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Review

Structural analysis of leucine-rich-repeat variants in proteins associated with human diseases

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Abstract. A number of human diseases have been shown to be associated with mutation in the genes encoding leucine-rich-repeat (LRR)-containing proteins. They include 16 different LRR proteins. Mutations of these proteins are associated with 19 human diseases. The mutations occur frequently within the LRR domains as well as their neighboring domains, including cysteine clusters. Here, based on the sequence analysis of the LRR domains and the known structure of LRR proteins, we describe some features of different sequence variants and discuss their adverse effects. The mutations in the cysteine clusters, which preclude the formation of sulfide bridges or lead to a wrong paring of cysteines in extracellular proteins or extracellular domains, occur with high frequency. In contrast, missense mutations at some specific positions in LRRs are very rare or are not observed at all.

Key words. Leucine-rich repeats; human diseases; cysteine clusters; typical LRR motif; RI-like LRR motif; Cryopyrin/Nalp3/PYPAF1; CARD15.

Introduction

Leucine-rich-repeat (LRR)-containing domains are present in 4748 proteins in the PFAM database (10 November 2004) (reviewed in [1–4]). LRR proteins have been identified in viruses (25), bacteria (403), archae (1) and eukaryotes (4319). Many LRR proteins are involved in protein-ligand interactions; these include plant immune response and the mammalian innate immune response (reviewed in [5]). Most LRRs are 20–30 amino acids long and the repeat number ranges from 2 to 52. The LRR proteins have been divided into seven classes [3]. One group of LRR proteins that includes small LRR proteoglycans (SLRP) has LRRs

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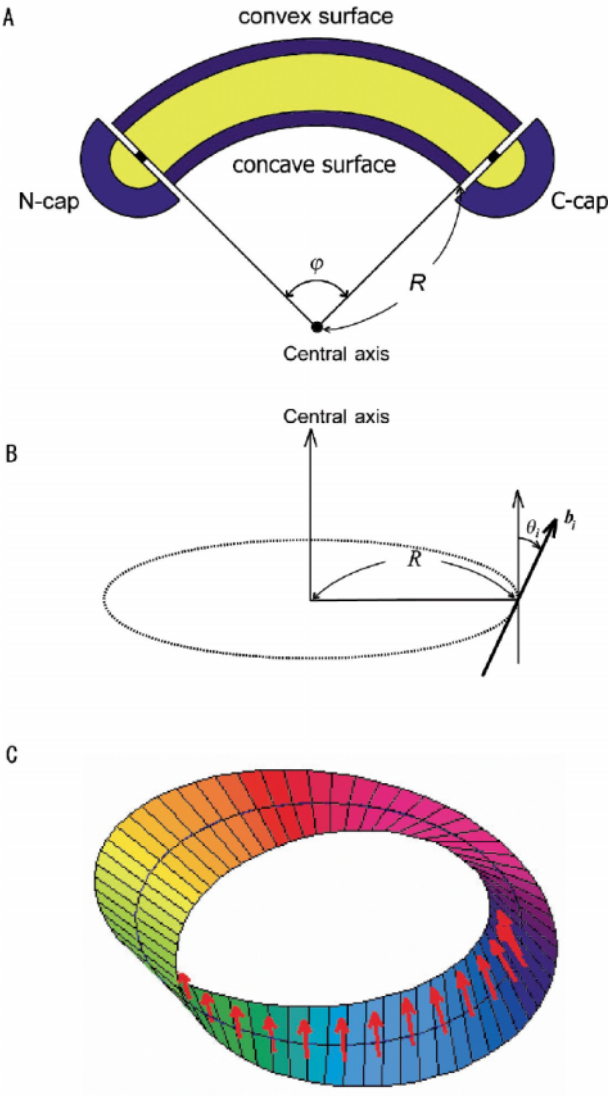

Figure 1. Schematic LRR arc shape and its geometrical parameters. (A) The radius of the arc (R) and the mean rotation angle about the central axis relating one β-strand to the next ($\overline{\varphi}$) . The hydrophobic core of the LRR arc is highlighted in yellow. The cap structures which shield the hydrophobic core at the N-terminus (N-cap) and at the C-terminus (C-cap) are indicated by half circles. 'φ' is the rotation angle of the LRR arc with the repeat number of LRRs, N. The average rotation angle ($\overline{\varphi}$) is given by $\overline{\varphi} = \varphi / (N\text{-}1)$. (B) The tilt angle of the i-th repeat (θ_i) between the β-strand direction vector of the i-th repeat ($\boldsymbol{b}_i$) and the central axis of the best-fit circle [154]. The linear slope in the plots of θ_i versus the i-the repeat (s) and repeat number per turn (N_t), where $N_t = 360/\overline{\varphi}$, gives the tilt angle of the parallel β-strand direction per turn (θ_t); $\theta_t = sN_t$ [154]. (C) An ideal Möbius strip and 3D representation of the vectors of individual β-strands in LRRs [154].

from more than one of the seven classes [4, 6]. All known LRRs adopt an arc shape (figs. 1, 2) [4].

A number of human diseases have been shown to be associated with mutation in the genes encoding LRR proteins (reviewed in [7–9]). They include NgR [10], LGI1 [11], Trk-A [12–14], polycystin 1/PKD1 [15, 16], nyctalopin [17, 18], FSHr [19–21], LH/CGr [22–24], TSHr [24, 25–27], keratocan [28, 29], GPIbα [30–32], GPIbβ [33–35], GPIX [36], LRRK2 [37], CIAS1 [38–42], CIITA [43, 44], and Nod2 [45, 46] (table 1). Mutations of these proteins are associated with schizophrenia [47], ADLTE/ADPEAF [48–58], CSNB1/XLCSNB [17, 18], CIPA[59, 60], ADPKD [61, 62], ODG1 [63–68], LCH [69], Graves disease [70], thyrotropin resistance [71–78], FGH [79], papillary cancer [80], hyperthyroidism [81–85], CNA2 [29, 86, 87], BSS [88–135], PT-vWD [136–139], Parkinson's disease [37, 140–144], CINCA/NOMID [39, 41, 42, 145–149], BLS II [43, 150–156] and Crohn's disease [45, 46, 157, 158] (table 1). The mutations occur frequently within the LRR domains as well as in their neighboring domains, including cysteine clusters at the N- and C-termini.

Here we focus on understanding the adverse effects of different sequence variants based on the sequence analysis of the LRR domains and the known structure of LRR proteins.

Structural principles and features of LRR proteins

All LRR repeats can be divided into a highly conserved segment and a variable segment. The highly conserved segment consists of an 11-residue stretch, LxxLxLxxNxL, or a 12-residue stretch, LxxLxLxxCxxL, in which 'L' is Leu, Ile, Val, or Phe, 'N' is Asn, Thr, Ser, or Cys, and 'C' is Cys or Ser [159]. Seven classes of LRRs have been proposed, characterized by different lengths and consensus sequences of the variable segments of repeats [159, 160]. They are 'RI-like', 'CC', 'bacterial', 'SDS22-like', 'plant specific', 'typical' and 'TpLRR' [159, 161]. Comparative analysis of the known structures of 17 different LRR proteins has revealed the following features [4].

1) Three residues at positions 3–5 in the highly conserved segments, LxxLxLxxNxL or LxxLxLxxCxxL, form a short β-strand. The β-strands stack parallel and then form an arc (fig. 2). The concave face consists of a parallel β-sheet, and the convex face is made of a variety of secondary structures such as α-helix, 3_{10}-helix, polyproline II helix, and an extended structure or a tandem arrangement of β-turns. In most LRR proteins the β-strands on the concave surface and (mostly) helical elements on the convex surface are connected by short loops or β-turns.
2) The seven classes of LRR motifs adopt a variety of structural units. Typical LRRs have the consensus sequence of LxxLxLxxNxLxxLpxxoFxzxLxx. Their variable segments mainly adopt polyproline II plus β-turn, consecutive β-turns or β-turn plus polyproline II. RI-like LRRs have the consensus

Table 1. Abbreviations and acronyms.

ADLTE	autosomal-dominant lateral temporal epilepsy
ADPEAF	autosomal-dominant partial epilepsy with auditory features
ADPKD	autosomal-dominant polycystic kidney disease type I
BLS-II	bare lymphocyte syndrome type II
BSS	Bernard-Soulier syndrome
CARD	caspase-activating recruitment domain
C-cap	C-terminal Cap shielding the hydrophobic core of the last LRR in LRRs
CIITA	MHC class II transactivator
CINCA	chronic infantile neurologic cutaneous and articular syndrome
CIPA	congenital insensitivity to pain with anhidrosis
CNA2	autosomal recessive cornea plana
CSNB1	congenital stationary night blindness type 1
FCAS	familial cold autoinflammatory syndrome
FCU	familial cold urticaria
FGH	familial gestational hyperthyroidism
FMPP	familial male precocious puberty
FSHr	follicle-stimulating hormone receptor
GPD	giant platelet disorder
GPI	glycosylphosphatidylinositol
GPIb	glycoprotein Ib
GPIb	glycoprotein Ib
GPIX	glycoprotein IX
LCH	Leydig cell hypoplasia
LGI1	leucine-rich glioma-activated protein 1
LH/CGr	leuteinizing hormone or choriogonadotropic hormone receptor
LRR	leucine-rich repeat
LRRCT	C-terminal cysteine clusters neighboring on LRRs
LRRK2	LRR kinase 2
LRRNT	N-terminal cysteine clusters neighboring on LRRs
MHA	May-Hegglin anomaly
MWS	Muckle-Wells syndrome
NACHT	nucleoside triphosphatase (NTPase) domain
N-cap	N-terminal Cap shielding the hydrophobic core of the first LRR in LRRs
Ngr	Nogo-66 receptor
NOMID	neonatal-onset multisystem inflammatory disease
ODG1	ovarian dysgenesis 1
OHSS	ovarian hyperstimulation syndrome
PKD1	polycystin 1
PT-vWD	pseudo-von Willebrand disease
SLRP	small LRR repeat proteoglycan
Trk-A	neurotrophic tyrosine kinase receptor type 1
TSHr	thyrotropin receptor
VDFS/DGS	velo-cardio-facial/DiGeorge syndrome

sequence LxxLxLxx(N/C)xLxxxgoxxLxxoLxxzxxx and CC LRRs have LxxLxLxxCxzxITDxxoxx-Laxzxcxx. Their variable segments mainly adopt α-helix. The consensus sequence of bacterial LRRs is LxxLxVxxNxLxxLP(e/d)LPxx, in which their variable segments mainly adopts the polyproline II helix. Their variable segments for SDS22-like LRRs with LxxLxLxxNxIxxIxxLxzxLxx mainly adopt the 3_{10}-

