ELECTRONIC SUPPLEMENTARY MATERIAL

Novel linkage peaks discovered for diabetic nephropathy in individuals with type 1 diabetes

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Supplementary Table 1 – Genotyping rates and allele counts for SNPs with genome-wide significant linkage LOD scores

SNP	*rsid*	*HOM A1*	*HET*	*HOM A2*	*Genotyping rate*
Chr2:165551404_A>G	rs17244632	256	1942	3821	100 %
Chr2:236452412_A>G	rs6717219	22	743	5254	100 %
Chr4:79304226_T>G	rs10033307	317	2113	3589	100 %
Chr4:85993738_C>T	rs4129430	336	2164	3515	99.93 %
Chr4:86000455_A>G	rs11097033	260	1956	3797	99.90 %
Chr4:86630512_A>G	rs1482085	1176	2922	1920	99.99 %
Chr4:91568501_T>G	rs10014992	1270	2974	1775	100 %
Chr20_51932381_T>G	rs200655	56	1028	4935	100 %
Chr20:51971152_T>C	rs200631	98	1327	4592	99,97 %
Chr22:27737024_C>T	rs1121442	49	1002	4967	99.99 %
Chr22:27740599_G>A	rs4820751	49	1002	4968	100 %

HOM A1: Number of the homozygous A1 allele carriers. HET: Number of the heterozygous A1-A2 carriers. HOM A2: Number of the homozygous A2 allele carriers.

Supplementary Table 2 – Regions with genome-wide significant linkage with either or both dominant or recessive inheritance models

Region	Marker	Recessive model Linkage LOD score (micro/macro/ESRD - normal AER, lead marker)	Dominant model Linkage LOD score (micro/macro/ESRD - normal AER, lead marker)
1q23	rs1858534	2.32	**3.40**
2q24.3	rs17244632	**3.31**	2.54
2q36.1	rs10205272	2.70	**3.61**
2q37.2	rs6717219	**3.63**	1.96
3p26.1	rs13075346	2.41	**3.38**
3p24.3	rs11720982	2.56	**3.37**
4q21.21	rs10033307	**3.62**	2.87
4q22	rs11097033	**3.80**	3.02
4q25	rs10014992	**3.41**	**3.40**
5q21.2	rs10060923	2.50	**3.37**
6p21-22	rs2239839	**7.42**	**6.17**
10p15.2	rs705468	2.73	**3.45**
12p11.22	rs2647384	**3.28**	**4.02**
17q25.3	rs7222861	2.97	**3.77**
20q13.2	rs200631	**3.58**	**3.38**
22q12.1	rs1121442	**3.63**	2.499

Supplementary Table 3 – Three of eight linkage peaks reached genome-wide significant linkage LOD scores analysis also with macro/ESRD phenotype as affected and normal AER as unaffected. Only regions within ± 2.5Mb original peaks were tested.

Region	Micro/macro/ESRD - normal AER (Lead marker)	Macro/ESRD - normal AER (Lead marker)
2q24.3	3.31 (rs17244632)	3.52 (rs4493277)
2q37.2	3.63 (rs6717219)	2.16 (rs6741321)
4q21.21	3.62 (rs10033307)	2.55 (rs1545805)
4q22	3.80 (rs11097033)	2.87 (rs1482085)
4q25	3.41 (rs10014992)	2.60 (89096641)
6p21-22	7.42 (rs2239839)	4.35 (rs9277334)
20q13.2	3.58 (rs200631)	2.67 (rs793034)
22q12.1	3.63 (rs1121442)	3.62 (rs7289240)

Supplementary Table 4 – Linkage LOD-scores by pedigree type

Region	Linkage LOD-score (all 177 pedigrees)	Linkage LOD-score on pedigrees with concordant individuals only (57 trees)	Linkage LOD-score on pedigrees with discordant individuals only (77 trees, only 1 individual with DN and 1 or more individual with normal AER)	Linkage LOD-score on complex pedigrees (9 trees with at least 2 concordant individuals and 1 discordant member)
2q24.3	3.31	3.14	0.05	0.01
2q37.2	3.63	3.36	0.01	0.17
4.21.21	3.62	2.36	0.06	0.32
4q22	3.80	3.90	0.05	0.07
4q25	3.41	2,83	0.13	0.24
rs707898 (6p21)	4.23	3.25	0.31	0.8
rs1264570 (6p21)	3.50	2.31	0.41	0.3
rs9262632 (6p21)	3.66	3.17	0.01	0.4
rs1265048 (6p21)	3.82	3.89	0.42	0.0
rs2596464 (6p21)	3.98	2.95	0.35	1.1
rs614549 (6p21)	3.37	2.31	0.40	0.9
rs2239839 (6p21)	7.42	6.95	0.35	0.1
rs259686 (6p21)	3.55	2.67	0.41	1.3
20q13.2	3.58	2.10	0.52	1.39
22q12.1	3.63	3.11	0.03	0.61

Supplementary Table 5 – The most significant variants linked/associated with T1D(1) and possibly overlapping linkage peaks from this study

SNP	Locus	Gene/SNP	Overlapping linkage peak for DN
rs2187668, rs7454108, rs1264813, rs2395029, rs3129889	6p21-22	HLA region	HLA region
rs689	11p15.5	INS	
rs2476601	1p13.2	PTPN22	
rs12722495, rs11594656	10p15.1	IL2RA	
rs2292239	12q13.2	ERBB3	
rs10509540	10q23.31	C10orf59/RNLS	
rs4948088	7p12.1	COBL	
rs7202877	16q23.1		
rs12708716	16p13.13	CLEC16A	
rs3087243	2q33.2	CTLA4	
rs1893217	18p11.21	PTPN2	
rs3024505	1q32.1	IL10	
rs9388489	6q22.32	CENPW/C6orf173	
rs1465788	Chr14:68.79Mb		
rs1990760	2q24.2, Chr2:162267541	IFIH1	DN LOD:3.4 for rs17244632 (Chr2:165.55Mb), the T1D associated rs1990760 is genotyped in GWAS, LOD-score is 0
rs3825932	15q25.1	CTSH	
rs425105	Chr19:46.70Mb		
rs763361	18q22.2	CD226	
rs4788084	16p12.1-p11.2	IL27	
rs17574546	Chr15:38.61Mb		
rs11755527	6q15	BACH2	
rs3788013	21q22.3	UBASH3A	
rs2069762	4q27	IL2	
rs2281808	Chr20:1629905		
rs5753037	Chr22:30.18Mb		DN LOD:3.6 for rs1121442 (Chr22:27.73Mb), the T1D associated rs5753037 is genotyped in GWAS, LOD-score is 0.003

Supplementary Table 6 – Variants with genome-wide significant or suggestive assocassociations with DKD on *Salem et al 2019* study (12), located within ± 2.5Mb of linkage peaks

