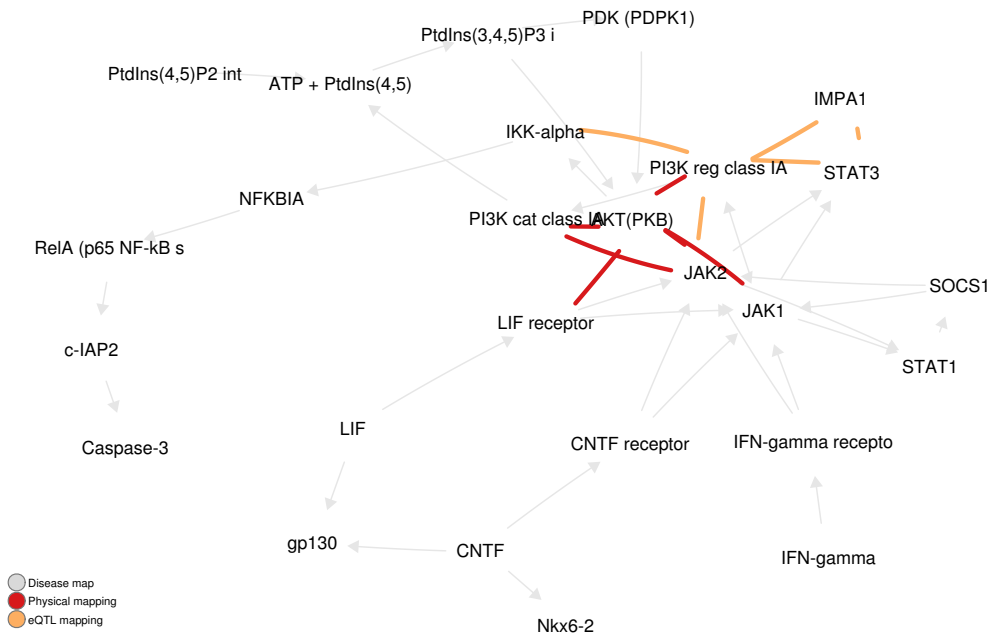
(e) DM 4593: Axonal degeneration in multiple sclerosis



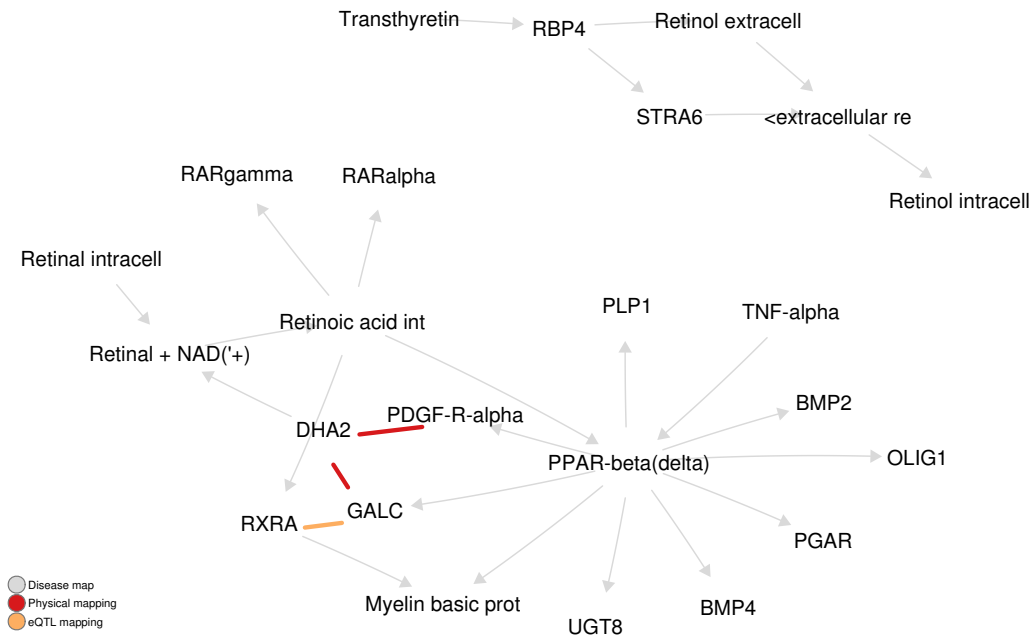
(f) DM 4693: Role of Thyroid hormone in regulation of oligodendrocyte differentiation in multiple sclerosis



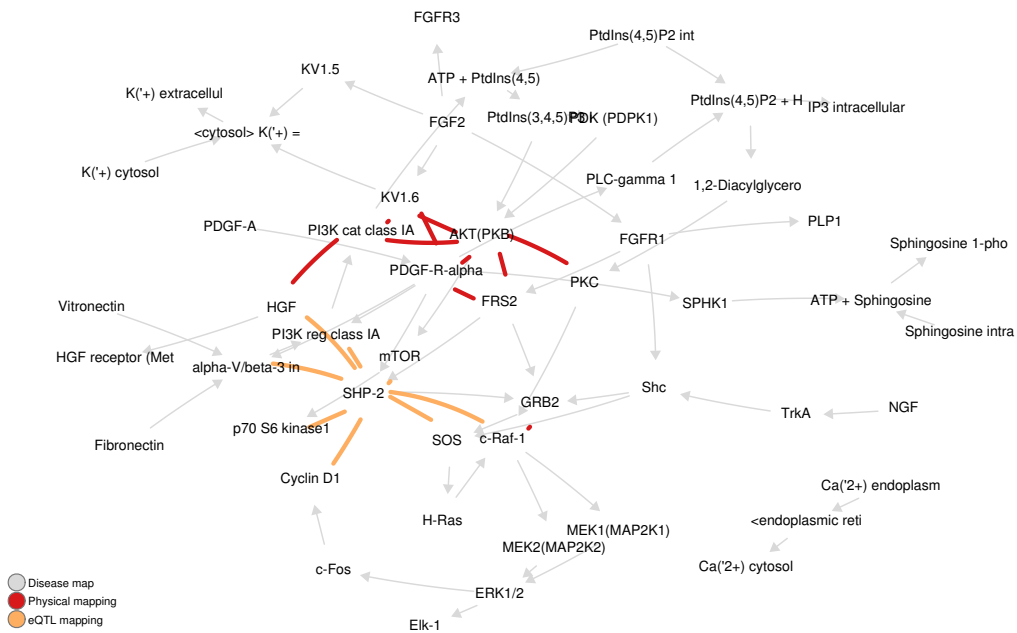
(g) DM 4703: Demyelination in multiple sclerosis



