

Behavioral characterization of low copy SOD1-G93A transgenic mice

Stefanie Flunkert, Roland Rabl, Ágnes Kasza, Vera Niederkofler, Ewald Auer, Birgit Hutter-Paier
QPS Austria GmbH, Neuropharmacology, Parkring 12, 8074 Grambach, Austria



BACKGROUND

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that results in the death of motor neurons in the brain and spinal cord. So far no effective treatments are available. Several causative genes are known and of these mutant superoxide dismutase 1 (SOD1) is by far the most frequent accounting for up to 20% of familial ALS cases. A range of human mutant SOD1 transgenic mouse models that model the human disease has been developed. The most widely used is the SOD1(G93A)¹Gur mouse, which expresses a human SOD1 transgene with a G93A mutation (Gurney et al., 1995). These mice become paralyzed in one or more limbs beginning around 12 weeks of age. Life expectancy is only four to six weeks after onset of the first symptoms. Although the SOD1-G93A mouse has been a bedrock for ALS research, there are some concerns about its use due to its very strong and early phenotype. The low copy number SOD1 mouse model might be a suitable alternative. It presents a delayed onset of the ALS phenotype compared to the original high copy number strain because of a reduction in transgene copy number.

The aim of this study was to evaluate the behavioral phenotype onset and survival of low copy number SOD1-G93A mice.

MATERIALS and METHODS

Low copy number SOD1-G93A mice (JAX #002300) of mixed sex were analyzed from week 24 to 30 for motor deficits. The Wire Suspension test was performed once a week while the Beam Walk, Rota Rod and Pasta Gnawing tests were performed at an age of 24, 27 and 30 weeks. Survival rates were calculated from the day of birth until the day of death or until the animal had to be euthanized due to reaching defined end-point criteria.

Our data revealed a weak phenotype in female SOD1-G93A low copy number mice. Deficits in muscle strength and motor coordination as analyzed by using the Wire Suspension test as well as the Beam Walk and the Pasta Gnawing test, respectively, were detectable starting at 24-25 weeks of age, although data were not always significant. In the Rota Rod no significant differences were observed up to an age of 30 weeks in female animals. In total, male mice exhibited a much milder or no behavioral phenotype. The life span of SOD1-G93A low copy animals was clearly shorter than that of non-transgenic littermates. While the first female SOD1-G93A low copy mice reached end-point criteria at 24 weeks of age, male SOD1-G93A mice did so 8 weeks later at 32 weeks of age.