Adjacent linkage peak	*SNP*	*rsid*	*Freq A1*	*OR*	*Beta*	*StdErr*	*Pvalue*
4q25	Chr4:92502825:t>c	rs538044833	0.9967	0.00665425*	-5.0125	0.9025	2.795×10^{-8}
	Chr4:92450033:a>g	rs556759477	0.9966	0.00804584	-4.8226	0.8864	5.316×10^{-8}
	Chr4:92450037:c>g	rs570462470	0.9966	0.00804584	-4.8226	0.8864	5.316×10^{-8}
	Chr4:92323157:a>t	rs555267119	0.9963	0.0174067	-4.0509	0.8280	9.961×10^{-7}
	Chr4:93945075:a>g	rs76955293	0.8859	1.17904	0.1647	0.0397	3.277×10^{-5}
	Chr4:93909727:a>t	rs12498874	0.1116	0.851207	-0.1611	0.0396	4.68×10^{-5}
22q12.1	Chr22:29150747:g>ggct	rs557914425	0.9964	0.0336077	-3.3930	0.7479	5.709×10^{-6}
	Chr22:28926297:a>g	rs182486743	0.9972	0.0502121	-2.9915	0.6754	9.452×10^{-6}
	Chr22:29371359:a>g	rs147328662	0.0035	12.9203	2.5588	0.5963	1.776×10^{-5}
	Chr22:29366285:t>c	rs141420500	0.0035	11.7048	2.4600	0.5819	2.358×10^{-5}
	Chr22:29179281:a>g	rs191062565	0.0035	11.6849	2.4583	0.5893	3.023×10^{-5}
	Chr22:29148035:t>c	rs145666781	0.0040	11.5248	2.4445	0.5915	3.588×10^{-5}
4q22	Chr4:88116799:a>g	rs143285834	36.5434	3.5985	0.7974	36.5434	6.403×10^{-6}
	Chr4:88244081:a>t	rs114937514	23.0877	3.1393	0.7334	23.0877	1.866×10^{-5}
2q24.3	Chr2:163931755:t>c	rs114789105	0.267563	-1.3184	0.3106	0.267563	2.189×10^{-5}
	Chr2:164814526:t>c	rs142210044	0.433311	-0.8363	0.2066	0.433311	5.156×10^{-5}
2q37.2	Chr2:234830322:ct>c	rs57417753	1.20877	0.1896	0.0451	1.20877	2.619×10^{-5}

*A raw OR based on the estimated allele counts in the Scottish cohort yields an OR of (10.9/716.1)/(20.0/3942.0)=3.0 for the rare allele.

Supplementary Table 7 – Significant eQTL associations from GTEx database for SNPs with genome-wide significant linkage for diabetic nephropathy

Tissue	SNP	Chr:pos, base change	Gene	P-value
Skeletal muscle	rs17244632	1:165551404 G>A	*SLC38A11*	3.7×10^{-7}
Tibial Nerve	rs10033307	4:79304226 T>G	*FRAS1*	5.6×10^{-14}
Esophagus – Muscularis	rs4129430	4:85993738 T>A	*WDFY3-AS2*	3.6×10^{-7}
Esophagus – Muscularis	rs11097033	4:86000455 G>A	*WDFY3-AS2*	7.3×10^{-10}
Tidal artery	rs11097033	4:86000455 G>A	*WDFY3-AS2*	2.3×10^{-5}
Tidal artery	rs1482085	4:86630512-A>G	*ARHGAP24*	1.3×10^{-5}
Aorta	rs1482085	4:86630512-A>G	*ARHGAP24*	1.8×10^{-4}
Adipose - Subcutaneous	rs1482085	4:86630512-A>G	*RP13-514E23.2*	3.62×10^{-8}

Supplementary Table 8 – Significant mQTL associations with SNPs with genome-wide significant linkage

SNP	Chr:pos, base change	MAF	Timepoint	CpG	CpG Pos	beta	Effect Size	P-value	Trans
rs4129430	4:85993738-C>T	0.246	Birth	cg04673465	4:85570164	-0.24230	0.02805	9.21×10^{-8}	N
rs1482085	4:86630512-A>G	0.357	Birth	cg06648395	17:77817382	0.24990	0.00070	5.98×10^{-8}	Y
rs1482085	4:86630512-A>G	0.357	Birth	cg22017213	4:86851225	0.28706	0.00627	3.30×10^{-11}	N
rs1482085	4:86630512-A>G	0.35	Childhood	cg20784207	4:86597598	-0.23339	0.02246	3.87×10^{-10}	N
rs10014992	4:91568501-T>G	0.412	Childhood	cg16885107	17:16310614	0.21143	0.00164	6.96×10^{-8}	Y
rs10014992	4:91568501-T>G	0.415	Adolescence	cg00160777	16:23764590	0.27451	0.14694	5.02×10^{-10}	Y
rs10014992	4:91568501-T>G	0.412	Childhood	cg00160777	16:23764590	0.23672	0.15598	5.06×10^{-8}	Y
rs10014992	4:91568501-T>G	0.408	Middle Age	cg00160777	16:23764590	0.25949	0.15387	3.62×10^{-8}	Y

Supplementary Table 9 – Genes and their functions in processes associated to DN under linkage peaks

Region	Plausible genes at the region	Gene function and significant associations
Genes close or under the genome-wide significant linkage peaks		
2q24.3	*GRB14*	*GRB14* encodes a small adapter protein called Growth factor receptor-bound protein 14 that directly binds to the activated insulin receptor and inhibits its tyrosine kinase activity (2). Genetic studies suggest association of the *GRB14* variant with insulin resistance, BMI and fat distribution (3-5).
2q37.2	*AGAP1*	The *AGAP1* gene encodes a GTPase activator protein, and is linked to Rac1 activation through Arf1, Arf5 and RhoA, linking the GTPase activator protein to the same pathway as the Rho GTPase Activating Protein 24 encoded by *ARHGAP24.*
4q21.21	*FRAS1*	The *FRAS1* gene encodes the Fras1 protein that is expressed in embryonic epidermal cells, localizing in their basement membrane. Mutations in the *FRAS1* cause a rare familial Fraser syndrome, which manifests as severe developmental problems in multiple organs and tissues including eyes, digits and the renal system (6). Fras1 has also been shown to be essential for the glomerular integrity and possibly also for the kidney development (7).
4q22	*ARHGAP24, PTPN13*	The *ARHGAP24* gene directly under the linkage peak at chromosome 4q22.1 (highest LOD 3.36) has been associated with familial focal segmental glomerulosclerosis (FSGS), a rare familial kidney disease, but not with DN (8). Furthermore, the orthologous Q156R mutation reduces the capability of mouse Arhgap24 to deactivate Rac1(8). Variant of the *PTPNP13* gene previously suggestively associated with DN (9).
4q25	*CCSER1*	Rare *CCSER1* intronic variants have been associated with DKD on one DNCRI meta-analysis' non-Finnish cohort, and CKD on HUNT cohort (10).
6p21-22	HLA-region, TNF-α, *AGER*, *LRRC16A*	Several genes on HLA-region studied as candidates for DN associations.
20q13.2	*TSHZ2*	*TSHZ2* has been associated with renal pelvis development in human and mice (11)
22q12.1	-	-

Supplementary table 10 – Replicated regions from previous studies. The two regions 3q25 and 22q11, from previous studies with the most prevalent evidence of linkage did not yield genome-wide significant linkage LOD score in this study.

