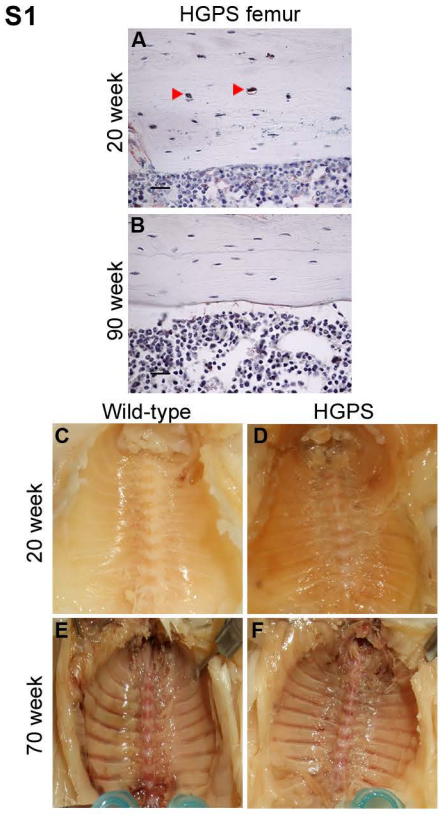

Figure S1. Very low transgenic expression and no defects in the bone. Immunohistochemical labelling for transgenic lamin A/progerin in the HGPS femur (A, B) showed that there were very few osteocytes that are positive for the transgene (arrowheads) at 20 weeks, and almost none in the 90 week old HGPS animals. Neither HGPS nor wild-type animals had any calluses at either 20 or 70 weeks of age (C-F). Scale bars: 20μm.

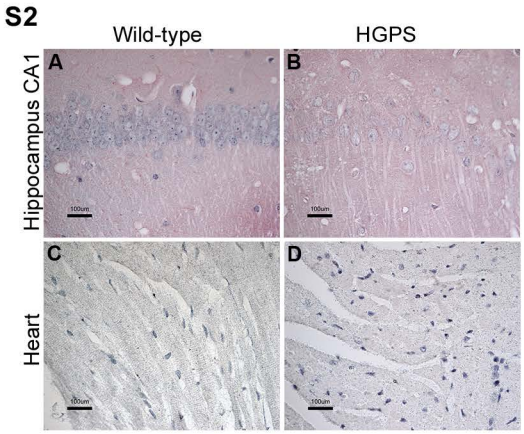

Figure S2. Immunohistochemical labelling of cleaved caspase-3 in the brain and heart tissue. To examine for the presence of apoptosis in the HGPS animals, 90-week old brain and 74-week old heart tissues were labelled with cleaved caspase-3 antibody. There were no positive labelling in both wild-type or HGPS animals. Scale bars: 100μm.

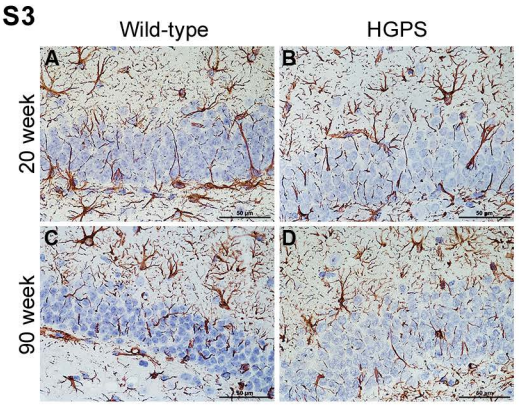

Figure S3. No astrocyte activation in the brain. Immunohistochemical labelling for glial fibrillary acidic protein showed no astrocyte activation in either HGPS or wild-type animals. Images are from the hilus region of the dentate gyrus. Scale bars: 50μm.

