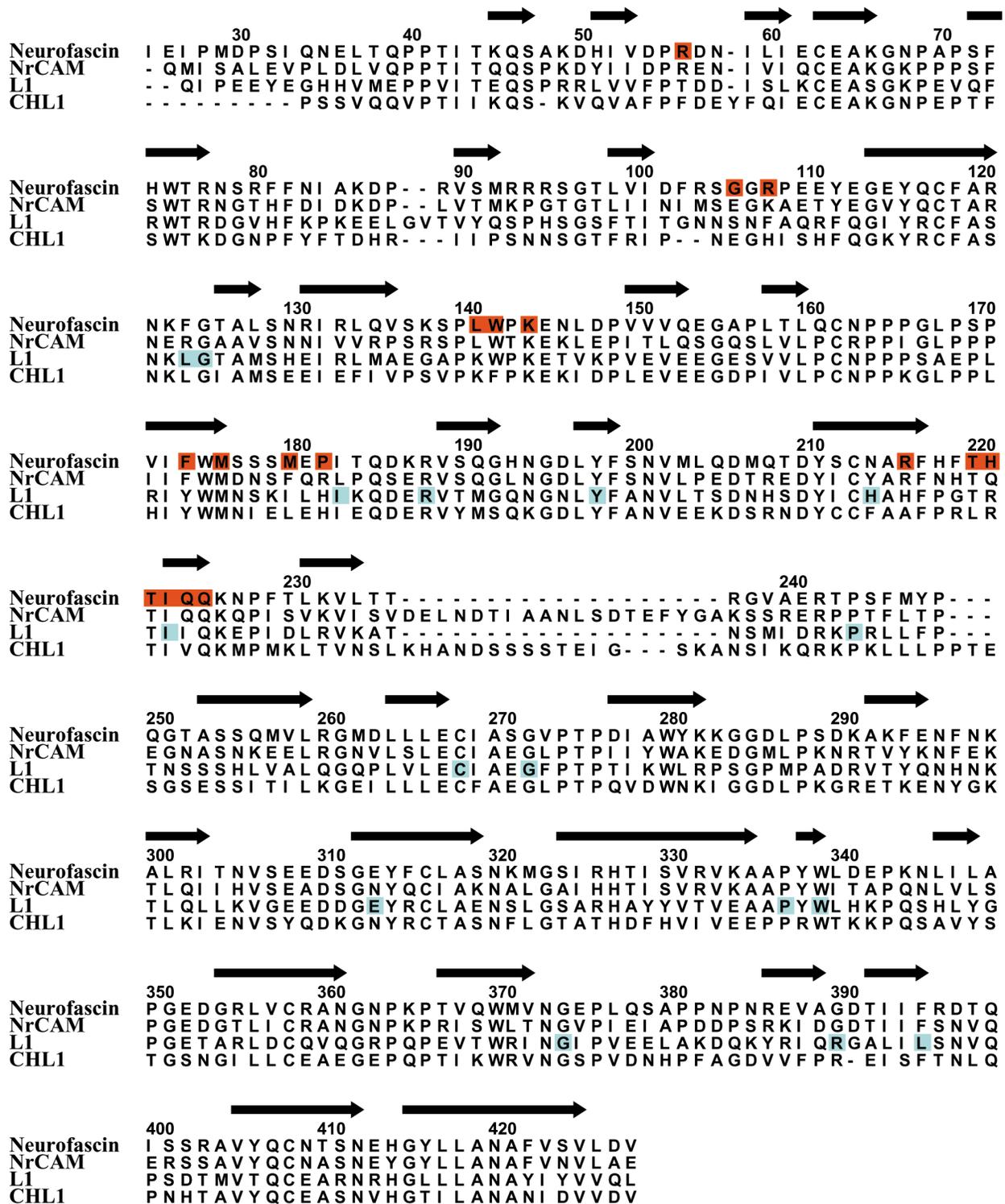Supplementary Figure S1. SIGMAA-weighted, 2*F*o-*F*c electron density map around the super-β-sheet inter-molecular interaction.