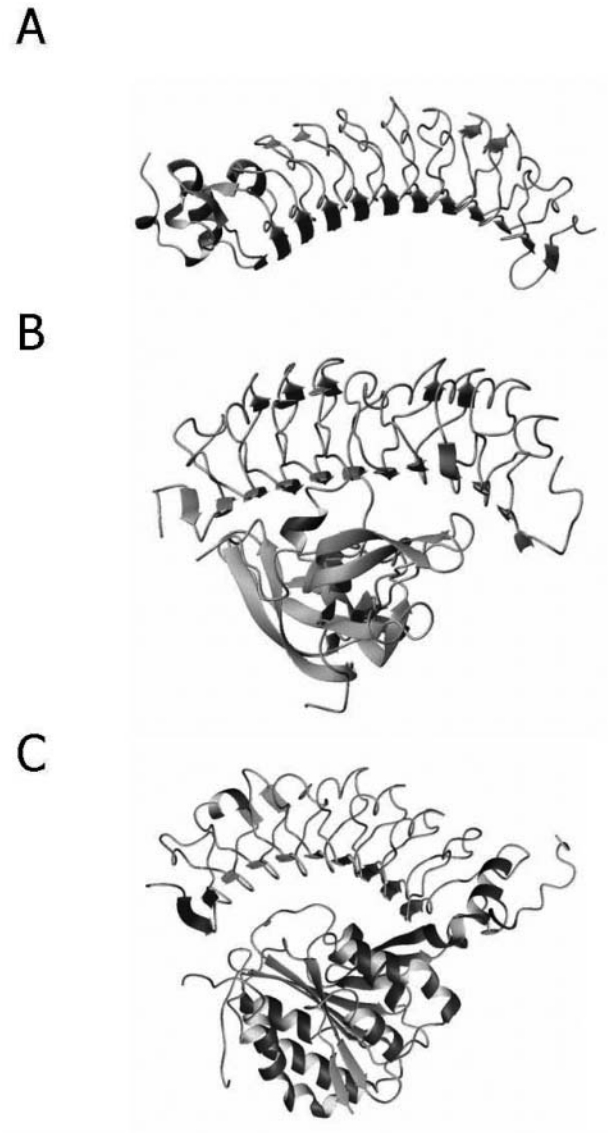

Figure 2. Ribbon diagrams of the known structures of LRRs domains within Nogo-66 receptor (NgR), FSHr and GPIbα. (A) NgR [1ozn]; (B) FSHr-FSH complex [1xwd]; (C) GPIbα-vWF complex [1m10]

helix. Similarly, the variable segments for plant-specific LRRs with LxxLxLxxNxL(t/s)gzxIPxxLGxLxzx mainly adopt 3_{10}-helix. Also, in individual LRRs the β-strand on the concave face at the N-terminus and the 3_{10}-helix on the convex face at the C-terminus are connected by a β-turn. Here residues identical or conservatively substituted in more than 50 and 30% of the repeats are shown in uppercase and lowercase, respectively, after Kobe and Kajava [3]. 'o' represents a nonpolar residue. 'x' represents nonconserved residues. 'z' indicates frequent deletions.

3) Conserved hydrophobic residues in the consensus sequences in individual classes contribute to the hydrophobic cores in the LRR arcs. Four leucine residues at positions 1, 4, 6 and 11 in the highly conserved segments, LxxLxLxxNxL, participate in the hydrophobic core in LRR arcs. Similarly, conserved hydrophobic residues in the variable segments of individual LRR classes participate in the hydrophobic core.
4) Most of the known LRR structures have a cap, which shields the hydrophobic core of the first LRR at the N-terminus (termed N-cap) or the last LRR at the C-terminus (C-cap) (fig. 1). In extracellular proteins or extracellular domains, the N-cap and C-cap frequently consist of cysteine clusters including (mostly) two- or four-cysteine residues and then form disulfide bonds [4]. Here the cysteine clusters on the N- and C-terminal sides of LRRs are termed LRRNT and LRRCT, respectively.
5) The LRR arc structures can be characterized by three parameters – the radius of the arc (R), the mean rotation angle about the central axis relating one β-strand to the next (φ), and the tilt angle of the parallel β-strand direction per turn (θ_t) (figs. 1A, B) [162]. The Rs of the LRR arcs of RI-like and CC LRRs are smaller those of bacteria-like, SDS22-like, typical and plant-specific LRRs. The observed values of R, $\varphi$and θ_t range from 15 to 47 Å, from 6 to 16º, and from –77 to 210º, respectively [162]. New data gave 227º for the maximum θ_t [4]. The LRR arcs with typical LRRs have the largest R. The spacing of adjacent β-strands, $D = 2\ R \sin(\varphi/2)$, is near constant.
6) The concave face of the LRR β-sheet in LRR proteins, including internalins, yopM and polygalacturonase-inhibiting protein, can be regarded as part of a Möbius strip (fig. 1C) [4, 162]. An ideal Möbius strip is a continuous one-sided surface that can be formed from a rectangular strip by rotating one end 180º and attaching it to the other end; it gives $\theta_t = \pm 180°$.
7) The crystal structures of eight complexes revealed that ligands interact on both the concave surface and the convex surface of the LRR arcs (fig. 2). The former induces relatively large structural changes, as seen in increases in R and θ_t.

Nogo-66 receptor (NgR) and schizophrenia

Schizophrenia is a severe mental disorder affecting 1% of the general population [163]. This disorder is highly heterogeneous and its pathophysiology is unknown at present. Family, twin and adoption studies provide strong evidence for a genetic component of the disorder, even though the transmission pattern is complex and genetically variable [164]. Two major types of evidence have focused the molecular genetic study of schizophrenia on chromosome 22q11 [165, 166].

A Nogo-66 receptor (NgR)

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LRRNT      1 MKRASAGGSRLLAWVLWLQAWQVAAPCPGACVCY   L18L
             NEPKVTTSCPQQGLQAVPVGIPAA
LRR1         SQRIFLHGNRI  SHVPAASFRACRN
LRR2         LTILWLHSNVL  ARIDAAAFTGLAL
LRR3         LEQLDLSDNAQL RSVDPATFHGLGR          R119W
LRR4         LHTLHLDRCGL  QELGPGLFRGLAA
LRR5         LQYLYLQDNAL  QALPDDTFRDLGN
LRR6         LTHLFLHGNRI  SSVPERAFRGLHS          R196H
LRR7         LDRLLLHQNRV  AHVHPHAFRDLGR
LRR8         LMTLYLFANNL  SALPTEALAPLRA
LRR9         LQYLRLNDNPW
Cons.seq.    LxxLxLxxNxL  xxaPxxAFxGLxx
LRRCT        VCDCRARPLWAWLQKFRGSSSEVPCSLPQRLAGR
             DLKRLAANDLQGCAVATGPYHPIWTGRATDEEPL
             GLPKCCQPDAADKASVLEPGRPASAGNALKGRVP
             PGDSPPGNGSGPRHINDSPFGTLPGSAEPPLTAV
             RPEGSEPPGFPTSGPRRRPGCSRKNRTRSHCRLG
             QAGSGGGGTGDSEGSGALPSLTCSLTPLGLALVL
             WTVLGPC 473
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B LGI1

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SIGNAL     1 MESERSKRMGNACIPLKRIAYFLCLLSALLLTEG  L26R
LRRNT        KKPAKPKCPAVCTCTKDNALCENARSIPRTVPPD  C42R, C42G, C46R
LRR1         VISLSFVRSGF TEISEGSFLFTPS
LRR2         LQLLLFTSNSF DVISDDAFIGLPH           A110D
LRR3         LEYLFIENNNI KSISRHTFRGLKS
LRR4         LIHLSLANNNL QTLPKDIFKGLDS           S145R
LRR5         LTNVDLRGNSF
Cons.seq.    LxxLxLxxNxF xxISxxAFxGLxS
LRRCT        NCDCKLKWLVEWLGHTNATVEDIYCEGPPEYKKR  C200R
             KINSLSSKDFDCIITE
EPTP         FAKSQDLPYQSLSIDTFSYLNDEYVVIAQPFTGK
             CIFLEWDHVEKTFRNYDNITGTSTVVCKPIVIET
             QLYVIVAQLFGGSHIYKRDSFANKFIKIQDIEIL  I298T, F318C
             KIRKPNDIETFKIENNWYFVVADSSKAGFTTIYK
             WNGNGFYSHQSLHAWYRDTDVEYLEIVRTPQTLR  E383A
             TPHLILSSSSQRPVIYQWNKATQLFTNQTDIPNM
             EDVYAVKHFSVKGDVYICLTRFIGDSKVMKWGGS  V432E
             SFQDIQRMPSRGSMVFQPLQINNYQYAILGSDYS  S473L
             FTQVYNWDAEKAKFVKFQELNVQAPRSFTHVSIN
             KRNFLFASSFKGNTQIYKHVIVDLSA 557
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C trk-A

