Supplementary materials

Two novel candidate genes for insulin secretion identified by comparative genomics of multiple backcross mouse populations

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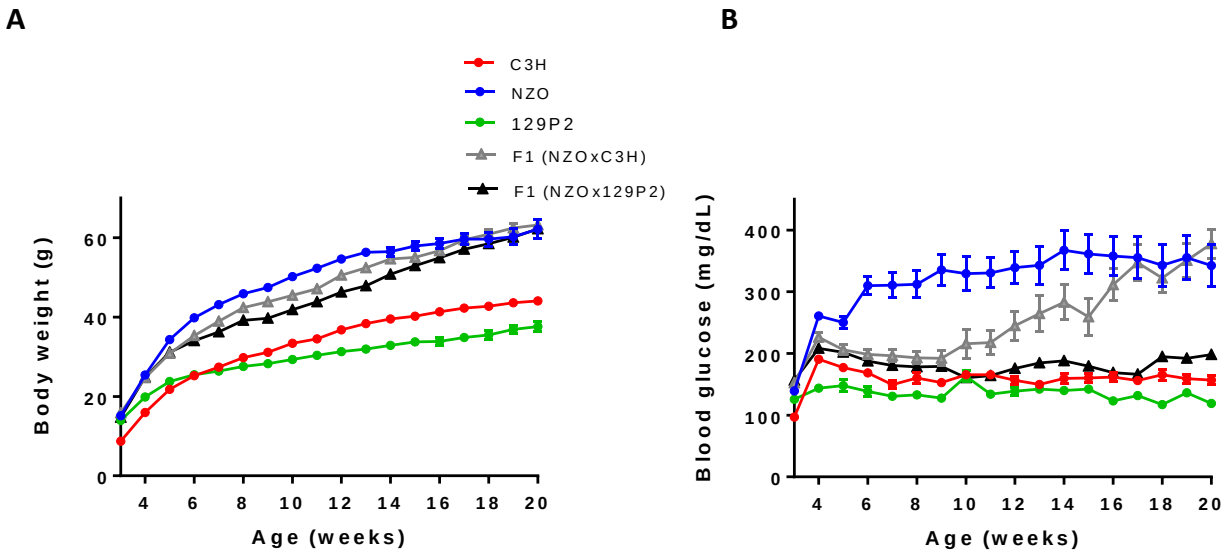

Figure S1: Metabolic characterization of parental mouse strains 129P2, C3H and NZO and both F_1 (NZOxC3H and NZOx129P2) generations. Body weight- (A) and blood glucose- (B) were measured weekly. Data represent mean values ± SEM of male mice (129P2: n=17; C3H: n=18; NZO: n=24-35; F_1(NZOxC3H): n=18; F_1(NZOx129P2): n=17).

