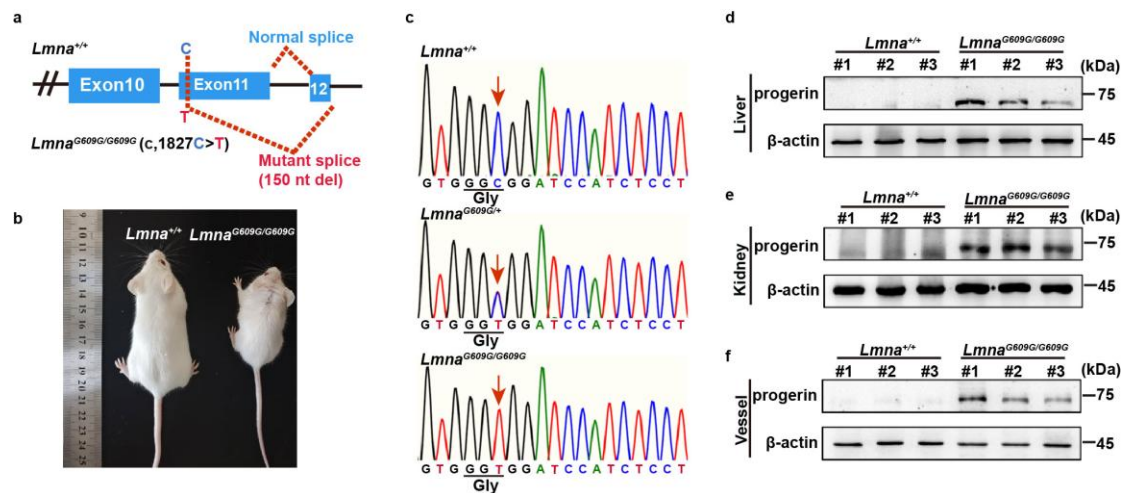
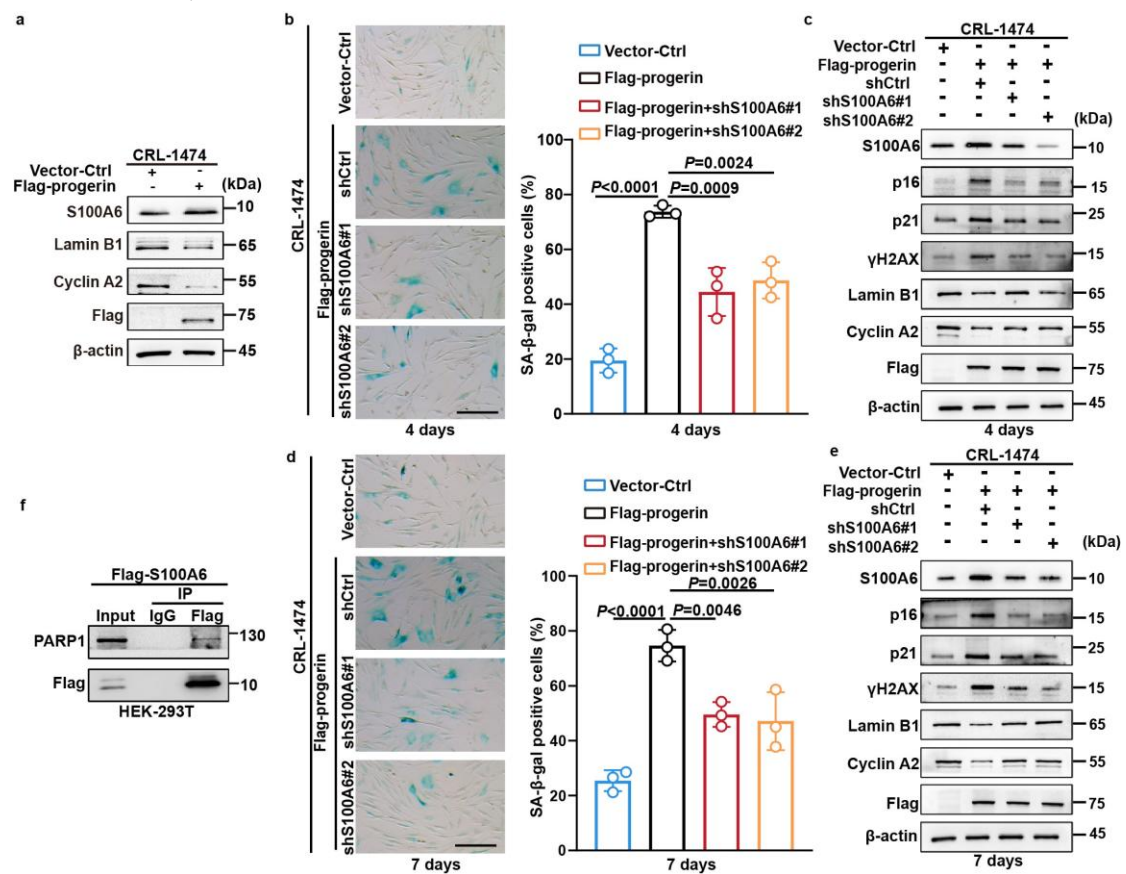