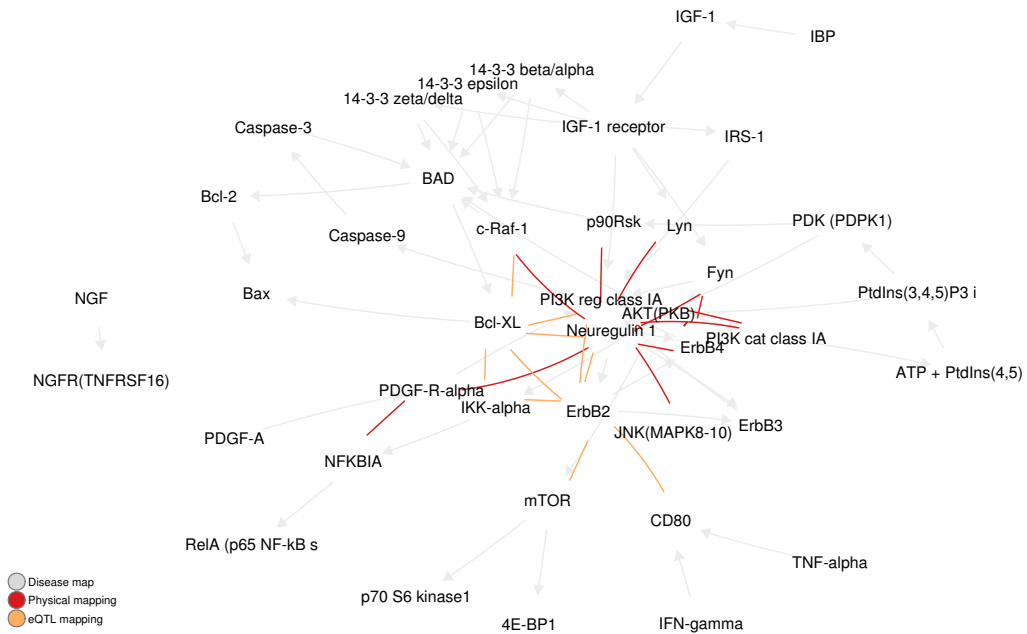
(h) DM 4791: Role of CNTF and LIF in regulation of oligodendrocyte development in multiple sclerosis



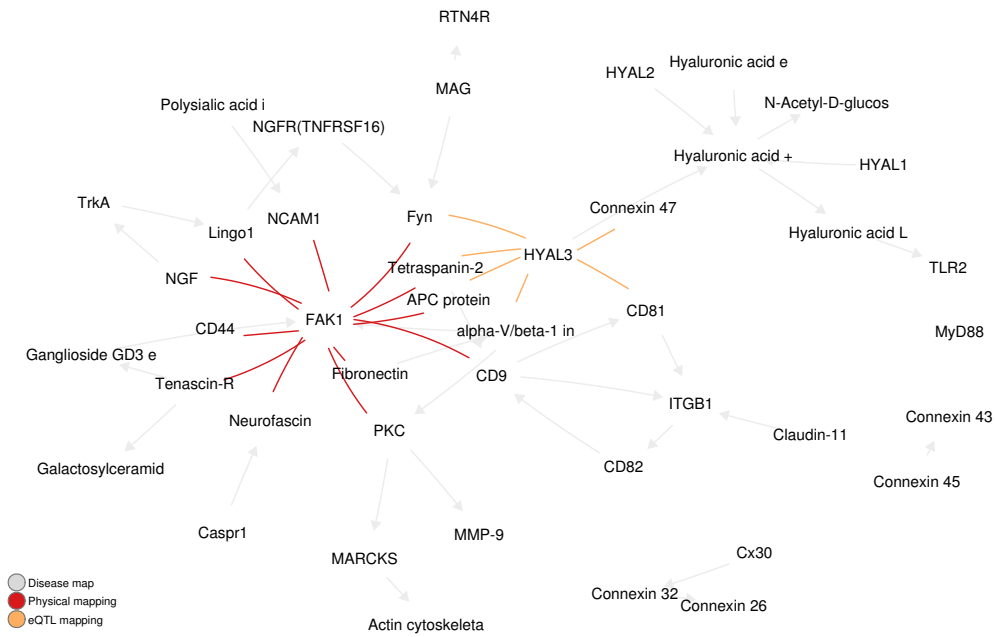
(i) DM 4794: Retinoic acid regulation of oligodendrocyte differentiation in multiple sclerosis



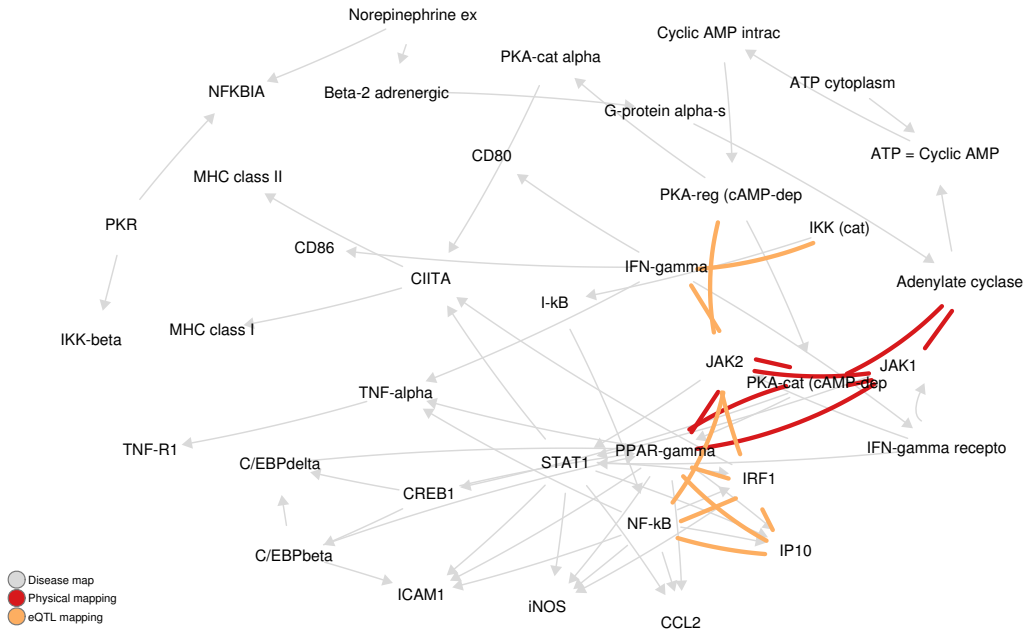
(j) DM 4843: Growth factors in regulation of oligodendrocyte precursor cells proliferation in multiple sclerosis