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SIGNAL     1 MLRGGRRGQLGWHSWAAGPGSLLAWLILASAG    Qstop
LRRNT        AAPCPDACCPHGSSGLRCTRDGALDSLHHLPGAEN N67fs
LRR1         LTELYIENQQHL QHLELRDLRGLGE
LRR2         LRNLTIVKSGL  RFVAPDAFHFTPR           L93P
LRR3         LSRLNLSFNAL  ESLSWKTVQGLS            S131fs
LRR4         LQELVLSGNPL
Cons.seq.    LxxLxLxxNxL  xxLxxxxaxxLxx
LRRCT        HCSCALRWLQRWEEEGLGGVPEQKLQCHGQGPLA  E164stop
             HMPNASCGV
IG-1         PTLKVQVPNASVDVGDDVLLRCQVEGRGLEQAGW  L213P
             ILTELEQSATVMKSGGLPSLGLTLANVTSDLNRK
             NLTCWAENDVGRAEVSVQVNVSFPASVQLHTAVE
             MHH
IG-2         WCIPFSVDGQPAPSLRWLFNGSVLNETSFIFTEF  Q308fs
             LEPAANETVRHGCLRLNQPTHVNNGNYTLLAANP  Y359stop
             FGQASASIMAAFMDNPFEFNPEDPIPVSFSPVDT
             NSTSGDPVEKKDETPFGVSVAVG 423
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D polycystin 1/PKD1

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SIGNAL     1 MPPAAPARLALALGLGLWLGALA             L13Q
LRRNT        GGPGRGCGPCEPPCLCGPAPGAACRVNCSGRGLR
             TLGPALRIPAD
LRR1         ATALDVSHNLL RALDVGLLANLSA            S75F, A88V
LRR2         LAELDISNNKI STLEEGIFANLFN
LRR3         LSEINLSGNPF
Cons.seq.    LxELDLSxNxa xxLxxGaaANLxx
LRRCT        ECDCGLAWLPRWAEEQQVRVVQPEAATCAGPGSL  W139C
             AGQPLLGIPLLDSGCGEEYVACLPDNSSGTVAAV
             SFSAAHEGLLQPEACSAFCFSTGQGLAALSEQGW
             CLCGAAQPSSASFACLSLCSGPPPPPAPTCRGPT
             LLQHVFPASPGATLVGPHGPLASGQLAAFHIAAP 300
             LPV
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E Nyctalopin

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SIGNAL     1 MKGRGMLVLLLHAVVLGLPSAWA
LRRNT        VGACARACPAACACSTVERGCSVRCDRAGLLRVP  C31S, R29-A36Del
             AELPCE
LRR1         AVSIDLDRNGL  RFLGERAFGTLPS           P57T, A64E
LRR2         LRRLSLRHNNL  SFITPGAFKGLPR           I101del
LRR3         LAELRLAHNGDL RYLHARTFAALSR           E114-A118Adel
LRR4         LRRLDLAACRL  FSVPERLLAELPA           A143P, P151L
LRR5         LRELAAFDNLF  RRVP.GALRGLAN           L155LSVPERLL, P175R
LRR6         LTHAHLERGRI  EAVASSSLQGLRR           L184P, A187K, R207RLLR
LRR7         LRSLSLQANRV  RAVHAGAFGDCGV           R209RCLR, L213Q, N216S
LRR8         LEHLLLNDNLL  AELPADAFRGLRR           L232P*A243-P246del
LRR9         LRTLNLGGNAL  DRVARAWFADLAE           N264K
LRR10        LELLYLDRNSI  AFVEEGAFQNLSG           L285P, F298S, Q299stop
LRR11        LLALHLNGNRL  TVLAWVAFQPGFF           L307P, N312S
LRR12        LGRLFLFRNPW
Cons.seq.    LxxLxLxxNxL  xxVxxxAFxxLxx
                          I
LRRCT        CCDCRLEWLRDWMEGSGRVTDVPCASPGSVAGLD   L347P, G370V
             LSQVTFGRSSDGLCVDPEELNLTTSSPGPSPEPA
             ATTVSRFSSLLSKLLAPRVPEVEEAANTTGGLANA
             SLSDSLSSRGVGGAGRQPWFLLASCLLPSVAQHV
             VFGLQMD  481
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F FSHr

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SIGNAL     1 MALLLVSLLAFLSLGSG
LRRNT        CHHRICHCS
LRRNT/LRR1   NRVFLCQESK.V  TEIPSDLPRNA
LRR2         AIELRFVLTK.L  RVIQKGAFSGFGD
LRR3         LEKIEISQNDVL  EVIEADVFSNLPK
LRR4         LHEIRIEKANNL  LYINPEAFQNLPN
LRR5         LQYLLISNTG.I  KHLPDVHKIHSLQ
LRR6         KVLLDIQDNINI  HTIERNSFVGLSFE        I160T
LRR7         SVILWLNKNG.I  QEIHNCAFNGTQ          A189V
LRR8         LDELNLSDNNNL  EELPNDVFHGASG
LRR9         PVILDISRTR.I  HSLPSYGLEN
LRR10        LKKLRARSTYNL  KKLPTLEKLVALME
Cons.seq.    LxxLxLxxTxxL  xxIpxxAFxxLxxz
                           S
LRRCT        ASLTYPSHCCAFANWRRQISELHPICNKSILRQ
             EVDYMTQTRGQRSSLAEDNESSYSRGFDMTYTE
             FDYDLCNEVVDVTCSPKPDAFNPCEDIMGYNILR 366
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G LH/CGr

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SIGNAL     1 MKQRFSALQLLKLLLLLQPPLPRALR
LRRNT        EALCPEPCNCVPDGALRCPGPTAG
LRR1         LTRLSLAYL.PV KVIPSQAFRGLNE
LRR2         VIKIEISQIDSL ERIEANAFDNLLN
LRR3         LSEILIQNTKNL RYIEPGAFINLPR           I114F
LRR4         LKYLSICNT.GI RKFPDVTKVFSSES          C131R, V144F
LRR5         NFILEICDNLHI TTIPGNAFQGMNNE
LRR6         SVTLKLYGN.GF EEVQSHAFNGTT            F194V
LRR7         LTSLELKENVHL EKMHNGAFRGATG
LRR8         PKTLDISST.KL QALPSYGLES
LRR9         IQRLIATSSYSL KKLPSRETFVNLLE
Cons.seq.    LxxLxLxxNxxL xxIpxxAFxxLxxz
                          T
LRRCT        ATLTYPSHCCAFRNLPTKEQNFSHSISENFSKQ
             CESTVRKVSNKTLYSSMLAESELSGWDYEYGFC
             LPKTPRCAPEPDAFNPCEDIMGYDFLR 363      C343S, E354K
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H TSHr

