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Supporting Information List

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Figure S1. Spoke model and matrix model for protein-protein interactions. (a) Spoke model only assumes interactions between absent and impacted proteins (black arrows); and (b) matrix model assumes extra interactions between all impacted proteins (green arrows), besides the interactions (black arrows) assumed in the spoke model.

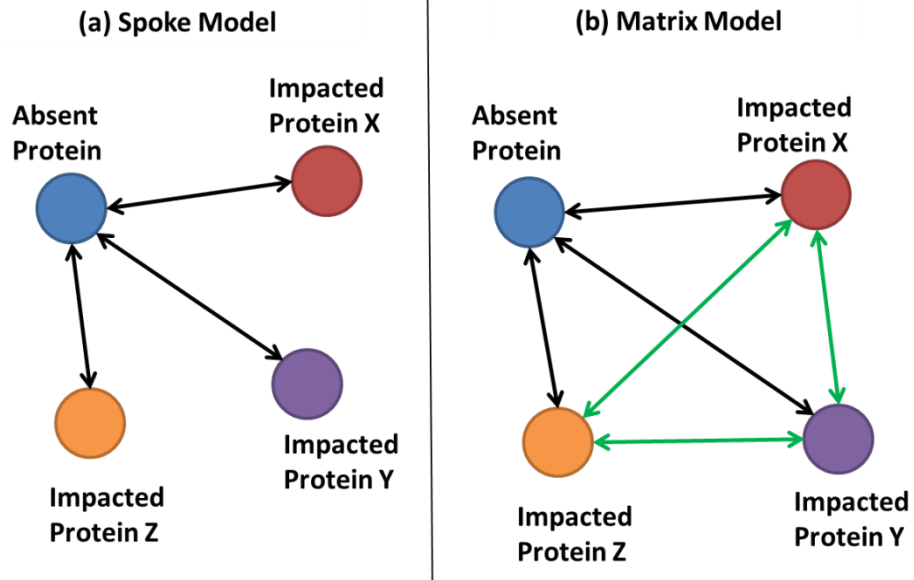
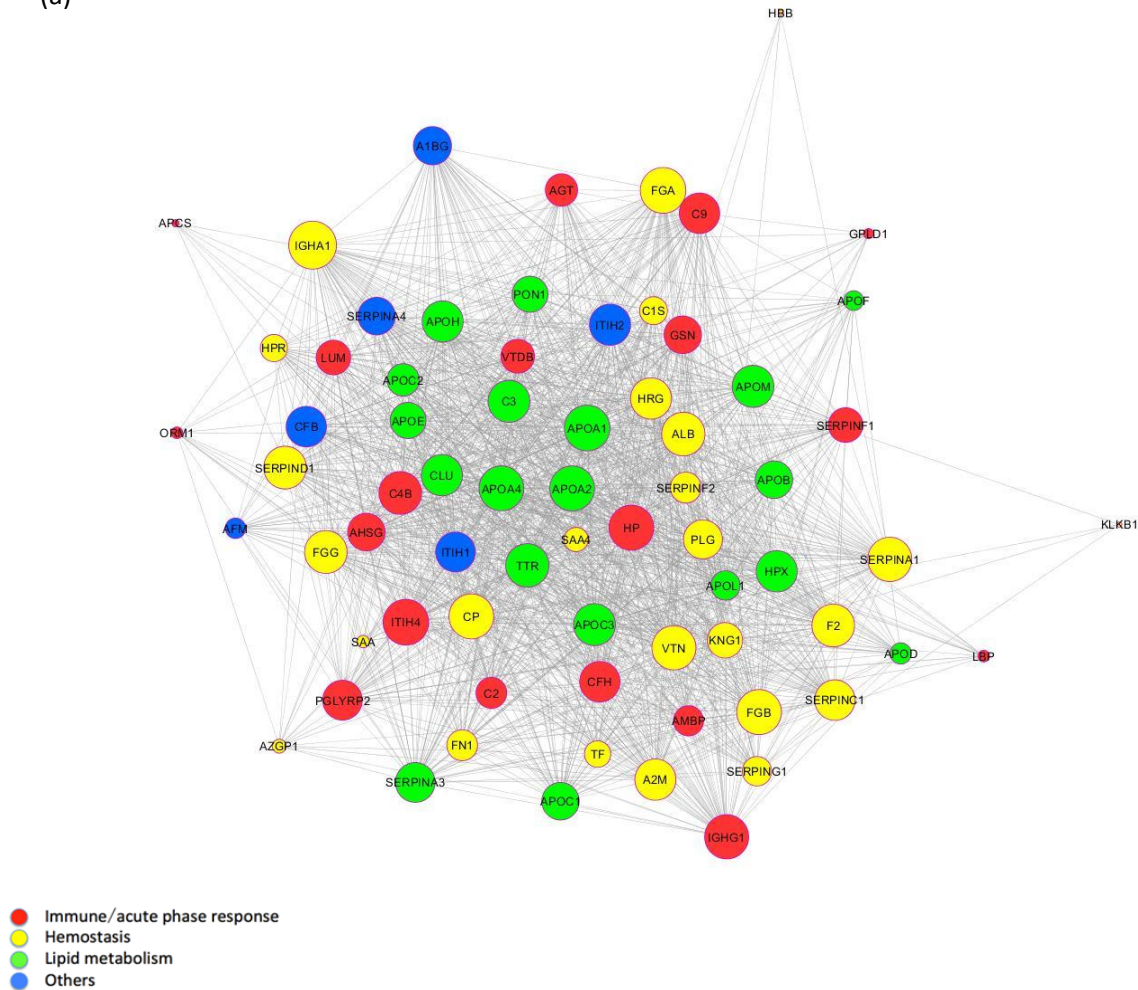
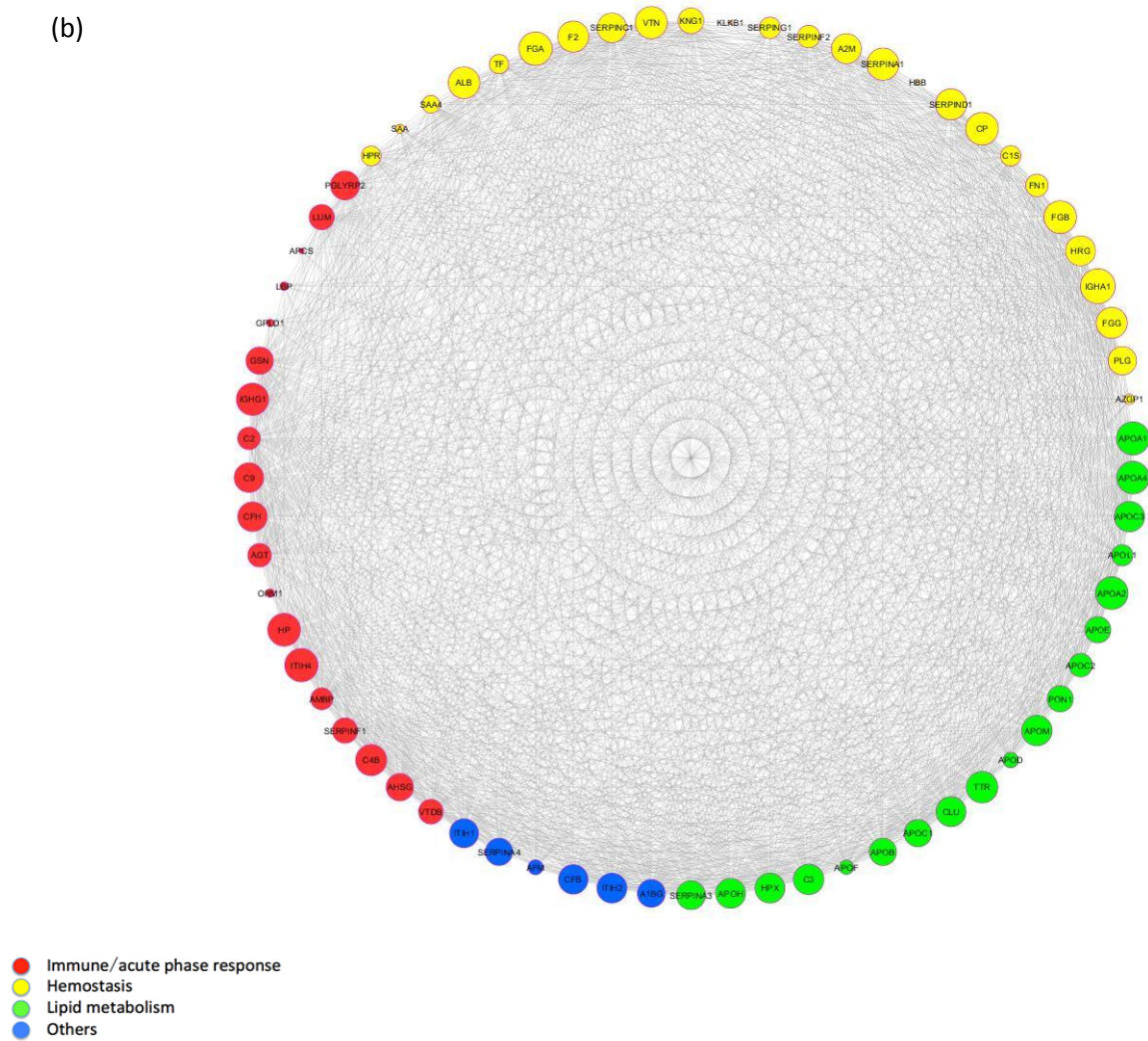


