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**Figure 1. Genomic organization of *LRP6* and pairwise LD analysis of SNPs. (A)**

Schematic representation of the *LRP6* genomic region showing the locations of SNPs.

Coding and noncoding sequences of exons are shown as closed and open boxes,

respectively. Details of the SNPs are provided in Table 1. **(B)** Values of  $D'$  (bold type)

and of  $r^2$  (nonbold type) for pairwise LD analysis in 92 control subjects. Three

estimated LD blocks are highlighted in gray.

**Figure 2. Genomic organization of *LRP5* and pairwise LD analysis of SNPs. (A)**

Schematic representation of the *LRP5* genomic region showing the locations of SNPs.

Coding and noncoding sequences of exons are shown as closed and open boxes,

respectively. Details of the SNPs are provided in Table 4. **(B)** Values of  $D'$  (bold type)

and of  $r^2$  (nonbold type) for pairwise LD analysis in 92 control subjects. Two

estimated LD blocks are highlighted in gray.

**Table 1.** Association analysis for SNPs of *LRP6* and Type 2 DM in the initial panel.

Position on chromosome 12	SNP name	rs number	Major allele	Minor allele	MAF		P value	Odds ratio (95% CI)
					Case	Control		
12314360	SNP6-1	rs7136900	G	A	0.08	0.10	0.042*	0.72 (0.52–0.99)
12304062	SNP6-2	rs10743980	C	T	0.19	0.23	0.019*	0.77 (0.61–0.96)
12279248	SNP6-3	rs7956971	T	C				
12267732	SNP6-4	rs11054731	G	A	0.28	0.31	0.106	
12256592	SNP6-5	rs17302049	A	G	0.22	0.20	0.241	
12253186	SNP6-6	rs1181332	A	G	0.05	0.05	0.837	
12241380	SNP6-7	rs2417086	A	G	0.19	0.24	0.008*	0.74 (0.59–0.93)
12224619	SNP6-8	rs10492120	C	T				
12222642	SNP6-9	rs2417085	T	C	0.16	0.18	0.186	
12214885	SNP6-10	rs7294695	G	C	0.19	0.21	0.293	
12193165	SNP6-11	rs2302685	T	C	0.06	0.05	0.333	
12166202	SNP6-12	rs2284396	C	T	0.18	0.22	0.094	
12159793	SNP6-13	rs7316466	T	C	0.16	0.16	0.984	

SNP position is indicated as base-pair number in NCBI build 127. MAF, minor allele frequency. P values for the difference in the minor allele frequency between cases and controls were calculated by the chi-square test; the odds ratio and 95% confidence interval (CI) were also calculated for the minor allele. Asterisks indicate P values of <0.05.

**Table 2.** Association analysis for rs2417086 (SNP6-7) and rs17302049 (SNP6-5).

dbSNP ID	Initial panel						Replication panel						
	<i>n</i>		MAF		OR	<i>P</i>	<i>n</i>		MAF		OR	<i>P</i>	
	Case	Control	Case	Control	(95% CI)		Case	Control	Case	Control	(95% CI)		
rs2417086	AA	400	215	0.19	0.24	0.74	0.008*	305	336	0.23	0.22	1.06	0.569
	AG	188	128			(0.59-0.93)		167	175			(0.86-1.31)	
	GG	20	23					30	29				
rs17302049	AA	364	231	0.22	0.20	1.15	0.241	322	329	0.22	0.23	0.92	0.451
	AG	214	113			(0.91-1.44)		170	188			(0.75-1.13)	
	GG	29	16					28	33				
Combined													
	<i>n</i>		MAF		OR		<i>P</i>						
Case	Control	Case	Control	(95% CI)		Case		Control					
705	551	0.21	0.22	0.89		0.130							
355	303			(0.77-1.03)									
50	52												
686	560	0.22	0.22	1.01		0.895							
384	301			(0.87-1.17)									
57	49												

MAF, minor allele frequency. *P* values for the difference in the minor allele frequency between cases and controls were calculated by the chi-square test; the odds ratio and 95% confidence interval (CI) were also calculated for the minor allele. Asterisks indicate *P* values of <0.05.

**Table 3.** Clinical characteristics of Type 2 DM subjects in the initial panel according to genotype for rs2417086 (SNP6-7) of LRP6.