1 Supplementary Figures



Supplementary Fig. 1. The identification of *Lmna*^{G609G/G609G} mice.

a. The corresponding mutation site on exon 11 of mouse *Lmna*^{G609G/G609G}, with blue and red dashed lines representing normal and mutated RNA splicing forms.
b. Representative picture of 12 weeks *Lmna*^{+/+} and *Lmna*^{G609G/G609G} mice.
c. Genotyping results of mice were identified by Sanger sequencing.
d-f. Western blot analysis of progerin in the liver (d), kidney (e) and vessel (f) tissues of *Lmna*^{G609G/G609G} mice, n=3.



Supplementary Fig. 2. The role of S100A6 knockdown in progerin-overexpressing CRL-1474 cells.

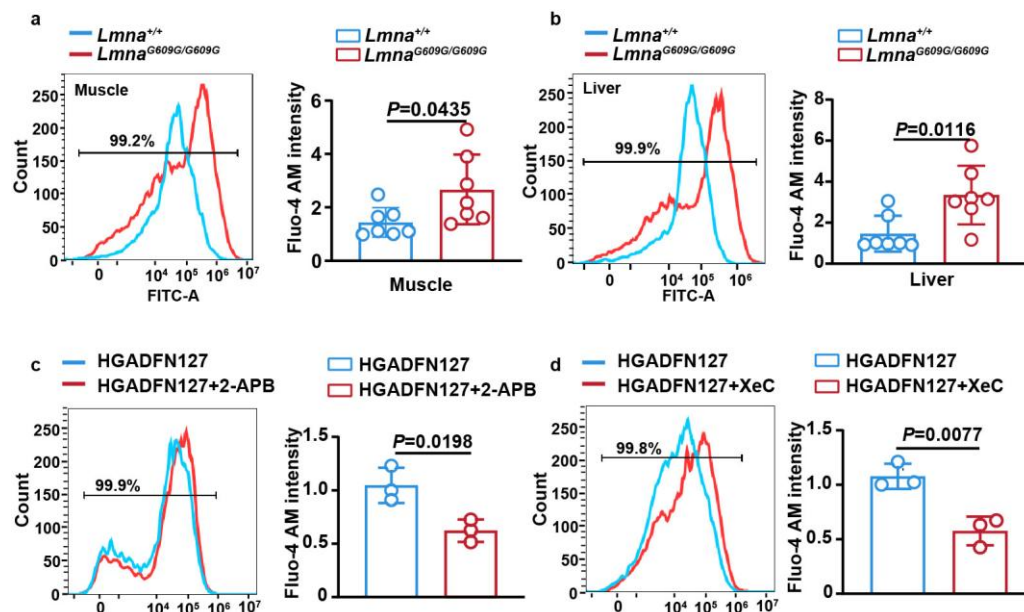
a. Western blot analysis of the protein levels of Cyclin A2, Lamin B1, and S100A6 in CRL-1474

cells overexpressing progerin. n=3 biological replicates.

b and d. CRL-1474 cells overexpressing progerin were transfected with shS100A6 for 4 days and 7days, followed by SA- β -gal staining. Scale bar: 100 μ m. The percentage of SA- β -gal positive cells was calculated in 1474 cells overexpressing progerin were transfected with shS100A6 for 4 days (b) and 7 days (d). n=3 biological replicates.

c and e. Western blot analysis of Cyclin A2, Lamin B1, IL-6, IL-8, γ H2AX, PARP1, and S100A6 in CRL-1474 cells overexpressing progerin were transfected with shS100A6 for 4 days (c) and 7 days (e). n=3 biological replicates.

f. Co-IP assay was performed to analyze the interaction between S100A6 and PARP1 in HEK-293T cells overexpressing Flag-S100A6. n=3 biological replicates. Source data are provided as Source Data File. All data are presented as mean $\pm$ S.D. Statistical significance was determined by one-way ANOVA analysis.

