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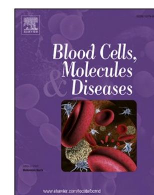

Hematologically important mutations: Leukocyte adhesion deficiency (second update)

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ABSTRACT

Leukocyte adhesion deficiency (LAD) is an immunodeficiency caused by defects in the adhesion of leukocytes (especially neutrophils) to the blood vessel wall. As a result, patients with LAD suffer from severe bacterial infections and impaired wound healing, accompanied by neutrophilia. In LAD-I, characterized directly after birth by delayed separation of the umbilical cord, mutations are found in *ITGB2*, the gene that encodes the β subunit (CD18) of the β_2 integrins. In the rare LAD-II disease, the fucosylation of selectin ligands is disturbed, caused by mutations in *SLC35C1*, the gene that encodes a GDP-fucose transporter of the Golgi system. LAD-II patients lack the H and Lewis Le^a and Le^b blood group antigens. Finally, in LAD-III, the conformational activation of the hematopoietically expressed β integrins is disturbed, leading to leukocyte and platelet dysfunction. This last syndrome is caused by mutations in *FERMT3*, encoding the kindlin-3 protein in all blood cells, involved in the regulation of β integrin conformation. This article contains an update of the mutations that we consider to be relevant for the various forms of LAD.

1. Introduction

Leukocyte adhesion deficiency (LAD) is an autosomal recessive disorder caused by decreased expression or functioning of CD18, the β_2 subunit of the leukocyte β_2 integrins [1]. This deficiency leads to severe impairment of leukocyte adhesion to the vascular wall and of leukocyte migration to sites of infection and inflammation. The patients suffer from recurrent, life-threatening bacterial and fungal infections and from

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Table 1
Mutations in the LAD-I gene *ITGB2* (cDNA numbering based on NM_000211.3).

Variant	Effect on protein	Amino-acid or mRNA change	LAD-I type	Families (alleles)	Reference	
Not determined	Deletion gene	No protein	LAD-I^0	1(1)	[7]	
Not determined	Deletion gene	No protein	LAD-I^0	1(1)	[7]	
Not determined	Deletion gene	No protein	LAD-I$^?$	1(1)	[7]	
Not determined	Deletion gene	No protein	LAD-I	1(1)	[36,37]	*
c.-3-767_58 + 51del[d]	Deletion	Deletion exon 2, including start codon	LAD-I^0	1(2)	[7]	
c.(−4 + 1–3-1) (993 + 1994–1)del	Deletion	Deletion exon 2_8, including start codon	LAD-I^0	1(1)	[36]	*
c.1A > T	Deletion	Startcodon lost	LAD-I^0	1(2)	[38]	*
c.2 T > A	Deletion	Start codon lost	LAD-I$^-$	1(1)	[7]	
c.41_58 + 2dup	Deletion (splice site)	Deletion exon 2? including start codon?	LAD-I$^-$	1(2)	[39]	*
c.49del	Frame shift	p.(Leu17Serfs*33)	LAD-I^0	1(2)	[7]	
c.59-10C > A[a]	Frame shift (splice site)	Ins 43 nts from intron 2 r.59-43_59-1ins43;59-10C > A p.(Cys19_Val20ins11fs *12)	LAD-I^0	1(1)	[7]	
c.59-1G > A	Frame shift (splice site)	Deletion exon 3? p.(Val20Glufs*9)?	LAD-I^0	3(4)	[40,41] Unpubl.	*
c.66_67del	Frame shift	p.(Gln23Glyfs*35)	LAD-I^0	1(1)	[7]	
c.77dup	Frame shift	p.(Lys27Glufs*32)	LAD-I^0	1(1)	[7]	
c.79A > T	Nonsense	p.(Lys27*)	LAD-I^0	3(4)	[7,42]	
c.82_95del	Frame shift	p.(Phe28Leufs*26)	LAD-I^0	1(1)	[43]	*
c.106 T > A	Missense	p.(Cys36Ser)	LAD-I^0	2(4)	[7,44]	
c.108_112del	Nonsense	p.(Cys36*)	LAD-I$^?$	1(2)	[45]	*
c.119_128del	Frame shift	p.(Gly40Alafs*7)	LAD-I^0	8(19)[b]	[742,46,]. Unpubl.	
c.120del	Frame shift	p.(Gly42Alafs*7)	LAD-I^0	1(1)	[7]	
c.130A > C	Missense	p.(Thr44Pro)	LAD-I^0	2(2)	[7,47]	
c.134G > A	Nonsense	p.(Trp45*)	LAD-I$^?$	2(4)	[40,48]	*
c.148-1G > A	Frame shift (splice site)	Deletion exon 4? p. (Asn50Alafs*8)?	LAD-I^0	1(2)[b]	Unpubl.	*
Not identified	Frame shift (splice site)?	r.148_328del p. (Asn50Alafs*8)	LAD-I^0	1(2)	[7]	
c.184 T > C	Missense	p.(Cys62Arg)	LAD-I$^?$	1(2)	[7]	
c.186C > A	Nonsense	p.(Cys62*)	LAD-I$^?$	5(12)	[7,49] Unpubl.	
c.199C > T	Nonsense	p.(Gln67*)	LAD-I^0	2(3)	[7]	
c.215del	Frame shift	p.(Gly72Alafs*32)	LAD-I^0	1(2)	[44]	*
c.268del	Frame shift	p.(Asp90Thrfs*13)	LAD-I$^-$	2(4)	[7,42]	
c.305_306del	Frame shift	p.(Lys102Serfs*39)	LAD-I^0	4(12)	[50]	*
c.314 T > C	Missense	p.(Leu105Pro)	LAD-I$^-$	1(2)[b]	[7]	
c.322C > T	Nonsense	p.(Arg108*)	LAD-I^0	8(15)	[36,38,44,51] Unpubl.	*
c.328 + 1G > A[a]	Frame shift (splice site)	Deletion exon 4 p.(Asn50Alafs*8)	LAD-I^0	1(1)	[7]	
c.329-37_461del[a]	Deletion	Deletion exon 5 p.(Gln111_Phe168del)	LAD-I^0	1(2)	[7]	
c.329-6C > A[a]	Deletion (splice site)	Deletion exon 5? p. (Gln111_Gly167del)?	LAD-I^0	2(4)	[7,52]	
c.329-2A > G[a]	Deletion (splice site)	Deletion exon 5? p.(Gln111_Gly167del)?	LAD-I^0	1(2)	[44]	*
c.382G > A	Missense	p.(Asp128Asn)	LAD-I$^{0/-}$	5(9)	[7 50,53,54]	
c.382G > T	Missense	p.(Asp128Tyr)	LAD-I$^{0/-}$	15(37)	[7,44,49,50-52,55,] Unpubl.	
c.388 T > C	Missense	p.(Tyr130His)	LAD-I^0	1(6)	[56]	*
c.389A > G	Missense	p.(Tyr130Cys)	LAD-I$^?$	1(1)	Unpubl.	*
c.392A > C[c]	Missense	p.(Tyr131Ser)	LAD-I^0	1(2)	[7]	
c.393 T > A	Nonsense	p.(Tyr131*)	LAD-I^0	1(2)	[44]	*
c.400G > A	Missense	p.(Asp134Asn)	LAD-I$^?$	1(1)	[7]	
c.400G > T	Missense	p.(Asp134Tyr)	LAD-I$^+$	1(2)	[57]	*
c.412 T > C	Missense	p.(Ser138Pro)	LAD-I$^+$	1(1)	[7]	
c.446 T > C	Missense	p.(Leu149Pro)	LAD-I$^-$	2(2)	[7]	

(*continued on next page*)

Table 1 (*continued*)