Figure S2. HDL-associated proteins interactome merged from 58 individual co-migration networks. The vertices of the network are the proteins detected in our current MS analysis and also on the 89 HDL protein watch list. Each edge between any protein pair is binary. The color indicated the known function group that a given protein belongs to. The size of each vertex was according to its network degree, reflecting its diversity of protein interactions. Different panels include multiple layouts (a) Organic layout, (b) Circle layout, and (c) Grid layout.

(a)



(b)



(c)

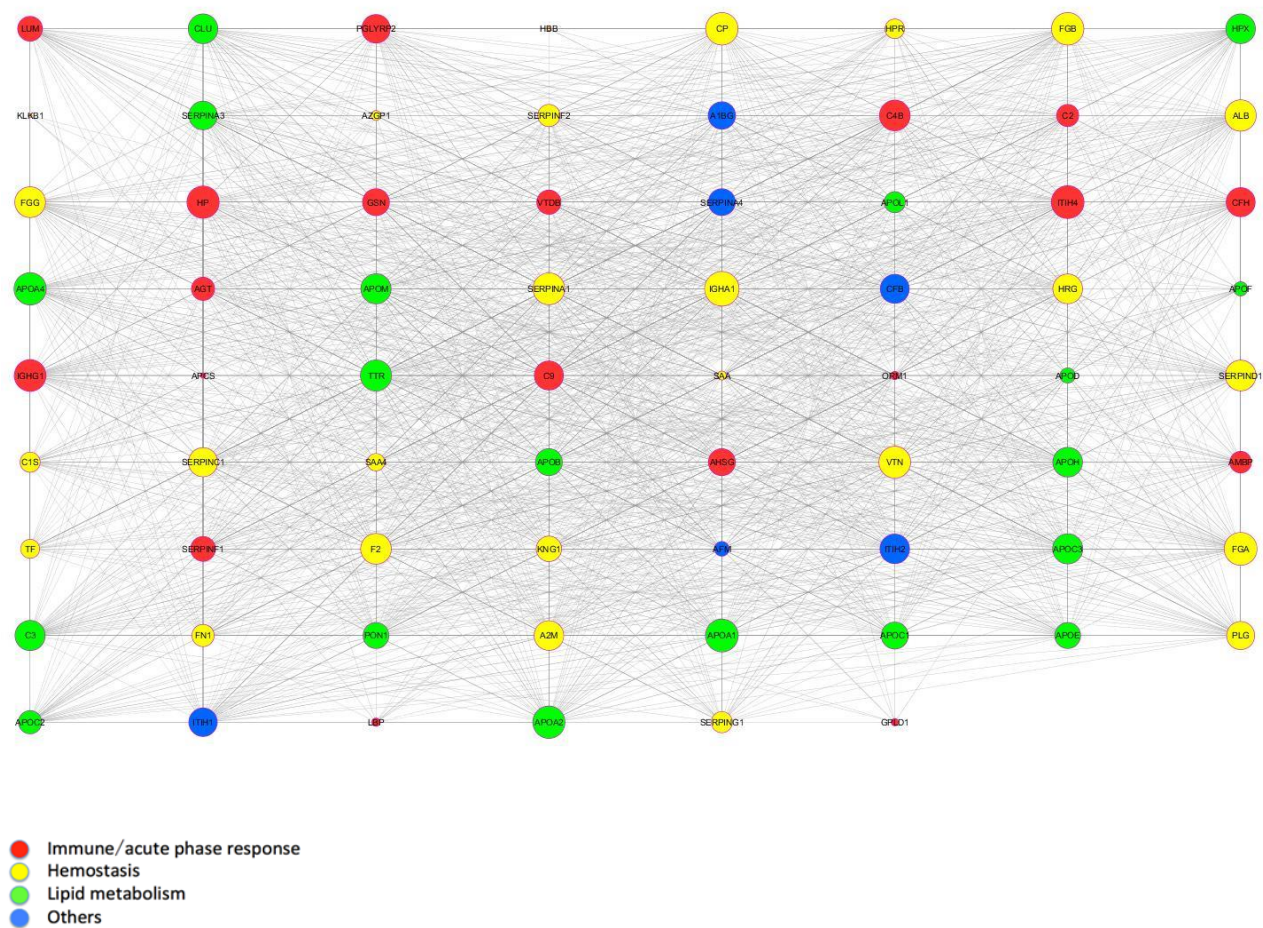
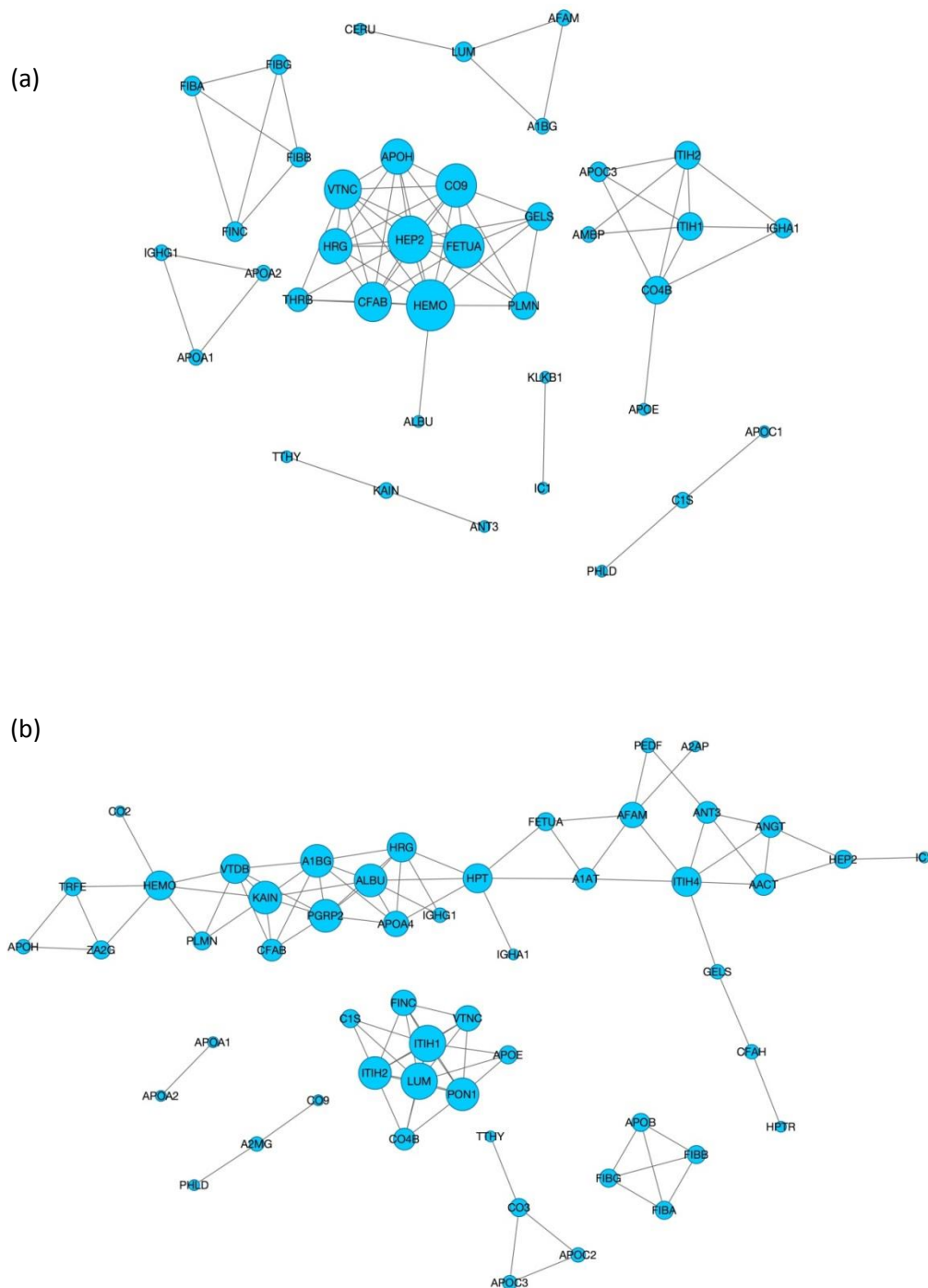


Figure S3. HDL proteome map constructed based on (a) GF separation experiment, (b) AE separation experiment, (c) IEF separation experiment, and (d) overlapping edges of three networks from all separation experiments. Size of a vertex reflects network degree of the vertex.