Region	Highest Linkage LOD score (Marker)
3q25	2.76 (rs1562487)
22q11	2.80 (rs738034)

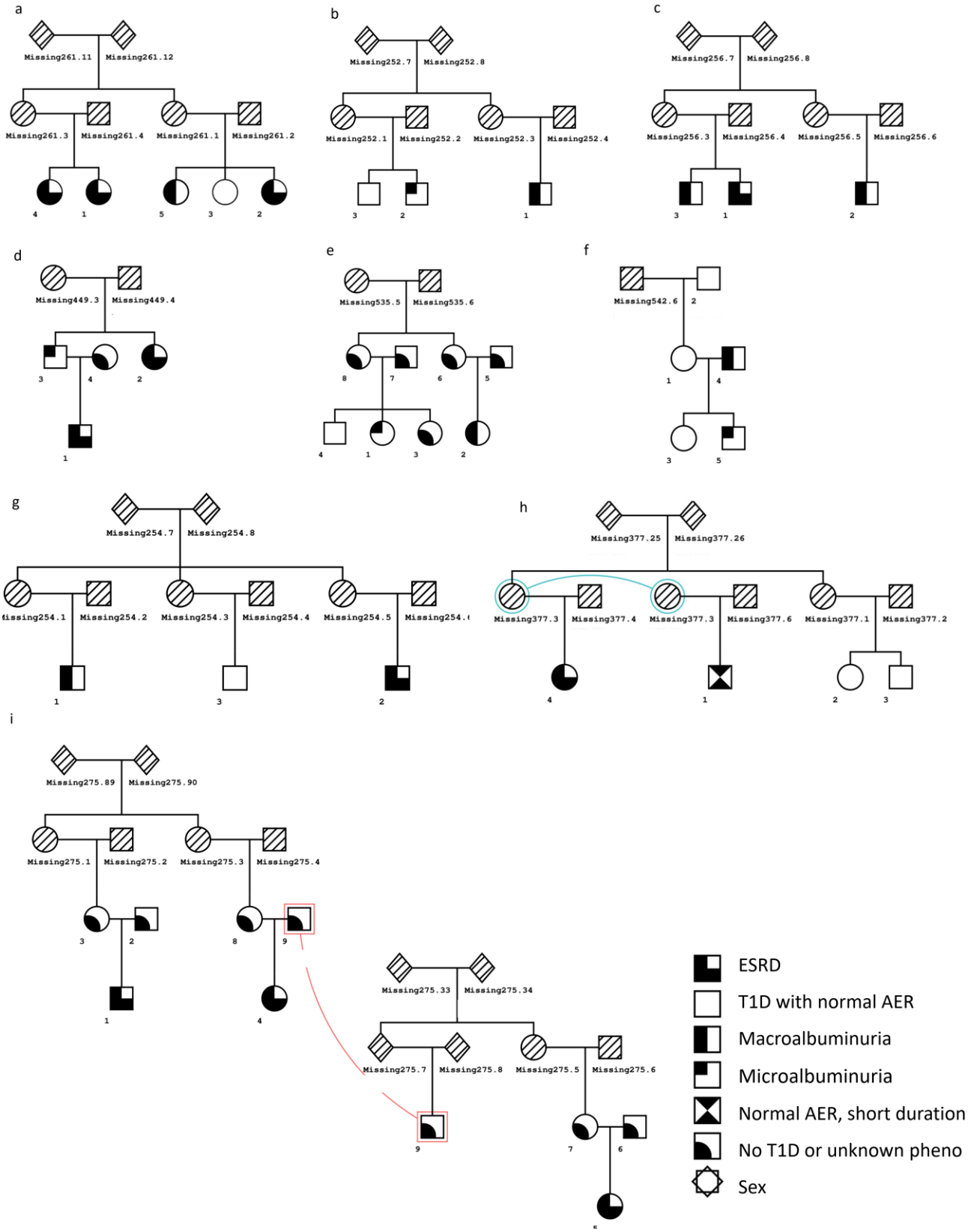
Supplementary Table 11 – Physicians and nurses at health care centers participating in the collection of FinnDiane patients.

FinnDiane Study Centers	Physicians and nurses
Anjalankoski Health Centre	S. Koivula, T. Uggeldahl
Central Finland Central Hospital, Jyväskylä	T. Forslund, A. Halonen, A. Koistinen, P. Koskiaho, M. Laukkanen, J. Saltevo, M. Tiihonen
Central Hospital of Åland Islands, Mariehamn	M. Forsen, H. Granlund, A-C. Jonsson, B. Nyroos
Central Hospital of Kanta-Häme, Hämeenlinna	P. Kinnunen, A. Orvola, T. Salonen, A. Vähänen
Central Hospital of Länsi-Pohja, Kemi	H. Laukkanen, P. Nyländen, A. Sademies
Central Ostrabothnian Hospital District, Kokkola	S. Anderson, B. Asplund, U. Byskata, P. Liedes, M. Kuusela, T. Virkkala
City of Espoo Health Centre	
Espoonlahti	A. Nikkola, E. Ritola
Tapiola	M. Niska, H. Saarinen
Samaria	E. Oukko-Ruponen, T. Virtanen
Viherlaakso	A. Lyytinen
City of Helsinki Health Centre	
Puistola	H. Kari, T. Simonen
Suutarila	A. Kaprio, J. Kärkkäinen, B. Rantaeskola
Töölö	P. Kääriäinen, J. Haaga, A-L. Pietiläinen
City of Hyvinkää Health Centre	S. Klemetti, T. Nyandoto, E. Rontu, S. Satuli-Autere
City of Vantaa Health Centre	
Korso	R. Toivonen, H. Virtanen
Länsimäki	R. Ahonen, M. Ivaska-Suomela, A. Jauhiainen
Martinlaakso	M. Laine, T. Pellonpää, R. Puranen
Myyrmäki	A. Airas, J. Laakso, K. Rautavaara
Rekola	M. Erola, E. Jatkola
Tikkurila	R. Lönnblad, A. Malm, J. Mäkelä, E. Rautamo
Heinola Health Centre	P. Hentunen, J. Lagerstam
Helsinki University Central Hospital, Department of Medicine, Division of Nephrology	A. Ahola, J. Fagerudd, M. Feodoroff, D. Gordin, O. Heikkilä, K Hietala, L. Kyllönen, J. Kytö, S. Lindh, K. Pettersson-Fernholm, M. Rosengård-Bärlund, M. Rönnback, A. Sandelin, A-R Salonen, L. Salovaara, L. Thorn, J. Tuomikangas, T. Vesisenaho, J. Wadén
Herttoniemi Hospital, Helsinki	V. Sipilä
Hospital of Lounais-Häme, Forssa	T. Kalliomäki, J. Koskelainen, R. Nikkanen, N. Savolainen, H. Sulonen, E. Valtonen
Iisalmi Hospital	E. Toivanen
Jokilaakso Hospital, Jämsä	A. Parta, I. Pirttiniemi
Jorvi Hospital, Helsinki University Central Hospital	S. Aranko, S. Ervasti, R. Kauppinen-Mäkelin, A. Kuusisto, T. Leppälä, K. Nikkilä, L. Pekkonen
Jyväskylä Health Centre, Kyllö	K. Nuorva, M. Tiihonen
Kainuu Central Hospital, Kajaani	S. Jokelainen, P. Kemppainen, A-M. Mankinen, M. Sankari
Kerava Health Centre	H. Stuckey, P. Suominen
Kirkkonummi Health Centre	A. Lappalainen, M. Liimatainen, J. Santaholma
Kivelä Hospital, Helsinki	A. Aimolahti, E. Huovinen