Variant	Effect on protein	Amino-acid or mRNA change	LAD-I type	Families (alleles)	Reference	
c.449G > A	Missense	p.(Gly150Asp)	LAD-I^{+}	1(1)	[7]	
c.474dup	Frame shift	p.(Glu159Argfs*27)	LAD-I^{0}	1(2)	[58]	*
c.499 + 1G > T[a]	Deletion (splice site)	Deletion exon 5? p.(Gln111_Gly167del)?	LAD-I^{0}	1(2)	[44]	*
c.499 + 1G > A[a]	Deletion (splice site)	Deletion exon 5? p.(Gln111_Gly167del)?	LAD-I^{0}	1(2)	[44]	*
c.500-12 T > G[a]	Frame shift (splice site)	Deletion part of exon 6 p.(Gly167Valfs*47)	LAD-I^{0}	1(2)	[7]	
c.505G > A	Missense	p.(Gly169Arg)	LAD-I^{0}	7(12)	[7,44,51,59,60]	
c.520A > G	Missense	p.(Lys174Glu)	LAD-I^{0}	1(1)	[7]	
c.532C > T	Missense	p.(Pro178Ser)	LAD-I^{-}	3(11)	[61] Unpubl.	*
c.533C > T	Missense	p.(Pro178Leu)	LAD-I^{0}	30(58) [b]	[7,36,38,41,43,44,50,51,56,62] Unpubl.	
c.557dup	Frame shift	p.(Leu187Alafs*78)	LAD-I^{0}	1(2)	[44]	*
c.562C > T	Nonsense	p.(Arg188*)	LAD-I^{0}	19(53)	[7,38,44,50,51,62,63] Unpubl.	
c.576dup	Frame shift	p.(Asn193Glnfs*72)	LAD-I^{0}	1(1)	[52]	*
c.602del	Frame shift	p.(Pro201Argfs*8)	LAD-I^{0}	1(1)	[7]	
c.614_615insA	Frame shift	p.(His206Alafs*59)	LAD-I^{0}	1(1)	[7]	
c.616C > T	Missense	p.(His206Tyr)	LAD-I^{0}	1(2)	[44]	*
c.658G > T	Nonsense	p.(Glu220*)	LAD-I^{0}	7(16)	[44,51]	*
c.691G > C	Missense	p.(Asp231His)	LAD-I$^{+/-}$	3(4)	[7,58]	
c.706G > T	Missense	p.(Gly236Trp)	LAD-I$^{?}$	1(2)	[63]	*
c.706G > A	Missense	p.(Gly236Arg)	LAD-I^{0}	2(3)	[52]	*
c.710 T > G	Missense	p.(Leu237Arg)	LAD-I^{0}	1(2)	[44]	
c.712G > A	Missense	p.(Asp238Asn)	LAD-I$^{?}$	1(1)	[7]	
c.715G > A	Missense	p.(Ala239Thr)	LAD-I^{0}	10(19) [b]	[7,44,52–54] Unpubl.	
c.725A > G	Missense	p.(Gln242Arg)	LAD-I^{0}	1(2)	[44]	
c.741 + 1del[a]	Deletion (splice site)	Deletion exon 6? p.(Glu248_Phe299del)?	LAD-I^{-}	1(1)	[36]	*
c.742-14C > A[a,c,d]	Deletion (splice site)	p.(Pro247_Glu248 insProSerSerGln)	LAD-I^{0}	2(2)	[7]	
c.742-1G > A[a]	Deletion (splice site)	Deletion exon 7? p.(Glu248_Phe299del)?	LAD-I^{0}	2(5)	[44]	*
c.(741 + 1742–1) (897 + 1898–1)del	Deletion	p.(Glu248_Phe299del)	LAD-I$^{?}$	1(2)	Unpubl.	*
c.751G > A	Missense	p.(Gly251Ser)	LAD-I^{0}	5(5)	[44]	*
c.754 T > C	Missense	p.(Trp252Arg)	LAD-I^{0}	2(4)	[7,55]	
c.755G > A	Nonsense	p.(Trp252*)	LAD-I^{0}	1(1)	[7]	
c.756G > C	Missense	p.(Trp252Cys)	LAD-I^{0}	2(3)	[44]	*
c.758G > A[f]	Missense	p.(Arg253His)	LAD-I^{0}	1(2)	[44]	*
c.769C > T	Missense	p.(Arg257Trp)	LAD-I$^{0/-}$	4(6)	[7,36,37,46] Unpubl.	
c.779_786dup	Insertion	p.(Thr263Cysfs*20)	LAD-I^{0}	1(2)	[50]	*
c.809C > T	Missense	p.(Ala270Val)	LAD-I$^{0/-/+}$	7(9)	[7,42,44,51] Unpubl.	
c.817G > A	Missense	p.(Gly273Arg)	LAD-I^{0}	21(35) [b]	[7,36,37,44,49–51,64,65]	
c.821dup	Frame shift	p.(Leu275Alafs*39)	LAD-I^{0}	3(6)	[40,44]	*
c.841_849del	Deletion	p.(Pro281_Asp283del)	LAD-I^{0}	1(1)	[36,37]	*
c.843del	Frame shift	p.(Asn282Thrfs*41)	LAD-I^{0}	2(3)	[7,52,54]	
c.844_846del	Deletion	p.(Asn282del)	LAD-I^{0}	1(2)	[66]	*
c.846C > A	Missense	p.(Asn282Lys)	LAD-I^{+}	1(2) [b]	[7]	
c.850G > A[c]	Missense	p.(Gly284Ser)	LAD-I$^{0/+}$	23(36)	[7,36,37,40,44,46,51] Unpubl.	
c.857G > T	Missense	p.(Cys286Phe)	LAD-I^{0}	1(2)	[48]	*
c.897 + 1G > A[a]	Frame shift (splice site)	Extension exon 7 with 64 or 298 nts from intron 7, or with whole intron 7, fs*26 or fs*44	LAD-I^{0}	21(43) [b]	[7,36,38,44,49,51,52,54,67] Unpubl.	
c.897 + 1G > C[a]	Splice site	Unknown	LAD-I^{0}	2(2)	[44,51]	*
c.897 + 1G > T[a]	Splice site	Unknown	LAD-I^{0}	1(2)	[52]	*
c.899A > T	Missense	p.(Asp300Val)	LAD-I^{0}	1(2)	[7]	
c.905C > T	Missense	p.(Pro302Leu)	LAD-I^{0}	1(1)	[7]	
c.920 T > G	Missense	p.(Leu307Arg)	LAD-I^{0}	1(2) [b]	Unpubl.	*
c.943_946dup[d]	Frame shift	p.(Ile316Lysfs*11)	LAD-I^{0}	3(6) [b]	[44] Unpubl.	*
c.953C > A	Missense	p.(Pro318His)	LAD-I^{-}	1(2)	[44]	*
c.954del	Frame shift	p.(Ile319Serfs*4)	LAD-I^{0}	1(1)	[68,69]	*
c.962C > A	Missense	p.(Ala321Glu)	LAD-I^{0}	2(4)	[44,51]	*
c.979_981del[d]	Deletion	p.(Val327del)	LAD-I^{0}	1(2)	[44]	*

(*continued on next page*)

Table 1 (*continued*)