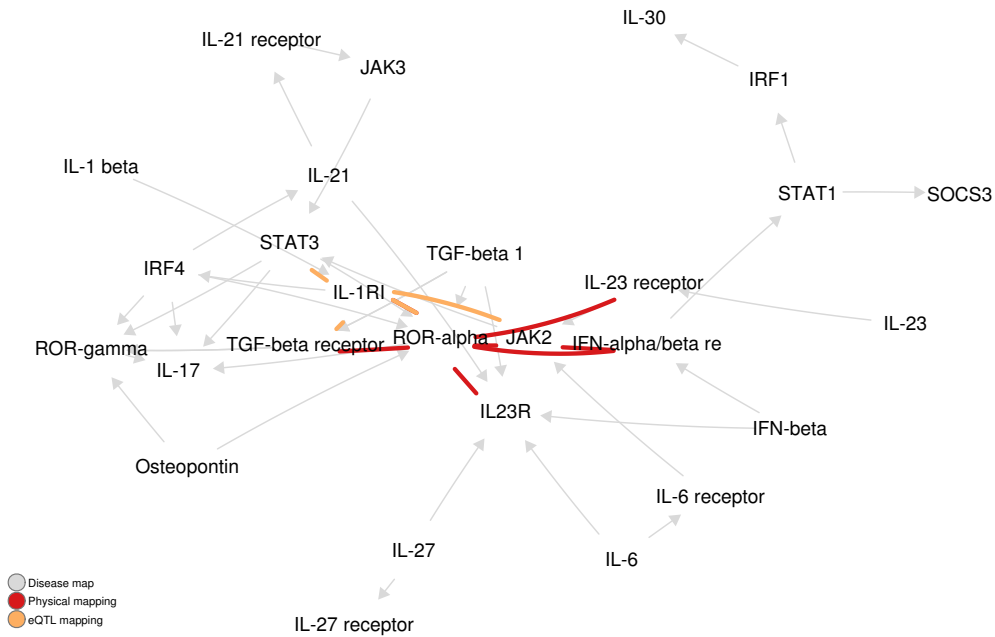
(k) DM 4846: Growth factors in regulation of oligodendrocyte precursor cells survival in multiple sclerosis



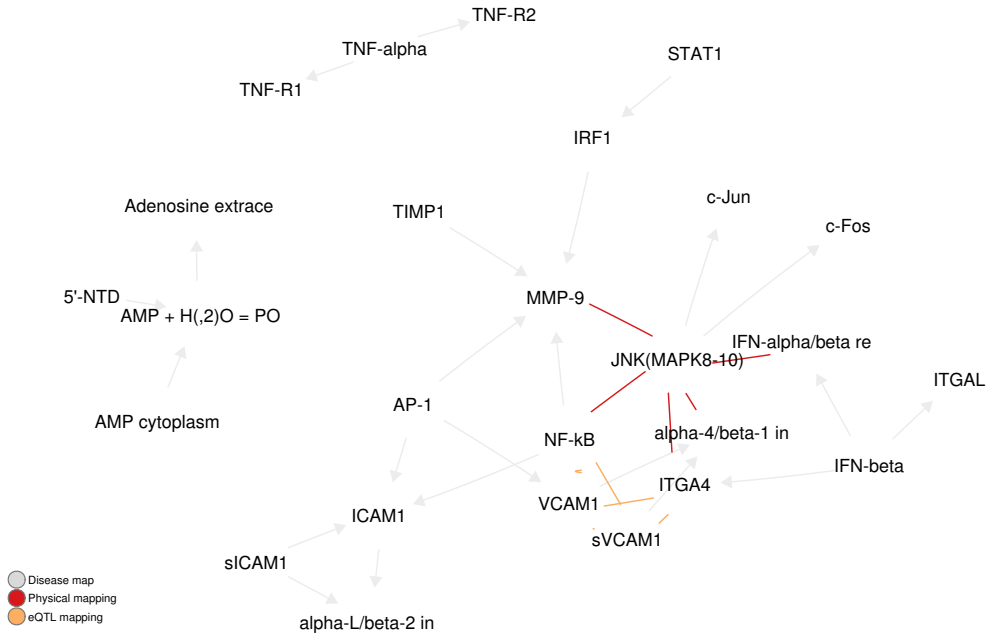
(l) DM 4901: Inhibition of remyelination in multiple sclerosis: role of cell-cell and ECM-cell interactions



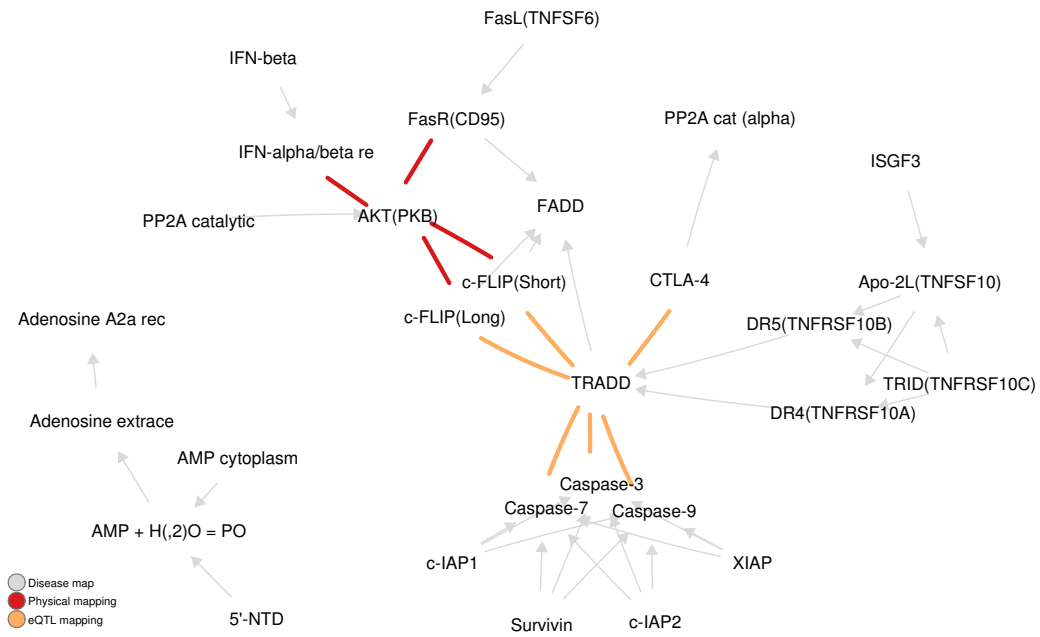
(m) DM 5199: Cooperative action of IFN- γ and TNF- α on astrocytes in multiple sclerosis