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SIGNAL     1 MRPADLLQLVLLLDLPRDLG
LRRNT        GMGCSSPPCECHQEEDFRVTCKDIQRIPSLPPS  D36H, C41S
LRR1         TQTLKLIET.HL  RTIPSHAFSNLPN
LRR2         ISRIYVSIDVTL  QQLESHSFYNLSK
LRR3         VTHIEIRNTRNL  TYIDPDALKELPL         R109Q
LRR4         LKFLGIFNT.GL  KMFPDLTKVYSTDI
LRR5         FFILEITDNPYM  TSIPVNAFQGLCNE         P162A, I167N
LRR6         TLTLKLYNN.GF  TSVQGYAFNGTK           K183R, F197I
LRR7         LDAVYLNKNKYL  TVIDKDAFGGVYSG         D219E
LRR8         PSLLDVSQT.SV  TALPSKGLEH
LRR9         LKELIARNTWTL  KKLPLSLSFLHLTR         L252P
Cons.seq.    LxxLxLxxTxxL  TxaPxxAFxxLxxz
                           N
LRRCT        ADLSYPSHCCAFKNQKKIRGILESLMCNESSMQ  S281I S281N, S281T
             SLRQRKSVNALNSPLHQEYEENLGDSIVGYKEK  R310C
             SKFQDTHNNAHYYVFFEEQEDEIIGFGQELKNP
             QEETLQAFDSHYDYTICGDSEDMVCTPKSDEFN  C390W
             PCEDIMG 413                        D410N
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I Keratocan

```
LRRNT      1 MAGTICFIMWVLFITDTVWSRSVRQVYEVHDSD
             DWTIHDFECPMECFCPPSF
LRRNT/LRR1   PTALYCENRGL KEIPAIPSR
LRR2         IWYLYLQNNLI ETIPEKPFENATQ
LRR3         LRWINLNKNKI TNYGIEKGALSQLKK
LRR4         LLFLFLEDNEL EEVPSPLPRS
LRR5         LEQLQLARNKV SRIPQGTFSNLEN
LRR6         LTLLDLQNNKL VDNAFQRDTFKGLKN          Q174stop
LRR7         LMQLNMAKNAL RNMPPRLPAN
LRR8         TMQLFLDNNSI EGIPENYFNVIPK            T215K
LRR9         VAFLRLNHNKL SDEGLPSRGFDVSS           N247S
LRR10        ILDLQLSHNQL TKVPRISAH
LRR11/LRRCT  LQHLHLDHNKI KSVNVSVICPSPSMLPAERDS   R313stop
                         FSYGPH
LRR12/LRRCT  LRYLRLDGNEI KPPIPMALMTCFRLLQAVII 352
Cons.seq.(1) axxLxaxxNxL xxaPxzIPxx
Cons.seq.(2) LxxLxLxxNxI xxIPxxxFxxaxxzzzzzzzz
                         zzzzzz
Cons.seq.(3) LxxLxLxxNxa zzxxxxaxxxxFxxaxxzz
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J GPIbα

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SIGNAL       MPLLLLLLLLPSPLHP
LRRNT      1 HPICEVSKVASHLEVNCDKRNLTALPPDLPKD
LRR1         TTILHLSENLL YTFSLATLMPYTR
LRR2         LTQLNLDRCEL TKLQVDGTLPV              L57F, C65R
LRR3         LGTLDLSHNQL QSLPLLGQTLPA
LRR4         LTVLDVSFNRL TSLPLGALRGLGE
LRR5         LQELYLKGNEL KTLPPGLLTPTPK            L129P
LRR6         LEKLSLANNNL TELPAGLLNGLEN            A156V
LRR7         LDTLLLQENSL YTIPKGFFGSHL             L179del
LRR8         LPFAFLHGNPW
Cons.seq.    LxxLxLxxNxL xxLPxGxaxxxxx
LRRCT        LCNCEILYFRRWLQDNAENVYVWKQGVDVKAMT  C209S,G233S, M239V
             SNVASVQCDNSDKFPVYKYPGKGCPTLGDEGDT
             DLYDYYPEEDTEGDKVRATRTVVKFPTKAHTTP
             WGLFYSWSTASLDSQMPSSLHPTQESTKEQTTF
             PPRWTPNFTLHMESITFSKTPKSTTEPTPSPTT  W343stop
             SEPVPEPAPNMTTLEPTPSPTTPEPTSEPAPSP
             TTPEPTPIPTIATSPTILVSATSLITPKSTFLT  S444stop
             TTKPVSLLESTKKTIPELDQPPKLRGVLQGHLE
             SSRNDPFLHPDWCCLLPL                 W498stop
TM           GFYVLGLFWLLFASVVLILLL
CYTOPLSAMIC  WVGHVKPQALDSGQGAALTTATQTTHLELQRGR
             QVTVPRAWLLFLRGSLPTFRSSLFLWVRPNGRV
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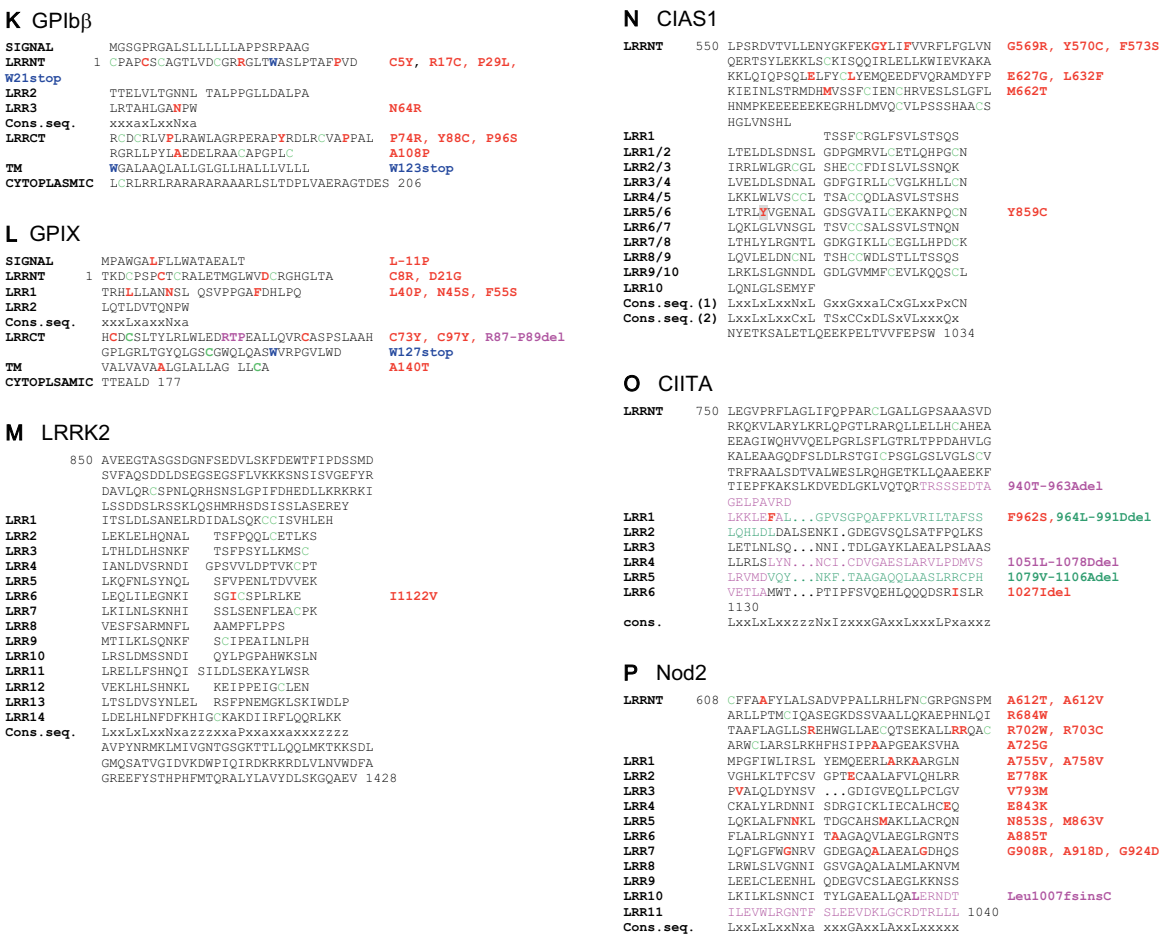

Figure 3. Sequence alignments of LRR domains in 16 proteins associated with human diseases. (A) NgR [Q9BZR6]; (B) LGI1 [O95970]; (C) trk-A [P04629]; (D) polycystin 1 [P98161]; (E) Nyctalopin [Q9GZU5]; (F) FSHr [P23945]; (G) LH/CGr [P22888]; (H) TSHr [P16473]; (I) keratocan [O60938]; (J) GPIbα [P07359]; (K) GPIbβ [P13224]; (L) GPIX [P14770]; (M) LRRK2 [AY792511]; (N) CIAS1 [Q96P20]; (O) CIITA [P33076]; (P) Nod2 [Q9HC29]. The complete amino acid sequences are shown for NgR with 473 residues (res.), LGI1 with 557 res., nyctalopin with 481 res., keratocan with 352 res., GPIbα with 626 res., GPIbβ with 206 res. and GPIX with 177 res. The partial aminio acid sequences including LRRs are shown for trk-A with 796 res., polycystin with 4303 res., FSHr with 695 res., LH/CGr with 699 res., TSHr with 764 res., LRRK2 with 2527 res., CIASI with 1034 res., CIITA with 1130 res. and Nod2 with 1040 res. Residues of missense mutations and the deletion of one residue (L179del in GPIbα) are highlighted in red boldface, and the residues on the concave surface or the convex surface are indicated by shaded boxes. Substituted residues due to nonsense mutations are highlighted in blue boldface. The deletions in which the lengths correspond to one LRR motif or larger than one LRR, and the deletion of three residues (R87–P89del in GPIX), are highlighted in pink or dark green boldface. Cys residues are highlighted in green boldface. Cons. seq. (1), (2) and (3) in keratocan are the consensus sequences of LRRs 1, 4, 7 and 10, LRRs 2, 5, 8 and 11, and LRRs 3, 6, 9 and 12, respectively. Cons. seq. (1) and (2) in CIAS1 are the consensus sequences of the LRRs with 28 and 29 residues, respectively. SIGNAL, signal peptide sequence; LRRNT, cysteine clusters on the N-terminal sides of LRRs; LRRCT, cysteine clusters on the C-terminal sides of LRRs; Cons. seq., consensus sequence of LRRs; TM, (putative) transmembrane region; CYTOPLASMIC, cytoplasmic domain; EPTP, epitempin domain; IG-1, the first immunoglobulin domain; IG-2, the second immunoglobulin domain.

The NgR gene [10] was identified as a candidate for schizophrenia susceptibility within the 22q11 deleted region [47]. Three mutant alleles were detected, including two missense changes (R119W and R196H), and one synonymous codon variant (L18L) (fig. 3A) [47].

The Nogo-66 receptor is a GPI-anchored, neuronal LRR protein that binds the myelin-associated proteins – Nogo-A, oligodendrocyte protein (OMGP) and myelin-associated glycoprotein (MAG) (reviewed in [167]). Seven of the eight LRRs in NgR are 24 residues long; LRR3 is 25 (fig. 3A). The LRRs are typical [4]. The crystal structure of human NgR has been determined [168, 169] (fig. 2A). The convex side in the LRR arc adopts a short extended structure similar to polyproline II that is flanked by a tandem arrangement of three β-turns. Thus, the variable segments of the LRRs may be represented as polyproline II plus β-turn [4, 154]. The radius of the LRR arc (R = 33.7 Å) is large [4, 162]. The tilt angle (θ_t = 132°) is relatively large.

The NgR LRR differs from other LRRs by having an internally buried phenylalanine at the end of each repeat sequence [168, 169]. Each Phe is surrounded by four Leu's, which form the hydrophobic core of the LRR arc. NgR's have both an N-cap and a C-cap. The N-cap contains four cysteines with the pattern of Cx_3CxCx_9C and forms two disulfide bonds (C27–C33 and C31–C44). The C-cap also contains four Cys's with the pattern of $CxCx_{20}Cx_{21}C$ in two disulfide bridges (C234–C259 and C236–C281).
Two missense mutations, R119W and R196H, associated with schizophrenia, are within the LRR domain of NgR [47]. The two mutated amino acids are located in the NgR surface, which is important for ligand binding. R119 is found at the edge between the convex and the concave part of the LRR arc, while R196 is located on its convex part [168, 169]. Sinibaldi et al. [47] noted that replacement of R119 with Trp causes a large steric change, and the removal of a positively ionizable side chain may alter the electrostatic potential of the receptor surface. Both effects may change the binding properties of the LRR3 domain. R196H is located in LRR6. The side chain of His is significantly different in shape from that of Arg. At neutral pH the His should not be protonated as is the Arg. The synonymous codon variant (L18L) is a putative splice site mutation.

Leucine-rich glioma-activated protein 1 (LGI1) and autosomal dominant lateral temporal epilepsy (ADLTE)/autosomal-dominant partial epilepsy with auditory features (ADPEAF)

Mutations in the LGI1 gene cause ADLTE/ADPEAF (reviewed in [170]). The LGI1 protein is a putative membrane-anchored protein of unknown function, which has LRR in the N-terminal sequence, flanked by LRRNT, and the epitempin EPTP repeat (fig. 3B) [11]. The majority of mutations are predicted to cause protein truncations; the remaining missense mutations alter conserved amino acids [48–58].
The structure of LGI1 is not available. The LRRs spanning residues 69–175 contain four and a half repeats (fig. 3B) and are typical. The variable segments of the LRRs likely adopt polyproline II plus β-turn. Also, all the Phe residues in the LRRs (F87, F111, F135 and F150) are internally buried. Moreover, the LRRCT and LRRNT show high similarity to those in NgR [168, 169]. The N-cap and C-cap likely adopt cap structures similar to those in NgR, and probably have two disulfide bonds (C42–C48 and C46–C55) at the LRRNT and two disulfide bonds (C177–C200 and C179–C221) at the LRRCT.
The Cys-to-Arg mutations (C42R, C46R and C200R) and C42G preclude the formation of sulfide bridges in the LRRNT [48–52, 53]. Two missense mutations, A110D and S145R, occur in the LRRs. A110 is likely buried in the LRR arc. This is consistent with the equivalent residue of the NgR structure [168, 169]. Thus, A100D may influence the hydrophobic core in the LRR arc. S145 at position 5 in the highly conserved segment is located on the concave surface (fig. 3B). S145R may changes the binding properties if LGI1 does interact with a ligand. L26R occurs in the signal peptide sequence [51]. The change of just a single amino acid reduces the solvent accessibility of the N-terminus. A transmembrane α-helix is present from amino acids 12–31, whereas in the mutated protein the transmembrane α-helix is totally abolished [51]. The C-terminal region consists of seven EPTP repeats. Five mutations occur in the EPTP repeats (fig. 3B) [48, 49, 52–54].