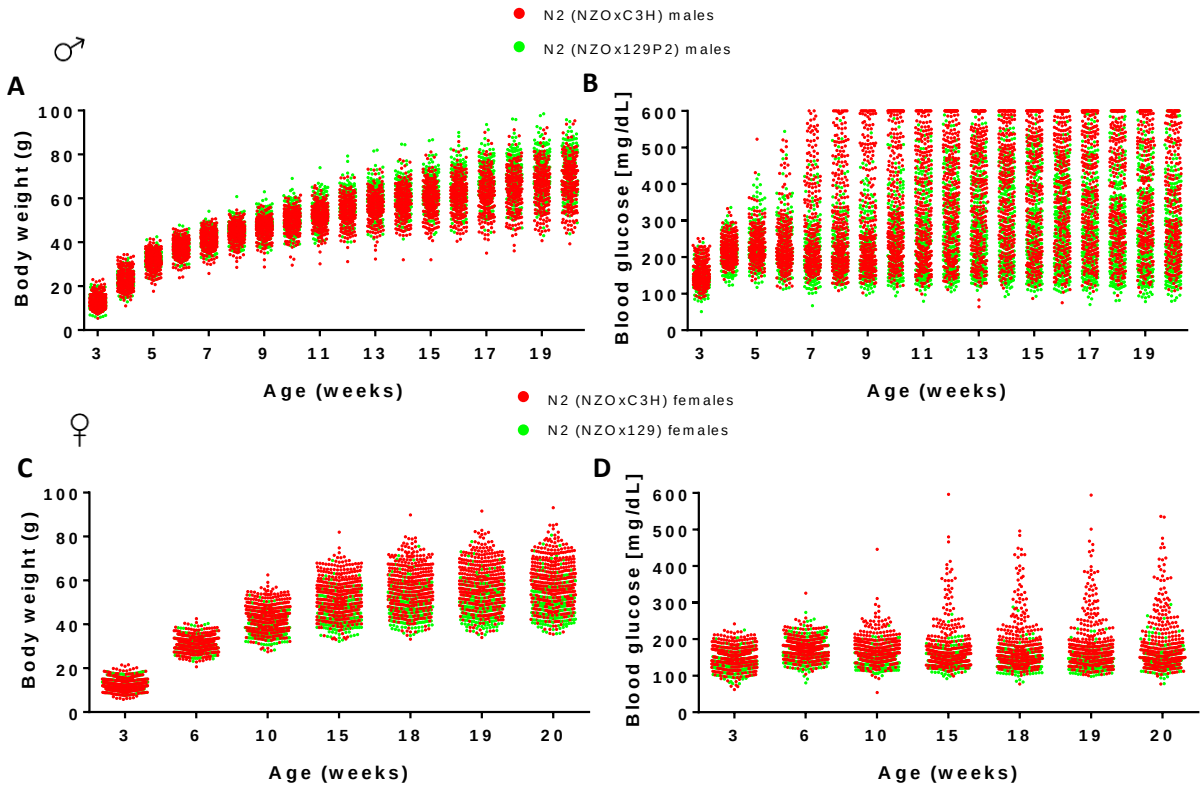

Figure S2: Metabolic characterization of males and females of both backcross populations, N_2(NZOx F_1(NZOxC3H)) and N_2(NZOx F_1(NZOx129P2)). Body weight- (A: males, C: females) and blood glucose- (B: males, D: females) was measured weekly for the males and at weeks 3, 6, 10, 15, and 18-20 for the females. Dots represent single animals. N_2(NZOx F_1(NZOxC3H)): n=269-329 males and 300-310 females, N_2(NZOx F_1(NZOx129P2)): n=285-291 males and 300-307 females.

Table S1: **Summary of QTL (LOD >4) from males and females of both backcross populations, N_2(NZOx F_1(NZOxC3H)) and N_2(NZOx F_1(NZOx129P2)).** The significance threshold was determined using a permutation test; the 95%-confidence interval was calculated by Bayesian method using R/qtl software. **N_2(NZOx F_1(NZOxC3H)), NxC**: n=269-329 males and 300-310 females, **N_2(NZOx F_1(NZOx129P2)), Nx129**: n=285-291 males and 300-307 females. BG, blood glucose; BW, body weight; C, C3H; Chr, chromosome; CI, confidence interval; f, female; FM, fat mass; FBG, fasting blood glucose; ins, insulin; LM, lean mass; LOD, logarithm of the odds; N, NZO; m, male; Pancr, Pancreas; Pos, Position.