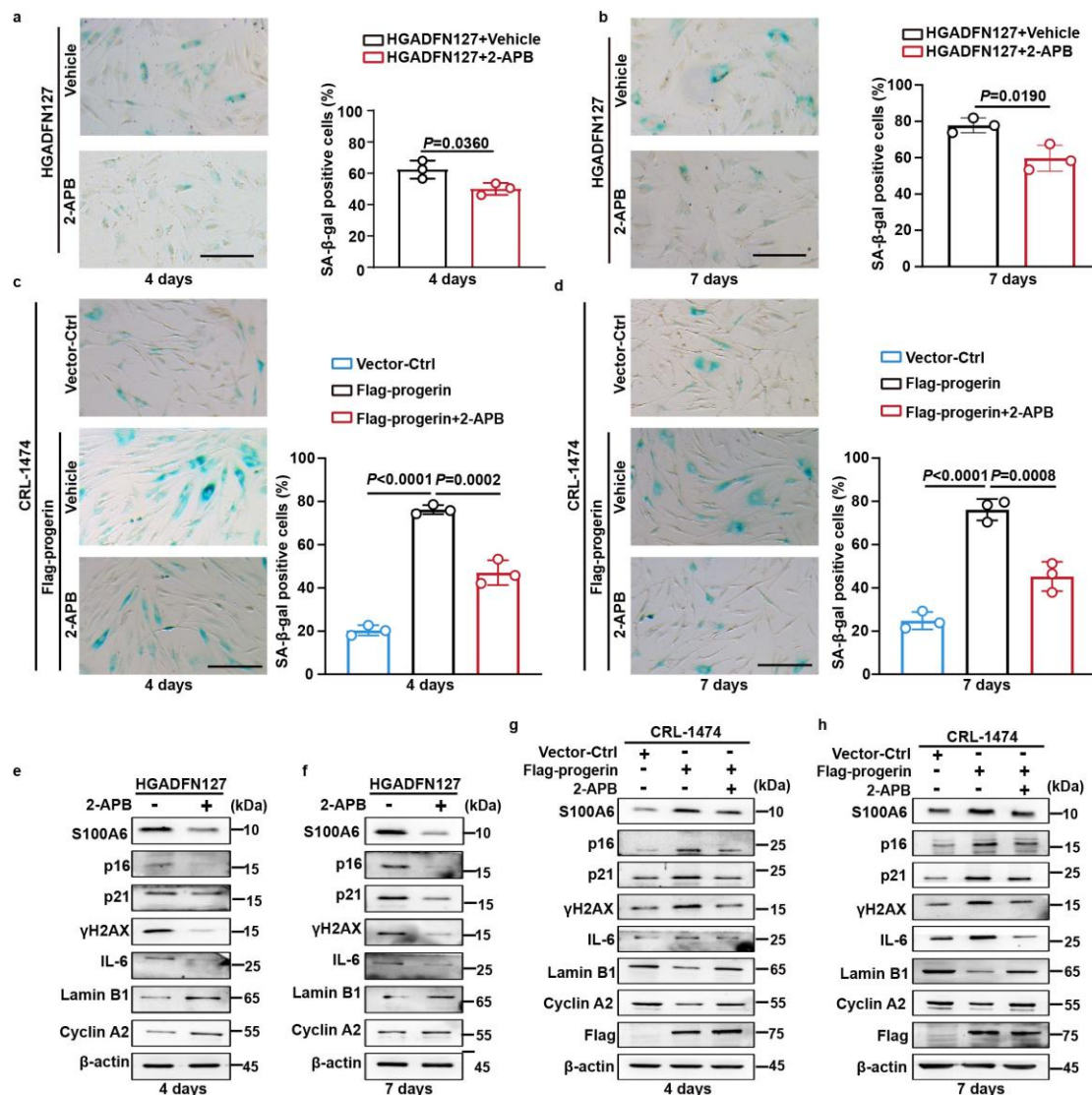


Supplementary Fig. 3. The Ca²⁺ levels in HGPS aging.

a-b. Flow cytometry detection of Ca²⁺ concentration in cells isolated from multi-tissues was performed using Fluo-4 AM, including the muscle (a) and liver (b) of *Lmna*^{+/+} and *Lmna*^{G609G/G609G} mice (n=7).

c. Flow cytometry detection of Ca²⁺ concentration in HGADFN127 cells transfected with 2-APB was performed using Fluo4-AM. n=3 biological replicates.

d. Flow cytometry detection of Ca²⁺ concentration in HGADFN127 cells transfected with Xec was performed using Fluo4-AM. n=3 biological replicates. Source data are provided as Source Data File. All data are presented as mean $\pm$ S.D. Statistical significance was determined two-tailed unpaired Student's *t*-test.