FinnDiane Study Centers	Physicians and nurses
Koskela Hospital, Helsinki	V. Ilkka, M. Lehtimäki
Kotka Heath Centre	E. Pälikkö-Kontinen, A. Vanhanen
Kouvola Health Centre	E. Koskinen, T. Siitonen
Kuopio University Hospital	E. Huttunen, R. Ikäheimo, P. Karhapää, P. Kekäläinen, M. Laakso, T. Lakka, E. Lampainen, L. Moilanen, L. Niskanen, U. Tuovinen, I. Vauhkonen, E. Voutilainen
Kuusamo Health Centre	T. Kääriäinen, E. Isopoussu
Kuusankoski Hospital	E. Kilkki, I. Koskinen, L. Riihelä
Laakso Hospital, Helsinki	T. Meriläinen, P. Poukka, R. Savolainen, N. Uhlenius
Lahti City Hospital	A. Mäkelä, M. Tanner
Lapland Central Hospital, Rovaniemi	L. Hyvärinen, S. Severinkangas, T. Tulokas
Lappeenranta Health Centre	P. Linkola, I. Pulli
Lohja Hospital	T. Granlund, M. Saari, T. Salonen
Loimaa Health Centre	A. Mäkelä, P. Eloranta
Länsi-Uusimaa Hospital, Tammisaari	I-M. Jousmaa, J. Rinne
Malmi Hospital, Helsinki	H. Lanki, S. Moilanen, M. Tilly-Kiesi
Mikkeli Central Hospital	A. Gynther, R. Manninen, P. Nironen, M. Salminen, T. Vänttinen
Mänttä Regional Hospital	I. Pirttiniemi, A-M. Hänninen
North Karelian Hospital, Joensuu	U-M. Henttula, P. Kekäläinen, M. Pietarinen, A. Rissanen, M. Voutilainen
Nurmijärvi Health Centre	A. Burgos, K. Urtamo
Oulankangas Hospital, Oulainen	E. Jokelainen, P-L. Jylkkä, E. Kaarlela, J. Vuolaspuro
Oulu Health Centre	L. Hiltunen, R. Häkkinen, S. Keinänen-Kiukaanniemi
Oulu University Hospital	R. Ikäheimo
Päijät-Häme Central Hospital	H. Haapamäki, A. Helanterä, S. Hämäläinen, V. Ilvesmäki, H. Miettinen
Palokka Health Centre	P. Sopanen, L. Welling
Pieksämäki Hospital	V. Javtsenko, M. Tamminen
Pietarsaari Hospital	M-L. Holmbäck, B. Isomaa, L. Sarelin
Pori City Hospital	P. Ahonen, P. Merensalo, K. Sävelä
Porvoo Hospital	M. Kallio, B. Rask, S. Rämö
Raahe Hospital	A. Holma, M. Honkala, A. Tuomivaara, R. Vainionpää
Rauma Hospital	K. Laine, K. Saarinen, T. Salminen
Riihimäki Hospital	P. Aalto, E. Immonen, L. Juurinen
Salo Hospital	A. Alanko, J. Lapinleimu, P. Rautio, M. Virtanen
Satakunta Central Hospital, Pori	M. Asola, M. Juhola, P. Kunelius, M-L. Lahdenmäki, P. Pääkkönen, M. Rautavirta
Savonlinna Central Hospital	E. Korpi-Hyövälti, T. Latvala, E. Leijala
South Karelia Central Hospital, Lappeenranta	T. Ensala, E. Hussi, R. Härkönen, U. Nyholm, J. Toivanen
Tampere Health Centre	A. Vaden, P. Alarotu, E. Kujansuu, H. Kirkkopelto-Jokinen, M. Helin, S. Gummerus, L. Calonius, T. Niskanen, T. Kaitala, T. Vatanen
Tampere University Hospital	I. Ala-Houhala, T. Kuningas, P. Lampinen, M. Määttä, H. Oksala, T. Oksanen, K. Salonen, H. Tauriainen, S. Tulokas
Tiirismaa Health Centre, Hollola	T. Kivelä, L, Petlin, L. Savolainen
Turku Health Centre	I. Hämäläinen, H. Virtamo, M. Vähätalo

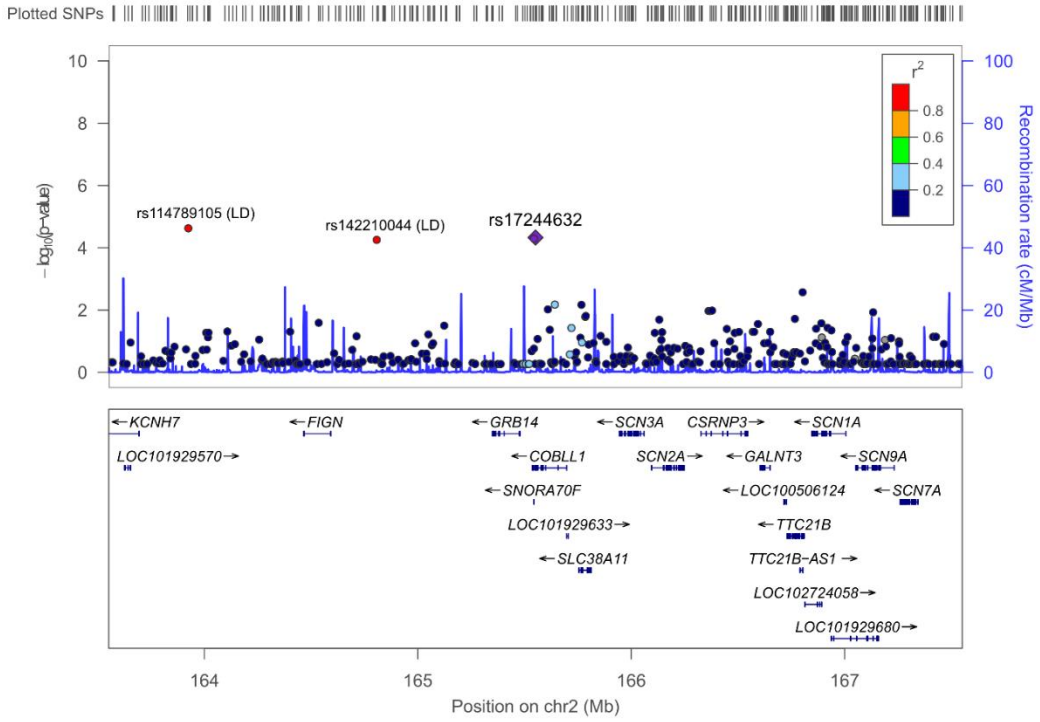
FinnDiane Study Centers	Physicians and nurses
Turku University Central Hospital	K. Breitholz, R. Eskola, K. Metsärinne, U. Pietilä, P. Saarinen, R. Tuominen, S. Äyräpää
Vaajakoski Health Centre	K. Mäkinen, P. Sopanen
Valkeakoski Regional Hospital	S. Ojanen, E. Valtonen, H. Ylönen, M. Rautiainen, T. Immonen
Vammala Regional Hospital	I. Isomäki, R. Kroneld, M. Tapiolinna-Mäkelä
Vaasa Central Hospital	S. Bergkulla, U. Hautamäki, V-A. Myllyniemi, I. Rusk