Neurotrophic tyrosine kinase receptor type 1 (Trk-A) and congenital insensitivity to pain with anhidrosis (CIPA)

Trk-A is required for high-affinity binding to nerve growth factor (NGF), neurotrophin-3 and neurotrophin-4/5 but not brain-derived neurotrophic factor (BDNF) [171, 172]. Known substrates for Trk-A are SHC1, PI 3-kinase, and PLCγ1. Mutation of Trk-A is a cause of CIPA (reviewed in [173]). CIPA is characterized by a congenital insensitivity to pain, anhidrosis (absence of sweating), absence of reaction to noxious stimuli, self-mutilating behavior and mental retardation.
Trk-A is a type I membrane protein; it has 796 residues [12–14]. The potential extracellular domain spanning residues 33–423 contains LRRs and two immunoglobulin-like domains (fig. 3C), and the cytoplasmic portion contains a tyrosine kinase domain. The LRRs residues 68–150 contain three and a half repeats and are a typical LRR. LRRCT and LRRNT have the patterns Cx_3CCx_8C and $CxCx_{21}Cx_{13}C$, respectively.
The mutations in trk-A, associated with CIPA, occur in the signal peptide sequence, the LRRNT, the LRRs, the immunoglobulin domains, the tyrosine kinase domain and the splice site [59, 60, 174].
Two missense mutations are L93P in the LRRs and L213P in the first immunoglobulin domain [59, 60]. L93 is located at position 1 in the highly conserved segment, suggesting that L93 is completely buried in the LRR arc. Kajava and Kobe [175] provided an insight about the origin of the LRR arcs. The repeats in pectate lyase form a β-helix structure [176]. The repeats consist of a (G/S)xxLxLxxNxL similar to the highly conserved segment in LRRs. They proposed that the first bulky nonpolar residue probably causes the LRR arc [175]. L93 is located at the short loop that connects the helical structure on the convex part (in LRR1) and the β-strand on the concave part (in LRR2). Structural changes due to L93P may spread throughout the polypeptide, thereby leading to changes in R, φ and θ_t.

Three mutations are a change of Gln, Glu or Tyr to a stop codon (Q9stop, E164stop or Y359stop), predicting a truncated protein [59, 60]. Three frameshift mutations – N67fs, S131fs and Q808fs – are located in the LRRNT, the first and second immunoglobulin domains, respectively [59, 60]. These should result in truncation of the trk-A polypeptide.

Polycystin 1 (PKD1) and autosomal dominant polycystic kidney disease type I (ADPKD)

Polycystin 1 (PKD1) is a giant protein with 4303 residues and contains a C-type lectin family domain, a GPS domain, LDL-receptor class A domain, LRRs, 16 PKD domains, and a PLAT and a REJ domain [15, 16]. Residues 24–3074 are a potential extracellular domain. PKD1 is involved in adhesive protein-protein and protein-carbohydrate interactions and interacts with PKD2. Mutations in polycystin 1 cause ADPKD, which is a common autosomal dominant genetic disease affecting about 1 in 1000 individuals (reviewed in [177]). ADPKD is characterized by progressive formation and enlargement of cysts in both kidneys, typically leading to end stage renal disease in adult life.

The LRRs contain two and a half repeats at the N-terminal part (fig. 3D) and are typical LRRs. The LRRNT and LRRCT have the patterns of $Cx_2Cx_3CxCx_7Cx_3C$ and $CxCx_{23}Cx_{20}C$, respectively. Sixty-one missense mutations in polycystin 1 are associated with ADPKD [P98161]. Three of the 61 occur in LRR1 (S75F and A88V) [61, 62] and in LRRCT (W139C) [61] (fig. 3D). Since the $CxCx_{23}Cx_{20}C$ pattern predicts two disulfide bonds (C129–C155 and C131–C176), W139C may lead to a wrong pairing of cysteines in disulfide bonds. S75 in LRR1 is located at the edge between the β-strand on the concave surface and the consecutive short loop. S75 in polycystin 1 corresponds to S39 in GPIbα, because both residues are located at position 7 in LRR1. The GPIbα structure reveals that S39 is surrounded by other polar residues [178–181]. It would appear that S75F requires local rearrangements. A88 is near the loop C-terminal to the convex part. We think that its side chain is partially buried. A88V would influence the loop structure. L13Q occurs in the signal peptide sequence [61]. This nonconservative change significantly affects the hydrophobicity of the signal peptide, suggesting that this mutation significantly impairs the function of this region.

Nyctalopin and congenital stationary night blindness type 1 (CSNB1)/X-linked congenital stationary night blindness (XLCSNB)

Nyctalopin [17–18] is a member of the SLRP family and belongs to class IV subfamily as well as chondroadherin [4]. Human nayctalopin is a GPI-anchored protein [182]. Defects in nyctolopin are the cause of CSNB1/XLCSNB, which is a rare inherited retinal disorder characterized by impaired scotopic vision, myopia, hyperopia, nystagmus and reduced visual acuity [17, 18]. CSNB1 is identified on the basis of electroretinogram responses by the absence of the rod β-wave but largely normal cone amplitudes.

Nyctolopin contains 11 and a half LRRs, flanked by LRRNT ($Cx_3Cx_3CxCx_6Cx_3C$) and LRRCT ($CCxCx_{19}C_{23}Cx_3C$) (fig. 3E) [197, 198]. These LRRs are typical, and most of the repeat lengths are 24. Thus, as seen in the NgR structure, the variable segments of the LRRs are likely represented by polyproline II plus β-turn [4, 162]. We predict that the structural parameters, R, φ and θ_t, of nyctalopin are similar to those of NgR.

Thirty-five mutations in nyctalopin are associated with CSNB1 (fig. 3E) [17, 18, 183, 184]. Twenty-one of the 23 occur in LRRs, while three in LRRNT and two in LRRCT. Mutations involving Pro residues occur frequently. These include P57T, A143P, P151L, P175R, L184P, L232P, L285P, L307P and L347P. Pro is a breaker of regular secondary structures such as α-helix or β-strand. It occurs in turns, nonrepetitive structures, at the ends of strands and helices [185]. The NgR structure predicts that P151 and P175 are contained in polyproline II. These novel Pro substitutions including P151L and P175R may have an influence on the conformation. The side chains of I101, L184, A187, L213, L232, L285, F298 and L307 are completely buried in the LRR arc. Seven missense mutations -L184P, A187K, L213Q, L232P, L285P, F298S and L307 – and the deletion of I101 (I101del) may influence the hydrophobic core. L184P and L232P correspond to L83P in trk-A, because the Leu's are located at position 1 in the highly conserved segment. All these mutations presumably cause changes in R, φ and θ_t, in which I101del, A187K and L213Q may induce relatively large structural changes. C31S likely precludes the formation of sulfide bridges, as seen in four Cys mutations in LGI1. Like Pro, Gly is associated with key bends in protein secondary structure. G370V may disturb the structural integrity of the C-cap structure. A64 in LRR1 is very near the LRRNT. Thus, A64E may influence the orientation of the N-cap structure. Three mutations – N216S, N264K and N312S – occur at position 9 in the highly conserved segment. Position 9 is generally occupied by Asn or Cys whose side chains form hydrogen bonds in the loop structure [2]. Replacement of the Asn's with Ser or Lys may change the hydrogen bond pattern in the loop.

The remaining seven mutations are nonsense mutations, insertions or the deletions of 3–8 amino acids. Q299stop lacks one and a half LRRs at the C-terminus. The deletion of five amino acid residues (E243–P246del) results in a breaking of the β-strand on the convex face, whereas four residues deletion (A243–P246del) results

in a shortening of the loop structure. Three insertions (L155LSVPERLL, R207RLLR and R209RCLR) presumably change or disrupt the loop structures. These mutations likely induce drastic structural changes in the N-cap structure or in the LRR arc, thereby leading to changes in R, φ and θ_t.

Follicle stimulating hormone receptor (FSHr) and ovarian dysgenesis 1 (ODG1)

Glycoprotein hormone receptors (GpHrs), FSHr [19–21], LH/CGr [22–24] and TSHr [24, 25–27], are receptors for follicle stimulating hormone (FSH), luteinizing hormone (LH) or human choriogonadotropic hormone (hCG), and thyrothropin (TSH), respectively, and are members of the rhodopsin-like G-protein-coupled receptor family. These GpHrs contain a large N-terminal (350–400 residues) ectodomain being an extracellular region that is responsible for high affinity and selective binding of the corresponding hormones.

These receptors with 695–764 residues are homologous to each other. The N-terminal ectodomain contains LRRs, flanked by LRRNT and LRRCT (fig. 3F). The LRRNT (residues 18–46) has a unique pattern consisting of Cx_4CxCx_6C, while the LRRCT is a chemokine-like domain [186].

Very recently, the structure of FSHr (residues 1–268) in complex with FSH was solved (fig. 2B) [187]. Unexpectedly, the LRRNT includes the first of the LRR repeats. This segment is further integrated into the structure by an antiparallel β-strand added before the inner β-sheet and by two disulfide bridges (Cys18 Cys25 and Cys23 Cys32). The curvature of FSHr is steeply graded; LRRs 7–10 have the signature arc-like curvature of LRR proteins, whereas LRRs 1–7 are nearly flat [187]. We calculated that the radius of the LRR arc (R = 36 37 Å) is larger and comparable to that of NgR [4, 162]. In contrast, the tilt angle (t = 32 to 50º) is negative and small. Most of the variable segments of the LRR may be represented as polyproline II plus β-turn or consecutive β-turns and in LRR5 adopt a 310-helix. Apart from LRR1, the overall fold of FSHr is likely to be conserved in LH/CGr and TSHr [187]. The LRRs in FSHr contain 10 repeats, while those in both LH/CGr and TSHr have 9 (figs. 3F H).