Variant	Effect on protein	Amino-acid or mRNA change	LAD-I type	Families (alleles)	Reference	
c.(993 + 1994–1) (1083 + 11,084–1)del	Deletion	Deletion exon 9 p.(Lys332_Lys362del)	LAD-I^{0}	1(2)	[70]	*
c.995_1004del	Frame shift	p.(Lys332Argfs*44)	LAD-I$^{?}$	1(1)	[7]	
c.1021G > C	Missense	p.(Ala341Pro)	LAD-I$^{0/-}$	1(1)	[7]	
c.1030G > T	Nonsense	p.(Glu344*)	LAD-I^{0}	1(2)	[52]	*
c.1034 T > C	Missense	p.(Leu345Pro)	LAD-I^{0}	1(2)	[71]	*
c.1037_1044delinsT	Frame shift	p.(Ser346Phefs*31)	LAD-I^{0}	1(2)	[72]	*
c.1052A > G[c]	Missense	p.(Asn351Ser)	Active LFA-I	1(1)	[7]	
c.1057_1059delinsTCCTCTAATTAATGT	Frame shift	p.(Val353del insSerSerAsn*)	LAD-I^{0}	1(2)	[51]	*
c.1057_1059delinsTCCTCTCATTAAGCAATGTGTCCTCTAATTAATGT	Frame shift	p.(Val353del insSerSerHis*)	LAD-I^{0}	3(5)	[7,51]	
c.1057_1062delinsTCCTCTAATTAATGTCAT[d]	Frame shift	p.(Val353Serfs*4)	LAD-I^{0}	1(4)	[44]	*
c.1083 + 3G > C[a]	Deletion (splice site)	Deletion exon 9 p.(Lys332_Asn361del)	LAD-I^{0}	2(10) [b]	[7]	
c.1083 + 4A > G[a]	Deletion (splice site)?	Deletion exon 9? p.(Lys332_Asn361del)?	LAD-I^{0}	1(2)	[44]	*
c.1084A > G[a]	Deletion (splice site)?	Deletion exon 9? p.(Lys332_Asn361del)?	LAD-I^{0}	1(1)	[7]	
c.1099del	Frame shift	p.(Val367Serfs*12)	LAD-I^{+}	2(4)	[46]	*
c.1143del	Frame shift	p.(Tyr382Thrfs*)	LAD-I^{-}	3(6) [b]	[7,52]	
c.1224 + 4A > G [a]	Deletion (splice site)?	Deletion exon 10? p.(Lys362_Pro408del)?	LAD-I^{+}	9(20)	[44,51,73]	*
c.1225_1272del[d]	Deletion/ splice site	p.(Ile409_Gln424del)	LAD-I^{0}	1(2)	Kambli20 44	*
c.(1224 + 11,225–1) (1412 + 11,225–1)del	Deletion/ splice site	Deletion exon 11 p.(Ile409Valfs*2)	LAD-I$^{?}$	1(2) [b]	[7]	
c.1256_1257del[d]	Frame shift	p.(Glu419Valfs*27)	LAD-I^{-}	1(2)	[7]	
c.1264C > T	Nonsense	p.(Gln422*)	LAD-I^{0}	2(4)	[44,51]	*
c.1283 T > G	Missense	p.(Ile428Ser)	LAD-I^{0}	1(1)	[44]	*
c.1336G > T	Nonsense	p.(Glu446*)	LAD-I^{0}	1(2)	[59]	*
c.1388_1390del insCA	Frame shift	p.(Gly463Alafs*66)	LAD-I$^{?}$	1(2)	[7]	
c.1401C > A	Nonsense	p.(Cys467*)	LAD-I^{0}	1(2)	[62]	*
c.1413-416_*415{0}	Deletion	Deletion exons 12 + 13 p.([Arg471Ser, Cys472_Ile626del])	LAD-I^{0}	1(2)	[7]	
c.1413–149_2080 + 839 delinsAAAA	Frame shift	Deletion exon 12_14 p.(Cys472Valfs*43)	LAD-I^{0}	3(5) [b]	[7,50] Unpubl.	
c.1413-396_?del27703	Deletion	Deletion exon 12_end p.(Arg471_Ser769del)	LAD-I^{0}	1(1)	[7]	
c.1421del	Frame shift	p.(Thr474Metfs*55)	LAD-I$^{?}$	1(1)	[7]	
c.1472_1475del	Frame shift	p.(Gln491Argfs*37)	LAD-I^{0}	1(2)	[44]	*
c.1498del	Frame shift	p.(Asp500Thrfs*29)	LAD-I^{0}	5(7) [b]	[7]	
c.1516del	Frame shift	p.(Cys506Alafs*23)	LAD-I^{0}	1(2)	[44]	*
c.1537_1538del	Frame shift	p.(Val513Leufs*24)	LAD-I^{0}	1(2)	[74]	*
c.1590C > G	Nonsense	p.(Tyr530*)	LAD-I^{0}	2(4) [b]	[7,44]	
c.1602C > A	Nonsense	p.(Cys534*)	LAD-I^{0}	4(6) [b]	[7]	
c.1621 T > C	Missense	p.(Cys541Arg)	LAD-I^{0}	1(2)	[44]	*
c.1622delGins ACAGCGCAGTTGTAGCGCAGACC	Frame shift	p.(Cys541Tyrfs*9)	LAD-I^{0}	1(2)	[7]	
Not idntified	Deletion/ Splice site?	r.1622_1657del[a] p.(Cys541_Gly553del insTrp)	LAD-I^{-}	1(1)	[7]	
c.1627C > T	Missense	p.(Arg543Cys)	LAD-I$^{?}$	1(1)	Unpubl.	*
c.1632C > G	Nonsense	p.(Tyr544*)	LAD-I^{0}	5(8)	[7,38,44,51]	
c.1645 T > C	Missense	p.(Cys549Arg)	LAD-I^{0}	1(2)	[75]	*
c.1657 + 1G > T[a]	Frame shift (splice site)	Deletion exon 13? p.(Gly553Alafs*6)	LAD-I$^{?}$	1(2) [b]	[76]	*
c.1658-2A > G[a]	Frame shift (splice site)	Deletion exon 13? p.(Gly553Alafs*6)	LAD-I^{+}	2(3)	[7,44]	
Not identified	Frame shift (splice site)?	r.1658_1877del Deletion exon 13 p.(Gly553Alafs*6)	LAD-I^{0}	1(1)	[7]	
c.1670G > C	Missense	p.(Cys557Ser)	LAD-I^{0}	3(5) [b]	[7] Unpubl.	
c.1685G > A[d]	Missense	p.(Cys562Tyr)	LAD-I^{0}	2(4)	[54,55,58]	*
c.1697del	Frame shift	p.(Pro566Argfs*18)	LAD-I$^{?}$	1(1)	Unpubl.	*
c.1745G > A[g]	Missense	p.(Cys582Tyr)	LAD-I^{0}	1(1)	[44]	*

(continued on next page)

Table 1 (*continued*)

Variant	Effect on protein	Amino-acid or mRNA change	LAD-I type	Families (alleles)	Reference	
c.1768 T > C	Missense	p.(Cys590Arg)	Active LFA-1, no CR3	4(7)	[7,44,54,77]	
c.1777C > T	Missense	p.(Arg593Cys)	Active LFA-1, no CR3	8(16) [b]	[7,44,50,51,54]	
c.1788C > A	Nonsense	p.(Cys596*)	LAD-I^0	2(2)	[36,37,65]	*
c.1794dup	Frame shift	p.(Asn599Glnfs*93)	LAD-I^0	1(1)	[36,37]	*
c.1798del	Frame shift	p.(Val600Tyrfs*33)	LAD-I^0	1(2)	[44]	*
c.1802G > T	Missense	p.(Cys601Phe)	LAD-I^0	1(1)	[68,69]	*
c.1821C > A	Nonsense	p.(Tyr607*)	LAD-I$^?$	3(6)	[54,58]	*
c.1822C > T	Nonsense	p.(Gln608*)	LAD-I$^?$	2(4)	[54]	*
c.1828C > A	Missense	p.(Pro610Thr)	LAD-I^0	1(1)	[44]	*
c.1834 T > C	Missense	p.(Cys612Arg)	LAD-I$^-$	1(2)	[7]	
c.1835G > T	Missense	p.(Cys612Phe)	LAD-I$^+$	1(2)	[78]	*
c.1840G > T	Nonsense	p.(Glu614*)	LAD-I^0	2(4)	[44]	*
c.1866 T > A	Nonsense	p.(Cys622*)	LAD-I^0	1(2)	[44]	*
c.1877 + 1G > A[a]	Frame shift (splice site)	Deletion exon 13? p.(Gly553Alafs*7)?	LAD-I^0	1(2)	Unpubl.	*
c.1877 + 2 T > C[a]	Frame shift (splice site)	Deletion exon 13? p.(Gly553Alafs*7)?	LAD-I^0	2(4)	[52,53]	*
c.1878-2A > C[a]	Frame shift (splice site)	Deletion exon 14? p.(Ser627Valfs*45)	LAD-I^0	3(6)	[44,51]	*
c.1878-1G > A[a]	Frame shift (splice site)	Deletion exon 14? p.(Ser627Valfs*45)?	LAD-I^0	1(2)	[44]	*
c.1888G > T	Nonsense	p.(Glu630*)	LAD-I^0	3(6)	[44,51]	
c.1907del	Frame shift	p.(Lys636Argfs*22)	LAD-I^0	3(8)	[7,52]	
c.1920del	Frame shift	p.(Lys641Argfs*17)	LAD-I^0	1(1)	[7]	
c.2055C > A	Nonsense	p.(Tyr685*)	LAD-I^0	1(1)	[44]	*
c.2070del[c]	Frame shift	p.(Asp690Glufs*25)	LAD-I^0	7(7)	[7] Unpubl.	
c.2077C > T	Nonsense	p.(Arg693*)	LAD-I^0	7(14) [b]	[7,44] Unpubl.	
c.2080 + 1del[a]	Frame shift (splice site)?	Deletion exon 14? p.(Ser627Valfs*44)?	LAD-I^0	1(1)	[7,47]	
c.(2080 + 1_2081–1)_*415{0}	Deletion	Deletion exon 15_16	LAD-I^0	1(4)	[56]	*
c.2146G > C	Missense	p.(Gly716Arg)	LAD-I^0	1(2)	[53]	*
c.2147G > C[e]	Missense	p.(Gly716Ala)	LAD-I^0	2(4)	[7,52]	
c.2147G > T	Missense	p.(Gly716Val)	LAD-I^0	1(1)	[44]	*
c.2200G > T	Nonsense	p.(Glu734*)	LAD-I$^-$	1(1)	[7]	
c.2248-2A > G[a]	Deletion (splice site)	p.(Asp750_Lys755del)	LAD-I$^{+/-}$	2(4)	[42,79]	*