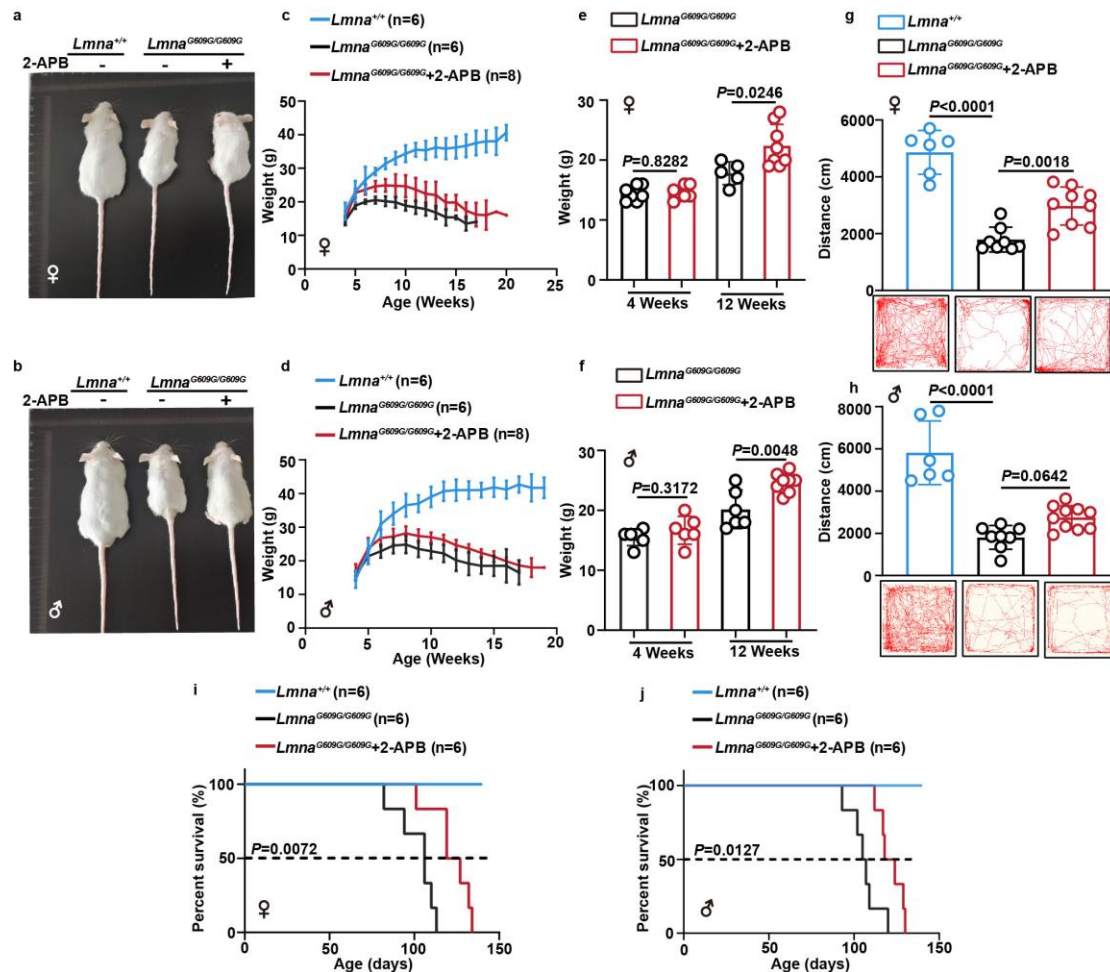
Supplementary Fig. 4. 2-APB delays senescence in HGPS cells.

a-b. HGADFN127 cells were treated with 2-APB for 4 days and 7 days, followed by SA-β-gal staining. Scale bar: 100 μm. The percentage of SA-β-gal positive cells was calculated in HGADFN127 cells treated with 2-APB for 4 days (a) and 7 days (b). n=3 biological replicates.

c-d. CRL-1474 cells overexpressing progerin treated with 2-APB for 4 days and 7 days, followed by SA-β-gal staining. Scale bar: 100 μm. The percentage of SA-β-gal positive cells was calculated in 1474 cells overexpressing progerin treated with 2-APB for 4 days (c) and 7 days (d). n=3 biological replicates.

e-f. Western blot analysis of Cyclin A2, Lamin B1, IL-6, IL-8, γH2AX, PARP1, and S100A6 in HGADFN127 cells treated with 2-APB for 4 days (e) and 7 days (f). n=3 biological replicates.

g-h. Western blot analysis of Cyclin A2, Lamin B1, IL-6, IL-8, γH2AX, PARP1, and S100A6 in CRL-1474 cells overexpressing progerin treated with 2-APB for 4 days (g) and 7 days (h). n=3 biological replicates. Source data are provided as Source Data File. All data are presented as mean±S.D. Statistical significance was determined by two-tailed unpaired Student's *t*-test (a-b) or one-way ANOVA analysis (c-d).



Supplementary Fig. 5. 2-APB ameliorates aging phenotypes and extends lifespan of *Lmna*^{G609G/G609G} mice.