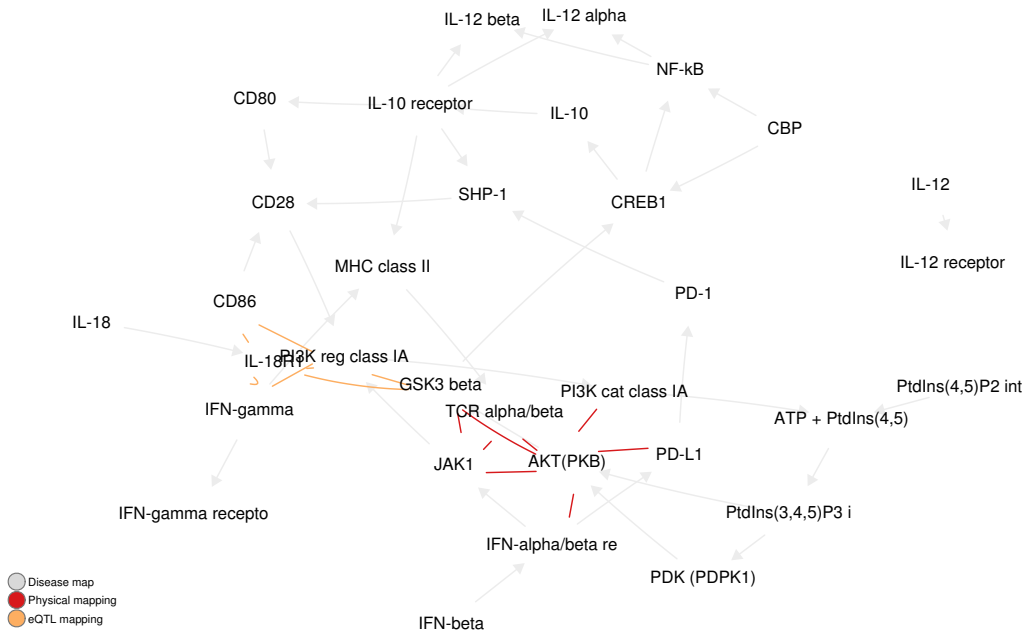
(n) DM 5288: Impaired inhibition of Th17 cell differentiation by IFN- β in multiple sclerosis



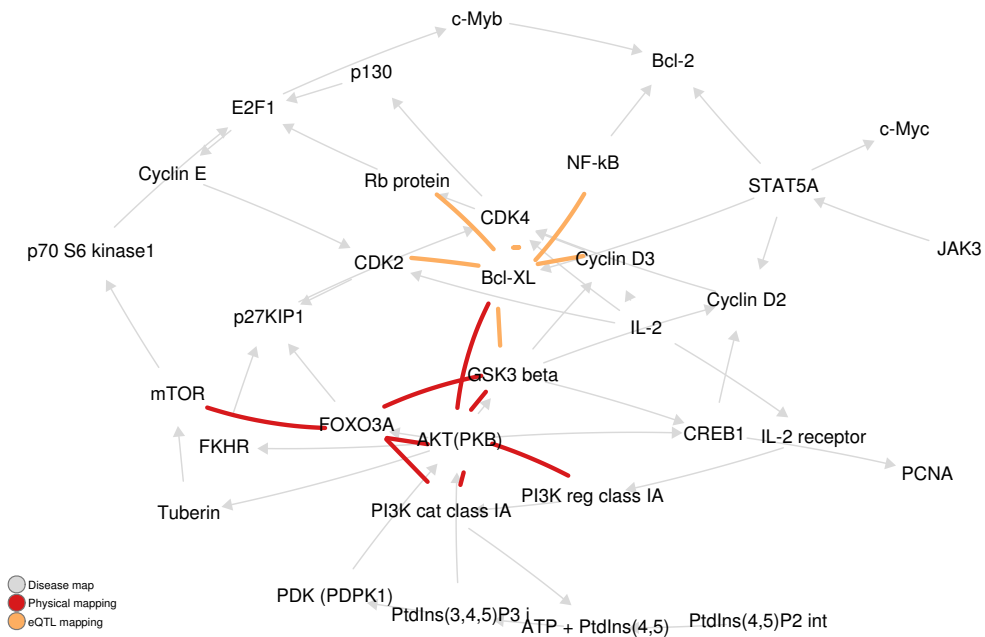
(o) DM 5378: Role of IFN- β in the improvement of blood-brain barrier integrity in multiple sclerosis