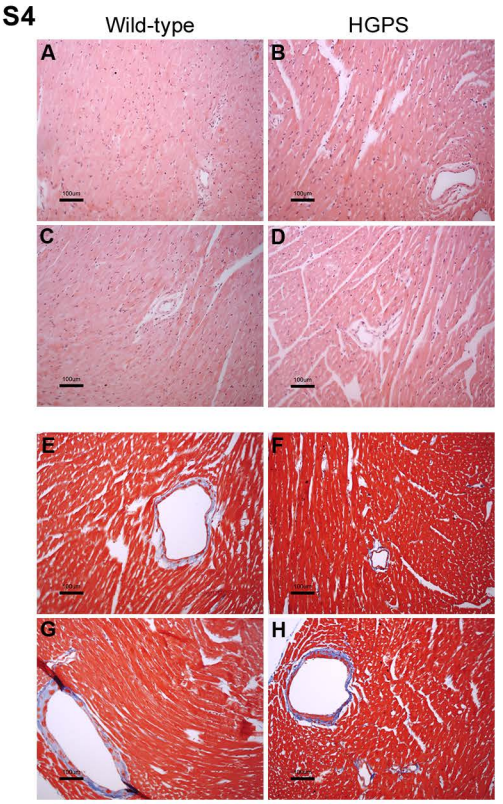

Figure S4. No defects in the heart. Haematoxylin and eosin (A-D) and Masson's trichrome (E-H) stainings showed that both HGPS and wild-type animals had no defects in the heart at 74 weeks of age. Images are from the ventricle (A, B, E, F) and the atrium (C, D, G, H). Scale bars: 100μm.

S5

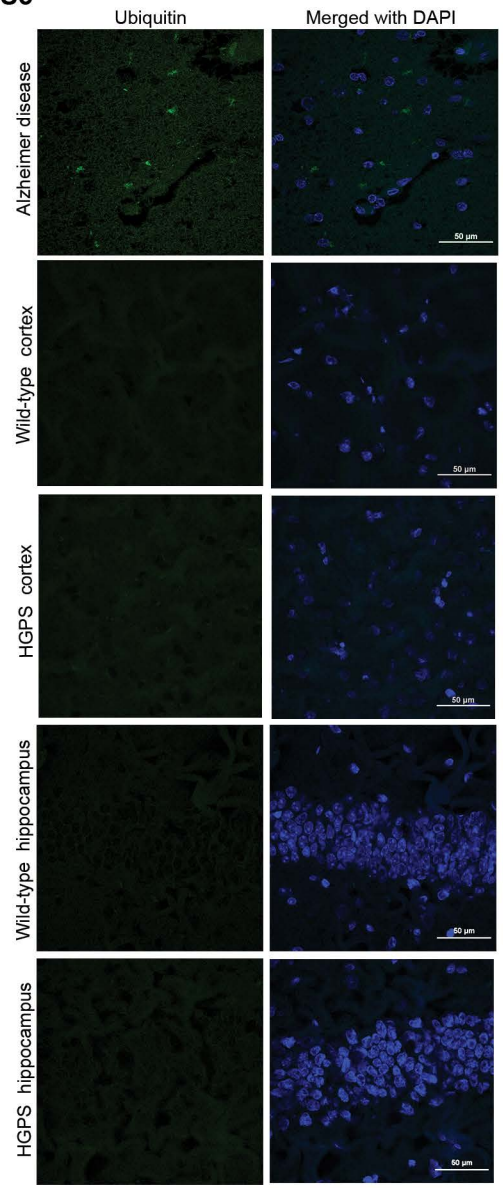

Figure S5. No evidence of protein inclusions in brain from HGPS animals. Immunofluorescent labelling for ubiquitin in sections from 90 week old brain tissue from wild-type and HGPS animals. Immunoreactivity for ubiquitin was seen in the positive control sample with brain tissue obtained postmortem from a patient with Alzheimer disease. Representative images from hippocampus are from the CA1 region. Scale bars: 50µm.

S6

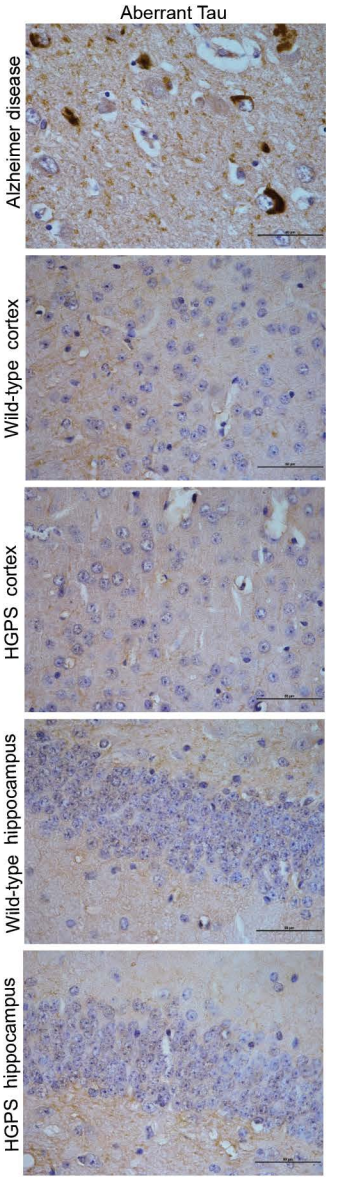

Figure S6. No evidence for presence of aberrant Tau in the brain from HGPS animals. Immunohistochemical labelling for aberrant Tau (using the MC-1 antibody) in sections from cortex and hippocampus of 90 week old wild-type and HGPS animals did not show signs of protein aggregates, suggestive of neurodegeneration. Positive control sample from postmortem brain tissue from a patient with Alzheimer disease showed staining of neurofibrillary tangles, neurophil threads and dystrophic neuritis. Representative images from hippocampus are from the CA1 region. Scale bars: 50µm.