Parameter	AA	AG	GG	P value
Sex (male/female)	234/166	107/81	8/12	
Age (years)	61 ± 10 (n = 400)	61 ± 10 (n = 188)	59 ± 12 (n = 20)	0.710
BMI (kg/m <sup>2</sup> )	23.8 ± 3.5 (n = 399)	23.9 ± 3.3 (n = 188)	25.0 ± 4.5 (n = 20)	0.245
PPG (mmol/l)	7.7 ± 2.5 (n = 307)	7.5 ± 2.0 (n = 139)	8.2 ± 2.8 (n = 19)	0.285
HOMA-IR*	2.90 ± 2.39 (n = 299)	3.14 ± 3.32 (n = 136)	2.79 ± 2.06 (n = 19)	0.920
HOMA-β*	54.0 ± 95.4 (n = 298)	60.5 ± 80.2 (n = 133)	44.3 ± 50.3 (n = 19)	0.342
Total cholesterol (mmol/l)*	5.3 ± 1.0 (n = 271)	5.2 ± 1.0 (n = 119)	5.4 ± 0.6 (n = 15)	0.614
HDL-cholesterol (mmol/l)*	1.4 ± 0.4 (n = 269)	1.4 ± 0.4 (n = 118)	1.3 ± 0.4 (n = 15)	0.832
LDL-cholesterol (mmol/l)*	3.3 ± 0.9 (n = 267)	3.2 ± 0.9 (n = 116)	3.3 ± 0.5 (n = 14)	0.689
Triglyceride (mmol/l)*	1.4 ± 0.8 (n = 271)	1.7 ± 2.6 (n = 119)	1.8 ± 1.3 (n = 15)	0.302
HbA <sub>1c</sub> (%)*	8.0 ± 1.9 (n = 400)	7.7 ± 1.7 (n = 187)	7.7 ± 1.7 (n = 20)	0.312

Data are means ± SD. P values were calculated by ANOVA. \*These parameters were log transformed before analysis.

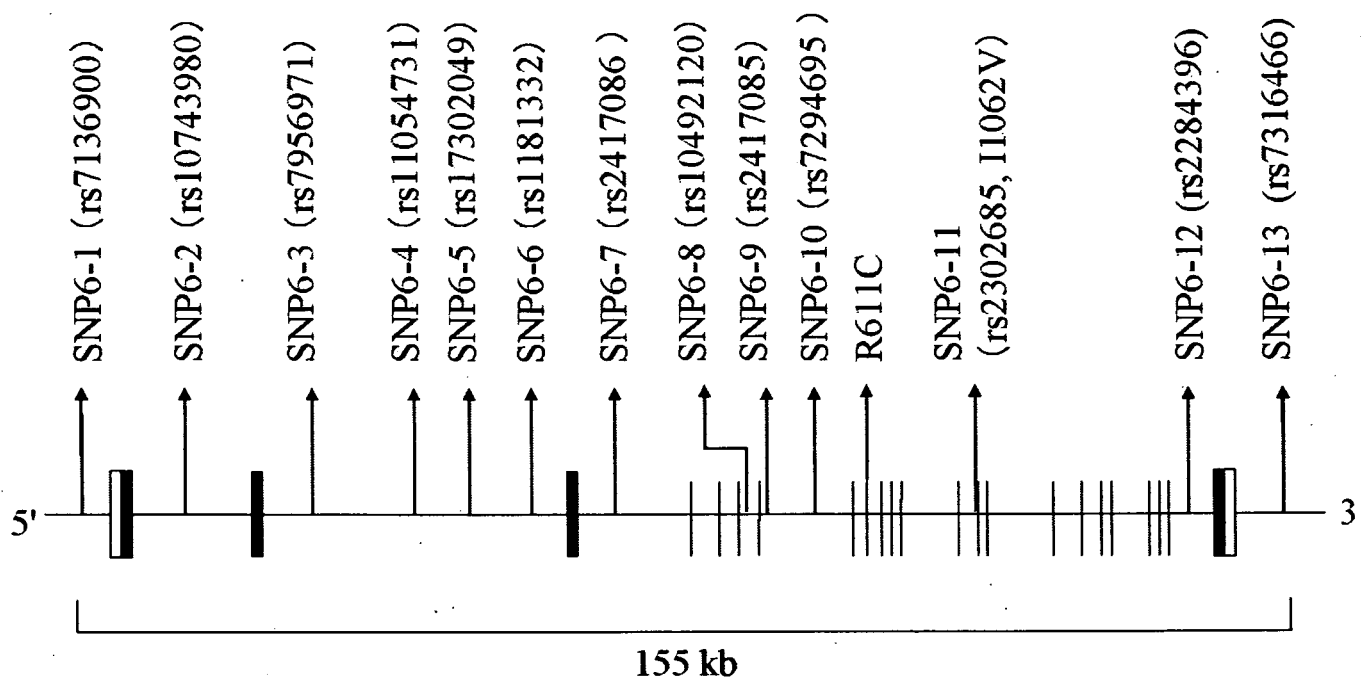
**Table 4.** Association analysis for SNPs of *LRP5* and Type 2 DM in the initial panel.