Mutations of FSHr cause ODG1 [63-68] and ovarian hyperstimulation syndrome (OHSS) [188]. ODG1 is an autosomal recessive disease characterized by primary amenorrhea, variable development of secondary sex characteristics and high serum levels of FSH and LH. Four missense mutations associated with ODG1 were identified [63–68]. Two of the four (I160T and A189V) occur in LRRs (fig. 3F), whereas the remaining two occur in the cytoplasmic region. One missense mutation, associated with OHSS, also occurs in the cytoplasmic region [188].

The structures of FSHr complexed with FSH allow us to make some inferences about structural effects due to the mutations I160T and A189V. The FSHr structure shows that the side chains of I160 and A189 are completely buried in the LRR arc. The complex shows FSH bound into the concave surface of the LRR arc in a manner that resembles a hand clasp (fig. 2B) [187]. In contrast, the two mutations concentrate on the convex part. It is reasonable to assume that the structural changes due to these mutations cause the changes in R, φ and θ_t.

Luteinizing hormone/choriogonadotropic hormone receptor (LH/CGr) and Leydig cell hypoplasia (LCH)

Mutations of LH/CGr cause LCH and familial male precocious puberty (FMPP) (reviewed in [189]). LCH is an autosomal recessive disease characterized by male pseudohermaphroditism. Eighteen mutations in LSHr associated with LCH have been described [69]. Six of the 18 occur in LRRs and in the LRRCT (fig. 3G). Comparison with the FSHr structure indicates that L114, V144 and F194 are all buried hydrophobic residues. L114F, V144F and F194V influence the hydrophobic core. As inferred in I160T in FSHr, the structural changes due to these mutations may cause the changes in R, φ and θ_t, This appears to be supported by the observation that F194V as well as C131R and E354K display decreased affinity for human CG [69]. C131R corresponds to S75F in polycystin 1 and A143P in nyctalopin. C343S might preclude the formation of sulfide bridges. E354K alters the electrostatic potential in the C-terminal part of the ectodomain.

The missense mutations associated with FMPP have been identified only in the cytoplasmic region [189].

Thyrotropin receptor (TSHr) and thyrotropin resistance, hypothyroidism, familial gestational hyperthyroidism (FGH), papillary cancer or Graves disease

Mutations of TSHr cause thyrotropin resistance, hypothyroidism, FGH, thyroid neoplasms (papillary and follicular cancers) and Graves disease [71–85]. Thyrotropin resistance leads either to congenital hypothyroidism or to euthyroidism with increased thyrotropin secretion, depending on the completeness of the defect. Subclinical hypothyroidism is a condition biochemically characterized by the association of normal free thyroid hormone levels and slight hyperthyrotropinemia.

Fifteen missense mutations of TSHr associated with these diseases were identified in the ectodomain [71–85]. The mutations linked to with thyrotropin resistance are

C41S, R109Q, P162A, L252P, I167N, R310C, C390W and D410N; S281I, S281N and S281T with hyperthyroidism; K183R with FGH; F197I and D219E with papillary cancer; and D36H with Graves disease.

Seven of the 15 occur in LRRs (fig. 3H). Two occur in LRRNT and 7 occur in LRRCT. The mutations involving Cys (C41S, R310C and C390W) preclude the formation of sulfide bridges or lead to a wrong paring of cysteines. Comparison with the FSHr structure indicates that I167, F197 and L252 are internally buried in the LRR arc. It is expected that these mutations induce similar effects in the LRR arc to I160T in FSHr, I114F, V144F and F194V in LH/CGr. P162 is located at the short loop. As noted, Pro is typically associated with key bends in protein secondary structure. P162A may change the short loop structure. K183R and D219E are conservative substitutions. Also, K183 lies on the concave surface and D219 on the convex surface. Thus, these two mutations induce little changes in the LRR arc. However, the side chain of Lys is significantly different in shape from that of Arg. K183R may change the pattern of hydrogen bonds in interactions with ligands. Such a situation may occur in R109Q. This insight appears to provide a structural rationale to the observed loss of specificity seen in K183R [190, 191]. In contrast, D219E remains unclear, since the ligands interact on the concave surface. It is not known whether there is a different ligand from TSH.

S281 belongs to a GpHr-specific YPSHCCAF sequence signature located downstream of the LRRs [192]. This segment has relatively high propensity for a turn structure. Thus, the three mutations at S281 probably induce a local 'loss of structure' [193] and/or may influence the C-cap structure. D410N is comparable with E354K in LSHr (figs. 3F, G). This suggests that the C-terminus of the ectodomain plays a common role in the function or the interactions with the hormones. D36H in the LRRNT may alter the electrostatic potential of the N-cap structure.

Keratocan and autosomal recessive cornea plana (CNA2)

Keratocan is an extracellular matrix and belongs to the SLRP family, which comprises five distinct subfamilies [28, 29]. The amino acid sequence of keratocan is similar to that of decorin [6], whose crystal structure has been determined [194]. Thus, it is likely that the overall fold of keratocan is very similar to that of decorin. The decorin structure revealed that one molecule contains 12 LRRs flanked a β-hairpin at the N-terminus and an additional β-strand at the end of LRR12. The long β-sheet consists of 13 β-strands. The radius (R = 28–29 Å) of the LRR arc in decorin is smaller than that of NgR [4]. However, it is larger than those of GPIbα [4, 162]. The tilt angle θ_t (57–60) is relatively small. The LRRs of keratocan vary in length from 20 to 38 residues and follow a short-long-long regular pattern throughout the molecule (fig. 3I) [6]. The first 9 LRRs show a (20/21)-24-(25/26) pattern. The last 3 LRRs also have a short-long-long pattern, this time 20-38-31. Keratocan contains probably 12 LRRs. The decorin structure indicates that the LRRNT likely forms two disulfide bonds (Cys42–Cys48 and Cys46–Cys58), whereas the LRRCT forms a disulfide bond (Cys313–Cys343).

Keratocan is responsible for CNA2 [29, 86, 87]. In cornea plana, the forward convex structure is flattened, leading to a decrease in refraction. CNA2 is a more severe, recessively inherited form and a rare disorder with a worldwide distribution, but a high prevalence in Finland. Four mutations, linked to CNA2, were identified [29, 86, 87]. Two out of the four are nonsense mutations (Q174stop and R313stop), predicting a truncated protein of 173 and 134 amino acids, respectively. The remaining two mutations are T215K in LRR8 and N247S in LRR9.

The hydrophobic pattern in a highly conserved segment of LRR8 (TMQLFLDNNSI) is not consistent with its consensus sequence, LxxLxLxxNxL. However, it is similar to those of LRR6 (146-KVLLLDIQDNI-156) and LRR7 (172-SVILWLNKNGI-182) in FSHr (figs. 3F, H). The FSHr structure reveals that Val147 and Val173 at position 2 are buried in the LRR arc [187]. Thus, it is predicted that in keratocan not T215 but M216 is internally buried. T215 is presumably located at the loop and alters the electrostatic potential of keratocan. N247 is located at position 9 in the highly conserved segment. Thus, N247S may change the hydrogen bond pattern in the loop, as seen in N216S, N264K and N312S in nyctalopin. Such a mutation is also seen in C75R in GPIbα, N64R in GPIbβ and N45S in GPIX (figs. 3I–K).

Glycoprotein Ibα (GPIbα) and Bernard-Soulier syndrome (BSS) or pseudo-von Willebrand disease (PT-vWD)

The glycoprotein (GP) Ib-V-IX complex is a platelet membrane receptor complex with a critical role in adhesion to the damaged vessel wall under conditions of higher shear stress (reviewed in [195]). The GPIb-V-IX complex consists of four LRR proteins–GPIbα, GPIbβ, GPIX and GpV–in the ratio 2:2:2:1. GPIbα binds the plasma glycoprotein von Willebrand factor (vWF), a multimeric ligand that together with GPIbα regulates adhesion of platelets to the subendothelium. GPIbα is also a receptor for thrombin. The integrity of the LRR domain of GPIb is essential for normal processing and

function of the GPIb-IX complex [196]. BSS is an autosomal recessive bleeding disorder caused by genetic abnormalities in the GPIb-V-IX complex [195]. More than 30 mutations of GPIbα, GPIbβ and GPIX have been described in BSS [122].

GPIbα contains eight LRRs whose repeat lengths range from 22 to 24 (fig. 3J) [30-32]. The structures of GPIbα complexed with vWF A1 and with thrombin have been determined (fig. 2C) [178-181]. The overall fold of GPIbα consists of a central domain of eight LRRs that is flanked by the N-terminal β-hairpin (residues C4–C17), the β-switch region (residues V227–S241) and the C-terminal anionic region (residues D269 to Y279) [178-181]. Two disulfide bonds, C209–C248 and C211–C264, are formed in the LRRCT. The radius (R = 22–24 Å) and θ_t (= 80–100°) of the LRR arc is smaller than those in NgR [4,154].