Deletions	Number of different alleles		Total number of alleles	
	41 alleles	(23.2 %)	121 alleles	(14.1 %)
Insertions	9 alleles	(5.1 %)	28 alleles	(3.3 %)
Indels	7 alleles	(4.0 %)	22 alleles	(2.6 %)
Nonsense mutations	25 alleles	(14.1 %)	176 alleles	(20.5 %)
Splice site mutations	33 alleles	(18.6 %)	136 alleles	(15.8 %)
Missense mutations	62 alleles	(35.0 %)	376 alleles	(43.8 %)
	In total 177 different allelic mutations		In total 861 identified alleles in 442 patients from 397 families	

o/- indicates that the mutant CD18 molecule supports differentially the expression of the different CD11/CD18 integrins. Unpubl. indicates personal communication from one or more authors.

c.1225-4_1268del48 (p.(Ile409Valfs*2)) [44].

More information can be found in the "Global Variome shared LOVD" *ITGB2* gene variant database (www.LOVD.nl/ITGB2).

[a] Positions of introns in *ITGB2*: intron 1 c.-4_-3; intron 2 c.58_59; intron 3 c.147_148; intron 4 c.328_329; intron 5 c.499_500; intron 6 c.741_742; intron 7 c.897_898; intron 8 c.993_994; intron 9 c.1083_1084; intron 10 c.1224_1225; intron 11 c.1412_1413; intron 12 c.1657_1658; intron 13 c.1877_1878; intron 14 c.2080_2081; intron 15 c.2247_2248.

[b] One or more patients presumed to be homozygous for this mutation.

[c] And reverse mutations in a small subset of lymphocytes [80].

[d] Corrected after consultation of the authors.

[e] Not certain of clinical significance since transfection of this mutant into a CD18-deficient B cell line induced near normal expression. Moreover, transfection into HEK293 cells together with CD11a induced normal expression and constitutive binding to ICAM-1, and transfection together with CD11b induced expression and constitutive binding to denatured BSA [33]. Possibly, this hyperadhesive activity reduces the migratory function of the leukocytes, thus predisposing a patient with this mutation to severe bacterial and fungal infections, as has been reported for another patient by Simpson et al. [81].

[f] Possibly a polymorphism: found only once, on the same allele together with c.322C>T (p.Arg108*) [44].

[g] Possibly a polymorphism: found only once, on the same allele together with.

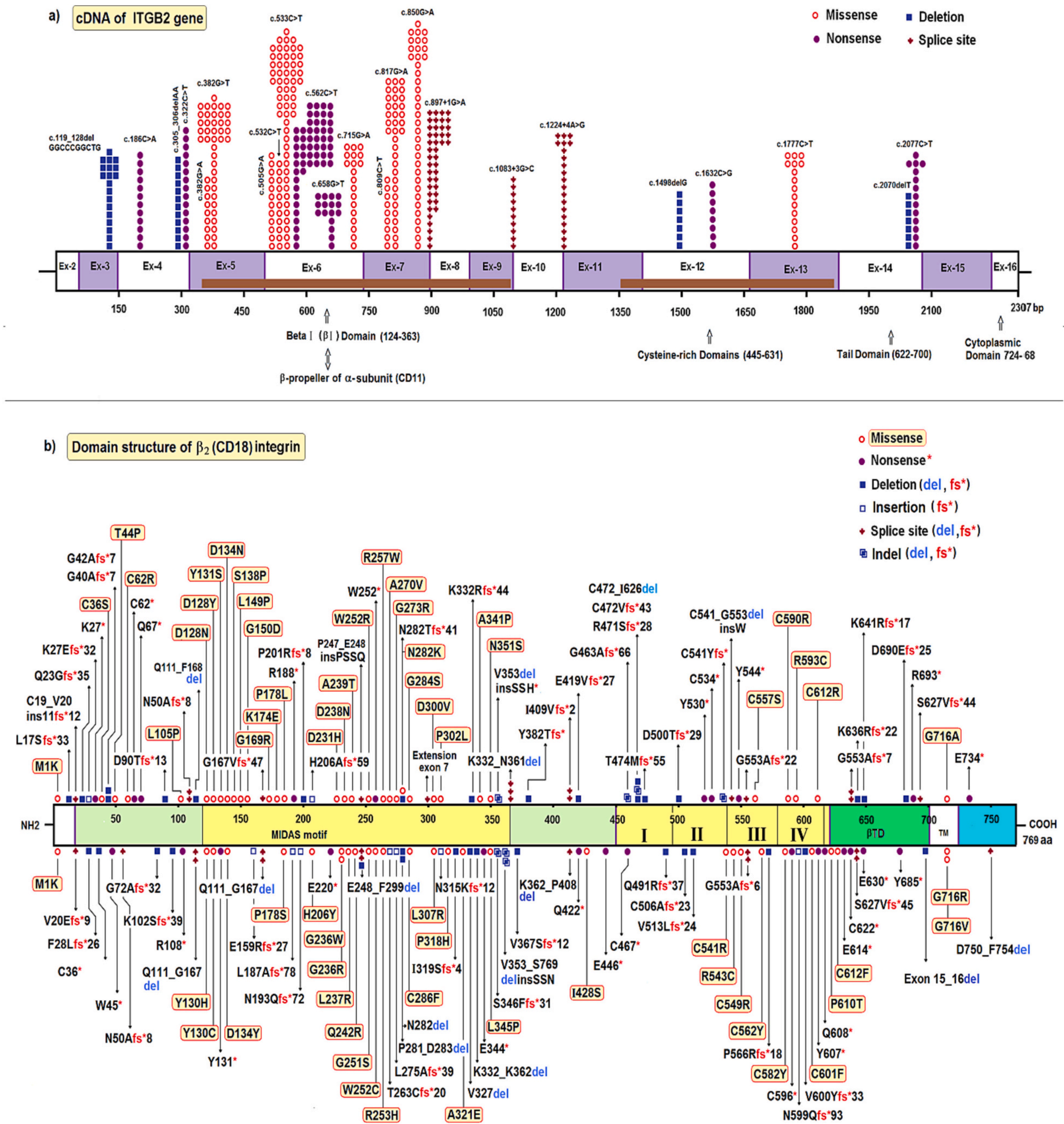

Fig. 1. Schematic overview of the mutations in *ITGB2* and the changes in the β_2 integrin protein.
a. The number of the 23 most frequently encountered mutated alleles, the type of mutation and their position along the exons of *ITGB2*, with active domains depicted in brown. Protein interaction sites are shown for some domains. Symbols, explained on the right, represent mutated alleles. Numbers refer to nucleotides in cDNA.
b. Domain structure of the β_2 integrin (CD18) and the location of each mutation, with active domains depicted in yellow, green and blue. Symbols, explained on the right, represent separate mutations. Numbers refer to amino acids in β_2 integrin.

Table 2
Polymorphisms in the LAD-I gene *ITGB2*.