Name	Sex	Chr	Trait	Peak Pos. (cM)	95% CI (cM)	Closest SNP-marker (Mbp)	Max. LOD	Week (max. effect)	Mean NZO/NZO	Mean C3H/NZO or NZO/129	cross
Nbg7p	m	7	BG	12	7-27	37.3	13.3	10	369 mg/dL	247 mg/dL	NxC
			BW	17	7-22	37.3	7.4	17	59.8 g	65.4 g	NxC
			LM	11	4-21	37.3	8.6	15	31.5 g	33.2 g	NxC
			Plasma ins	17	13-25	37.3	4.8	21	6.5 µg/L	11.3 µg/L	NxC
Nbg7d	m	7	BG	26	23-29	76.7	12.5	10	374 mg/dL	252 mg/dL	NxC
Nbg4d	m	4	BG	44	38-47	97.3	7.4	17	230 mg/dL	306 mg/dL	Nx129
			Liver weight	46	40-63	108.8	5.5	21	567 mg	592 mg	Nx129
Nbg15p	m	15	BG	23	18-30	63.3	6.7	15	410 mg/dL	310 mg/dL	NxC
Nbg15d	m	15	BG	41	34-47	98	6.5	10	349 mg/dL	272 mg/dL	NxC
Nbg7fem	f	7	BG	1	0-7	16.6	6.8	20	214 mg/dL	169 mg/dL	NxC
Nbg4d	m	4	BG	42	38-52	119	6.6	20	291 mg/dL	389 mg/dL	NxC
			Pancr ins	45	44-51	119	4.2	21	12.9 µg/mg	6.2 µg/mg	NxC
			Plasma ins	40	44-62	119	4.3	21	10.8 µg/L	7.2 µg/L	NxC
Nbg5	m	5	BG	34	14-43	63.4	6.5	7	293 mg/dL	225 mg/dL	NxC
Nbg4p	m	4	BG	28	23-31	58.1	5.8	17	234 mg/dL	307 mg/dL	Nx129
Nbg6	m	6	BG	51.7	33-52	139	4.6	12	394 mg/dL	312 mg/dL	NxC
Nbg18	m	18	BG	12.2	6-18	43.9	4.3	3	164 mg/dL	148 mg/dL	NxC
Nbg8	m	8	BG	11	2-18	41.1	4.3	10	346 mg/dL	279 mg/dL	NxC
Nbg7_2	m	7	BG	26.7	5-35	56.7	4.2	18	299 mg/dL	235 mg/dL	Nx129
Nbg14	m	14	FBG	0	0-7	11.0	4.1	21	215 mg/dL	164 mg/dL	Nx129
Nbw4	m	4	BW	32	16-41	91.0	8.2	19	69.1 g	62.7 g	NxC
Nbw10fem	f	10	BW	7.2	5-11	89.1	9.3	6	32.1 g	29.5 g	NxC
Nbw4fem	f	4	BW	15	8-27	53	7.5	19	62.1 g	56 g	NxC
Nbw14fem	f	14	BW	23	17-30	63.6	5.2	6	31.8 g	29.8 g	NxC
Nbw13fem	f	13	BW	29.0	0-29	74.4	4.2	6	31.8 g	30 g	NxC
Nbw16male	m	16	BW	1	0-25	11.5	4.1	6	38.1 g	36.3 g	NxC
Nlm10fem	f	10	LM	6	3-11	89.1	8.3	6	20.3 g	19.2 g	NxC
Nlm3	m	3	LM	51.7	32-52	86.2	7.4	6	27 g	25.6 g	NxC

Name	Sex	Chr	Trait	Peak Pos. (cM)	95% CI (cM)	Closest SNP-marker (Mbp)	Max. LOD	Week (max. effect)	Mean NZO/NZO	Mean C3H/NZO or NZO/129	cross
Nlm2	m	2	LM	54	36-61	113.7	5.9	15	34.7 g	33.2 g	Nx129
Nlm10	m	10	LM	8	0-14	89.1	5.6	6	26.9 g	25.6 g	NxC
Nlm2_2	m	2	LM	29	22-44	84	4.2	6	26.7 g	25.6 g	NxC
Nfm4fem	f	4	FM	15	8-25	53	7.5	15	28.7 g	24.7 g	NxC
Nfm14fem	f	14	FM	23	17-32	63.5	6.3	6	10.6 g	9.2 g	NxC
Nfm10fem	f	10	FM	7.2	3-10	89.1	6.3	10	20.6 g	17.8 g	NxC
Nfm14	m	14	FM	26	6-32	77.5	4.9	6	10.1 g	8.9 g	NxC
Nfm6fem	f	6	FM	20	5-50	64.2	4.4	6	10.5 g	9.3 g	NxC

Table S2: Coding non-synonymous single nucleotide polymorphisms (Cn-SNPs) in the critical QTL region of *Nbg7p*. The Sanger database (REL-1505 - GRCm38; https://www.sanger.ac.uk) was queried for SNPs where C3H/HeJ differed from both NZO/HlLtJ and 129P2/OlaHsd. SNPs were analyzed for their potential impact on protein function using the 'Sorting Tolerant From Intolerant' (SIFT) algorithm[1)]. Reference allele in bold face. As SIFT score below 0.05 predicts a deleterious impact of the substitution.