Seventeen mutations of GPIbα have been described in BSS [88-135]. Eleven of the 17 generate a truncated protein. One mutation is the deletion of Leu at residue 179 (L179del) in LRR7 (fig. 3J). The remaining five are missense mutations in the LRRs and in the LRRCT. C209S precludes the formation of sulfide bridges in the LRRCT. L57, L129 and L179 are all buried hydrophobic residues [178-181]. Thus, the mutations–L57F, L129P and L179del–may influence the hydrophobic core in the LRR arc. C65 is at the central part of the loop. C65F corresponds to N247S in keratocan, N64R in GPIbβ, and N45S in GPIX. These mutations may change the hydrogen bond pattern in the loop, as noted. A156 lies on the C-terminal side of the β-strand and is partially buried. It is possible that A156V influences the R, φ and θ_t of the LRR arc. Three nonsense mutations–W343stop, S444stop and W498stop–occur in a pro/thr/ser-rich domain.

In addition to BSS, mutations of GPIbα are associated with PT-vWD, which is an autosomal dominant bleeding disorder caused by hyperactivation of a receptor on the platelet surface [136-139]. The abnormal receptor, GPIbα, displays increased affinity for its ligand, vWF. Two missense mutations, G233V [136, 137] and M239V [138, 139] (fig. 3J), which cause PT-vWD, are located in the β-switch region.

The structure of the GPIbα-vWF A1 complex containing 'gain-of-function' mutations, GPIbα-M239V and A1-R543Q, is available (fig. 2C) [179, 181]. At the larger interfaces, differences in interaction associated with the GPIbα-M239V plate-type VWD mutation are minor and localized but feature discrete γ-turn conformers at the loop end of the β-hairpin structure. It is important to note that the side chain of Met is more flexible than that of Val. Like Pro, Gly is associated with key bends in protein secondary structure. G233V likely disturbs the structural integrity of the β-switch structure.

Glycoprotein Ibβ (GPIbβ) and Bernard-Soulier syndrome (BSS), giant platelet disorder (GPD) or velo-cardio-facial/DiGeorge syndrome (VCFS/DGS)

Mutations in PGIbβ are also linked to GPD [119, 121] and VCFS/DGS [109]. VCFS is a congenital anomaly disorder. GPD is a rare and heterogeneous group characterized by abnormally large platelets and thrombocytopenia, and often associated with a tendency to bleeding [121]. Examples of GPD are BSS and May-Hegglin anomaly (MHA).

GPIbβ [33-35] contains one and a half LRR repeats that are flanked by LRRNT and LRRCT (fig. 3K). Because the highly conserved segment repeats twice, at least two β-strands are likely formed. Tang et al. [120] have proposed a model for GPIbβ, based on sequence similarity to the known structures of NgR and GPIbα. In the model, the LRRNT with the pattern of Cx_3CxCx_6C forms two disulfide bonds, C1–C7 and C5–C14; the LRRNT has been suggested to pair C1–C14 and C5–C7 [113, 122]. In addition, LRRCT with $CxCx_{22}Cx_{22}C$ also forms two sulfide bonds (C68–C93 and C70–C116). The two proposed sulfide bonds at LRRNT are consistent with the known structure of *Drosophila* Slit [1w8a], because it has the pattern of LRRNT that is similar to that in GPIbβ.

Eleven missense mutations in PGIbβ, linked to BSS, have been reported [122]. Three of the 11 (del122q11.2, P29L and P96S) are linked to VCFS as well as BSS [122] and 3 missense mutations (R17C, Y88C, and A108P) to GPD [114, 119, 121].

Four mutations involve Pro residues (P29L, P74R, P96S and A108P). As well as mutations involving Pro residue in nyctalopin and TSHr, these Pro substitutions likely affect the conformation of GPIbβ and alter its normal interactions with GPIbα and GPIX, or both [120]. Three mutations involve Cys residues, C5Y and R17C in LRRNT, and Y88C in LRRCT. These mutations preclude the formation of sulfide bridges or lead to a wrong pairing of cysteines. N64 in LRR2 is at position 9 in the highly conserved segment, which is occupied by Asn or Cys in most LRRs. Like N216S, N264K and N312S in nyctalopin, N247S in keratocan and C65R in GPIbα, N64R may change the hydrogen bond pattern in the loop structure. In addition, N64R may influence the C-cap structure. W21stop and W123stop generate truncated proteins lacking the C-terminal domain. Also a 13 bp deletion in the signal peptide-coding sequence was reported [135]. The deletion would cause a frame-shift, resulting in the appearance of a stop codon following an indifferent polypeptide sequence.

Glycoprotein IX (GPIX) and Bernard-Soulier syndrome (BSS)

GPIX is homologous to GPIbβ [36]. Thus, the overall fold of GPIX is likely very similar to that of GPIbβ. In contrast to the GPIbβ, LRRNT is predicted to form two sulfide bonds, C4–C10 and C8–C22, while, in LRRCT, C73–C97 and C75–C118 should form sulfide bonds (fig. 3L).
Eleven missense mutations in PGIX, linked to BSS, were reported [122]. Three mutations of the eleven involve Cys residues, C8R in the LRRNT, and C73Y and C97Y in the LRRCT. They prevent the formation of sulfide bridges, as seen in GPIbβ. Three mutations–L40P, N45S, and F55S–occur in LRR1. L40P and F55S influence the hydrophobic core in the LRR arc, because L40 and F55 are located at positions 4 and 19, respectively, in the typical LRR consensus that are occupied by strong hydrophobic residues. N45S corresponds to N247S in keratocan, C65R in GPIbα, N64R in GPIX, and N853S in Nod2, showing that all these mutations keep the loop structures. Deletion of the R87-T88-P89 sequence may destroy or change the C-cap structure. D21G alters the electrostatic potential of GPIX and thus may influence the N-cap. W127stop lacks the C-terminal domain.
The remaining mutations are L-11P in the signal peptide sequence [134] and A140T in the transmembrane region [132]. The former presumably leads to an abnormal conformation and, hence, incorrect insertion of GPIX into the endoplasmic reticulum and/or to defective signal peptide cleavage, both of which are required for correct transport to the cell membrane [134]. The latter does not induce intracellular GP Ib/IX complex degradation, but prevents its insertion in the cytoplasmic membrane of platelets and CHO cells [132].

Leucine-rich repeat kinase 2 (LRRK2) and Parkinson's disease

Parkinson's disease is a common neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons of the substantia nigra, associated with the formation of fibrillar aggregates composed of α-synuclein and other proteins (Lewy bodies and Lewy neurites) (reviewed in [197]). In most cases, Parkinson's disease occurs as sporadic disease of unknown etiology, but in rare instances, point mutations or multiplications of the α-synuclein gene cause autosomal-dominant parkinsonism.
A novel gene on chrosomosome 12 was identified as the PARK8 locus linked to familial parkinsonism [37, 140]. Zimprich et al. [37] have found six disease-segregating mutations (five missense and one putative splice site mutation) in a gene encoding a large, multifunctional protein, LRRK2. LRRK2 has 2527 residues containing a ROC and a COR domain that both belong to the Ras/GTPase superfamily, LRRs, tyrosine kinase catalytic domain, and a WD40 domain associated with pre-mRNA (messenger RNA) processing and cytoskeleton assembly. The LRRs with 957–1130 residues contain 13 repeats 20–29 residues long (fig. 3M). Most of the LRRs appear to belong to the typical class.
Only one mutation, I1122V, has been observed in the LRRs [37]. I1122 corresponds to a conserved hydrophobic residue in the variable segment and thus affects the hydrophobic core. However, the structural change due to I1122V may be minor, because the volumes of the two side chains differ by only a methyl group.

Cold autoinflammatory syndrome 1 protein (CIAS1) and chronic infantile neurologic cutaneous and articular syndrome (CINCA)/Neonatal-onset multisystem inflammatory disease (NOMID)

Mutations of CIAS1/cryopyrin/NALP3/PYPAF1 are associated with several genetic autoinflammatory conditions: CINCA/NOMID, FCU/FCAS, and MWS (table 1) (reviewed in [198]). These diseases cause recurrent episodes of inflammatory attacks associated with arthritis, fever and rash.
CIAS1 may function as a potential inducer of apoptosis and interacts selectively with apoptosis-associated specklike protein containing a CARD domain. CIAS1 with 1034 residues contains PYRIN, NACHT and LRR [38-42]. PYRIN, also called DAPIN, PAAD or PYD, appears to be involved in apoptosis and inflammation [199]. It is homologous to CARD [200, 201], whose three-dimensional (3D) structures reveal a highly conserved compact bundle of six-anti-parallel α-helices as common domain fold [202]. CARD was first described as a homology region in the N-terminus of the death adaptor protein RAIDD and the caspases ced-3 and ICH1. This domain is widespread among apoptotic signaling molecules, and a possible function in caspase recruitment has been proposed [200]. NACHT is a nucleoside triphosphatase (NTPase) domain and consists of seven distinct conserved motifs, including the ATP/GTPase specific P-loop, the Mg^{2+} binding site (Walker A and B motifs, respectively) and five more specific motifs [203].
The LRRs have 724–1008 residues and contain 10 repeats (fig. 3N). These 10 LRRs alternate 28 or 29 residues each, thereby forming higher-order repeating units, each 57 residues long, as seen in ribonuclease inhibitor [4]. The LRR clearly belongs to RI-like class. The LRR structure in CIAS1 is predicted to be very similar to that of ribonuclease inhibitor [204]. Also a flanking region is present between the NACHT and LRR domain. It can be regarded as an LRRNT with six Cys's.