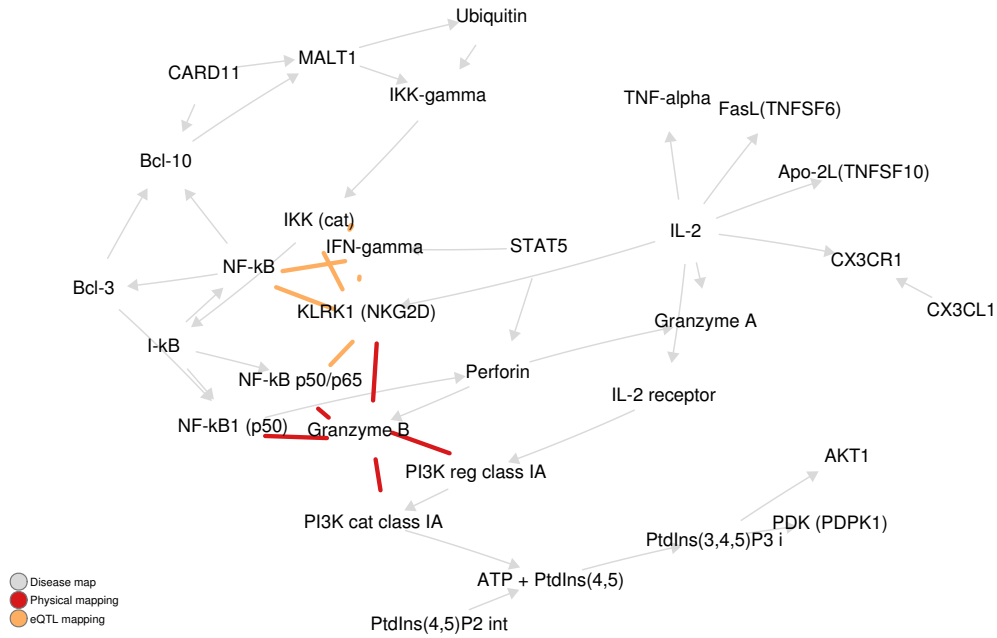
(p) DM 5398: Role of IFN- β in activation of T cell apoptosis in multiple sclerosis



(q) DM 5518: Role of IFN- β in inhibition of Th1 cell differentiation in multiple sclerosis



(r) DM 5601: IL-2 as a growth factor for T cells in multiple sclerosis



(s) DM 5611: Role of IL-2 in the enhancement of NK cell cytotoxicity in multiple sclerosis

Figure 1: Representation of the 2% top-scoring interactions for physical and eQTL mappings on the original disease maps.

C Statistical significance of the observed network characteristics

Table 2: Enrichment analysis results for four network characteristics: connectedness, complementarity, centrality and commonality.

internal ID	Connectedness		Complementariy			Centrality	Commonality		
	physical mapping	eQTL mapping	1 vertex	2 vertices	3 vertices	maximal degree	1 edge	2 edges	3 edges
3302	0.019	0.021	0.705	0.254	0.038	0.147	0.542	0.149	0.022
3305	1.000	1.000	0.294	0.013	0.000	1.000	0.354	0.035	0.000
3306	0.061	0.060	0.792	0.335	0.054	0.001	0.761	0.357	0.099
4455	0.000	0.000	0.988	0.905	0.679	0.000	0.822	0.499	0.224
4593	0.001	0.014	0.392	0.056	0.004	0.724	0.368	0.072	0.007
4693	0.000	0.000	0.728	0.314	0.072	0.000	0.619	0.246	0.069
4703	0.000	0.000	0.649	0.208	0.033	0.750	0.479	0.126	0.020
4791	0.008	0.011	0.778	0.340	0.070	0.407	0.728	0.333	0.096
4794	0.161	1.000	0.241	0.011	0.000	1.000	0.233	0.028	0.001
4843	0.000	0.000	0.836	0.477	0.171	0.014	0.551	0.179	0.037
4846	0.000	0.000	0.938	0.699	0.361	0.000	0.782	0.447	0.191
4901	0.000	0.002	0.947	0.729	0.391	0.000	0.561	0.187	0.040
5199	0.000	0.000	0.726	0.291	0.057	0.134	0.785	0.439	0.183
5288	0.004	0.014	0.791	0.366	0.082	0.009	0.697	0.307	0.090
5378	0.012	0.011	0.673	0.215	0.026	0.341	0.561	0.172	0.030
5398	0.012	0.004	0.779	0.346	0.074	0.052	0.567	0.178	0.034
5518	0.002	0.002	0.723	0.283	0.050	0.251	0.665	0.275	0.074
5601	0.001	0.002	0.847	0.472	0.146	0.032	0.713	0.338	0.109
5611	0.004	0.004	0.687	0.245	0.037	0.405	0.602	0.210	0.048

D Content of resulting subnetworks in therapeutic targets

Table 3: Number of drug targets in the resulting subnetworks for each disease map and its statistical significance.

internal ID	Number of included drug targets	<i>p</i> -value
3302	0	1.000
3305	0	1.000
3306	1	0.378
4455	2	0.380
4593	6	0.009
4693	2	0.382
4703	0	1.000
4791	2	0.154
4794	1	0.222
4843	2	0.808
4846	2	0.500
4901	2	0.265
5199	1	0.875
5288	2	0.728
5378	4	0.024
5398	2	0.347
5518	4	0.275
5601	1	0.768
5611	0	1.000