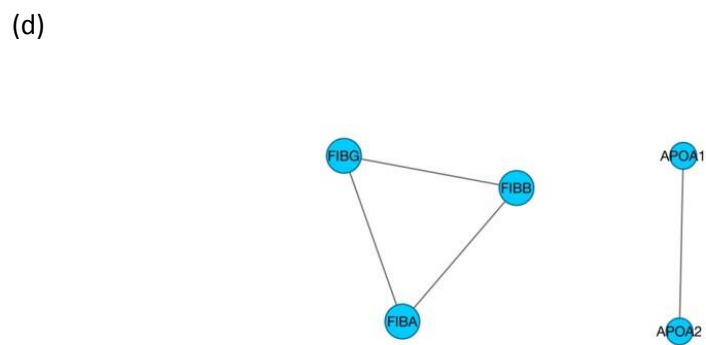
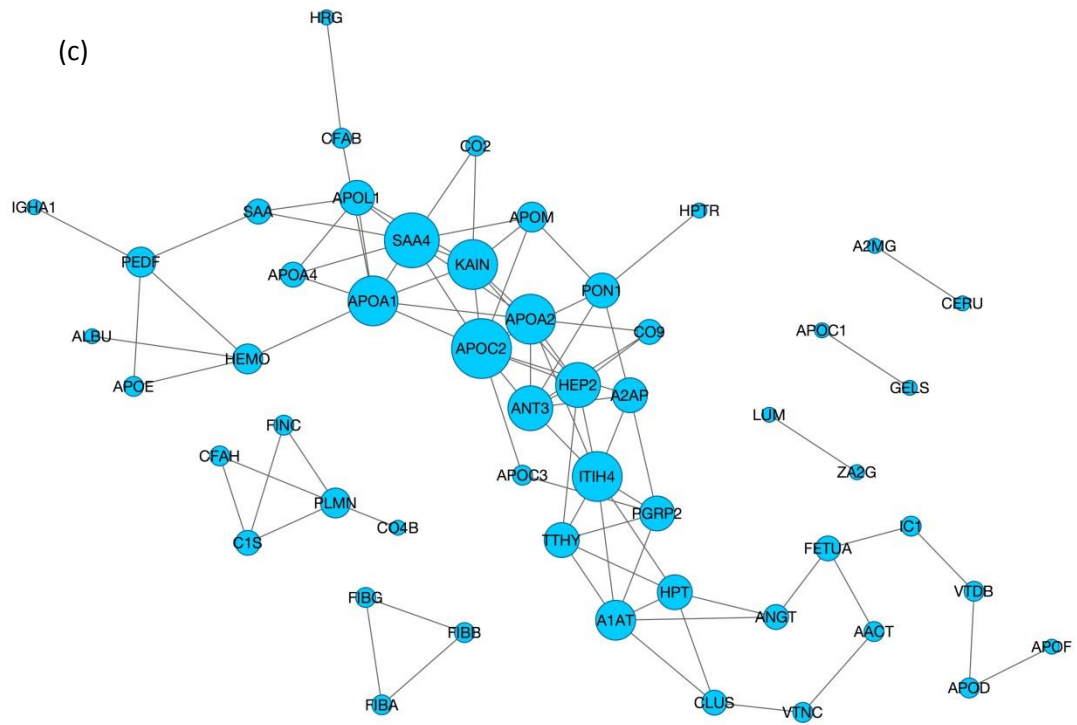


Figure S4. Migration pattern analysis for mouse gene knockout experiments. Due to the absence of proteins, the characteristics of certain subparticles are likely to change so as to alter the migration patterns of relevant proteins in the subparticles. (a) Assume protein P_x in the same subparticle with absent protein, differences of distribution may be discovered between WT and KO mice. (b) Assume protein P_y does not co-exist with absent proteins in any subparticle, its migration pattern is unlikely to change. As such, we are able to identify those impacted proteins, as the evidences for the composition of certain subparticles.