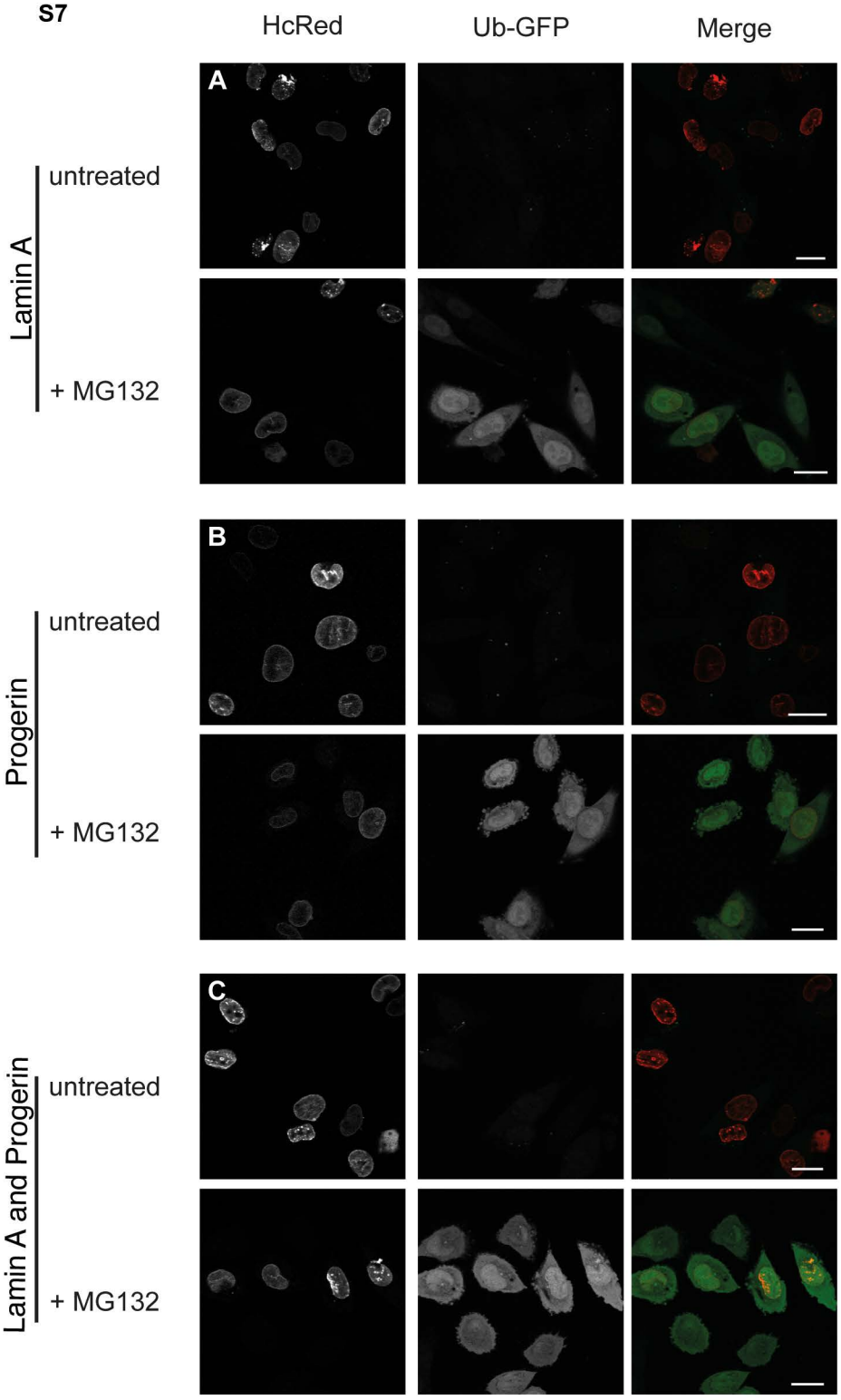

Figure S7. Expression of progerin does not cause functional impairment of the ubiquitin/proteasome system. Wild-type lamin A and two vectors that express either progerin or progerin and lamin A were transiently expressed in a human cell line (Me1JuSo) stably expressing a GFP-based substrate of the ubiquitin/proteasome system (Ub-GFP). Reporter Me1JUSO Ub-GFP stable cell line were transfected with HcRed-tagged Lamin A (A) and HcRed-Progerin (B) or HcRed-Lamin A and HcRed-Progerin (C). The cells were left untreated (upper panels) or treated for 5 hours with 10 μM proteasome inhibitor MG132 to allow accumulation of the GFP reporter substrate. Scale bars: 20μm.