Supplementary Figure 1 – Structures of nine complex pedigrees

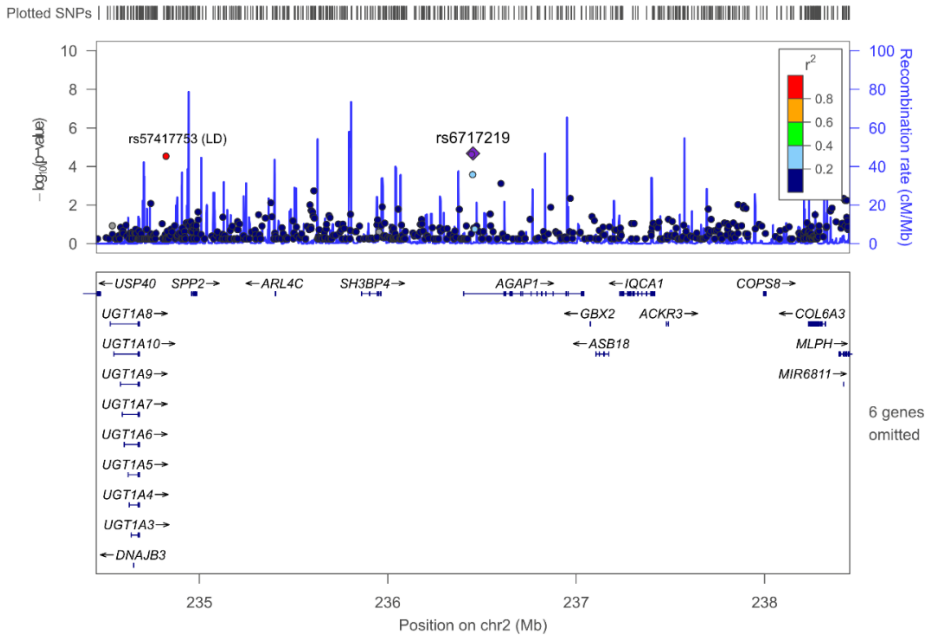


Supplementary Figure 2 – LocusZoom regional association plots for linkage peaks. The y-axis indicates the -$\log_{10}$(p-values), instead of LOD scores, for both linkage and association results. The purple diamonds show DN linkage P-value for the lead SNP in our current linkage study, whereas the red circles with rs-numbers display association P-values from *Salem et al. 2019*. The remaining SNPs are coloured according to their r^2 correlation with the lead SNP.