Most of the missense mutations that are associated with diseases lie within in exon 3, which encodes the NACHT and LRRNT domains [147]. Only one missense mutation within LRR domain, Y859C, which causes CINCA, has been identified [149]. Y859 lies on the concave surface, as seen in S145R in LGI1 and K183R in TSHr. Thus, it is likely that the structural change due to the substitution is very minor. However, it may display increased or decreased affinity for its ligand. Three mutations–E627F, L632F and M662T–near the LRRs may influence the N-cap structure.

MHC class II transactivator (CIITA) and Bare lymphocyte syndrome type II (BLS II)

Mutations of CIITTA are associated with BLS II (reviewed in [205]). CIITA does not bind DNA, but instead serves as a scaffold or interaction interface for DNA-binding transcription factors that recognize the MHC class II promoter; these include NF-Y, RFX and CREB. In addition, CIITA also coordinates the recruitment of histone modifying enzymes and contains a histone acetylase domain within its own N-terminus. CIITA is a potent transcriptional activator that is specific in its induction of genes important for the function of antigen-presenting cells, including MHC class II, HLA-DM, MHC class 1 and plexin-A1.

CIITA is 1130 residues long and contains an acidic region, proline/serine/threonine rich region, NACHT and LRR [43, 44]. Dendritic cell-specific variants of CIITA contain an additional N-terminal CARD [206]. The C-terminal LRR domain affects nuclear translocation [207, 208], self-association [209-211] and transactivation [207]. We found that the LRRs consist of residues 957–1130 and contain five and a half repeats; it has previously been reported that the LRRs repeat at least four times (fig. 3O) [207, 208] and belongs to RI-like class. An LRRNT appears to be present between the NACHT and LRRs domains, as seen in CIAS1.

Mutations of CIITA fall into three basic groups: splice site, nonsense and missense [205]. Two nonsense mutations, E381stop and W688stop, result in truncated proteins [150, 153]. Six mutations occur in the C-terminal LRR and its neighboring sequences [43, 150, 155, 156]. Five of the six result in exon skipping of one of the LRRs. F962 that is located at position 6 in the highly conserved segment is likely buried in the LRR arc. F962S may affect the hydrophobic core. The variable segment of the last LRR appears to function as a C-cap. The loss of Ile at residue 1027 may influence the C-cap structure. Three mutations lead to a loss of 28 amino acids at the protein level, including amino acids 964–991, 1051–1078 and 1079–1106. Interestingly, the length of the deletions corresponds to one LRR motif. One mutation, 940T-963Adel, is located in the putative N-cap and the highly conserved segment in LRR1. These four mutations induce a drastic structural change of the LRR arcs.

Nod2 and Crohn's disease

Nod2/CARD15 is a member of the CED4/APAF1 family of apoptosis regulators [45, 46] and activates nuclear factor NF-κB [212]. Nod2 is 1040 residues long and contains two CARDs, NACHT and LRRs. The LRRs have 755–1040 residues and contain 11 repeats (fig. 3P) [45, 46]. Ten of the 11 LRRs are 28 residues long and belong to RI-like class. Also, Nod2 has an LRRNT.

Mutations in Nod2, which render the molecule insensitive to muramyl dipeptide (MDP) and unable to induce NF-κB activation when stimulated, are associated with susceptibility to Crohn's disease, ulcerative colitis and Blau syndrome (reviewed in [213]). Three mutations, R702W, G908W and the frameshift mutation 1007fs (Leu1007fsinsC), are significantly associated with Crohn's disease, and other mutations cosegregate with disease in up to 30–50% of patients, depending on the population studied (fig. 3P) [45, 46, 157, 158]. The Nod2 mutations, associated with Blau syndrome, occur in only the NACHT domain [214]. In the LRRNT and LRRs, three mutations–R703W, A755V and A885V–are associated with ulcerative colitis, in addition to Crohn's disease.

Albrecht et al. [215] predicted the structure of the LRR domain based on the known structure of ribonuclease inhibitor. The complex of the NACHT and LRR domains was also modeled. G908R is located near the predicted interaction interface of the two domains [215]. This mutation is close to the residues D225 and N226 of RanGAP, which interact with K130 of Ran [215]. Therefore, they [215] proposed that G908R can affect downstream signaling from the peptidoglycan-sensing LRR units to the CARD domain through the NACHT domain.

The Leu1007fsinsC mutation results in premature stopping with a protein 1007 instead of 1040 amino acids. The variable segment of the last LRR appears to function as a C-cap. This mutation results in a drastic structural change with a truncated LRR domain of Nod2 [215]. The mutations, R702W, R703C and A725G, near the LRRs may influence the N-cap structure.

N853S is located at position 9 in the highly conserved segment. The corresponding mutations are observed in other LRR proteins, as noted. M863 is likely buried in the LRR arc. Thus, M863V may influence the hydrophobic core in the LRR arc. As noted in M239V observed in GPIbα, there is a difference in flexibility between the side chains of Met and Val. This may have an effect on the LRR structure in V793M and M863V. Seven mutations–R684W, R702C, E778K, E843K, G908R, A980D

LRR class		Highly conserved segment											Variable segment																
	Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
"Typical"	Cons. seq.	**L**	**x**	**x**	**L**	**x**	**L**	**x**	**x**	**N**	**x**	**L**	**x**	**x**	**L**	**p**	**x**	**x**	**o**	**F**	**x**	**x**	**L**	**x**	**x**				
	Frequency	6	1	0	5	3	0	6	0	6	1	0	1	0	4	2	0	2	2	5	1	0	0	0	0				
"RI-like"	Cons. seq.	**L**	**x**	**x**	**L**	**x**	**L**	**x**	**x**	**N**	**x**	**L**	**x**	**x**	**x**	**G**	**A**	**x**	**A**	**L**	**A**	**x**	**x**	**L**	**x**	**x**	**x**	**x**	**x**
	Frequency	0	1	0	0	1	1	0	1	1	0	0	0	1	1	1	0	0	1	1	1	0	0	2	1	0	0	1	0

Figure 4. Frequency of mutations at each position in the consensus sequences of Typical LRR and RI-like LRR. The variable segment of RI-like LRR is the consensus sequence of LRRs in Nod2. The lengths of the consensus sequences of typical and RI-like LRR are 24 and 28 residues, respectively. Each position is indicated by the numbering.

and G924D–may alter the electrostatic potential in Nod2, as seen in other LRR proteins. Six mutations involve Ala residues (A612T, A612V, A725G, A755V, A758V and A855T).

Concluding remarks

The LRR variants in proteins reported to date, associated with human diseases, are observed in two limited classes: typical and RI-like classes. Occurrence frequency of the missense mutations of LRRs and their neighboring domains in proteins are summarized in figure 4. Mutations at position 3 and 11 in the highly conserved segment have not been observed at all. Mutations in the N-cap and C-cap occur with high frequency. The missense mutations, deletions or insertions are roughly classified into five groups.

1) The first are the mutations in the N-cap and C-cap. These mutations involve cysteine residues and, in extracellular proteins or extracellular domain, preclude the formation of sulfide bridges or lead to a wrong paring of cysteines in LRRNT and LRRCT. These mutations likely disturb the integrity of the N-cap or Cap structure.
2) The second are mutations whose amino acids contribute to hydrophobic cores of the LRR arcs. These mutations may influence the hydrophobic cores throughout the polypeptide, thereby leading to changes in the structural parameters, R, φ and θ_i, of the LRR arcs. Their amino acids observed are located at positions 1, 4, 14 and 19 in the consensus sequence of the typical class, and at positions 6, 19 and 23 in that of RI-like class (fig. 4).
3) The third are the mutations whose amino acids lie on the concave or convex surface. It is likely that structural changes due to these mutations are very minor. However, the mutations alter the electrostatic potential of LRRs and/or the hydrogen bond pattern of their side chains in interactions with ligands. Their amino acids are located at positions 5 and 17 in the typical LRR, and at position 5 in the RI-like LRR (fig. 4).
4) The fourth are the mutations that are located at the loops that connect the β-strand on the concave part and the helical structure on the convex part. The mutations may be subdivided in three cases. First, the mutations occur at position 9 in the highly conserved segments, which is usually occupied by Asn or Cys. This mutation may influence the loop structures through hydrogen bond patterns (fig. 4). Second, the mutations occur at position 7 in the highly conserved segment, which is located at the edge of the loop (fig. 4). The structural effect of this mutation is not clear; although there is a possibility of local rearrangements. The remainders are the mutations that may alter the electrostatic potential of the LRR arcs.
5) The fifth are the deletions whose lengths correspond to one LRR motif or larger than one LRR, the insertions of 3–8 amino acid residues or the nonsense mutations that result in truncated proteins. These mutations induce a drastic structural change of the LRR arcs.

Finally, the above mutations likely induce changes in affinity to ligands or in interactions with other domain within individual proteins and sometimes cause loss of function. We anticipate that these insights and results will be useful for drug design against the human diseases.

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