E MetaCore disease maps

E.1 Disease map 3305

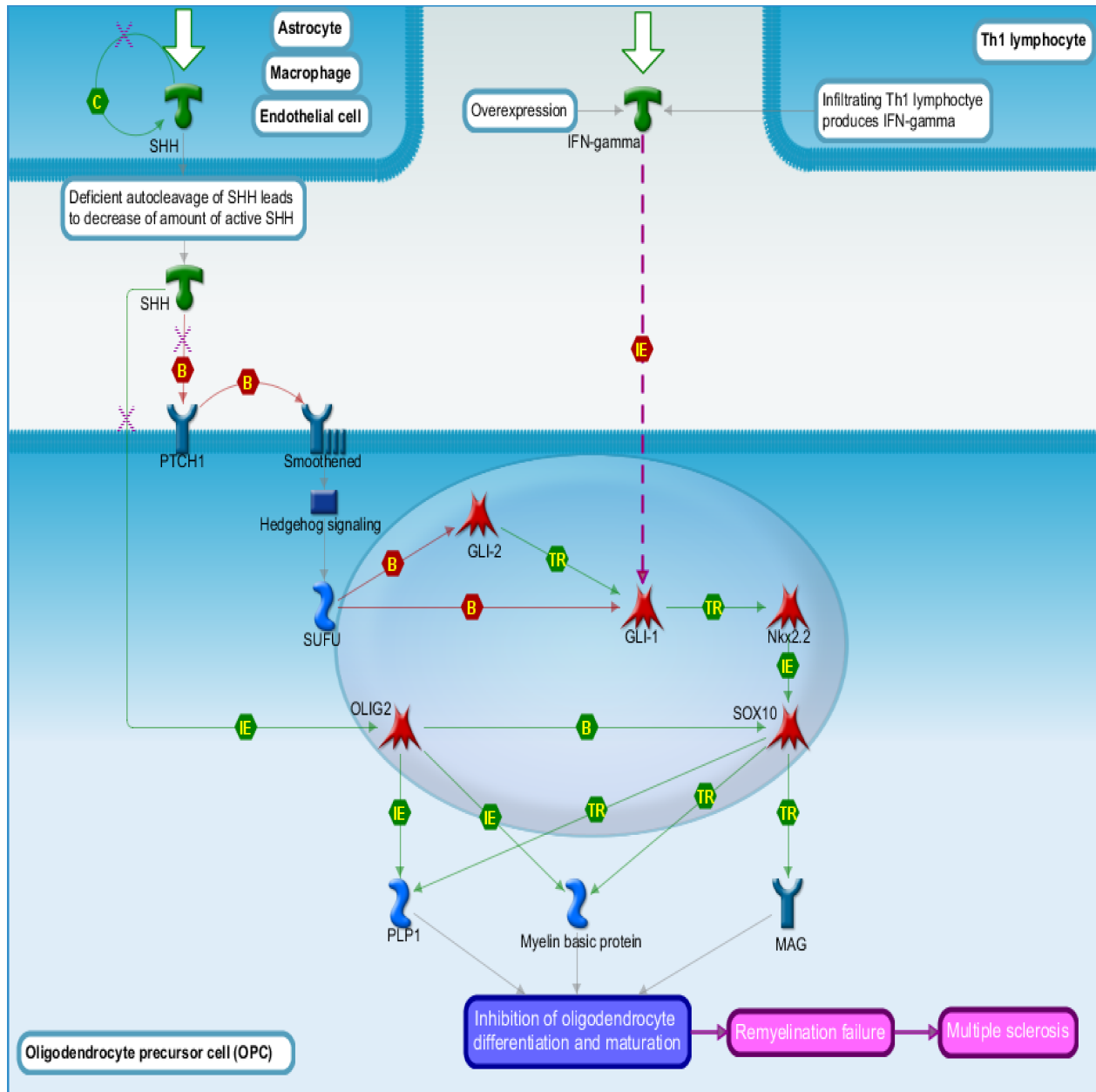


Figure 2: Sonic Hedgehog signaling in oligodendrocyte precursor cells differentiation in multiple sclerosis (DM 3305).

E.2 Disease map 4455

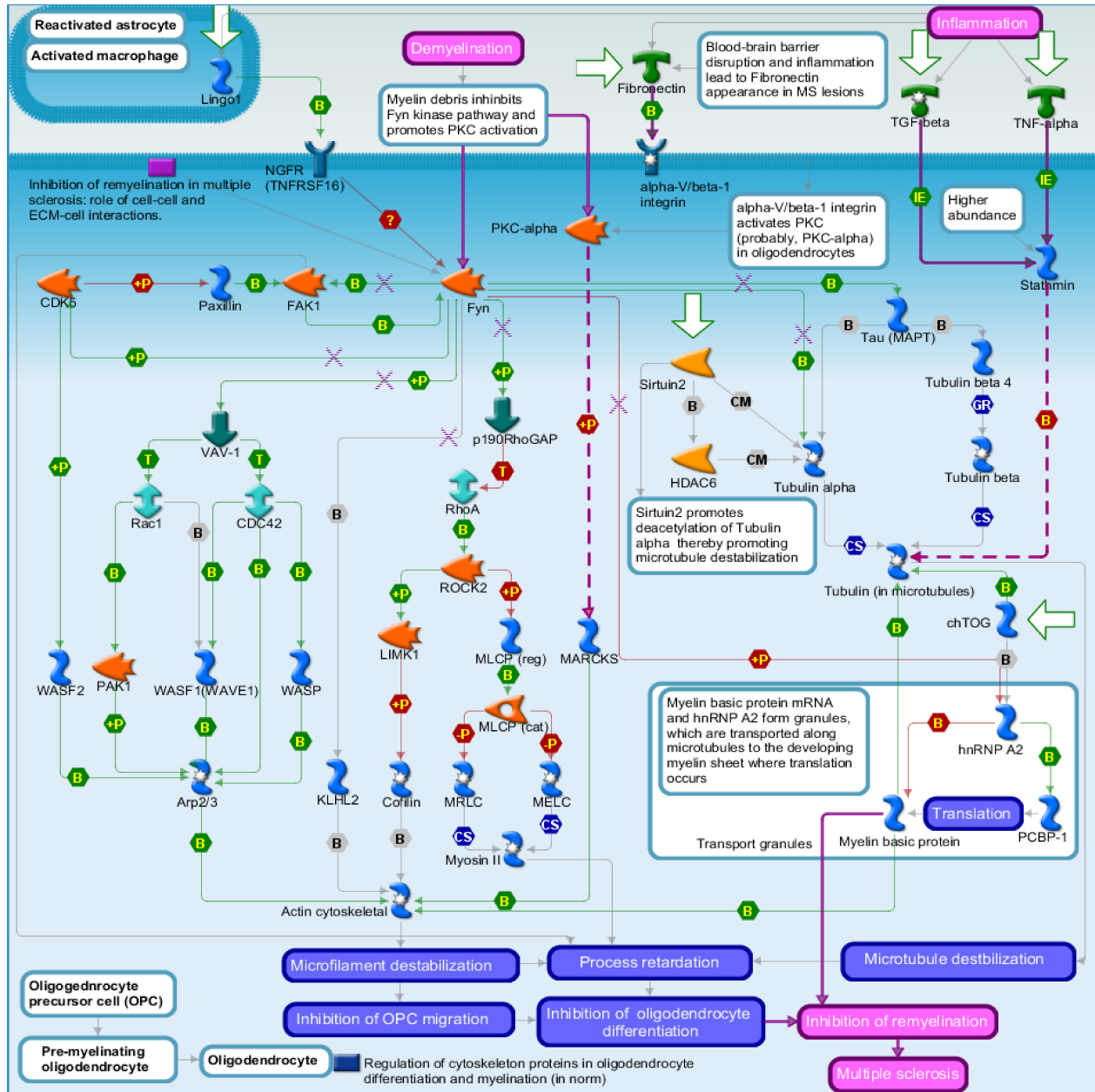


Figure 3: Inhibition of remyelination in multiple sclerosis: regulation of cytoskeleton proteins (DM 4455).

