ScienceAdvances

AAAS

Supplementary Materials for

The GH receptor exon 3 deletion is a marker of male-specific exceptional longevity associated with increased GH sensitivity and taller stature
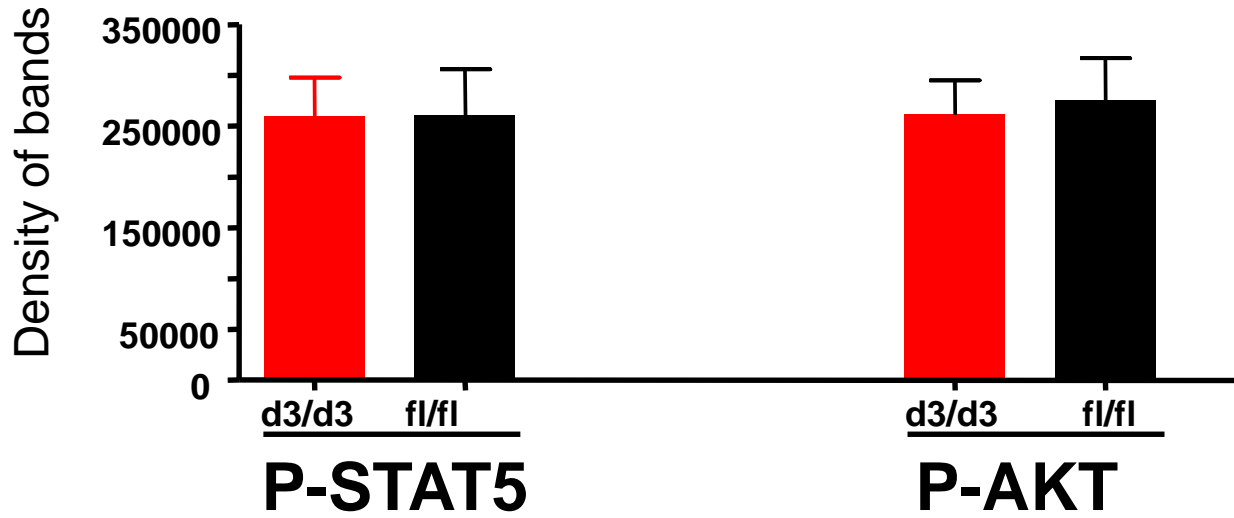
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fig. S1. Phosphorylation of STAT5 and AKT in homozygous WT and *d3-GHR* transformed lymphocytes from male AJ centenarians. No effect on the phosphorylation of STAT5 and AKT, suggesting a unique, pathway-specific effect of the *d3-GHR* polymorphism on GH signaling with decreased constitutive activation but enhanced GH-driven signaling.

table S1. Analysis (allelic, dominant, additive, and recessive models) of various variables (means ± SE), includes all AJs groups (*n* = 567) and adjusted for gender, age, and group. d3- Homozygote deletion, WT-Wild type, Het-Heterozygote, Pval- p value.