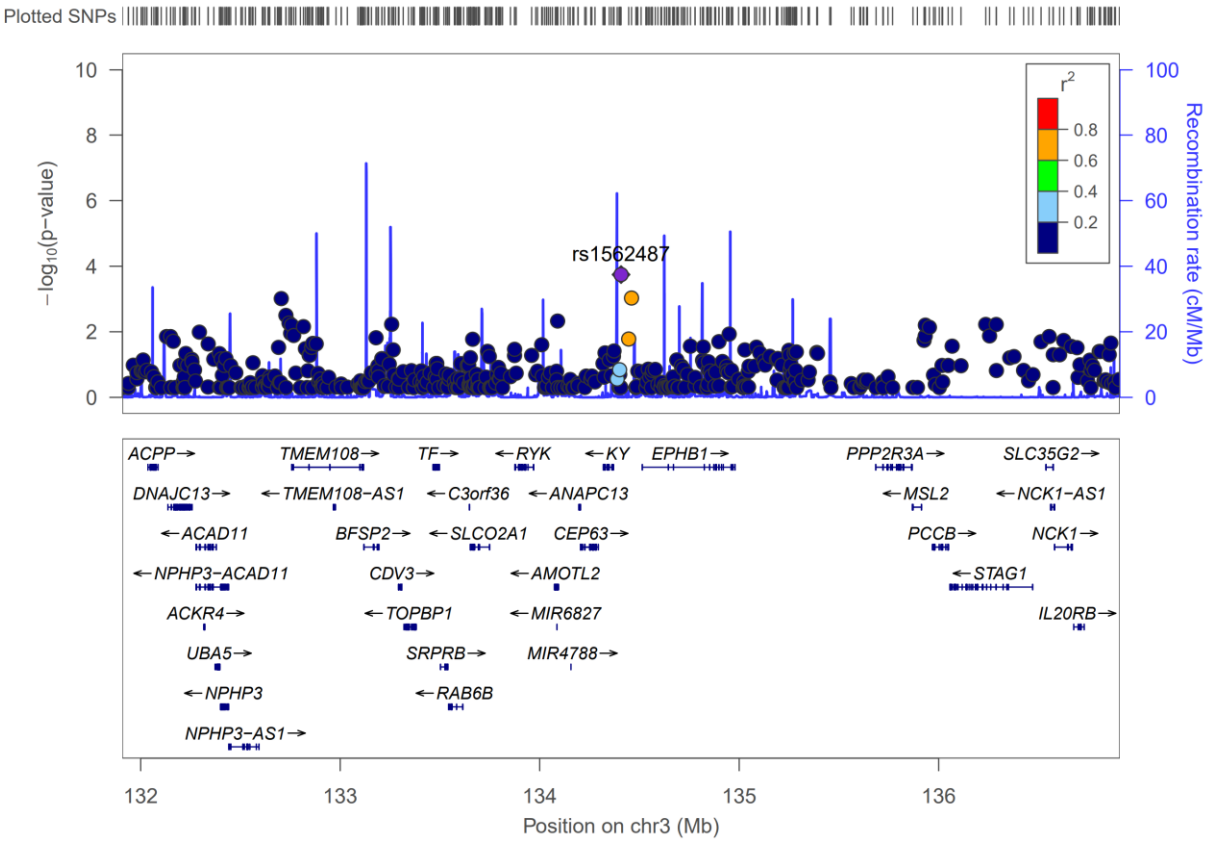
A - Chr2: 163.5-167.5



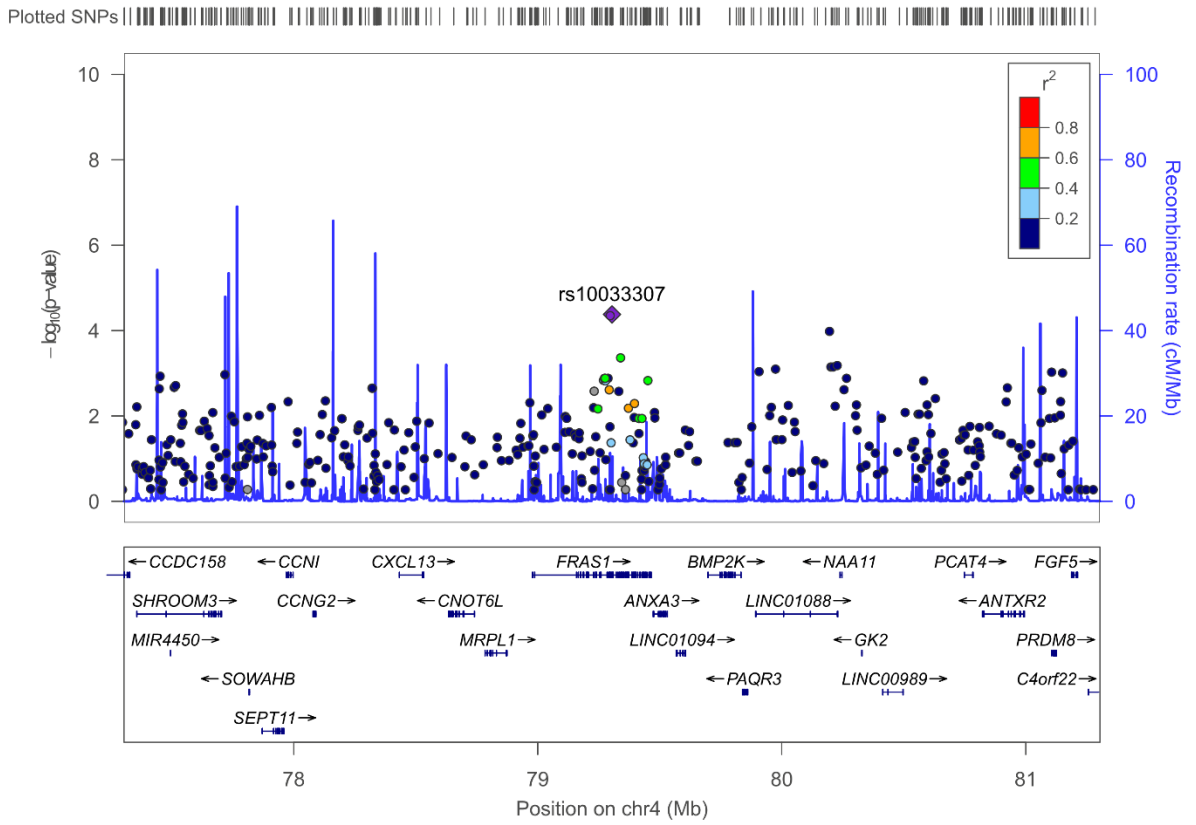
B - Chr2: 234.5-238.5Mb



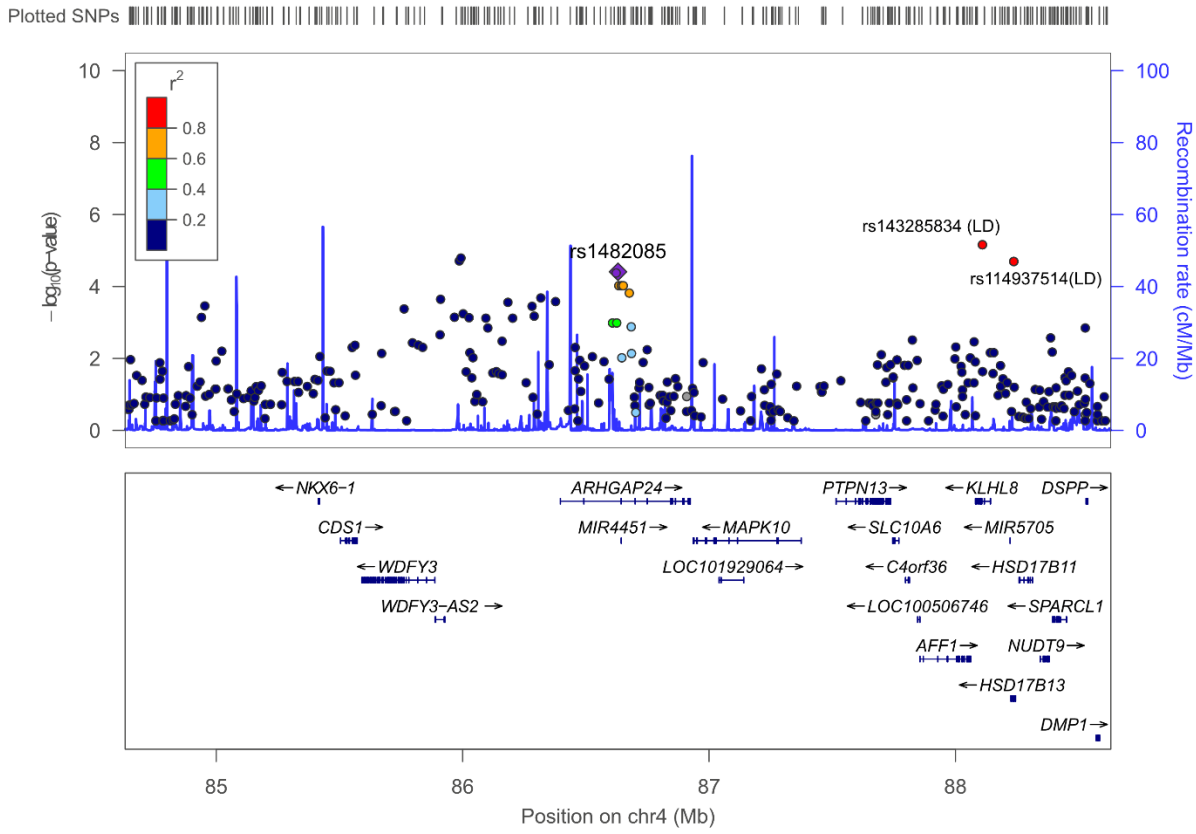
C - Chr3: 132-137Mb



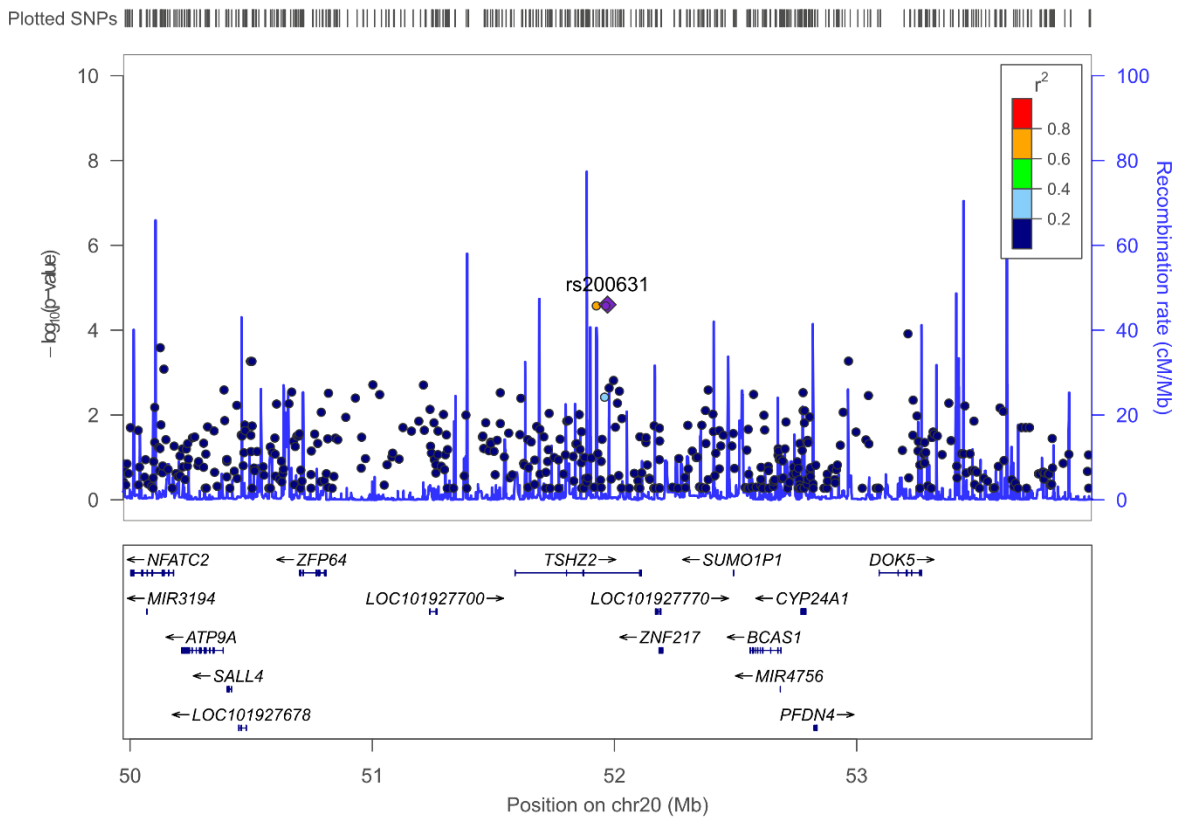
D - Chr4: 79.3 & 80.3



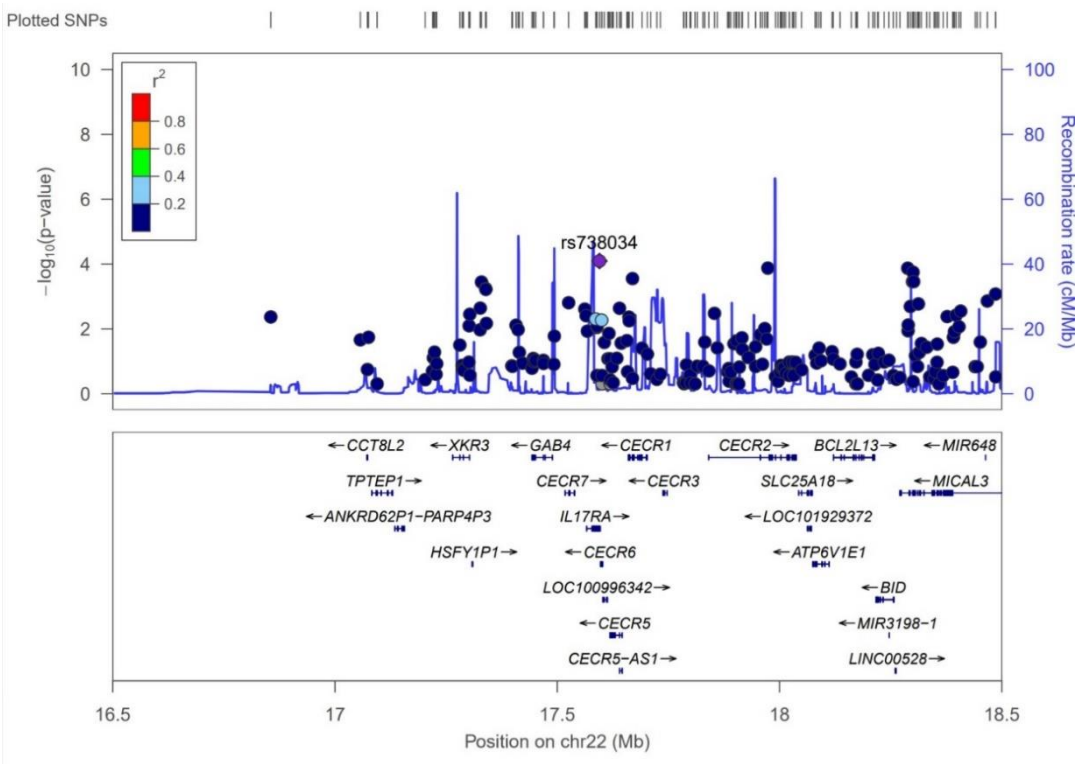
E - Chr4: 84 – 88Mb



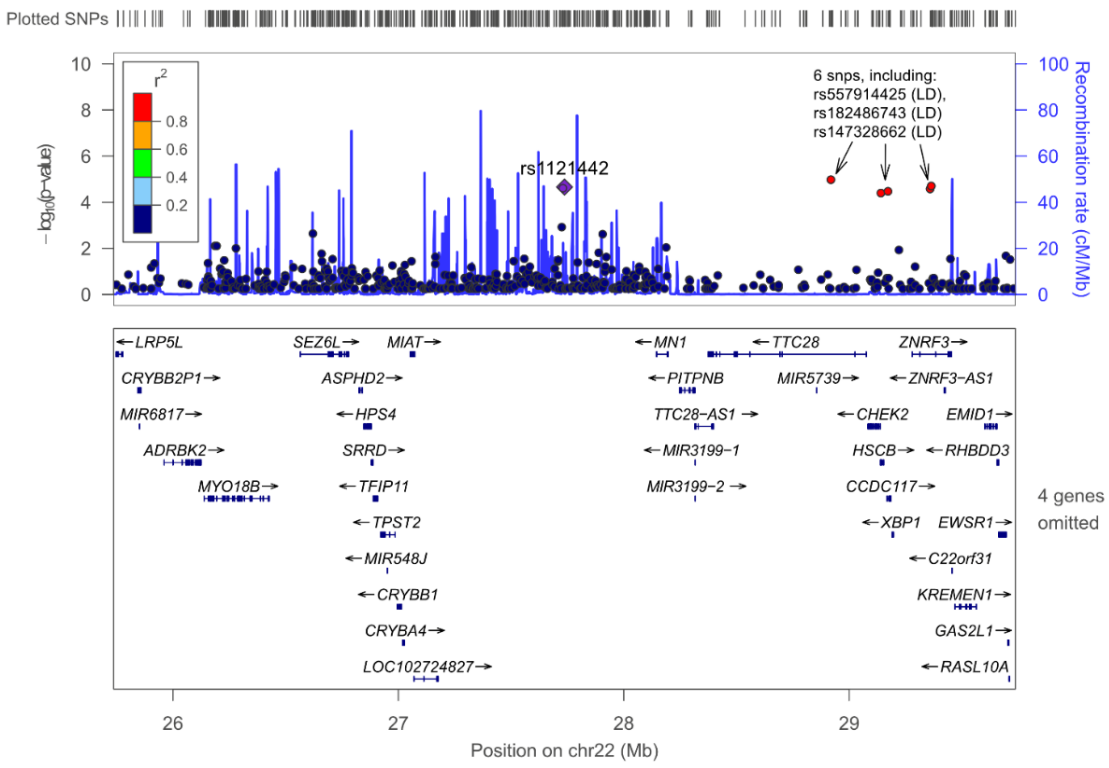
F - Chr 20: 51.9 Mb



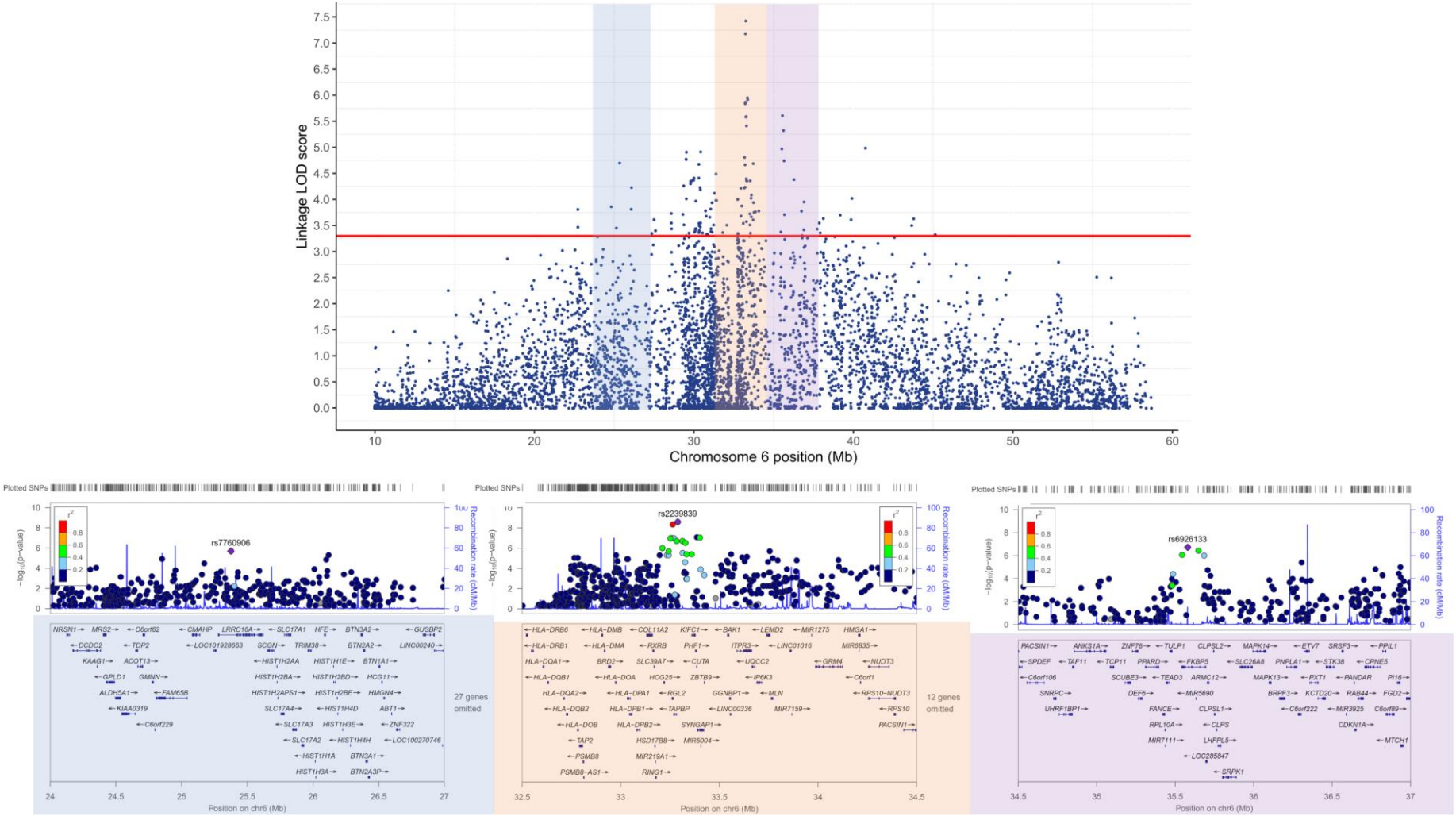