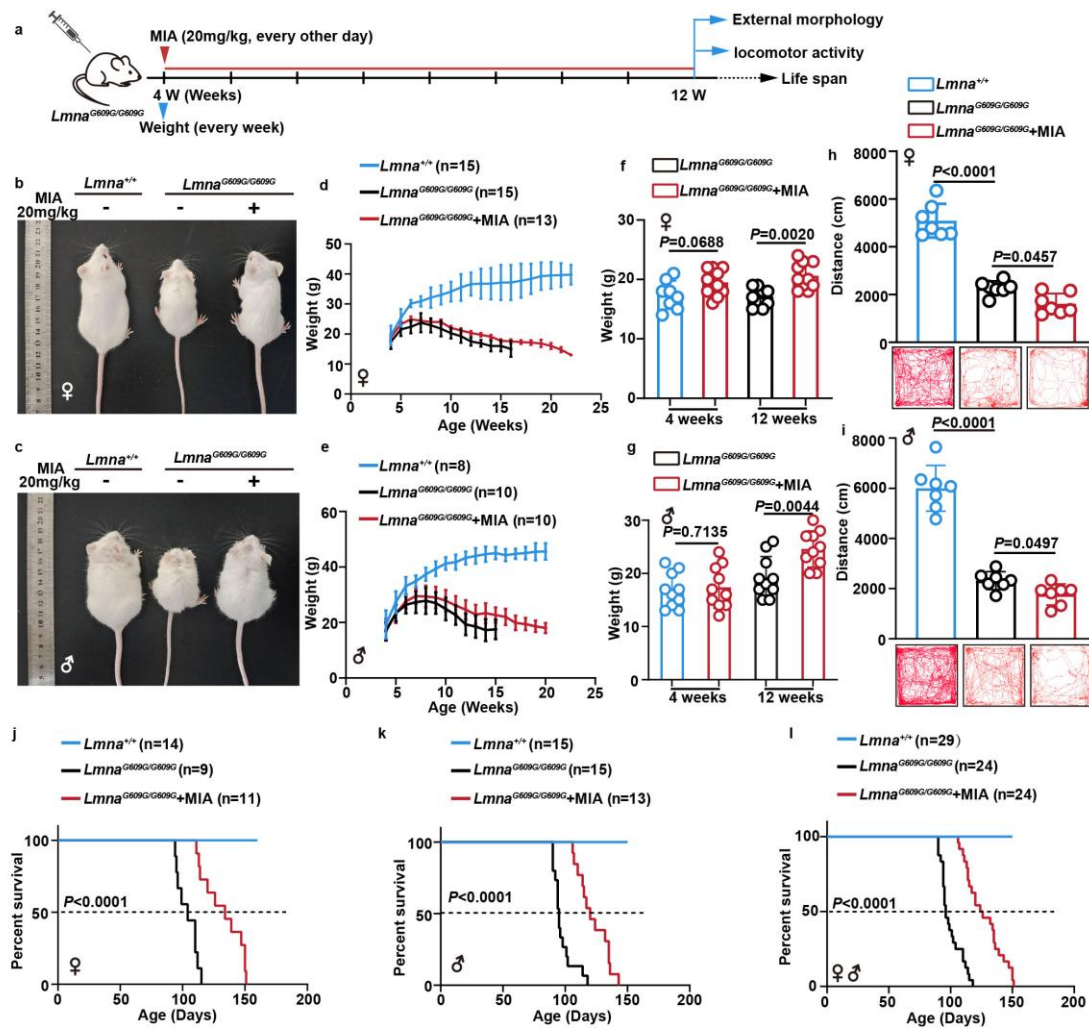
a-b. Representative photographs of *Lmna*^{G609G/G609G} female (a) and male (b) mice (12 weeks), treated with or without 2-APB.

c-d. The progression of body weight in *Lmna*^{G609G/G609G} female (c) and male (d) mice, treated with or without 2-APB, was detected from 4 weeks after birth (n = 6).

e-f. Comparison of body weight at 4 and 12 weeks in female (e, n=7,7) and male (f, n=6,6) *Lmna*^{G609G/G609G} mice, treated with or without 2-APB.

g-h. The open field test was used to assess the motion capabilities of *Lmna*^{G609G/G609G} female (g, n=6,8,9) and male (h, n=6,8,10) mice (12 weeks), with or without 2-APB treatment.

i-j. Kaplan-Meier survival curves of *Lmna*^{G609G/G609G} female (i, n=6) and male (j, n=6) mice, both with and without 2-APB treatment. Source data are provided as Source Data File. All data are presented as mean±S.D. Statistical significance was determined by two-tailed unpaired Student's *t*-test (e-f) or one-way ANOVA analysis (g-h).



Supplementary Fig. 6. 20 mg/kg MIA ameliorates aging phenotypes and extends lifespan of *Lmna*^{G609G/G609G} mice.

a. Experimental setup for 20 mg/kg MIA treatment: 4-week-old *Lmna*^{G609G/G609G} mice received intraperitoneal injections of MIA at a dose of 20 mg/kg every other day. Age-matched *Lmna*^{+/+} mice served as controls and were given intraperitoneal injections of 0.9% saline on the same schedule. Body weights were monitored weekly. Locomotor activity was assessed in 12-week-old mice. Created in BioRender. Tian, L. (2026) <https://BioRender.com/991l4u9>.

b-c. Representative photographs of *Lmna*^{G609G/G609G} female (b) and male (c) mice (12 weeks), treated with or without 20 mg/kg MIA.

d-e. The progression of body weight in *Lmna*^{G609G/G609G} female (d, n=15, 15, 13) and male (e, n=8, 10, 10) mice, treated with or without 20 mg/kg MIA, was detected from 4 weeks after birth.