Variant	Amino acid change	MAF (gnomAD)	Reference
c.-403C>T (promoter)	p.?	*** (Afr/Afr Am *)	[7]
c.-111T>C (5′ UTR)	p.?	0.2163	[7,82]
c.13C>T	p.(Arg5Cys)	***	[102]
c.24G>T	p.(Leu8=)	0.2098	[7]
c.28G>A	p.(Ala10Thr)	*** (South Asian *)	[102]
c.31C>T	p.(Leu11=)	*	[102]
c.117G>A	p.(Ser39=)	*	[82] [102]
c.147+16A>G	p.?	*	Unpubl.
c.162G>A	p.(Pro54=)	**	[7]
c.229G>A	p.(Asp77Asn)	** (Afr/Afr Am *)	[7]
c.328+15G>A	p.?	0.1540	[7]
c.329-6C>T	p.?	**(Afr/Afr Am *)	[102]
c.499+7C>T	p.?	*	[7]
c.500-29C>T	p.?	0.1706	[7]
c.500-11G>T	p.?	0.1593	[7]
c.587A>C[a]	p.(Lys196Thr)	N/A	Unpubl.
c.732C>T	p.(Ala244=)	***	[102]
c.742-13G>A	p.?	0.1241	[7]
c.807C>T	p.(Phe269=)	***	[102]
c.810G>A	p.(Ala270=)	**(0.01841)	[102]
c.819G>A	p.(Gly273=)	0.2427	[7,82] [102]
c.906A>G	p.(Pro302=)	*	[102]
c.994-47G>A	p.?	0.2291	[7]
c.1002C>T	p.(Thr334=)	** (Afr/Afr Am *)	[102]
c.1026G>C	p.(Val342=)	**(Afr/Afr Am *)	[102]
c.1101C>A	p.(Val367=)	0.2243	[7,82]
c.1172C>T	p.(Thr391Met)	***	[102]
c.1323T>C	p.(Val441=)	0.6871	[7]
c.1497G>A	p.(Lys499=)	***	[102]
c.1542C>T	p.(Cys514=)	**(East Asian and Afr/Afr Am *)	[102]
c.1635C>T	p.(Asn545=)	**	[102]
c.1756C>T	p.(Arg586Trp)	**	[7]
c.1888G>A	p.(Glu630Lys)	** (Eur Finnish *)	[102]
c.1893C>T	p.(Cys631=)	**	[102]
c.2058C>G	p.(Leu686=)	** (East Asian and European *)	[102]
c.*145C>A	p.?	0.1373	[102]

Variants described based on coding DNA reference sequence NM_000211.3 (see www.LOVD.nl/ITGB2). MAF, minor allele frequency; =, silent variation; gnomAD, genome aggregation database; [a] Originally published as an LAD-I¯ mutation [83]. Unpubl. indicates personal communication from one or more authors.
MAF scores: *** <0.001; ** <0.01; * <0.1.

impaired wound healing. Characteristic features are delayed separation of the umbilical cord and strong leukocytosis, especially neutrophilia, during periods of infection. Many LAD patients die at young age despite intensive antibiotic therapy. Hematopoietic cell transplantation is the treatment of choice. LAD is a rare immunodeficiency, but the exact incidence is not known.

The integrins are transmembrane receptors composed of α and β subunits that mediate cellular adhesive interactions throughout the body. All together 18 α and 8 β subunits have been identified, loosely organized into integrin families. The β_2 integrins form a family of four heterodimeric proteins, only expressed on leukocytes, with one of four α subunits coupled to a common β_2 subunit CD18: $\alpha_L\beta_2$ (LFA-1 or CD11a/CD18); $\alpha_M\beta_2$ (Mac-1 or CR3, CD11b/CD18); $\alpha_X\beta_2$ (p150,95 or CD11c/CD18) and $\alpha_D\beta_2$ (CR4 or CD11d/CD18), the latter only being expressed on macrophages. Decreased expression of the common β_2 subunit leads to a similar decrease in the expression of all four α subunits on the leukocyte surface. The four β_2 integrins act as adhesion proteins, mediating adhesion of leukocytes to other cells and to extracellular matrix proteins. The α subunits and the β_2 subunit are transmembrane proteins, intracellularly connected to the leukocyte cytoskeleton. Binding to extracellular ligands leads to a conformational change of the β_2 integrins, increased binding of intracellular target proteins and downstream signal transduction to cell spreading and altered gene expression, cell proliferation, differentiation and apoptosis ("outside-in" signaling). Leukocyte activation, e.g. as a result of chemokine binding to chemokine receptors, antigen binding to the T-cell receptor (TCR) or ligand binding to selectins, induces conformational changes in the extracellular regions of the β_2 integrins, leading to a higher affinity for their ligands ("inside-out" signaling) [2,3].

In this article the word "mutation" is used for a genetic variation that causes a substantial (>50 %) decrease in beta-2 integrin, GDP-fucose transporter 1 or kindling-3 protein expression, and thus results in LAD. Genetic variations that have less impact on protein expression and do not cause LAD are regarded as polymorphisms.

2. Classical LAD-I

In the most common form of LAD, called LAD-I (OMIM #116920), mutations are found in *ITGB2* (integrin beta-2), the gene located at 21q22.3 (OMIM *600065) that encodes the β_2 integrin protein. Usually, this leads to the absence or decreased expression of the β_2 integrins on the leukocyte surface, but sometimes a normal expression of nonfunctional β_2 integrins is found. As a result, LAD-I patients are unable to efficiently prevent outgrowth of bacterial and fungal infections: their neutrophils accumulate in the blood stream but fail to reach the sites of infections in the tissues. In addition, these patients also show increased incidence of periodontitis. This is due to tissue neutropenia-induced macrophage production of IL-23 as well as microbial induction of IL-23 and IL-17 in inflamed periodontitis lesions, and subsequent induction of G-CSF and chemoattractants which in vain attempts to attract neutrophils. Therefore, the IL-23 levels remain high and continue to induce IL-17 and related inflammation [4–6].

In a previous publication we listed 86 mutations found in *ITGB2* of LAD-I patients [7]. In the present publication 91 newly identified

Table 3
Mutations and polymorphisms in the LAD-II gene *SLC35C1* (cDNA numbering based on NM_018389.5).

Variant	Effect on protein	Amino-acid change	LAD type	Families (alleles)	Reference	
c.91G>T	Nonsense	p.(Gln31*)	LAD-II^{0}	1(2)	[14,84]	*
c.145T>A	Missense	p.(Trp49Arg)	LAD-II^{0}	1(4)	[85]	*
c.177_179del	Deletion	p.(Asn59del)	LAD-II^{0}	1(1)	[13]	*
c.247_249del	Deletion	p.(Val83del)	LAD-II^{0}	1(1)	[13]	*
c.267del	Frame shift	p.(Gly90Alafs*38)	LAD-II^{0}	1(2)	[86]	*
c.439C>T	Missense	p.(Arg147Cys)	LAD-II^{0}	1(2)	[7]	
c.503_505del	Deletion	p.(Phe168del)	LAD-II^{-}	4(6)	[9,14,15,84,87,88]	*
c.588del	Frame shift	p.(Trp196Cysfs*35)	LAD-II^{0}	1(2)	[7]	
c.703_705del	Deletion	p.(Asn235del)	LAD-II^{0}	1(2) [c]	Unpubl.	*
c.878C>T	Missense	p.(Pro293Leu)	LAD-II^{0}	1(1)	[9]	*
c.887A>G	Missense	p.(His296Arg)	LAD-II^{0}	1(2)	[89]	*
c.891T>G	Missense	p.(Asn297Lys)	LAD-II^{0}	1(1)	[15]	*
c.923C>G	Missense	p.(Thr308Arg)	LAD-II^{0}	2(4)	[7]	
c.942C>G	Nonsense	p.(Tyr314*)	LAD-II^{0}	1(2)	[9,87,88]	*
c.969G>A	Nonsense	p.(Trp323*)	LAD-II^{0}	1(2)	[7]	
c.1010A>G	Missense	p.(Tyr337Cys)	LAD-II^{0}	1(2)	[7]	
c.718A>G	Missense (SNP) [a]	p.(Ile240Val) [b]	MAF (gnomAD) *		[7] [102]	
c.1047G/A	Silent (SNP)	p.(Pro349=)	MAF (gnomAD) ** (Afr/Afr Am *)		[102]	

In total 19 patients from 16 families, with 16 different mutations.
SNP, single nucleotide polymorphism; =, silent variation; MAF, minor allele frequency; gnomAD, genome aggregation database.
Unpubl. indicates personal communication from one or more authors.
MAF scores: *** <0.001; ** <0.01; * <0.1.
More information can be found in the"Global Variome shared LOVD" SLC35C1 gene variant database (www.LOVD.nl/SLC35C1).
[a] May also be error in the GenBank accession number AF323970 [90].
[b] Corrected after consultation of the authors.
[c] Patient presumed to be homozygous for this mutation.

mutations have been added (Table 1, marked with * in the last column). Mutations that have not been previously published elsewhere are marked as "Unpubl.". Most of the single nucleotide variations are found in a ~240-residue domain that is highly conserved in all β integrin subunits and encoded by exons 5–9 of *ITGB2* (Fig. 1). This "βI domain", together with its αI counterpart, constitutes the major ligand-binding site of the β_2 integrins. Both I domains also contain a metal ion-dependent adhesion site (MIDAS motif) consisting of an Asp-X-Ser-X-Ser sequence.