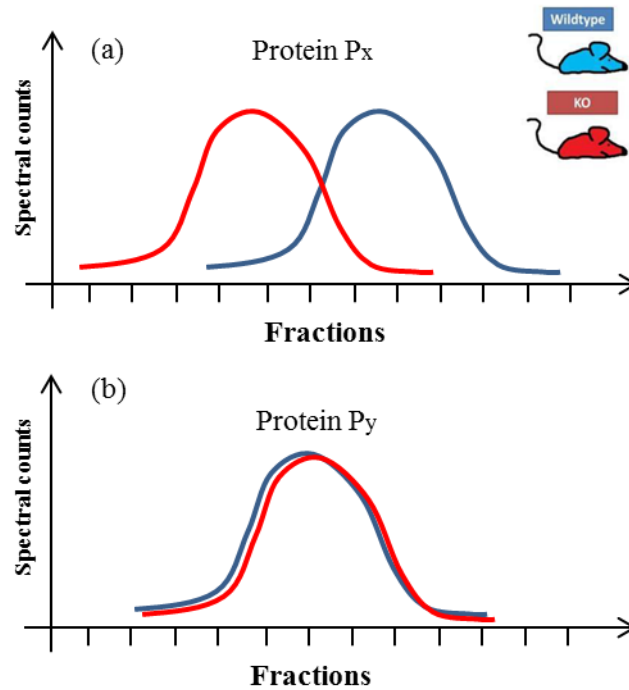
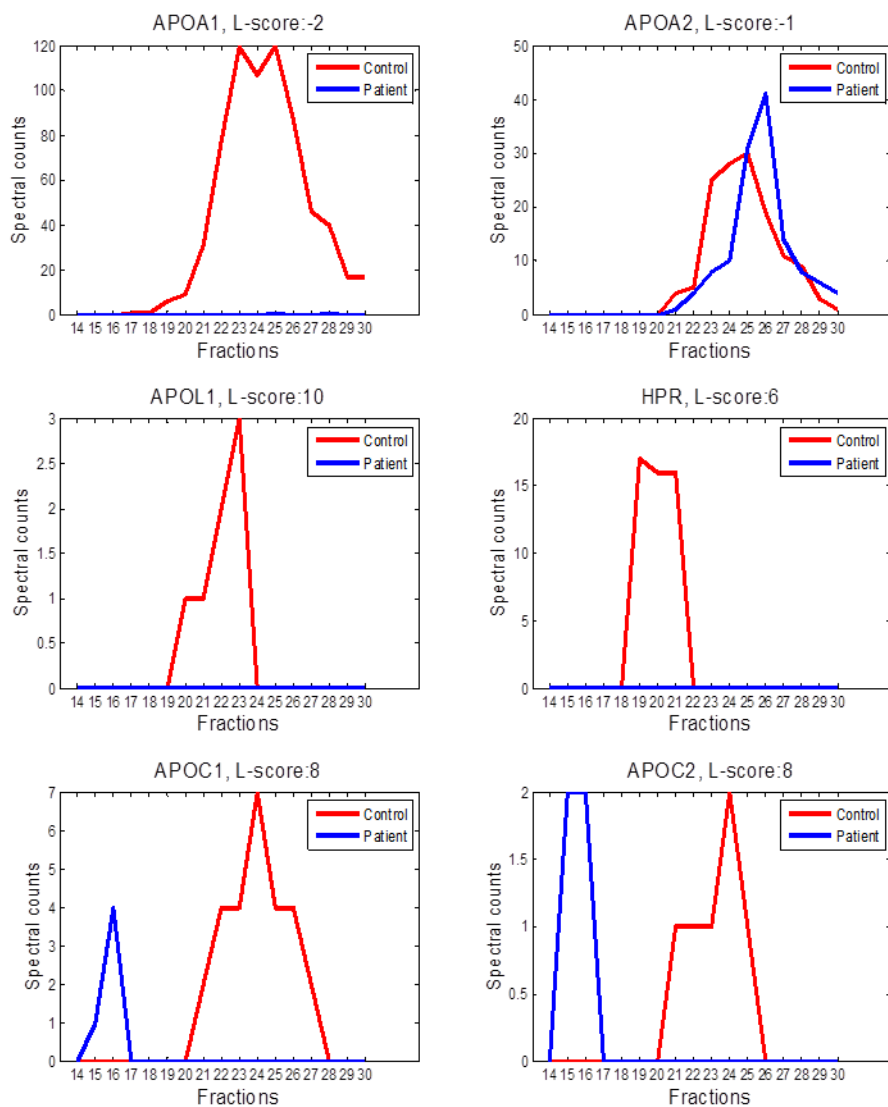


Figure S5. Examples of migration pattern comparison between the apoA-I deficient patient and the normal control. Distribution pattern comparisons were demonstrated for apoA-I, apoA-II, apoL-I, HPR, apoC-I, and apoC-II, respectively.