E.3 Disease map 5199

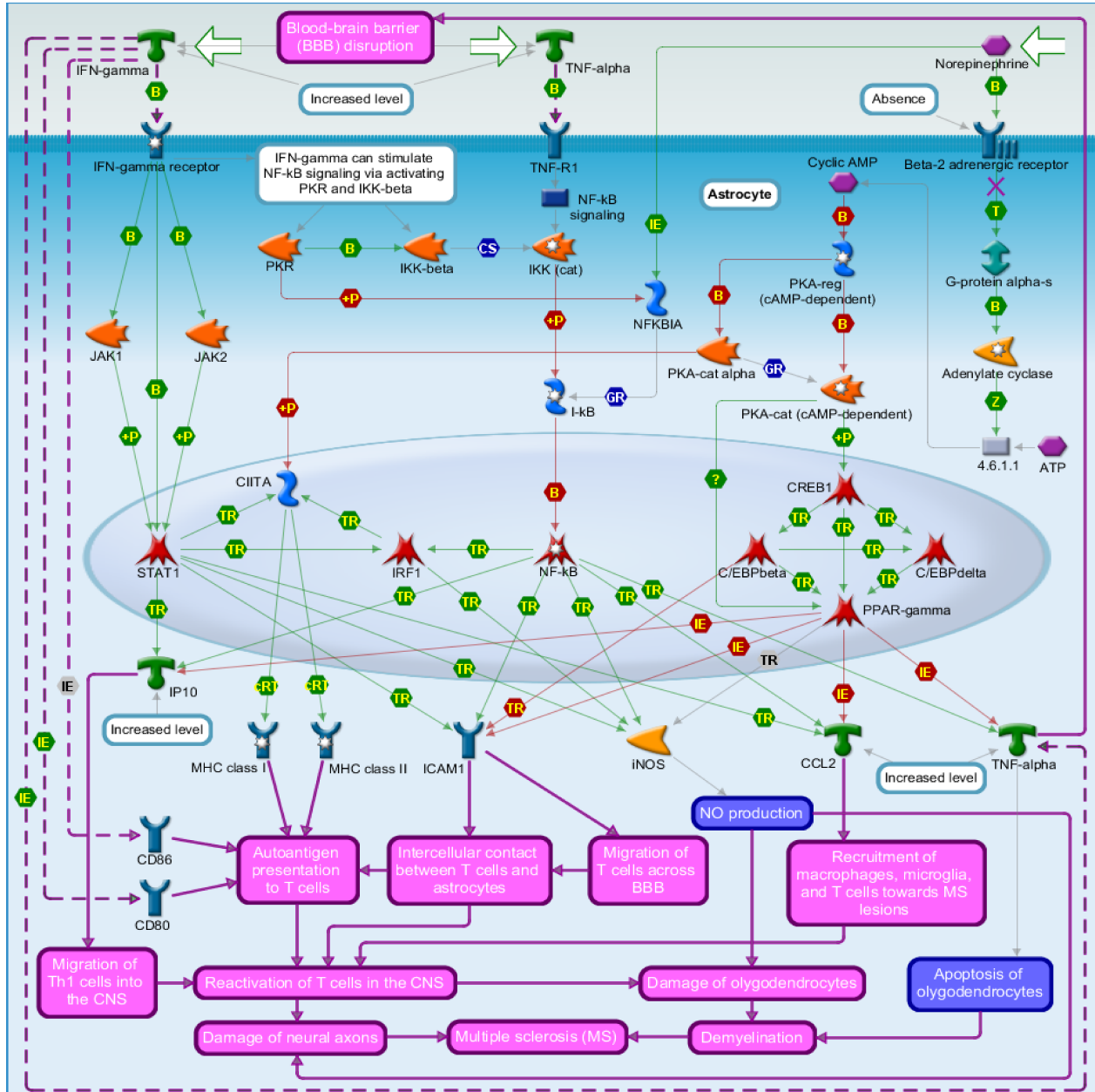


Figure 4: Cooperative action of IFN-gamma and TNF-alpha on astrocytes in multiple sclerosis (DM 5199).

F Filtering pipeline

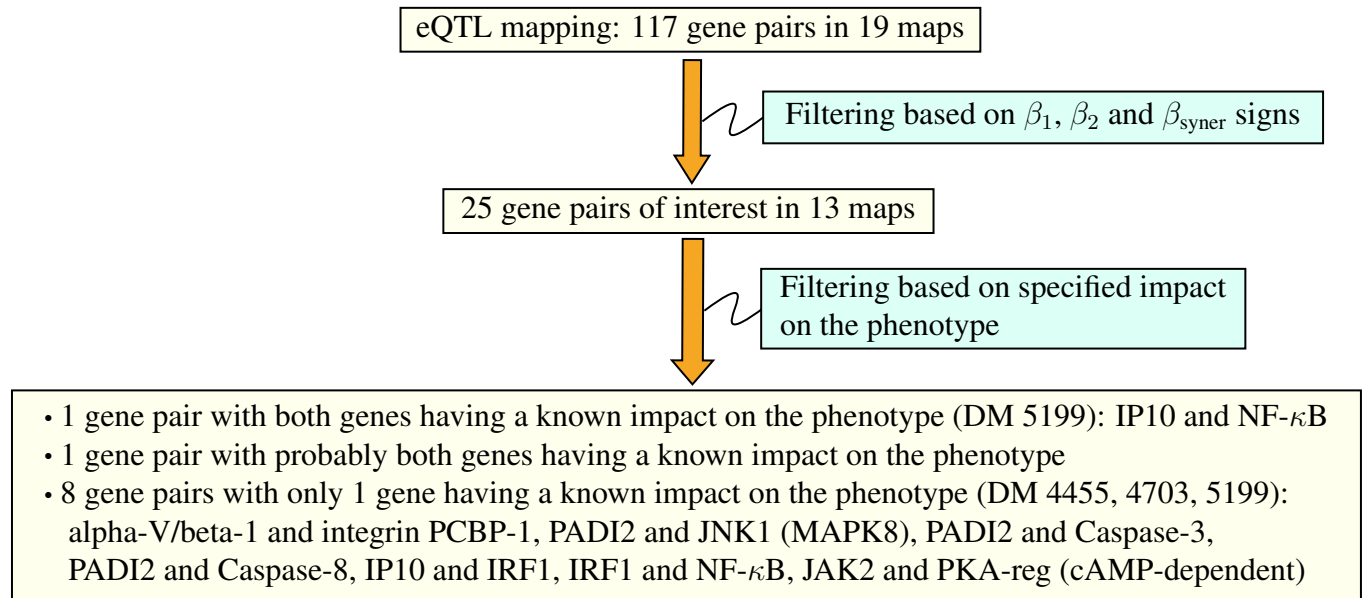


Figure 5: Filtering process for gene pairs identified by eQTL mapping.