Position Chr. 7	Symbol	dbSNP	129P2/ OlaHsd	C3H/ HeJ	NZO/ HlLtJ	Protein position	Amino acid exchange	SIFT (score)
30,056,835	*Zfp82*	rs51511420	G	**A**	G	304	V [Val] ⇒ A [Ala]	tolerated (0.16)
30,751,848	*Sbsn*	rs52020542	A	**G**	A	96	S [Ser] ⇒ N [Asn]	tolerated (1)
30,867,466	*Cd22*	rs48887107	C	**T**	C	796	T [Thr] ⇒ A [Ala]	tolerated (0.35)
31,359,121	*Scgb2b3*	rs32370064	G	**A**	G	86	F [Phe] ⇒ L [Leu]	tolerated (0.84)
31,360,167	*Scgb2b3*	rs46476185	C	**T**	C	61	K [Lys] ⇒ E [Glu]	tolerated (1)
35,627,419	*Ankrd27*	rs13471230	C	**T**	C	730	S [Ser] ⇒ P [Pro]	tolerated (1)
43,567,335	*Zfp658*	rs47840949	C	**T**	C	43	V [Val] ⇒ A [Ala]	tolerated (1)
43,572,611	*Zfp658*	rs51924694	T	**G**	T	103	R [Arg] ⇒ S [Ser]	tolerated (0.35)
43,572,940	*Zfp658*	rs48214912	A	**G**	A	213	S [Ser] ⇒ N [Asn]	tolerated (1)
43,572,961	*Zfp658*	rs107750661	A	**G**	A	220	G [Gly] ⇒ D [Asp]	tolerated (0.53)
43,572,987	*Zfp658*	rs46297319	A	**C**	A	229	P [Pro] ⇒ T [Thr]	tolerated (1)
43,573,008	*Zfp658*	rs47601314	G	**A**	G	236	N [Asn] ⇒ D [Asp]	tolerated (0.45)
43,573,021	*Zfp658*	rs49887463	G	**T**	G	240	L [Leu] ⇒ R [Arg]	tolerated (0.51)
43,573,029	*Zfp658*	rs46416895	G	**A**	G	243	T [Thr] ⇒ A [Ala]	tolerated (0.74)
43,573,030	*Zfp658*	rs51202651	G	**C**	G	243	T [Thr] ⇒ R [Arg]	tolerated (0.64)
43,573,708	*Zfp658*	rs49446471	C	**A**	C	469	E [Glu] ⇒ A [Ala]	tolerated (0.37)
43,573,968	*Zfp658*	rs49517688	G	**A**	G	556	I [Ile] ⇒ V [Val]	tolerated (0.26)
43,590,358	*Zfp719*	rs46898788	G	**C**	G	457	H [His] ⇒ D [Asp]	tolerated (0.49)
43,659,249	*Siglece*	rs47694652	C	**T**	C	227	N [Asn] ⇒ D [Asp]	tolerated (0.1)
43,660,062	*Siglece*	rs46346803	C	**A**	C	24	V [Val] ⇒ G [Gly]	tolerated (0.77)
44,016,001	*Klk1b26*	rs39690593	T	**C**	T	111	T [Thr] ⇒ I [Ile]	tolerated (0.22)
44,016,121	*Klk1b26*	rs46793621	A	**C**	A	151	T [Thr] ⇒ K [Lys]	tolerated (0.31)
44,016,267	*Klk1b26*	rs46049640	C	**T**	C	168	S [Ser] ⇒ P [Pro]	tolerated (1)
44,016,819	*Klk1b26*	rs37656890[2)]	T	**A**	T	229	N [Asn] ⇒ Y [Tyr][3)]	deleterious (0)
44,054,487	*Klk1b27*	rs48236844	T	**C**	T	18	A [Ala] ⇒ V [Val]	tolerated (0.63)
44,739,565	*Zfp473*	rs240887143	A	**C**	A	44	W [Trp] ⇒ L [Leu]	tolerated (1)

[1)] Kumar, P., S. Henikoff and P. C. Ng, 2009 Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat Protoc 4: 1073-1081. [2)] Sanger panel strains with T allele (N⇒ Y) for rs37656890: 129P2/OlaHsd, A/J, BALB/cJ, CAST/EiJ, DBA/1J, DBA/2J, I/LnJ, LEWES/EiJ, LP/J, MOLF/EiJ, NZB/B1NJ, NZO/HlLtJ, NZW/LacJ, Sea/GnJ, St/bJ, WSB/EiJ; [3)] Residue not conserved among related kallikreins (e.g. W [Trp] in *Klk1b22*, *Klk1*, *Klk1b9*; I [Ile] in *Klk1b11*, *Klk1b21*, *Klk1b16*), not conserved across species (rat, human).