	Allelic-O-C			Dominant-O-C			Additive-O-C				Recessive-O-C		
	d3	None	Pval	Het and d3/d3	WT	Pval	d3/d3	Het	WT	Pval	d3	WT and Het	Pval
IGF-I (ng/ml)	123+/-4.27	134+/-2.96	0.052	123+/-4.57	138+/-5.09	0.03	122+/-11.3	123+/-5.05	139+/-5.13	0.10	125+/-11.2	130+/-3.61	0.67
IGF-II (ng/ml)	794+/-29.8	806+/-20.4	0.79	789+/-33.6	821+/-36.4	0.98	834+/-86.8	782+/-35.6	821+/-36.5	0.78	834+/-86.2	800+/-25.7	0.49
IGFBP-1 (ng/ml)	25.5+/-2.57	15.9+/-1.74	0.01	24.6+/-3.12	13.4+/-2.73	0.03	29.3+/-5.39	23+/-3.51	13.4+/-2.73	0.06	29.3+/-5.44	17.4+/-2.37	0.09
IGFBP-2 (mg/dl)	13.8+/-0.98	13.1+/-0.67	0.97	13.5+/-1.1	13.2+/-1.14	0.99	15.6+/-2.39	12.9+/-1.22	13.2+/-1.14	0.99	15.6+/-2.39	13.1+/-0.84	0.93
IGFBP-3 (ng/ml)	2449+/-59.1	2489+/-40.6	0.90	2433+/-65.5	2526+/-69.4	0.59	2539+/-149	2408+/-71.9	2526+/-69.4	0.60	2539+/-149	2470+/-50.9	0.52
IGFBP-4 (ng/ml)	375+/-11.3	381+/-7.7	0.91	375+/-12.6	384+/-14	0.80	376+/-34.4	375+/-13.4	384+/-14.1	0.93	376+/-34.2	379+/-9.65	0.83
IGF-I/IGFBP-3 ratio	0.07+/-0.002	0.07+/-0.001	0.20	0.07+/-0.002	0.07+/-0.003	0.12	0.07+/-0.005	0.07+/-0.002	0.07+/-0.002	0.30	0.07+/-0.005	0.07+/-0.002	0.78
GHBP (pM)	1011+/-32.6	1220+/-27.2	0.004	1041+/-34.3	1397+/-58.2	0.002	699+/-110	1078+/-35.6	1397+/-58.2	0.0008	699+/-110	1169+/-31.0	0.009
Height (Inch)	66.5+/-0.16	66.4+/-0.1	0.47	66.3+/-0.17	66.5+/-0.18	0.89	67.3+/-0.42	66.1+/-0.19	66.5+/-0.18	0.11	67.3+/-0.42	66.3+/-0.13	0.05
Weight (Pound)	151+/-1.44	152+/-0.97	0.62	151+/-1.56	152+/-1.66	0.68	153+/-3.93	150+/-1.70	152+/-1.66	0.87	153+/-3.93	151+/-1.20	0.66

table S2. Analysis (allelic, dominant, additive, and recessive) of various variables (means ± SE), includes AJ centenarian (C) and control (C) groups (*n* = 344) and adjusted for gender, age, and group. d3- Homozygote deletion, WT-Wild type, Het-Heterozygote, Pval- p value.

	Allelic-C-C			Dominant-C-C			Additive-C-C				Recessive-C-C		
	d3	Het, WT	Pval	Het,d3/d3	WT	Pval	d3/d3	Het	WT	Pval	d3	Het, WT	Pval
IGF-I (ng/ml)	108+/-4.99	120+/-3.51	0.07	108+/-5.41	127+/-6.16	0.02	107+/-13.5	108+/-5.83	127+/-6.17	0.06	107+/-13.7	117+/-4.33	0.82
IGF-II (ng/ml)	746+/-38.9	774+/-25.3	0.98	751+/-43.4	783+/-45.2	0.99	681+/-140	758+/-45	783+/-45.6	1.00	681+/-139	769+/-32.3	0.97
IGFBP-1 (ng/ml)	33.7+/-5.44	23.3+/-4.06	0.13	32.3+/-7.65	21+/-6.05	0.39	38.7+/-9.74	29.8+/-8.35	21+/-6	0.28	38.7+/-9.46	24.7+/-5.79	0.11
IGFBP-2 (mg/dl)	18.3+/-1.66	17.4+/-1.17	0.78	17.5+/-1.93	18+/-1.95	0.72	23.3+/-4.2	16.3+/-2.11	18+/-1.96	0.93	23.3+/-4.18	17.2+/-1.53	0.98
IGFBP-3 (ng/ml)	2240+/-80.3	2339+/-58.6	0.64	2229+/-93.9	2402+/-96.6	0.42	2303+/-194	2213+/-102	2402+/-96.9	0.62	2303+/-193	2307+/-76.6	0.78
IGFBP-4 (ng/ml)	420+/-14	415+/-8.99	0.88	419+/-15.4	414+/-16.4	0.61	443+/-55.3	417+/-15.3	414+/-16	0.13	443+/-55.1	416+/-11	0.07
IGF-I/IGFBP-3 ratio	0.06+/-0.003	0.07+/-0.002	0.38	0.06+/-3e-3	0.07+/-3e-3	0.20	0.06+/-0.01	0.06+/-0.003	0.07+/-0.003	0.38	0.06+/-0.01	0.07+/-2e-3	0.88
GHBP (pM)	844+/-35.2	965+/-33.0	0.052	871+/-36.7	1102+/-86.5	0.006	556+/-122	902+/-38.2	1102+/-86.5	0.01	556+/-122	971+/-36.1	0.14
TSH (mIu/l)	2.34+/-0.13	2.27+/-0.09	0.73	2.33+/-2.25	0.14+/-0.15	0.74	2.42+/-0.37	2.31+/-0.15	2.25+/-0.15	0.94	2.42+/-0.37	2.28+/-0.11	0.84
Height (Inch)	66.2+/-0.21	66.4+/-0.14	0.97	66.1+/-0.23	66.6+/-0.24	0.46	67+/-0.6	65.9+/-0.25	66.6+/-0.24	0.22	67+/-0.6	66.3+/-0.17	0.19
Weight (Pound)	143+/-1.68	144+/-1.14	0.60	143+/-1.82	145+/-1.97	0.75	143+/-4.69	143+/-1.95	145+/-1.97	0.78	143+/-4.68	144+/-1.42	0.49