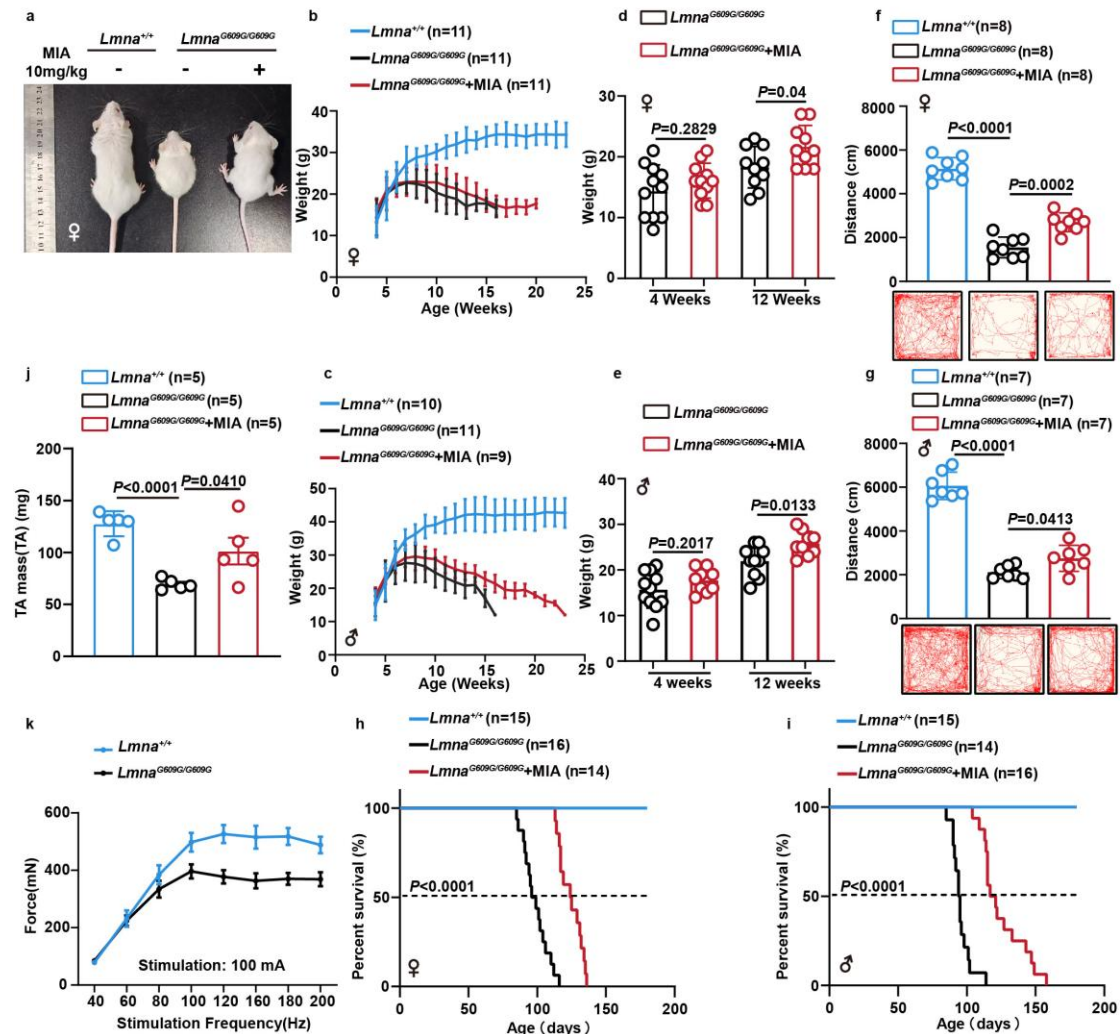
f-g. Comparison of body weight at 4 and 12 weeks in female (f, n=8, 10) and male (g, n=10, 10) *Lmna*^{G609G/G609G} mice, treated with or without 20 mg/kg MIA.

h-i. The open field test was used to assess the motion capabilities of *Lmna*^{G609G/G609G} female mice (h, n=7, 7, 7) and male (i, n=7, 7, 7) mice (12 weeks), with or without 20 mg/kg MIA treatment.

j-k. Kaplan-Meier survival curves of *Lmna*^{G609G/G609G} female (j, n=14, 9, 11) and male (k, n=15, 15, 13) mice, both with and without 20 mg/kg MIA treatment.

l. Kaplan-Meier survival curves for *Lmna*^{+/+} and *Lmna*^{G609G/G609G} mice, treated with or without 20 mg/kg MIA, were analyzed (n=29, 24, 24). Source data are provided as Source Data File. All data

88 are presented as mean±S.D. Statistical significance was determined by two-tailed unpaired Student's
89 *t*-test (f-g) or one-way ANOVA analysis (h-i).



91 **Supplementary Fig. 7. 10 mg/kg MIA ameliorates aging phenotypes and extends lifespan of**
92 ***Lmna*^{G609G/G609G} mice.**

93 a. Representative photographs of *Lmna*^{G609G/G609G} female mice (12 weeks) treated with or without
94 10 mg/kg MIA.

95 b-c. The progression of body weight in *Lmna*^{G609G/G609G} female (b, n=11,11,11) and male (c,
96 n=10,11,9) mice, treated with or without 10 mg/kg MIA, was detected from 4 weeks after birth.