Table S3: Indel polymorphisms in the critical QTL region of *Nbg7p*. The Sanger database (REL-1505 - GRCm38; https://www.sanger.ac.uk) was queried for Indel polymorphisms where C3H/HeJ differed from both NZO/HILtJ and 129P2/OlaHsd. All indels fulfilling the criteria mapped in intronic or intergenic regions.

Position Chr. 7	Symbol	dbSNP	129P2/OlaHsd	C3H/HeJ	NZO/HlLtJ	Variant type
30,872,402	*Cd22*	rs229282204; rs214494659	GATTCATTCATTC ATTCATTC	GATTCATTCATTC ATTC	GATTCATTCATTC ATTCATTCATTC	Intronic variant
44,818,214	*Atf5*	rs212982150; rs258293738	CTT	C	CTTTTTTTT	upstream gene variant
44,943,226	*Tsks*	rs213087291; rs243384591	C	CG	CGGGG	5'UTR variant
45,644,050	*Mamstr*	rs265585922	ACATACATACATA CATACATAC	ACATACATAC	AATACATACATAC	Intronic variant
45,696,569	*Car11*	rs229863154	GTTTGTTTGGT	GT	GTTTGTTTGGT	upstream gene variant
45,906,491	*Tmem143*	rs259428117	CTTT	CTT	CT	Intronic variant

Table S4: Previously published QTL for diabetes-related traits identified in crossbreedings with the NZO strain. Data were obtained from the online databases www.diabesitygenes.org[1)] and www.obesitygenes.org[2)]. Chr, chromsome; bw, body weight; fat%, relative fat content; CI, confidence interval; BC, backcross, IC, intercross. Bold, overlap to present study.

QTL name	Chr.	CI (Mbp)	Trait	Max. LOD	Cross	Cross type	Reference
Nob3	1	104-195	bw	16.1	NZO/HIBomDife x C57BL/6JRI	IC	Vogel *et al.* 2009
Nzoq1	1	10-76	bw	9.4	NZOHlLt x NON/Lt	BC	Reifsynder *et al.* 2000
Obq7	1	42-71	fat%	6.9	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
Obq8	1	122-162	fat%	6.4	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
Obq9	1	157-172	fat%	6.7	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
D1Mit411	1	26-76	insulin	4.6	NON/Lt x NZO/H1Lt	BC	Reifsynder *et al.* 2000
D1Mit411	1	26-76	glucose	4.9	NON/Lt x NZO/H1Lt	BC	Reifsynder *et al.* 2000
Nob5	1	133-168	bw	3.6	NZO/HIBomDife x C57BL/6JRI	BC	Vogel *et al.* 2018
Obq10	2	94-121	fat%	7.9	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
Nidd1/36	4	79-109	glucose	6.5	NZO/Hl x NON	IC	Leiter *et al.* 1998
Nidd/SJL	**4**	**100-147**	**glucose**	**3.6**	**NZO/HIBomDife x SJL**	**BC**	**Plum *et al.* 2000**
D5Mit81	5	50-109	fat%	3.9	NON/Lt x NZO/H1Lt	BC	Reifsynder *et al.* 2000
Nob1	5	29-89	bw	4.4	NZO/HIBomDife x SJL	BC	Kluge *et al.* 2000
Nob1	5	29-89	fat weight	3.0	NZO/HIBomDife x SJL	BC	Kluge *et al.* 2000
Obq11	5	4-28	fat%	4.4	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
Obq12	5	38-56	fat%	5.3	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
D6Mit275	6	35-67	bw	2.5	NZOHlLt x NON/Lt	BC	Reifsynder *et al.* 2000
Obq13	6	49-57	fat%	9.3	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
Obq14	6	94-107	fat%	9.2	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
D6Mit275	6	32-72	insulin	1.9	NZOHlLt x NON/Lt	BC	Reifsynder *et al.* 2000
Obq15	7	75-99	fat%	8.1	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
Dis1	**7**	**35-101**	**insulin**	**13.1**	**NZO/Wehi x C57BL/6J**	**BC**	**Andrikopoulos *et al.* 2016**
D9Mit128	9	32-61	insulin	3.2	NZO/Hl x NON	IC	Leiter *et al.* 1998
Nidd3/16	11	20-105	glucose	11.9	NZO/Hl x NON	IC	Leiter *et al.* 1998
Nidd3/24.2	11	20-105	insulin	8.9	NZO/Hl x NON	IC	Leiter *et al.* 1998
Nzoq2	12	87-102	bw	3.1	NZOHlLt x NON/Lt	BC	Reifsynder *et al.* 2000
Nzoq2	12	87-112	fat%	4.9	NZOHlLt x NON/Lt	BC	Reifsynder *et al.* 2000
D12Mit204	12	79-89	insulin	3.0	NZO/Hl x NON	IC	Leiter *et al.* 1998
D15Mit26	15	33-73	bw	2.7	NZOHlLt x NON/Lt	BC	Reifsynder *et al.* 2000
D15Mit159	15	70-104	insulin	3.6	NZOHlLt x NON/Lt	BC	Reifsynder *et al.* 2000
Obq4b	17	10-26	fat%	8.8	SM/J x NZO/HlLt	IC	Taylor *et al.* 2001
D18Mit60	18	17-49	fat%	2.5	NZOHlLt x NON/Lt	BC	Reifsynder *et al.* 2000
Nidd2	18	12-45	glucose	5.0	NZO/Hl x NON	IC	Leiter *et al.* 1998