table S3. Groups analysis of various variables (means ± SE) adjusted for gender and age within AJs. d3-Homozygote deletion, WT-Wild type, Het-Heterozygote, Pval- p value.

	Control (N=147)			Offspring (N=223)			Centenarian (N=197)		
	d3	WT and Het	Pval	d3	WT and Het	Pval	d3	WT and Het	Pval
IGF -1(ng/ml)	123+/-26.2	140+/-6.8	0.45	147+/-18.5	149+/-6.07	0.70	90.1+/-16.0	96.7+/-5.56	0.97
IGF-II (ng/ml)	799+/-56.5	790+/-36.1	0.74	880+/-45.8	881+/-34.6	0.67	695+/-55.2	757+/-36.7	0.68
IGFBP-1 (ng/ml)	6.36+/-4.55	8.31+/-2.07	0.59	15.8+/-2.53	8.75+/-1.59	0.01	37.1+/-4.31	28.7+/-3.25	0.12
IGFBP-2 (mg/dl)	3.83+/-0.53	4.8+/-0.32	0.60	6.94+/-0.61	6.84+/-0.42	0.67	25.4+/-2.33	25.8+/-1.68	0.90
IGFBP-3 (ng/ml)	2660+/-126	2586+/-81.2	0.61	2736+/-94.4	2676+/-62.3	0.71	2034+/-86.4	2192+/-62.2	0.31
IGFBP-4 (ng/ml)	347+/-17.8	321+/-11.7	0.75	306+/-17.9	309+/-13.5	0.70	503+/-20.7	514+/-13	0.61
IGF-I/IGFBP-3 ratio	0.07+/-4e-3	0.07+/-2e-3	0.94	0.07+/-3e-3	0.07+/-2e-3	0.44	0.06+/-3e-3	0.06+/-2e-3	0.23
GHBP (pM)	1137+/-274	1224+/-67.8	0.91	906+/-194	1447+/-50.8	0.02	297+/-111	689+/-34.9	0.01
Height (Inch)	67.5+/-1.08	67.8+/-0.26	0.93	67.7+/-0.57	66.4+/-0.18	0.21	66.8+/-0.7	64.7+/-0.23	0.05
Weight (Pound)	170+/-10.2	167+/-2.42	0.69	166+/-6.7	162+/-2.13	0.95	133+/-4.63	125+/-1.56	0.41

table S4. Analysis (allelic, dominant, additive, and recessive models) of various variables (means ± SE), includes AJ offspring (O) and control (C) (*n* = 370) and adjusted for gender, age, and group. d3- Homozygote deletion, WT-Wild type, Het-Heterozygote, Pval- p value.