G Physical mapping

Table 4: Pairs of genes identified by physical mapping, and selected on the basis of their SNPs' consequence as a protein dysfunction.

internal ID	Gene pair	Type of interaction
3305	GLI-1 and SUFU	direct interaction between the genes, but unspecified impact on MS
4703	AKT (PKB) and MEKK1 (MAP3K1)	no direct interaction between the genes, but AKT has a specified impact on MS
5611	Granzyme B and KLRK1 (NKG2D)	no direct interaction between the genes, and unspecified impact on MS
	Granzyme B and PI3K cat class IA	no direct interaction between the genes, and unspecified impact on MS

H eQTL mapping

Table 5: Compiled results of gene pairs identified by epistasis, and filtered according to the scheme in Fig 2, with their specified or unknown impact on MS.

internal ID	Title	Interacting gene pair		β_x	β_y	β_{syner}	Specified impact on MS (activation or inhibition)
3302	Notch signaling in oligodendrocyte precursor cell differentiation in multiple sclerosis	RBP-J (CBF1)	kappa ADAM17	1.40	1.37	0.02	no
3305	SHH signaling in oligodendrocyte precursor cells differentiation in multiple sclerosis						
3306	Inhibition of oligodendrocyte precursor cells differentiation by Wnt signaling in multiple sclerosis	Beta-catenin	GSK3 beta	1.27	1.84	0.00	no
4455	Inhibition of remyelination in multiple sclerosis: regulation of cytoskeleton proteins	alpha-V/beta-1 integrin	PCBP-1	1.27	0.96	0.01	probably yes for alpha-V/beta-1 integrin
4593	Axonal degeneration in multiple sclerosis						
4693	Role of Thyroid hormone in regulation of oligodendrocyte differentiation in multiple sclerosis						
4703	Demyelination in multiple sclerosis	PADI2	JNK1(MAPK8)	-1.42	-1.58	-0.02	PADI2 enhances in disease
4703	Demyelination in multiple sclerosis	PADI2	Caspase-3	-1.56	-1.96	-0.01	PADI2 enhances in disease
4703	Demyelination in multiple sclerosis	PADI2	Caspase-8	-1.47	-1.21	-0.03	PADI2 enhances in disease
4703	Demyelination in multiple sclerosis	JNK1(MAPK8)	Caspase-8	-1.58	-1.21	-0.01	no
4791	Role of CNTF and LIF in regulation of oligodendrocyte development in multiple sclerosis	IMPA1	STAT3	1.41	1.10	0.02	no
4791	Role of CNTF and LIF in regulation of oligodendrocyte development in multiple sclerosis	PI3K reg class IA	STAT3	1.40	1.10	0.05	no

4794	Retinoic acid regulation of oligodendrocyte differentiation in multiple sclerosis							
4843	Growth factors in regulation of oligodendrocyte precursor cells proliferation in multiple sclerosis	alpha-V/beta-3 integrin	SHP-2	1.34	1.97	0.07	no	
4843	Growth factors in regulation of oligodendrocyte precursor cells proliferation in multiple sclerosis	SHP-2	c-Raf-1	1.63	1.63	0.09	no	
4846	Growth factors in regulation of oligodendrocyte precursor cells survival in multiple sclerosis	ErbB2	Neuregulin 1	1.10	1.58	0.11	no	
4846	Growth factors in regulation of oligodendrocyte precursor cells survival in multiple sclerosis	Neuregulin 1	Bcl-XL	-1.49	-1.17	-0.02	no	
4901	Inhibition of remyelination in multiple sclerosis: role of cell-cell and ECM-cell interactions	Fyn	HYAL3	-1.99	-1.38	-0.07	no	
5199	Cooperative action of IFN- γ and TNF- α on astrocytes in multiple sclerosis	IP10	IRF1	1.41	1.12	0.09	yes for IP10	
5199	Cooperative action of IFN- γ and TNF- α on astrocytes in multiple sclerosis	IP10	NF- κ B	1.39	0.98	0.09	yes for both genes	
5199	Cooperative action of IFN- γ and TNF- α on astrocytes in multiple sclerosis	IRF1	NF- κ B	1.16	0.88	0.07	yes for NF- κ B	
5199	Cooperative action of IFN- γ and TNF- α on astrocytes in multiple sclerosis	JAK2	PKA-reg (cAMP-dependent)	1.14	1.25	0.02	yes for JAK2	
5288	Impaired inhibition of Th17 cell differentiation by IFN-beta in multiple sclerosis	IL-1RI	ROR-alpha	-1.16	-1.29	-0.09	yes (probable)	
5378	Role of IFN-beta in the improvement of blood-brain barrier integrity in multiple sclerosis							
5398	Role of IFN-beta in activation of T cell apoptosis in multiple sclerosis	CTLA-4	TRADD	-1.61	-2.61	-0.04	no	
5398	Role of IFN-beta in activation of T cell apoptosis in multiple sclerosis	Caspase-3	TRADD	-1.96	-2.21	-0.07	no	

5518	Role of IFN-beta in inhibition of Th1 cell differentiation in multiple sclerosis	IFN- γ	PI3K reg class IA	1.29	1.40	0.07	no
5518	Role of IFN-beta in inhibition of Th1 cell differentiation in multiple sclerosis	GSK3 beta	IL-18R1	1.39	1.36	0.02	no
5518	Role of IFN-beta in inhibition of Th1 cell differentiation in multiple sclerosis	PI3K reg class IA	CD86	-0.96	-1.13	-0.18	no
5601	IL-2 as a growth factor for T cells in multiple sclerosis	GSK3 beta	Bcl-XL	-0.85	-1.17	-0.03	no
5611	Role of IL-2 in the enhancement of NK cell cytotoxicity in multiple sclerosis						