[1)]Schmidt, C., N.P. Gonzaludo, S. Strunk, S. Dahm, J. Schuchhardt, F. Kleinjung, S. Wuschke, H.G. Joost, and H. Al-Hasani. 2008. A meta-analysis of QTL for diabetes-related traits in rodents. Physiological genomics. 34:42-53;
[2)] Wuschke, S., S. Dahm, C. Schmidt, H. G. Joost and H. Al-Hasani, 2007 A meta-analysis of quantitative trait loci associated with body weight and adiposity in mice. Int J Obes (Lond) 31: 829-841.

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Table S5: Previously published QTL for diabetes-related traits identified in crossbreedings with 129 strains. Data were obtained from the online databases www.diabesitygenes.org[1)] and www.obesitygenes.org[2)]. Chr, chromsome; bw, body weight; fat%, relative fat content; CI, confidence interval; BC, backcross, IC, intercross.

QTL name	Chr.	CI (Mbp)	Trait	Max. LOD	Cross	Cross type	Reference
Obq2	1	10-42	fat%	6.0	129/SvEms-p+ x EL/Suz	IC	Taylor and Phillips 1996
Obq17	1	112-143	fat%	2.3	C57BL/6J x 129S1/SvImJ	IC	Ishimori *et al.* 2004
D1Mit19	1	39-107	insulin	3.6	C57BL/6J x 129/Sv	IC	Kido *et al.* 2000
D1Mit270	1	153-193	insulin	2.9	PERA/Ei x C57BL/6.129S7-Ldlr	BC	Seidelmann *et al.* 2005
Bwq5	2	129-160	bw	4.4	129P3/J x C57BL/6ByJ	IC	Reed *et al.* 2003
Adip2.2	2	146-177	fat weight	3.1	129P3/J x C57BL/6ByJ	IC	Reed *et al.* 2003
D2Mit151	2	13-145	insulin	5.6	C57BL/6J x 129/Sv	IC	Kido *et al.* 2000
D3Mit278	3	52-92	insulin	3.2	C57BL/6J x 129S6/SvEvTac	IC	Almind and Kahn 2004
Mob2a	6	0-31	fat%	2.6	C57BL/6J x 129S1/SvImJ	IC	Ishimori *et al.* 2004
D6Mit201	6	127-150	insulin	2.8	C57BL/6J x 129/Sv	IC	Kido *et al.* 2000
Obq1	7	54-86	fat%	8.4	129/SvEms-p+ x EL/Suz	IC	Taylor and Phillips 1996
Obq16	8	86-108	fat%	10.0	C57BL/6J x 129S1/SvImJ	IC	Ishimori *et al.* 2004
Bwq6	9	95-124	bw	4.0	129P3/J x C57BL/6ByJ	IC	Reed *et al.* 2003
Adip5a	9	29-60	fat weight	4.0	129P3/J x C57BL/6ByJ	IC	Reed *et al.* 2003
D10Mit42	10	48-102	insulin	5.6	C57BL/6J x 129/Sv	IC	Kido *et al.* 2000
D11Mit199	11	82-122	insulin	3.0	C57BL/6J x 129S6/SvEvTac	IC	Almind and Kahn 2004
D12Mit182	12	0-31	fat%	2.9	C57BL/6J x 129S1/SvImJ	IC	Ishimori *et al.* 2004
D12Mit231	12	55-95	insulin	3.1	C57BL/6J x 129/Sv	IC	Kido *et al.* 2000
D12Mit231	12	78-115	glucose	2.7	C57BL/6J x 129S6	IC	Almind *et al.* 2003
D13Mit144	13	77-117	insulin	4.3	PERA/Ei x C57BL/6.129S7-Ldlr	BC	Seidelmann *et al.* 2005
D14Mit55	14	9-49	glucose	2.2	C57BL/6J x 129S6	IC	Almind *et al.* 2003
D14Mit75	14	92-117	glucose	2.3	C57BL/6J x 129S6	IC	Almind *et al.* 2003
D14Mit55	14	9-49	insulin	5.6	C57BL/6J x 129S6	IC	Almind *et al.* 2003
D14Mit192	14	51-90	glucose	3.3	PERA/Ei x C57BL/6.129S7-Ldlr	BC	Seidelmann *et al.* 2005
D14Mit52	14	11-51	insulin	3.0	C57BL/6J x 129S6/SvEvTac	IC	Almind and Kahn 2004
D15Mit13	15	0-23	glucose	3.3	C57BL/6J x 129S6/SvEvTac	IC	Almind and Kahn 2004
Adip9	16	71-99	fat weight	3.3	129P3/J x C57BL/6ByJ	IC	Reed *et al.* 2003