97 d-e. Comparison of body weight at 4 and 12 weeks in female (d, n=11,11) and male (e, n=11,9)
98 *Lmna*^{G609G/G609G} mice, treated with or without 10 mg/kg MIA.

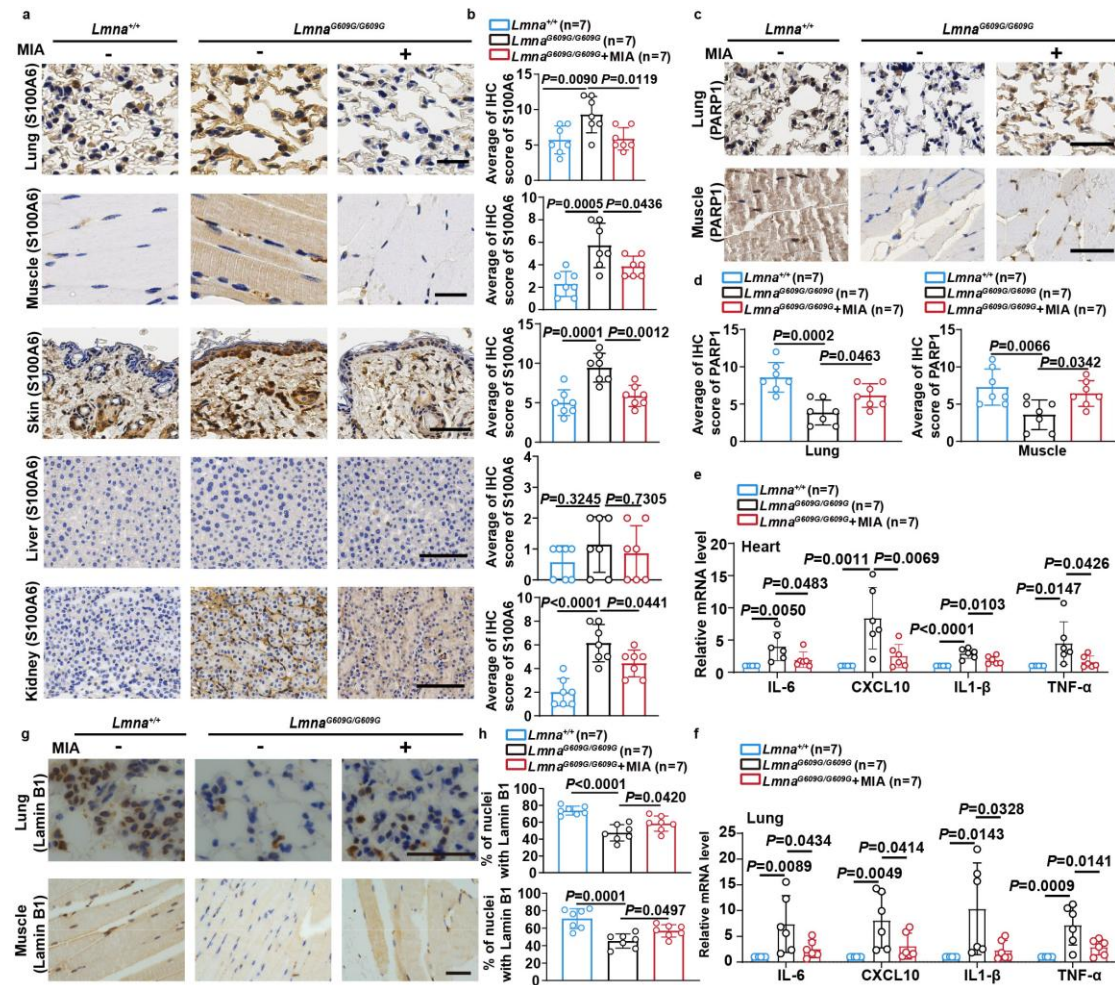
99 f-g. The open field test was used to assess the motion capabilities of *Lmna*^{G609G/G609G} female mice
100 (f, n=8,8,8) and male (g, n=7,7,7) mice (12 weeks), with or without 10 mg/kg MIA treatment.

101 h-i. Kaplan-Meier survival curves of female (h, n=15,16,14) and male (i, n=15,14,16)
102 *Lmna*^{G609G/G609G} mice, with and without 10 mg/kg MIA treatment.

103 j. The tibialis anterior muscle mass of *Lmna*^{G609G/G609G} mice, treated with or without 10 mg/kg MIA,
104 were measured at 12 weeks (n=5,5,5).

105 k. Force–frequency relationship in tibialis anterior muscle from *Lmna*^{+/+} and *Lmna*^{G609G/G609G} mice
106 (n=6,6). Source data are provided as Source Data File. All data are presented as mean±S.D.

Statistical significance was determined by two-tailed unpaired Student's *t*-test (d-e) or one-way ANOVA analysis (f,g,j).