Table 2 contains information on apparently benign polymorphisms that have been recognized in *ITGB2*.

Disease-causing variations in one of the four human β_2 integrin alpha chains have not been identified.

3. LAD-II

Two other, extremely rare forms of LAD also exist. Patients with LAD-II (OMIM #266265) have a defect in the fucosylation of various cell surface glycoproteins, some of which function as ligands for L-selectin [8,9]. As a result, the initial "rolling" of leukocytes over the endothelial vessel wall in areas of inflammation, which is mediated by reversible contact between L-selectins on the leukocytes and *E*- or P-selectins on the endothelial cells with their respective sialylated fucosyl ligands on the opposite cells, is disturbed. Both via intracellular signaling and by slowing down the leukocytes, this rolling allows integrins to bind their ligand on endothelial cells, which is needed for stable adhesion. Thus, in LAD-II, one mechanism of β_2-integrin activation is lacking, leading to decreased leukocyte adhesion to the vessel wall and decreased trans-endothelial migration into the tissues. However, the chemokine and TCR pathways of β_2-integrin activation are still operative, and the infectious episodes in LAD-II patients are therefore in general less severe than those seen in LAD-I patients. On the other hand, the fucosylation defect affects not only selectin ligands but also other essential glycoproteins, leading to severe mental and growth retardation.

The molecular defect in LAD-II has been identified as a deficiency in a GDP-fucose transport protein in the Golgi system [10,11]. This protein is encoded by *SLC35C1* (Solute carrier family 35 member C1) at 11p11.2 (OMIM *605881). Table 3 lists the mutations found in this gene in 16 families with LAD-II patients. Two of these mutations concern NM_018389.4:c.439C>T p.(Arg147) and c.923C>G p.(Thr308), both highly conserved amino acids in the family of nucleotide-sugar transporters group 2 and suggested to be involved in substrate recognition [12].

Supplementation of fucose led to a substantial clinical improvement and correction of hypofucosylation in the patient homozygous for the Arg147Cys mutation, whereas it was of no benefit to the patients homozygous for the Thr308Arg mutation [10,11,13]. Two brothers have been identified with a partial deficiency in N-glycan fucosylation [14]. These patients did have a short stature and mental retardation, but no frequent serious bacterial infections, no Bombay blood group and no neutrophilia. A global decrease but not absolute lack of fucosylation of N-glycans was noted. The H (Bombay) antigen and CD15s were present at lower expression, and decreased granulocyte rolling was observed on vascular *E*-selectin. The canonical leukocyte P- and E-selectin ligand PSGL-1 showed normal expression by Western blot but no expression of the CD15s determinant.

Subsequent reports have described four additional patients with this milder form of LAD-II, indicated in Table 3 as LAD-II^{-} [9,15]. All six patients share the presence of the NM_018389.4:c.503_505del p.(Phe168del) variant of the GDP fucose transporter, in combination with various other, strongly disabling variants [9]. Probably, the Phe168del variant constitutes a partial functional fucose transporter with enough residual activity to prevent severe bacterial or fungal infections and the Bombay blood phenotype, but ineffective in preventing growth and

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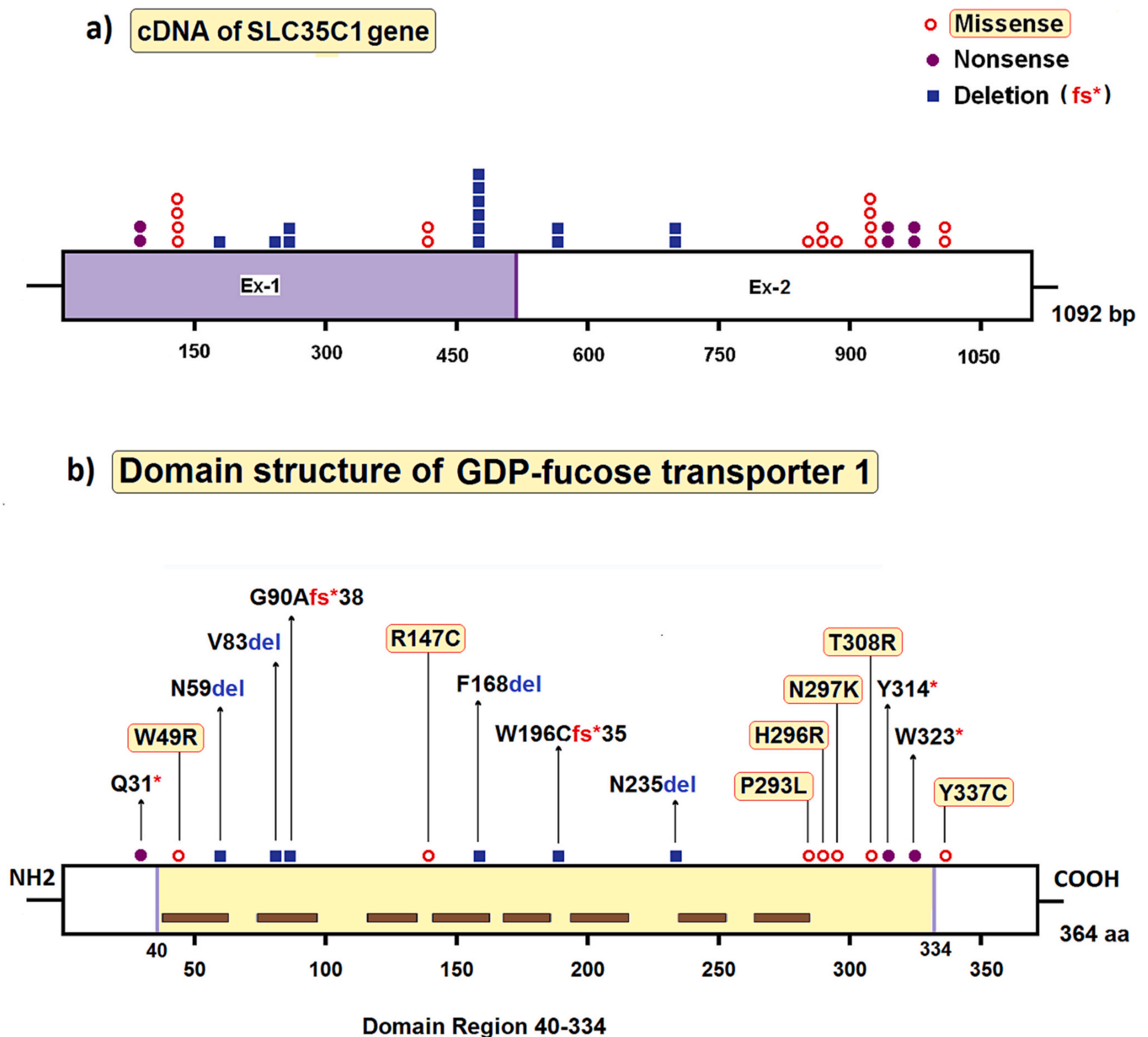

Fig. 2. Schematic overview of mutations in *SLC35C1* and the changes in the GDP-fucose transporter 1protein.
a. The number of mutated alleles, the type of mutation and their position along the exons of *SLC35C1*. Symbols, explained on the right, represent mutated alleles. Numbers refer to nucleotides in cDNA.
b. Domain structure of GDP-fucose transporter 1 and the location of each mutation, with active domains depicted in yellow 40–334, and trans membrane points depicted in brown. Symbols, explained on the right, represent separate mutations. Numbers refer to amino acids in GDP-fucose transporter 1.

developmental retardation [9,14,15]. Oral fucose supplementation had a slight, positive effect on speech and cognition, CD15 expression and core fucosylation of serum glycoproteins in the only mild variant LAD-II patient treated in this fashion [9]. Fig. 2 shows the mutations found in *SLC35C1* in 16 families with LAD-II patients. Published polymorphisms in *SLC35C1* are listed in Table 3.