	Allelic-O-C			Dominant-O-C			Additive-O-C				Recessive-O-C		
	d3	Het and WT	Pval	Het and d3/d3	N/N	Pval	d3/d3	Het	WT	Pval	d3	He and WT	Pval
IGF-I(ng/ml)	142+/-5.51	146+/-3.72	0.43	143+/-5.97	148+/-6.4	0.51	141+/-15.1	143+/-6.46	148+/-6.41	0.71	141+/-15.1	146+/-4.61	0.49
IGF-II (ng/ml)	843+/-35.8	831+/-24.7	0.55	830+/-40.6	842+/-44.8	0.71	949+/-113	815+/-43	842+/-44.9	0.68	949+/-112	827+/-31.3	0.38
IGFBP-1 (ng/ml)	14.7+/-2.54	8.66+/-1.64	0.02	14.9+/-3.02	6.84+/-2.44	0.01	13.9+/-5.31	15.3+/-3.44	6.84+/-2.47	0.04	13.9+/-5.61	9.84+/-2.35	0.50
IGFBP-2 (mg/dl)	5.98+/-0.46	6.12+/-0.31	0.94	5.65+/-0.51	6.54+/-0.52	0.59	7.8+/-1.18	5.17+/-0.56	6.54+/-0.52	0.36	7.8+/-1.18	5.9+/-0.38	0.29
IGFBP-3 (ng/ml)	2712+/-77.5	2648+/-52.5	0.51	2683+/-85.7	2650+/-89.1	0.73	2883+/-204	2643+/-93.1	2650+/-89.2	0.66	2883+/-203	2646+/-66.1	0.37
IGFBP-4 (ng/ml)	324+/-13.7	316+/-9.62	0.58	322+/-15.5	313+/-17.8	0.76	343+/-43.1	320+/-16.5	313+/-17.9	0.68	343+/-42.7	317+/-12.1	0.38
IGF/BP3 ratio	0.07+/-0.002	0.07+/-0.002	0.55	0.07+/-3e-3	0.07+/-3e-3	0.78	0.07+/-0.01	0.07+/-0.003	0.07+/-0.003	0.70	0.07+/-0.01	0.07+/-0.002	0.40
GHBP (pM)	1238+/-45.1	1405+/-35.7	0.02	1261+/-47.3	1518+/-71.4	0.01	977+/-157	1288+/-49.0	1518+/-71.4	0.01	977+/-157	1366+/-41.0	0.04
Height (Inch)	67.2+/-0.19	67+/-0.12	0.45	67.2+/-0.2	66.9+/-0.2	0.66	67.7+/-0.52	67.1+/-0.22	66.9+/-0.2	0.59	67.7+/-0.52	67+/-0.15	0.31
Weight (Pound)	166+/-2.00	164+/-1.30	0.69	166+/-2.16	163+/-2.21	0.66	167+/-5.62	165+/-2.32	163+/-2.21	0.91	167+/-5.62	164+/-1.62	0.89

table S5A. Genotyping efforts among the four cohorts (*n* = 841): AJ (*n* = 567, 56% female), OOA 152 males, CHS 61 males, and FLLS 61 males.

	Entire Cohort			Genotyped reported Individuals		
	N	%F	Age range	N	%F	Age range
Ashkenazi Jews (AJ)	567	56	43-109	567	56	43-109
Old Order Amish (OOA)	1078	59	25-98	152	0	21-85
Cardiovascular Health Study (CHS)	5888	57	64-98	61	0	75-95
French Long Lived Study (FLLS)	706	0	34-110	61	0	70-109

table S5B. Crude measurements of various variables (means ± SE) in the three AJs (*n* = 567) study groups.

	Control (N=147)	Offspring (N=223)	Centenarian (N=197)
Age at recruitment	71+/-0.71	68.4+/-0.52	97.6+/-0.23
% of female (N)	36(53)	51(114)	48 (95)
IGF-I (ng/ml)	139+/-6.45(121)	149+/-5.99(194)	96+/-5.24(138)
IGF-II (ng/ml)	920+/-23(71)	952+/-21.2(86)	846+/-24.5(57)
IGFBP-1 (ng/ml)	14.2+/-2.24(25)	11.8+/-1.44(70)	30.1+/-2.58(66)
IGFBP-2 (mg/dl)	6.76+/-0.81(96)	6.13+/-0.35(158)	24.2+/-1.45(127)
IGFBP-3 (ng/ml)	2610+/-59.4(109)	2733+/-51(197)	2157+/-54.9(157)
IGF-I/IGFBP-3 ratio	0.07+/-0.002(109)	0.07+/-0.002(197)	0.06+/-0.002(157)
IGFBP-4 (ng/ml)	375+/-10.1(72)	357+/-9.95(86)	515+/-10.5(57)
GHBP (pM)	1220+/-64.8(78)	1413+/-52.8(140)	651+/-35.9(93)
Height (Inch)	67.8+/-0.33(141)	66.5+/-0.28(200)	64.9+/-0.3(150)
Weight (Pound)	167+/-2.74(143)	163+/-2.35(218)	126+/-1.88(184)

table S6. PCR procedure using primers.

Primer	Sequence
G1	5'-TGTGCTGGTCTGTTGGTCTG
G2	5'-AGTCGTTCCTGGGACAGAGA
G3	5'-CCTGGATTAACACTTTGCAGACTC