Position on Chromosome 11	SNP name	rs number	Major allele	Minor allele	MAF		<i>P</i> value
					Case	Control	
67838979	SNP5-1	rs312016	C	T	0.48	0.48	0.920
67845407	SNP5-2	rs4988300	G	T	0.25	0.24	0.626
67857932	SNP5-3	rs7944040	C	T	0.14	0.15	0.584
67897990	SNP5-4	rs638051	A	G	0.26	0.28	0.442
67920032	SNP5-5	rs4930573	C	G	0.22	0.23	0.591
67938604	SNP5-6	rs314750	A	G	0.33	0.36	0.244
67949266	SNP5-7	rs556442	A	G	0.37	0.40	0.171
67957871	SNP5-8	rs3736228	C	T	0.29	0.30	0.587
67966294	SNP5-9	rs3781579	T	C	0.16	0.16	0.820

SNP position is indicated as base-pair number in NCBI build 127. MAF, minor allele frequency. *P* values for the difference in the minor allele frequency between cases and controls were calculated by the chi-square test.

# Figure 1 Zenibayashi et al

A.



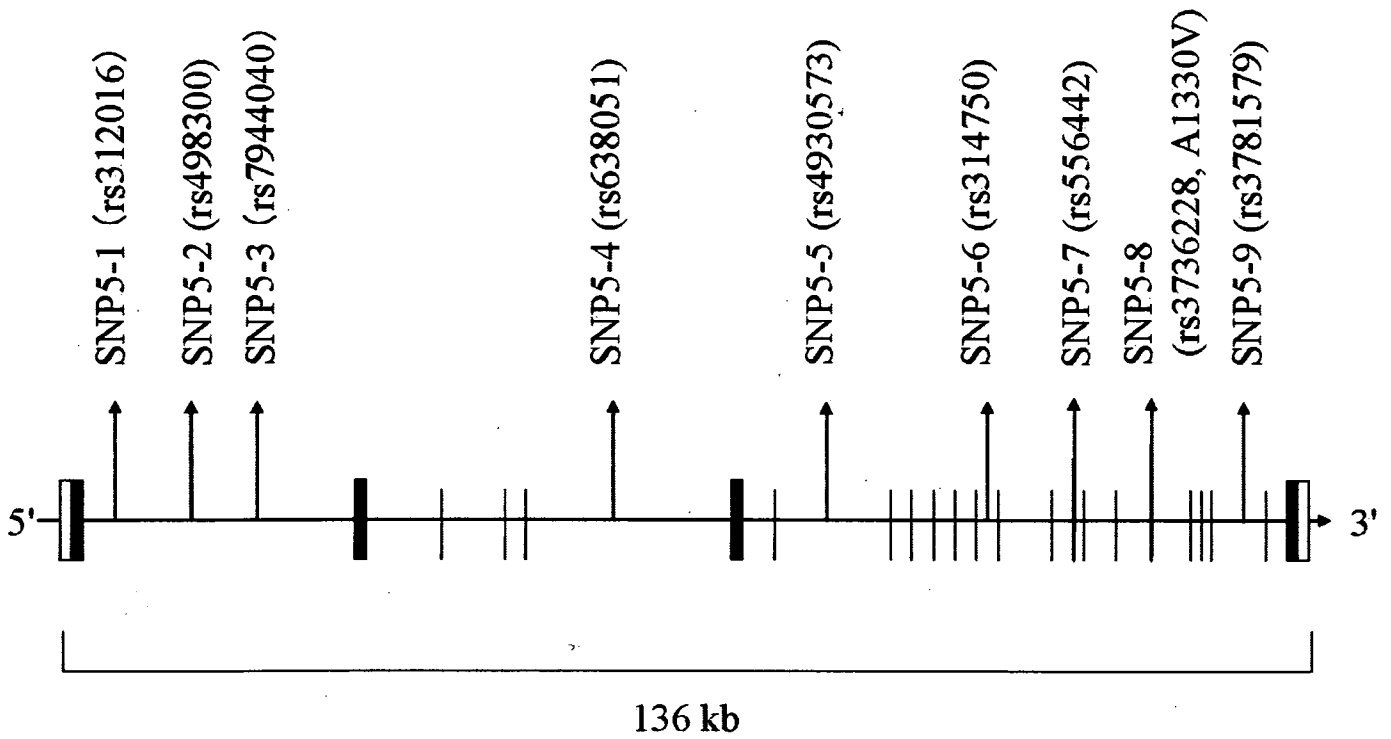
B.