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                30            40              50          60          70
Neurofascin  I E I P M D P S I Q N E L T Q P P T I T K Q S A K D H I V D P R D N - I L I E C E A K G N P A P S F
NrCAM        - Q M I S A L E V P L D L V Q P P T I T Q Q S P K D Y I I D P R E N - I V I Q C E A K G K P P P S F
L1           - - Q I P E E Y E G H H V M E P P V I T E Q S P R R L V V F P T D D - I S L K C E A S G K P E V Q F
CHL1         - - - - - - - - - - P S S V Q Q V P T I I K Q S - K V Q V A F P F D E Y F Q I E C E A K G N P E P T F

                            80            90          100          110          120
Neurofascin  H W T R N S R F F N I A K D P - - R V S M R R R S G T L V I D F R S G G R P E E Y E G E Y Q C F A R
NrCAM        S W T R N G T H F D I D K D P - - L V T M K P G T G T L I I N I M S E G K A E T Y E G V Y Q C T A R
L1           R W T R D G V H F K P K E E L G V T V Y Q S P H S G S F T I T G N N S N F A Q R F Q G I Y R C F A S
CHL1         S W T K D G N P F Y F T D H R - - - I I P S N N S G T F R I P - - N E G H I S H F Q G K Y R C F A S

                        130          140          150          160          170
Neurofascin  N K F G T A L S N R I R L Q V S K S P L W P K E N L D P V V V Q E G A P L T L C N P P P G L P S P
NrCAM        N E R G A A V S N N I V V R P S R S P L W T K E K L E P I T L Q S G Q S L V L P C R P P I G L P P P
L1           N K L G T A M S H E I R L M A E G A P K W P K E T V K P V E V E E G E S V V L P C N P P P S A E P L
CHL1         N K L G I A M S E E I E F I V P S V P K F P K E K I D P L E V E E G D P I V L P C N P P K G L P P L

                    180          190          200          210          220
Neurofascin  V I F W M S S S M E P I T Q D K R V S Q G H N G D L Y F S N V M L Q D M Q T D Y S C N A R F H F T H
NrCAM        I I F W M D N S F Q R L P Q S E R V S Q G L N G D L Y F S N V L P E D T R E D Y I C Y A R F N H T Q
L1           R I Y W M N S K I L H I K Q D E R V T M G Q N G N L Y F A N V L T S D N H S D Y I C H A H F P G T R
CHL1         H I Y W M N I E L E H I E Q D E R V Y M S Q K G D L Y F A N V E E K D S R N D Y C C F A A F P R L R

                    230                                                  240
Neurofascin  T I Q Q K N P F T L K V L T T - - - - - - - - - - - - - - - - - - - - - - - - R G V A E R T P S F M Y P - - -
NrCAM        T I Q Q K Q P I S V K V I S V D E L N D T I A A N L S D T E F Y G A K S S R E R P P T F L T P - - -
L1           T I I Q K E P I D L R V K A T - - - - - - - - - - - - - - - - - - - N S M I D R K P R L L F P - - -
CHL1         T I V Q K M P M K L T V N S L K H A N D S S S S T E I G - - - S K A N S I K Q R K P K L L L P P T E

            250          260          270          280          290
Neurofascin  Q G T A S S Q M V L R G M D L L L E C I A S G V P T P D I A W Y K K G G D L P S D K A K F E N F N K
NrCAM        E G N A S N K E E L R G N V L S L E C I A E G L P T P I I Y W A K E D G M L P K N R T V Y K N F E K
L1           T N S S S H L V A L Q G Q P L V L E C I A E G F P T P T I K W L R P S G P M P A D R V T Y Q N H N K
CHL1         S G S E S S I T I L K G E I L L L E C F A E G L P T P Q V D W N K I G G D L P K G R E T K E N Y G K

            300          310          320          330          340
Neurofascin  A L R I T N V S E E D S G E Y F C L A S N K M G S I R H T I S V R V K A A P Y W L D E P K N L I L A
NrCAM        T L Q I I H V S E A D S G N Y Q C I A K N A L G A I H H T I S V R V K A A P Y W I T A P Q N L V L S
L1           T L Q L L K V G E E D D G E Y R C L A E N S L G S A R H A Y Y V T V E A A P Y W L H K P Q S H L Y G
CHL1         T L K I E N V S Y Q D K G N Y R C T A S N F L G T A T H D F H V I V E E P P R W T K K P Q S A V Y S

            350          360          370          380          390
Neurofascin  P G E D G R L V C R A N G N P K P T V Q W M V N G E P L Q S A P P N P N R E V A G D T I I F R D T Q
NrCAM        P G E D G T L I C R A N G N P K P R I S W L T N G V P I E I A P D D P S R K I D G D T I I F S N V Q
L1           P G E T A R L D C Q V Q G R P Q P E V T W R I N G I P V E E L A K D Q K Y R I Q R G A L I L S N V Q
CHL1         T G S N G I L L C E A E G E P Q P T I K W R V N G S P V D N H P F A G D V V F P R - E I S F T N L Q

            400          410          420
Neurofascin  I S S R A V Y Q C N T S N E H G Y L L A N A F V S V L D V
NrCAM        E R S S A V Y Q C N A S N E Y G Y L L A N A F V N V L A E
L1           P S D T M V T Q C E A R N R H G L L L A N A Y I Y V V Q L
CHL1         P N H T A V Y Q C E A S N V H G T I L A N A N I D V V D V
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Supplementary Figure S2. The structure-based sequence alignment of the Ig1-Ig4 regions of the L1 family cell adhesion molecules. The neurofascin residues at the adhesion interface are shaded in red. The L1 pathological mutations are shaded in cyan.