LAD-III.

Finally, patients have been described with a defect in the “inside-out” signaling of leukocytes required for activation of β_2 integrins into structures that bind their ligands with high affinity [10]. These patients, in addition to infections, also present with a bleeding disorder, indicating that the signaling defect also affects the β_3 integrin fibrinogen receptor $\alpha_{IIb}\beta_3$ on blood platelets. In some patients osteopetrosis has been noted [16–20]; this has been attributed to overproduction of bone and cartilage by kindlin-3 negative mesenchymal stem cells and/or decreased bone resorption by mutated kindlin-3-containing osteoclasts [21].

The molecular defect of this variant form of LAD (LAD-III, previously known as LAD-I/variant, OMIM #612840) has been assigned to mutations in *FERMT3* (fermitin family homolog 3) at 11q13.1 (OMIM *607901), the gene encoding kindlin-3, a protein involved in inside-out signaling to all blood cell-expressed β integrins (β_1, β_2 and β_3) [22–25]. Kindlin-3 has been claimed to be expressed not only in hematopoietic cells, but also in endothelial cells [26]; however, this claim has not been confirmed, despite several attempts.

A discussion has raged in the literature about the importance of a genetic variation in the gene encoding CalDAG-GEF1 (a guanine nucleotide exchange factor for Rap1, involved in integrin activation) in some patients with LAD-III, in addition to mutations in *FERMT3* found in these patients [22,23,27]. However, since the functional defect in such patients can be corrected by reconstitution with kindlin-3 but not by reconstitution with CalDAG-GEF1 [25], this variation in CalDAG-GEF1

Table 4
Mutations in the LAD-III gene *FERMT3* (cDNA numbering based on NM_031471.6).

Variant	Effect on protein	Amino-acid or mRNA change	LAD type	Families (alleles)	Reference	
c.48G>A	Nonsense	p.(Trp16*)	LAD-III	2(6)	[7,40]	
c.126del	Frame shift	p.(Ile42Metfs*6)	LAD-III	2(4)	[40,48]	*
c.161-2A>C[a]	Frame shift (splice site)	p.(Asn54Argfs*142)	LAD-III	1(2)	[7]	
c.238_244dup	Frame shift	p.(Lys82Thrfs*67)	LAD-III	1(2)	[7]	
c.286C>T	Nonsense	p.(Gln96*)	LAD-III	1(2)	[91]	*
c.305T>C	Missense	p.(Leu102Pro)	LAD-III	1(2)	[44]	*
c.687G>A	Nonsense	p.(Trp229*)	LAD-III	4(11)	[7,46,92] Unpubl.	
c.687G>T	Missense	p.(Trp229Cys)	LAD-III	1(4)	[44]	*
c.756G>C	Missense	p.(Lys252Asn)	LAD-III	1(2)	Unpubl.	*
c.821A>G	Missense	p.(Gln274Arg)	LAD-III	1(2)	[44]	*
c.830G>A	Nonsense	p.(Trp277*)	LAD-III	1(2)	Unpubl.	*
c.873G>A	Missense	p.(Met291Ile)	LAD-III	1(1)	[93]	*
c.895-3T>G	Deletion (splice site)?	Deletion exon 8? p.(Tyr319_Leu343del)?	LAD-III	1(2)[c]	Unpubl.	*
c.921del	Frame shift	p.(Ser307Argfs*21)	LAD-III	1(2)	Unpubl.	*
c.922G>A	Missense	p.(Gly308Arg)	LAD-III	1(1)	[7]	
c.1069C>T	Nonsense	p.(Arg357*)	LAD-III	1(4)	[46]	*
c.1173del	Frame shift	p.(Asp393Thrfs*29)	LAD-III	2(4)	[94] Unpubl.	*
c.1275del[a]	Frame shift	p.(Glu426Argfs*3)	LAD-III	1(1)	[7]	
c.1312-1G>A	Deletion (splice site)	p.(Glu438_Gln439del) or deletion exon 12 p.(Glu438_Gln515del)	LADIII	1(2)	[95]	*
c.1331G>A	Nonsense	p.(Trp444*)	LAD-III	1(2)	[44]	*
c.1426C>T	Nonsense	p.(Gln476*)	LAD-III	1(4)	[96]	*
c.1525C>T	Nonsense	p.(Arg509*)	LAD-III	15(36)	[7,97] Unpubl.	
c.1543C>T	Nonsense	p.(Gln515*)	LAD-III	3(6)[c]	[98]	*
c.1585C>T[b]	Nonsense	p.(Gln529*)	LAD-III	1(2)	[20]	*
c.1671-2A>G[a]	Frame shift (splice site)	Deletion exon 14 p.(Phe558Trpfs*141)	LAD-III	1(2)	[7]	
c.1717C>T	Nonsense	p.(Arg573*)	LAD-III	3(7)	[7]	
c.1721T>C	Missense	p.(Leu574Pro)	LAD-III	1(2)	Unpubl.	*
c.1784A>C	Missense	p.(Gln595Pro)	LAD-III	1(2)	[99]	*
c.1788G>A	Nonsense	p.(Trp596*)	LAD-III	1(1)	[100]	*
c.1790del	Frame shift	p.(Asn597Metfs*173)[c]	LAD-III	1(2)	[101]	*
c.1989del	Frame shift	p.(*664Gluext*105) (Non-stop variant)	LAD-III	1(1)	[100]	*

In total 60 patients from 52 families, with 31 different mutations.
Unpubl. indicates personal communication from one or more authors.
More information can be found in the "Global Variome shared LOVD" FERMT3 gene variant database (www.LOVD.nl/FERMT3).
[a] Position of introns in *FERMT3*: intron 1 c.-15_-14; intron 2 c.160_161; intron 3 c.394_395; intron 4 c.514_515; intron 5 c.683_684; intron 6 c.786_787; intron 7 c.894_895; intron 8 c.1029_1030; intron 9 c.1079_1080; intron 10 c.1204_1205; intron 11 c.1311_1312; intron 12 c.1545_1546; intron 13 c.1670_1671; intron 14 c.1812_1813.
[b] Corrected after consultation of the authors.
[c] One or more patients presumed to be homozygous for this mutation.

is of no importance for the functional defect in LAD-III patients. Instead, patients with only a variation in the CalDAG-GEF1 gene *RASGRP2* present with a bleeding disorder caused by a reduced ability to activate Rap1 and to perform proper $\alpha_{IIb}\beta_3$ integrin inside-out signaling, but this functional deficiency is limited to platelets and megakaryocytes and does not affect leukocytes [28].

Table 4 and Fig. 3 list the mutations found in *FERMT3* in 52 families with LAD-III patients. A hotspot of NM_031471.5:c.1525C>T p.(Arg509*) mutations in *FERMT3* points to a founder effect, since these mutations are all found in Turkish families originating from Anatolia. Polymorphisms in *FERMT3* are listed in Table 5.

4. LAD-IV (cystic fibrosis)

In 2016 Sorio et al. described an adhesion defect specific for monocytes from patients with cystic fibrosis (CF) [29]. These monocytes showed a clear defect in adhesion to intercellular adhesion molecule-1 (ICAM-1, a ligand for LFA-1 and Mac-1), to fibrinogen (a ligand for Mac-1), and to vascular cell adhesion molecule-1 (VCAM-1, a ligand for $\alpha_4\beta_1$ integrins) upon stimulation of these cells by formyl-methionyl-leucyl-phenylalanine (fMLF), a chemoattractant and integrin activator. Lymphocytes and neutrophils from CF patients did not show this defect in adhesion. Chemotaxis by CF monocytes induced by fMLF was also disturbed. Drugs that correct the expression of the cystic fibrosis transmembrane conductance regulator (CFTR) protein on the surface of CF monocytes reconstituted monocyte adhesion, and a drug that inhibits the function of this chloride transport protein reduced adhesion of monocytes from healthy individuals. In mice, monocytes with a Phe805del mutation in *Cftr* did not accumulate in bronchial alveolar lavage fluid upon endotracheal installation of the murine chemoattractant protein-1 (MCP-1), in contrast to wild-type monocytes.