A global score-based analysis method. This works as an alternative method in our method development. In this method, we first performed the cluster analysis. We performed a global co-migration correlation analysis and constructed a global interaction network (correlation threshold: 0.8) for each method of fractionation (**Fig. S3a-c**); Then, we focused on proteins that co-associate in all three methods of fractionation (**Fig. S3d**). As shown in **Fig. S3d**, focusing on only the proteins that co-associate in all three methods results in largely disconnected components with very few consensus links between the proteins. Apparently, interactions between apoA-I: apoA-II or FGA-FGB-FGG are the most confident edges among all three methods, indicating possible subspecies. This analysis shows that although the co-associated PPIs among all three methods did identify the most apparent PPIs in the network, it was unable to uncover more biologically meaningful HDL subspecies.

Table S1. Identified 183 HDL subspecies based on 58 local co-migration networks.

Size	Subspecies		
3	APOA1	APOA2	HPX
3	APOA1	APOA4	ITIH1
3	APOA2	APOH	HPX
3	APOA2	HPX	VTN
3	APOA1	CLU	HPR
3	APOA1	APOL1	CLU
3	APOA1	APOL1	HPR
3	APOL1	CLU	HRG
3	APOL1	HPR	HRG
3	APOA1	APOE	SERPING1
3	APOA1	APOE	ITIH1
3	APOA1	CLU	FGA
3	APOA1	HP	HPR
3	APOA1	APOC3	PON1
3	APOE	SERPING1	IGHA1
3	APOA1	APOE	HP
3	APOA1	HP	ITIH1
3	APOE	SERPING1	KNG1
3	AMBP	APOE	HP
3	APOA1	APOA4	IGHG1
3	APOA1	APOC3	HP
3	ALB	FGB	FGG
3	APOA4	IGHG1	VTDB
3	A1BG	SERPINA3	AFM
3	APOA1	AHSG	GSN
3	APOA1	HPX	SERPIND1
3	SERPINC1	TTR	VTDB
3	ALB	APOA1	APOA4
3	APOH	AHSG	KNG1
3	ALB	APOA4	SERPINA4
3	APOA1	APOA2	IGHG1
3	SERPINA3	AFM	LUM
3	ALB	APOA1	AHSG
3	C2	LUM	PON1
3	SERPINC1	APOA4	SERPINA4
3	APOA1	AHSG	HPX
3	SERPINA1	APOA2	IGHG1
3	APOA1	HPX	TF
3	ALB	APOA1	APOC1

3	ALB	APOA1	CFB
3	APOA1	APOA4	APOC1
3	APOA1	APOA4	AHSG
3	APOA1	HPX	IGHG1
3	ALB	APOC1	PGLYRP2
3	APOA4	APOC1	PGLYRP2
3	HPX	IGHG1	PLG
3	A1BG	APOA4	HRG
3	HPX	PLG	VTDB
3	HPX	IGHG1	VTDB
3	FGG	HP	IGHA1
3	HRG	IGHG1	PGLYRP2
3	APOA1	CLU	SERPIND1
3	APOA1	APOC2	GPLD1
3	APOA1	APOA2	APOC1
3	APOA1	APOA4	FGA
3	APOA1	APOC3	APOE
3	APOA1	IGHG1	TTR
3	APOE	FGB	FGG
3	APOA1	CFH	TTR
3	ALB	APOA1	APOC3
3	APOA1	APOE	F2
3	AMBP	ITIH1	VTN
3	APOA1	APOA2	CP
3	APOA1	APOA2	ITIH1
3	CLU	APCS	F2
3	APOA1	APOC3	CLU
3	APOA1	APOA2	APOC3
3	APOA1	APOC1	CLU
3	APOA1	APOC2	APOC3
3	APOA1	FGA	PON1
3	APOC1	CLU	FGB
3	APOC1	CLU	FGG
3	SERPINA1	FGB	FGG
3	APOA1	CLU	TF
3	APOA1	APOA2	FGA
3	APOA1	FGA	HP
3	ALB	APOA1	GSN
3	APOA1	APOA4	TF
3	APOA1	ITIH1	TTR
3	SERPINA1	APOA2	VTN
3	APOA1	CP	IGHG1
3	ALB	APOA1	HPX