Supplementary Table 1

Table 1. Only 5 genes changed by 2-folds in HGPS mice. Exon array analysis of the hippocampus from the HGPS animals showed that there were only 5 genes that increased or decreased by 2-folds compared to the wild-type animals (highligted in pink). There were 46 genes that showed 1.5-fold change compared to the wild-type.

Gene name	Gene symbol	Fold change	*P* value	q-value
inter-alpha trypsin inhibitor, heavy chain 2	Itih2	2.14	0.035	0.400
proteoglycan 4	Prg4	2.08	0.030	0.396
histone cluster 1, H2bk	Hist1h2bk	2.06	0.043	0.400
kallikrein 1-related peptidase b9	Klk1b9	-2.16	0.018	0.390
olfactory receptor 102	Olfr102	-2.23	0.015	0.390
fatty acid binding protein 5, epidermal	Fabp5	1.83	0.005	0.380
solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	Slc6a12	1.83	0.029	0.394
CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated)	Cd74	1.80	0.036	0.400
myelin protein zero-like 2	Mpzl2	1.75	0.032	0.398
cyclin-dependent kinase inhibitor 1A (P21)	Cdkn1a	1.64	0.006	0.380
RIKEN cDNA 1700010M22 gene	1700010M22Rik	1.63	0.036	0.400
lysozyme 2	Lyz2	1.62	0.038	0.400
solute carrier family 22 (organic cation transporter), member 2	Slc22a2	1.62	0.045	0.400
insulin-like growth factor binding protein 7	Igfbp7	1.61	0.050	0.400
musculoskeletal, embryonic nuclear protein 1	Mustn1	1.59	0.011	0.390
vimentin	Vim	1.58	0.025	0.392
lactate dehydrogenase B	Ldhb	1.57	0.009	0.390
fibronectin 1	Fn1	1.57	0.019	0.390
ribosomal protein S20	Rps20	1.55	0.015	0.390
histocompatibility 2, class II antigen A, alpha	H2-Aa	1.55	0.050	0.400
neuronal PAS domain protein 4	Npas4	1.54	0.025	0.394
solute carrier family 22 (organic anion transporter), member 8	Slc22a8	1.54	0.045	0.400
polymerase I and transcript release factor	Ptrf	1.52	0.041	0.400
lipocalin 2	Lcn2	1.52	0.032	0.398
polymerase (RNA) II (DNA directed) polypeptide H	Polr2h	1.51	0.033	0.398
cellular retinoic acid binding protein II	Crabp2	1.51	0.025	0.393
armadillo repeat containing, X-linked 5	Armcx5	-1.50	0.002	0.380
cDNA sequence BC003266	BC003266	-1.52	0.039	0.400
late cornified envelope 3B	Lce3b	-1.54	0.038	0.400
olfactory receptor 1196	Olfr1196	-1.60	0.036	0.400
transducin (beta)-like 1X-linked receptor 1	Tbl1xr1	-1.61	0.0001	0.136
arylacetamide deacetylase-like 1	Nceh1	-1.63	0.002	0.380
Hermansky-Pudlak syndrome 3 homolog (human)	Hps3	-1.63	0.00003	0.116
olfactory receptor 610	Olfr610	-1.64	0.026	0.394
olfactory receptor 1270	Olfr1270	-1.64	0.028	0.394
high-mobility group nucleosome binding domain 5	Hmgn5	-1.65	0.002	0.380
olfactory receptor 1491	Olfr1491	-1.66	0.029	0.394
phosphodiesterase 7A	Pde7a	-1.67	0.0002	0.254
glycogenin	Gyg	-1.71	0.0002	0.269
MAS-related GPR, member A4	Mrgpra4	-1.74	0.030	0.396
vomeronasal 1 receptor 232	Vmn1r232	-1.77	0.049	0.400
vomeronasal 1 receptor 225	Vmn1r225	-1.79	0.002	0.380
interferon alpha 12	Ifna12	-1.85	0.002	0.380
RRS1 ribosome biogenesis regulator homolog pseudogene	4632415L05Rik	-1.90	0.001	0.380
neuroligin 1	Nlgn1	-1.92	0.0001	0.136
helicase-like transcription factor	Hltf	-1.95	0.0003	0.286