[1)] Schmidt, C., N.P. Gonzaludo, S. Strunk, S. Dahm, J. Schuchhardt, F. Kleinjung, S. Wuschke, H.G. Joost and H. Al-Hasani. 2008. A meta-analysis of QTL for diabetes-related traits in rodents. Physiological genomics. 34:42-53;
[2)] Wuschke, S., S. Dahm, C. Schmidt, H. G. Joost and H. Al-Hasani, 2007 A meta-analysis of quantitative trait loci associated with body weight and adiposity in mice. Int J Obes (Lond) 31: 829-841.

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Table S6: Previously published QTL for diabetes-related traits identified in crossbreedings with the C3H/He strain. Data were obtained from the online databases www.diabesitygenes.org[1)]. Chr, chromsome; bw, body weight; CI, confidence interval; IC, intercross. IPGTT, interperitoneal glucose tolerance test; Bold, overlap to present study.

QTL name	Chr.	CI (Mbp)	Trait	Max. LOD	Cross	Cross type	Reference
D2Mit48	2	136-176	IPGTT	8.3	C57BL/6J x C3H/He	IC	Kayo *et al.* 2000
D4Mit15	**4**	**46-129**	**IPGTT**	**5.4**	**C57BL/6J x C3H/He**	**IC**	**Kayo *et al.* 2000**
Nidd3nsyins	6	108-148	insulin	4.7	NSY x C3H/He	IC	Ueda *et al.* 1999
Nidd3nsy36	6	108-148	IPGTT	2.7	NSY x C3H/He	IC	Ueda *et al.* 1999
Gluhos3	9	20-59	IPGTT	6.7	C57BL/6J x C3H/He	IC	Toye *et al.* 2005
Nidd1nsy24	11	45-85	IPGTT	9.5	NSY x C3H/He	IC	Ueda *et al.* 1999
Nidd4nsy	11	0-36	IPGTT	5.8	NSY x C3H/He	IC	Ueda *et al.* 1999
Gluhos2	11	0-68	IPGTT	5.2	C57BL/6J x C3H/He	IC	Toye *et al.* 2005
D13Mit148	13	90-121	IPGTT	4.2	C57BL/6J x C3H/He	IC	Kayo *et al.* 2000
Gluhos1	13	92-120	IPGTT	5.0	C57BL/6J x C3H/He	IC	Toye *et al.* 2005
D13Mit262	13	94-121	IPGTT	4.8	C57BL/6J x C3H/He	IC	Toye *et al.* 2005
Nidd2nsyins	14	35-74	insulin	4.5	NSY x C3H/He	IC	Ueda *et al.* 1999
Nidd2nsy24	14	35-74	IPGTT	3.6	NSY x C3H/He	IC	Ueda *et al.* 1999

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