3	APOA1	APOA2	TF
3	APOA1	FGA	F2
3	APOA1	HP	TTR
3	ALB	FGB	HPX
3	APOA1	FGA	IGHG1
3	SERPINA1	C9	HP
3	SERPINA1	FGG	HP
3	GSN	HPX	HRG
3	FGA	FGB	IGHG1
3	APOA1	CFB	HPX
3	CFB	SERPINF1	SAA
3	APOA1	APOE	APOL1
3	ALB	APOH	FGG
3	APOH	FGG	SERPINF1
3	APOH	FGG	SAA
3	APOE	APOL1	C2
3	APOL1	C2	SAA4
3	APOA1	APOA2	F2
3	APOA1	APOA4	APOC2
3	APOA1	APOC1	APOE
3	APOA1	APOC2	PON1
3	SERPINC1	C9	SERPIND1
3	SERPINC1	APOH	APOM
3	SERPINC1	APOM	SERPIND1
3	APOA1	APOA2	APOA4
3	APOA1	APOF	CP
3	APOA1	SERPIND1	HPR
3	APOA2	APOH	ITIH2
3	C9	PGLYRP2	PON1
3	APOA2	APOA4	ITIH2
3	ALB	HPX	SERPINA4
3	HPX	SERPINA4	SAA4
3	APOA1	APOC3	LBP
3	APOA1	AHSG	HP
3	CFB	HPX	SERPINA4
3	APOA1	HPX	SERPING1
3	APOA1	APOC2	F2
3	APOA1	CLU	HP
3	APOH	APOL1	PGLYRP2
3	APOA1	CFB	IGHG1
3	ALB	APOC3	HRG
3	APOC3	HRG	LBP
3	SERPINA1	FGB	F2

3	AHSG	LUM	AZGP1		
3	APOA1	APOC3	HPX		
4	APOA2	HPX	HRG	VTN	
4	APOA1	APOL1	CLU	HPR	
4	ALB	APOA1	APOE	SERPING1	
4	APOA2	SERPING1	IGHA1	KNG1	
4	AMBP	APOC1	APOC3	HP	
4	APOA1	APOC1	APOC3	HP	
4	APOA1	AHSG	HPX	SERPIND1	
4	APOA1	APOA2	IGHG1	TTR	
4	APOA2	HP	HRG	SERPINA4	
4	APOA1	HPX	IGHG1	TF	
4	ALB	APOA1	APOC1	CFB	
4	ALB	APOA1	APOA2	APOC1	
4	ALB	APOA1	SERPIND1	HPR	
4	ALB	APOA1	APOC1	HPR	
4	APOA1	APOA2	IGHG1	F2	
4	APOA1	APOE	IGHG1	F2	
4	APOA1	CLU	IGHG1	F2	
4	APOA1	APOA2	CLU	F2	
4	APOC2	APOC3	FGG	VTN	
4	ALB	APOA1	APOA4	HPX	
4	APOA1	APOC1	APOE	GSN	
4	APOA1	APOC3	FGA	IGHG1	
4	ALB	APOA1	APOC1	GSN	
4	ALB	APOA1	APOC1	HPX	
4	APOA1	APOC3	F2	TTR	
4	APOE	APOL1	C2	SAA4	
4	SERPINC1	APOM	C9	PGLYRP2	
4	APOA1	CFB	HP	TTR	
4	APOA4	HPX	SERPINA4	SAA4	
4	AGT	SERPING1	TTR	VTN	
4	APOA1	CFB	HPX	TTR	
4	APOA1	APOA2	CFB	TTR	
4	SERPINC1	APOM	C9	SERPIND1	
4	ALB	HPX	SERPINA4	SAA4	
4	SERPINA3	AHSG	HP	HRG	
4	APOA1	SERPING1	IGHG1	TTR	
4	APOA1	FGA	IGHG1	TTR	
4	APOA1	HPX	SERPING1	IGHG1	
4	APOA1	HPX	SERPING1	TTR	
5	APOA1	APOA2	APOC3	SERPING1	IGHG1
5	APOA1	APOA2	APOA4	IGHG1	PON1

5	SERPINA3	AMBP	APOA2	IGHG1	TTR
5	ALB	APOA1	APOC1	APOL1	HPR
5	APOA1	APOA2	APOE	IGHG1	F2
5	APOA1	APOA2	APOC3	F2	TTR
5	APOA1	APOA2	CLU	F2	TTR
5	APOA2	APOC3	APOM	F2	TTR
5	APOA2	APOM	CLU	F2	TTR
5	APOC3	APOM	PGLYRP2	F2	TTR
5	APOC1	APOE	APOL1	IGHA1	SAA4
5	APOA4	APOE	APOL1	IGHA1	SAA4
5	APOA4	APOE	APOL1	HPX	SAA4
5	APOA1	AHSG	HP	SERPING1	TTR
5	APOA1	APOA2	APOA4	HPX	SERPIND1
5	APOA1	APOA2	CFB	HP	TTR
5	APOA1	APOC3	CFB	CLU	TTR