$D' \setminus r^2$	SNP6-1	SNP6-2	SNP6-3	SNP6-4	SNP6-5	SNP6-6	SNP6-7	SNP6-8	SNP6-9	SNP6-10	SNP6-11	SNP6-12	SNP6-13
SNP6-1		0.20	0.19	0.08	0.00	0.39	0.20	0.00	0.00	0.13	0.16	0.13	0.00
SNP6-2	<b>0.75</b>		1.00	0.60	0.09	0.18	0.94	0.64	0.64	0.61	0.11	0.58	0.32
SNP6-3	<b>0.73</b>	<b>1.00</b>		0.60	0.09	0.19	0.94	0.66	0.66	0.60	0.11	0.58	0.33
SNP6-4	<b>0.56</b>	<b>0.93</b>	<b>0.93</b>		0.12	0.08	0.60	0.35	0.35	0.38	0.02	0.36	0.18
SNP6-5	<b>-0.19</b>	<b>-1.00</b>	<b>-1.00</b>	<b>-1.00</b>		0.02	0.09	0.06	0.06	0.06	0.01	0.06	0.03
SNP6-6	<b>0.88</b>	<b>1.00</b>	<b>1.00</b>	<b>0.79</b>	<b>-1.00</b>		0.18	0.13	0.13	0.14	0.52	0.13	0.10
SNP6-7	<b>0.75</b>	<b>0.97</b>	<b>0.97</b>	<b>0.93</b>	<b>-1.00</b>	<b>1.00</b>		0.64	0.64	0.56	0.11	0.53	0.31
SNP6-8	<b>0.02</b>	<b>0.96</b>	<b>0.96</b>	<b>0.85</b>	<b>-1.00</b>	<b>0.71</b>	<b>0.96</b>		1.00	0.31	0.16	0.30	0.52
SNP6-9	<b>0.02</b>	<b>0.96</b>	<b>0.96</b>	<b>0.85</b>	<b>-1.00</b>	<b>0.71</b>	<b>0.96</b>	<b>1.00</b>		0.31	0.16	0.30	0.52
SNP6-10	<b>0.58</b>	<b>0.80</b>	<b>0.80</b>	<b>0.76</b>	<b>-0.82</b>	<b>0.84</b>	<b>0.77</b>	<b>0.65</b>	<b>0.65</b>		0.12	0.97	0.62
SNP6-11	<b>0.60</b>	<b>0.80</b>	<b>0.80</b>	<b>0.45</b>	<b>-1.00</b>	<b>0.76</b>	<b>0.80</b>	<b>0.84</b>	<b>0.84</b>	<b>0.82</b>		0.17	0.26
SNP6-12	<b>0.58</b>	<b>0.78</b>	<b>0.77</b>	<b>0.73</b>	<b>-0.81</b>	<b>0.84</b>	<b>0.74</b>	<b>0.65</b>	<b>0.65</b>	<b>1.00</b>	<b>1.00</b>		0.66
SNP6-13	<b>-0.13</b>	<b>0.71</b>	<b>0.71</b>	<b>0.65</b>	<b>-0.71</b>	<b>0.57</b>	<b>0.70</b>	<b>0.75</b>	<b>0.75</b>	<b>0.95</b>	<b>1.00</b>	<b>1.00</b>	



# Figure 2 Zenibayashi et al

A.



B.

D' \ r <sup>2</sup>	SNP5-1	SNP5-2	SNP5-3	SNP5-4	SNP5-5	SNP5-6	SNP5-7	SNP5-8	SNP5-9
SNP5-1	0.27	0.12	0.07	0.00	0.00	0.00	0.00	0.00	0.00
SNP5-2	<b>-0.97</b>	0.48	0.08	0.00	0.03	0.03	0.01	0.00	0.00
SNP5-3	<b>-0.86</b>	<b>0.91</b>	0.17	0.01	0.02	0.03	0.00	0.01	0.01
SNP5-4	<b>-0.44</b>	<b>0.31</b>	<b>0.60</b>	0.01	0.00	0.00	0.01	0.01	0.01
SNP5-5	<b>0.09</b>	<b>-0.07</b>	<b>0.15</b>	<b>-0.13</b>	0.20	0.15	0.21	0.13	0.13
SNP5-6	<b>0.06</b>	<b>0.24</b>	<b>0.26</b>	<b>0.07</b>	<b>0.61</b>	<b>0.78</b>	<b>0.57</b>	<b>0.22</b>	<b>0.22</b>
SNP5-7	<b>0.00</b>	<b>0.26</b>	<b>0.34</b>	<b>0.09</b>	<b>0.59</b>	<b>0.97</b>	<b>0.62</b>	<b>0.25</b>	<b>0.25</b>
SNP5-8	<b>0.05</b>	<b>0.12</b>	<b>0.10</b>	<b>0.08</b>	<b>0.54</b>	<b>0.86</b>	<b>0.98</b>	<b>0.14</b>	<b>0.14</b>
SNP5-9	<b>-0.09</b>	<b>-0.08</b>	<b>0.08</b>	<b>-0.32</b>	<b>0.46</b>	<b>0.80</b>	<b>0.94</b>	<b>0.57</b>	<b>0.57</b>