Integrin expression on the surface of CF patient monocytes was normal, suggesting that the defect concerns the activation of β_1 and β_4 integrins in the CF monocytes. Indeed, in these cells, the fMLF-triggered activation of Ras homolog gene family member A (RhoA) and of cell division control protein 42 (CDC42), two small rho GTPases involved in integrin inside-out activation [30] was found to be impaired. Thus, this defect, suggested to be called LAD-IV in an editorial [31], resembles LAD-III as an integrin activation defect. As far as we know, the suggestion to include this deficiency in the family of LADs has not been accepted. Mutations in *CFTR* leading to the CF clinical syndrome can be found in the HGMD database at www.hgmd.cf.ac.uk/ac/search.php.

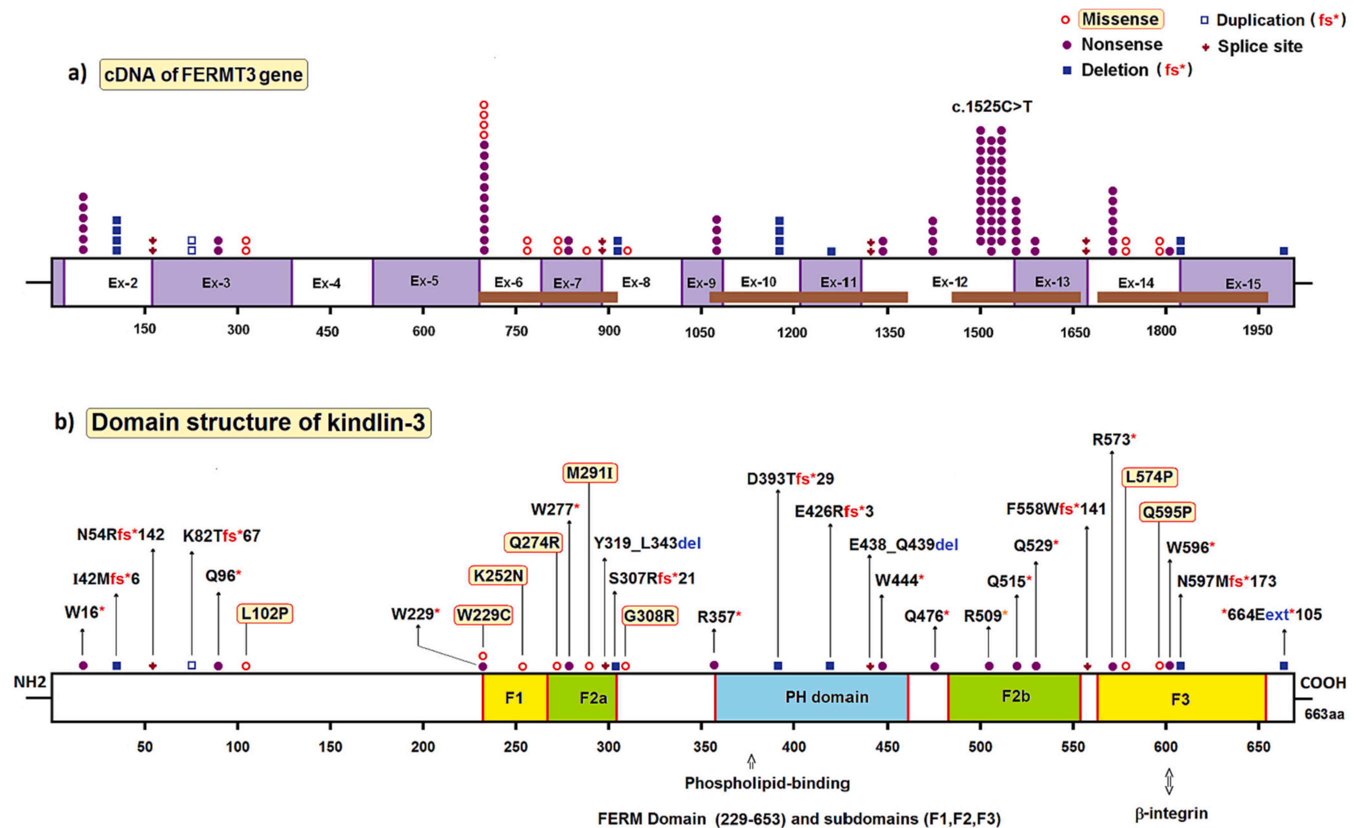

Fig. 3. Schematic overview of mutations in *FERMT3* and the changes in the kindlin-3 protein.
a. The number of mutated alleles, the type of mutation and their position along the exons of *FERMT3*. Symbols, explained on the right, represent mutated alleles. Numbers refer to nucleotides in cDNA.
b. Domain structure of kindlin-3 and the location of each mutation, with active domains depicted in yellow, green and blue. Protein interaction sites are shown for some domains. Symbols, explained on the right, represent separate mutations. Numbers refer to amino acids in kindlin-3.

5. Final remarks

Additional information about LAD in general can be found in a recent review [32] and in the cited literature. In Table 1 we have used the notation LAD-I^0, LAD-I$^-$ and LAD-I$^+$ for differentiating the various phenotypes of LAD-I. In this nomenclature the superscript symbol indicates whether the protein is present at <5 % of normal expression (°), diminished in expression ($^-$), i.e. between 5 % and 20 % of normal expression, or normally present but nonfunctional ($^+$). This information is based on immune reactivity of the patients' leukocytes with monoclonal antibodies analyzed by flow cytometry and sometimes on similar analyses of COS cells co-transfected with mutant CD18 molecules and wild-type CD11 molecules. In case this information is not known, this is indicated as ($^?$). In a number of cases functionality of the mutant CD18

Table 5
Polymorphisms in the LAD-III gene *FERMT3*.

Variant	Amino acid change	MAF (gnomAD)	Reference
c.119C>T	p.(Ser40Leu)	***	[94]
c.130G>A	p.(Gly44Arg)	**	[102]
c.249C>T	p.(Tyr83=)	*** (Afr/Afr Am **)	[102]
c.405C>T	p.(His135=)	**	[102]
c.527C>T	p.(Ala176Val)	***	[102]
c.684-5C>G	p.?	** (Afr/Afr Am *)	[102]
c.729C>T	p.(Ala243=)	*	[102]
c.736G>A	p.(Ala246Thr)	***	[102]
c.895-4C>T	p.?	*	[102]
c.930G>C	p.(Val310=)	**	[102]
c.1320G>A	p.(Gln440=)	** (Afr/Afr Am *)	[102]
c.1393G>A	p.(Glu465Lys)	** (South Asian *)	[102]
c.1404C>T	p.(Ala468=)	***	[102]
c.1449G>A	p.(Pro483=)	0.116	[102]
c.1506C>T	p.(Leu502=)	0.1777	[102]
c.1692C>T	p.(Asp564=)	** (South Asian 0.02)	[102]
c.1917G>A	p.(Thr639=)	**	[102]

Variants described based on coding DNA reference sequence NM_031471.6 (see www.LOVD.nl/FERMT3.
=, silent variation; MAF, minor allele frequency according to genome aggregation database. MAF scores: *** <0.001; ** <0.01; * <0.1.

proteins was tested in cellular adherence assays to β_2 ligands [33]. Similarly, in Table 3, the mild form of LAD-II has been indicated as LAD-II^-, in contrast to the severe form LAD-II^0.

The nucleotide numbering system we have used is based on the cDNA sequence and follows the convention that +1 is the A of the ATG initiation codon. The NCBI reference sequence numbering used is indicated in the headings of the Tables. This numbering is in accordance with the Matched Annotation from NCBI and EMBL-EBI (MANE). The notation of the variations follows the recommendations of the Human Genome Variation Society [34] (see also www.hgvs.org/varnomen). The description of the DNA and protein variants have been checked with the Mutalyzer program (www.mutalyzer.nl) [35]. More information on patients with a certain genetic LAD variation can be found in the Leiden Open Variation Database (LOVD): databases.lovd.nl/shared. Additional information can also be found in the HGMD database at www.hgmd.cf.ac.uk/ac/search.php.

CRediT authorship contribution statement

The authors state that they have nothing to declare.

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