G - Chr22: 16.5-18.5Mb



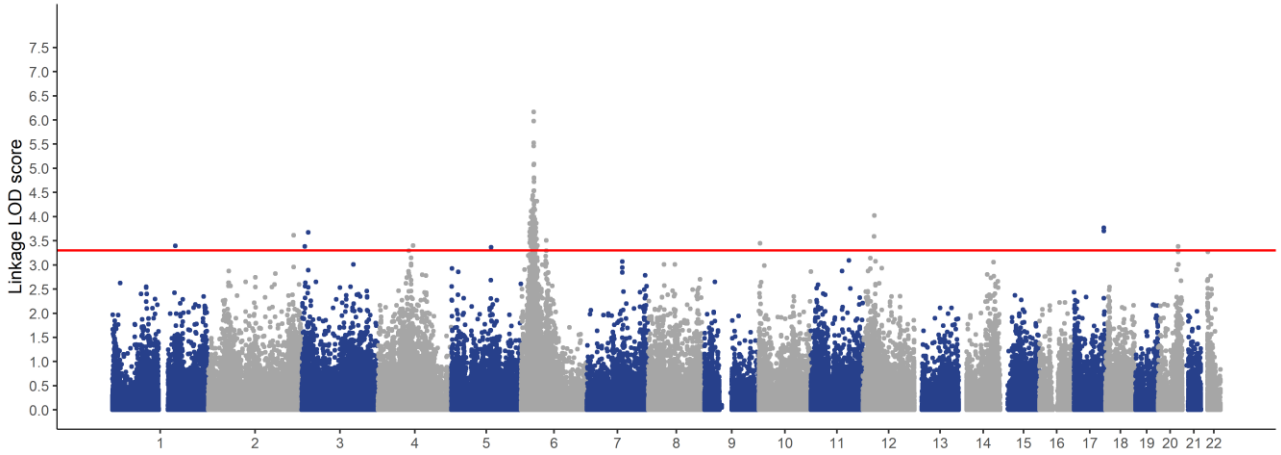
H - Chr 22: 27.3 Mb


Plotted SNPs
r²
0.8
0.6
0.4
0.2
rs1121442
6 snps, including:
rs557914425 (LD),
rs182486743 (LD)
rs147328662 (LD)
Recombination rate (cM/Mb)
LRP5L
SEZ6L
MIAT
MN1
TTC28
ZNRF3
CRYBB2P1
ASPHD2
PITPNB
MIR5739
ZNRF3-AS1
MIR6817
HPS4
TTC28-AS1
CHEK2
EMID1
ADRBK2
SRRD
MIR3199-1
HSCB
RHBDD3
MYO18B
TFIP11
MIR3199-2
CCDC117
TPST2
XBP1
EWSR1
MIR548J
C22orf31
CRYBB1
KREMEN1
CRYBA4
GAS2L1
LOC102724827
RASL10A
4 genes
omitted
Position on chr22 (Mb)

Supplementary Figure 3 – Manhattan plot of chromosome 6p, showing LOD-score on the y-axis. Small LocusZoom plots on the bottom show a closer view of the regions highlighted in blue, red and purple.



Supplementary Figure 4 - Manhattan plot of genome-wide linkage analysis with dominant inheritance model



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