Hemolin   Dscam   Axonin-1   Neurofascin
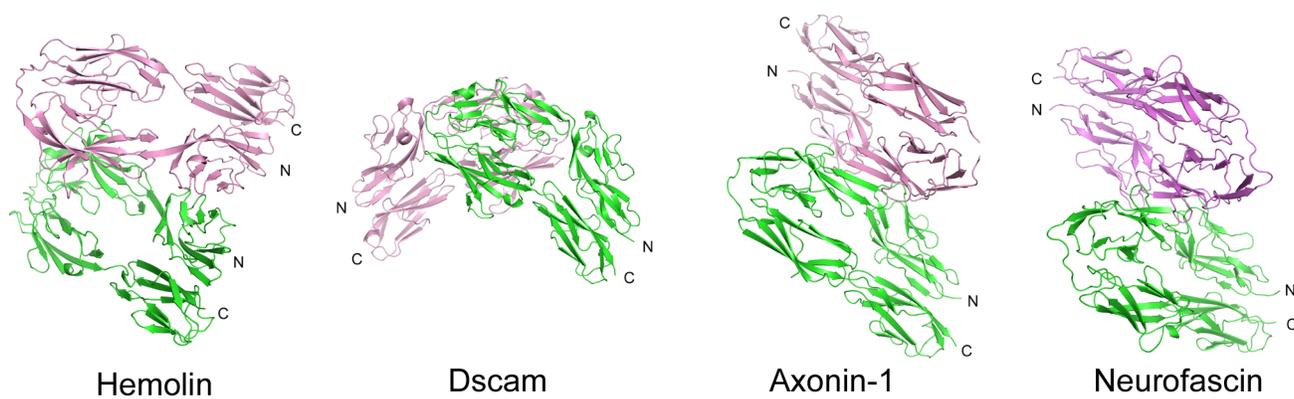
Supplementary Figure S3. The comparison of the homophilic recognition modes of the horseshoe headpieces of the Ig superfamily adhesion molecules. PDB ID: 1BIH for hemolin, 2V5M for Dscam, and 2OM5 for axonin-1. The green copies of the interacting molecules are in the same orientation as references.
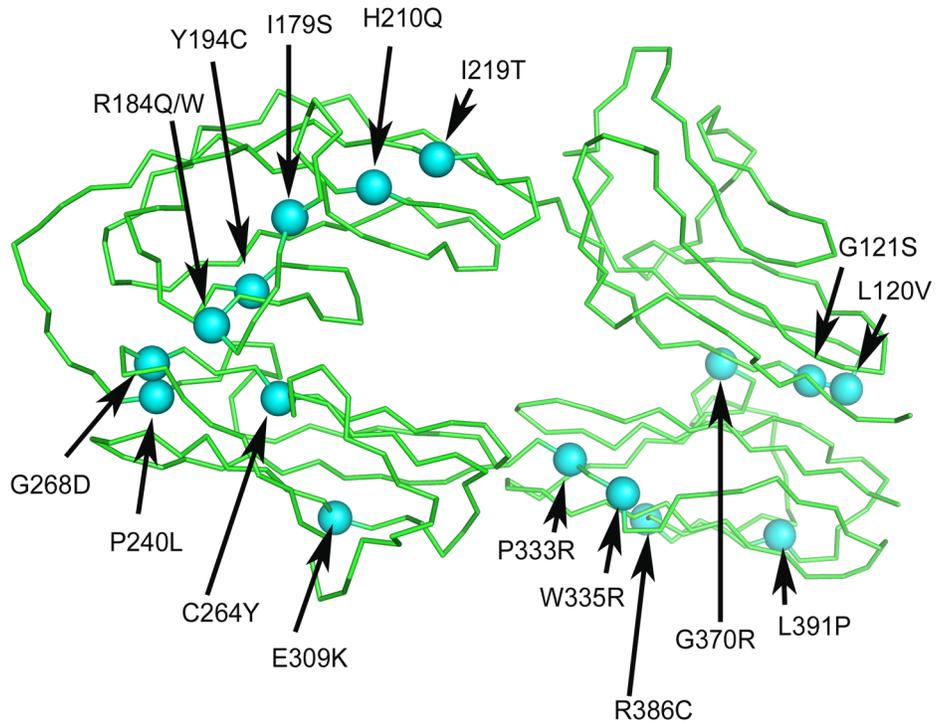
Supplementary Figure S4. Mapping the pathological mutations of L1 on the NF$_{Ig1\text{-}4}$ structure.