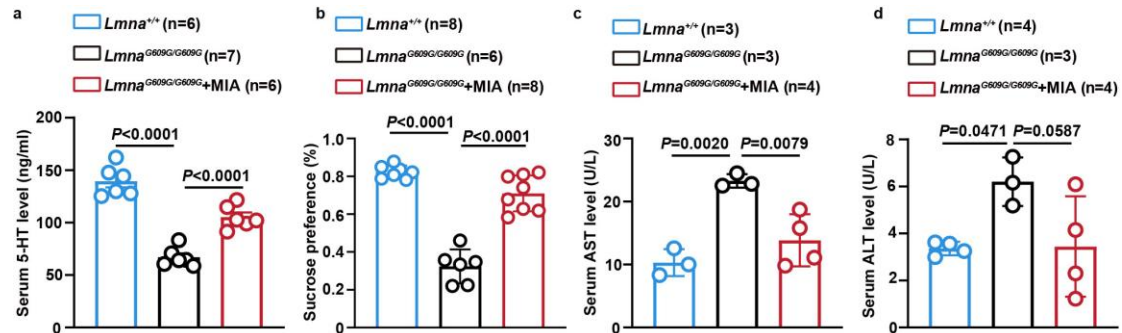
Supplementary Fig. 8. 10 mg/kg MIA ameliorates progeroid phenotypes of *Lmna*^{G609G/G609G} mice.

a-b. IHC of S100A6 in lung, muscle, skin, liver and kidney of *Lmna*^{G609G/G609G} mice (12 weeks), treated with or without 10 mg/kg MIA (a, Scale bars, 100 μm; n = 7,7,7). The quantification scores of S100A6 (b).

c-d. IHC of PARP1 in lung and muscle of *Lmna*^{G609G/G609G} mice (12 weeks), treated with or without 10 mg/kg MIA (c, Scale bars, 100 μm; n = 7,7,7). The quantification scores of S100A6 in lung and muscle (d).

e-f. Quantitative RT-PCR analysis of IL6, CXCL10, IL-1β and TNF-α mRNA levels in heart (e) and lung (f) of *Lmna*^{G609G/G609G} mice, with or without MIA treatment (n=6,6,6).

g-h. IHC of Lamin B1 in lung and muscle of *Lmna*^{G609G/G609G} mice (12 weeks), treated with or without 10 mg/kg MIA (g, Scale bars, 50 μm; n = 7,7,7). The quantification scores of Lamin B1 in lung and muscle (h). Source data are provided as Source Data File. All data are presented as mean±S.D. Statistical significance was determined by or one-way ANOVA analysis.

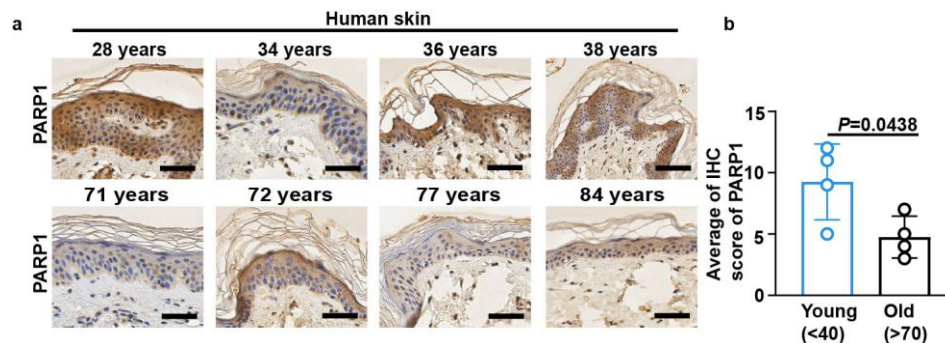


Supplementary Fig. 9. Effect of 10 mg/kg MIA on the concentration of 5-HT in the serum, sucrose preference, AST and ALT of *Lmna*^{G609G/G609G} mice.

a. The concentration of 5-HT in the serum of *Lmna*^{G609G/G609G} mice (12 weeks), treated with or without 10 mg/kg MIA, was detected using the ST/5-HT ELISA Kit (n=6,7,6).

b. Sucrose preference in *Lmna*^{G609G/G609G} mice (12 weeks), treated with or without 10 mg/kg MIA (n=8,6,8).

c-d. The serum AST (c, n=3,3,4) and ALT levels (d, n=4,3,4) were detected using the Aspartate Aminotransferase Assay Kit and Alanine aminotransferase Assay kit (C010-2-1, C009-2-1, Nanjing Jiancheng Bioengineering) in *Lmna*^{G609G/G609G} mice treated with or without 10 mg/kg MIA. Source data are provided as Source Data File. All data are presented as mean±S.D. Statistical significance was determined by one-way ANOVA analysis.



Supplementary Fig. 10. Fig. 8 Expression of PARP1 in the human skin tissues.

a-b. IHC of PARP1 in the human skin tissues of different ages (a, Scale bars, 50 µm; n = 4). The quantification scores of PARP1 (b). Source data are provided as Source Data File. All data are presented as mean±S.D. Statistical significance was determined by two-tailed unpaired Student's *t*-test.