Wire Suspension

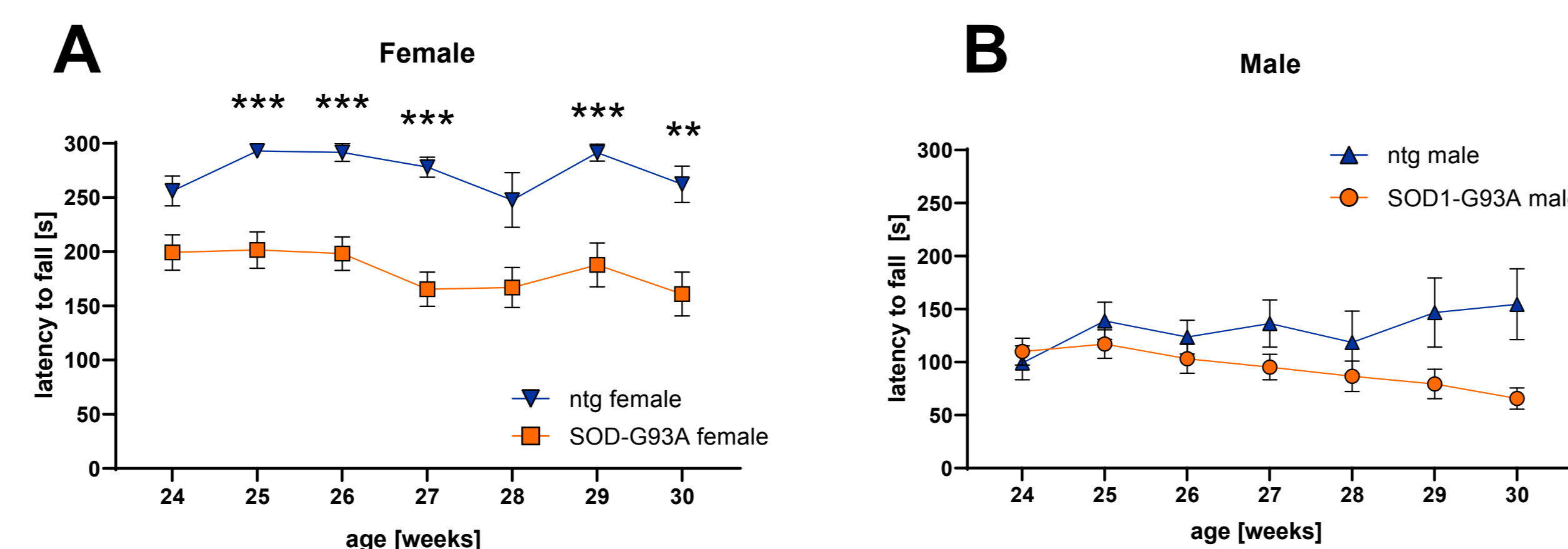


Figure 1. Wire suspension: Mean latency to fall off the wired grid of female (A) and male (B) SOD1-G93A mice tested over age. Female SOD1-G93A mice showed a significantly reduced wire hanging time starting at 25 weeks of age compared to non-transgenic littermates. Mean \pm SEM. Mixed-effects analysis with Bonferroni's *post hoc* test; ** $p < 0.01$; *** $p < 0.001$.

Meet QPS at Booth
#1464

Poster #E11

For more information about the model
please visit: www.qpsneuro.com
or send us an e-mail:
office-austria@qps.com

RESULTS

Beam Walk

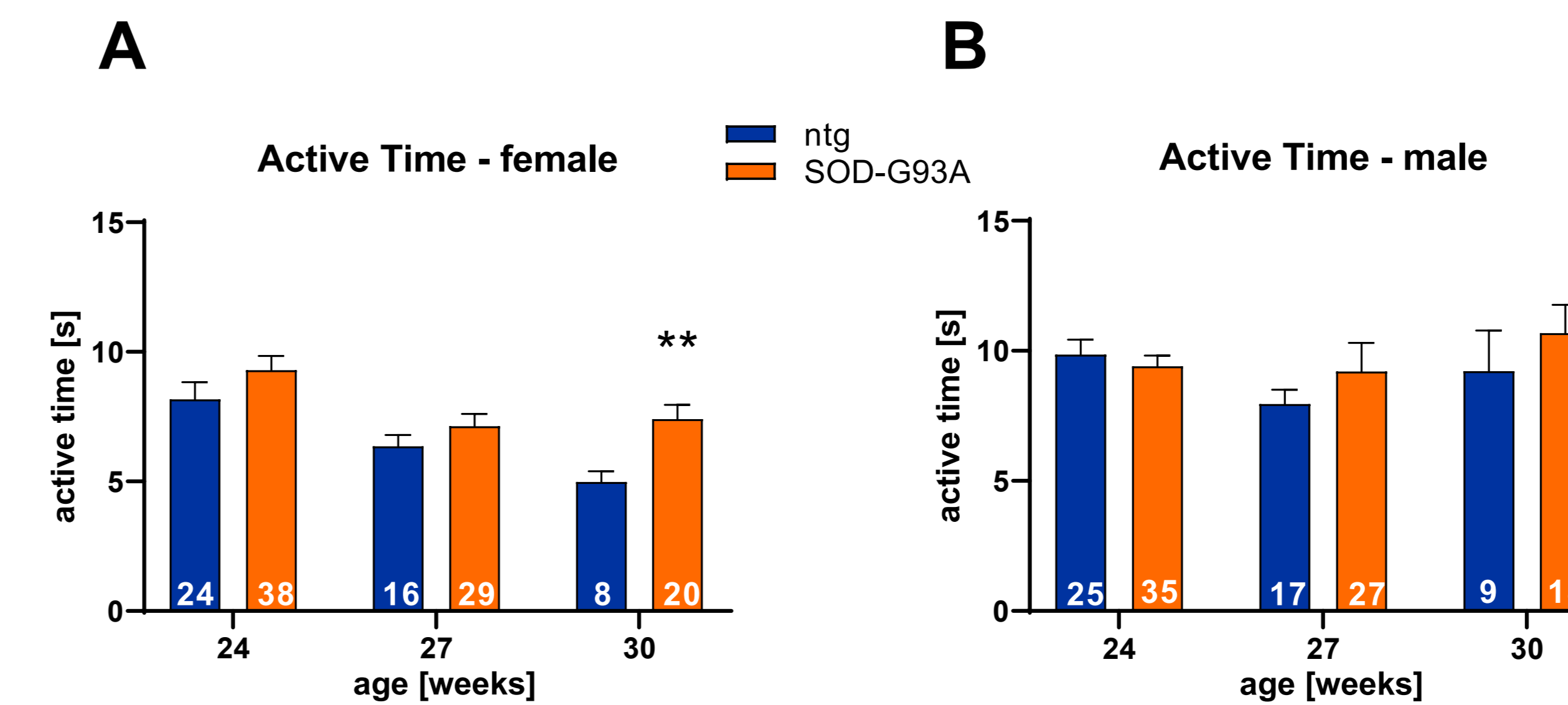


Figure 2. Beam Walk: Time to traverse the 13 mm square beam of female (A) and male (B) SOD1-G93A mice. Female SOD1-G93A mice take longer to cross the beam than non-transgenic littermates. Mean \pm SEM. Mixed-effects analysis with Bonferroni's *post hoc* test; ** $p < 0.01$.

Pasta Gnawing

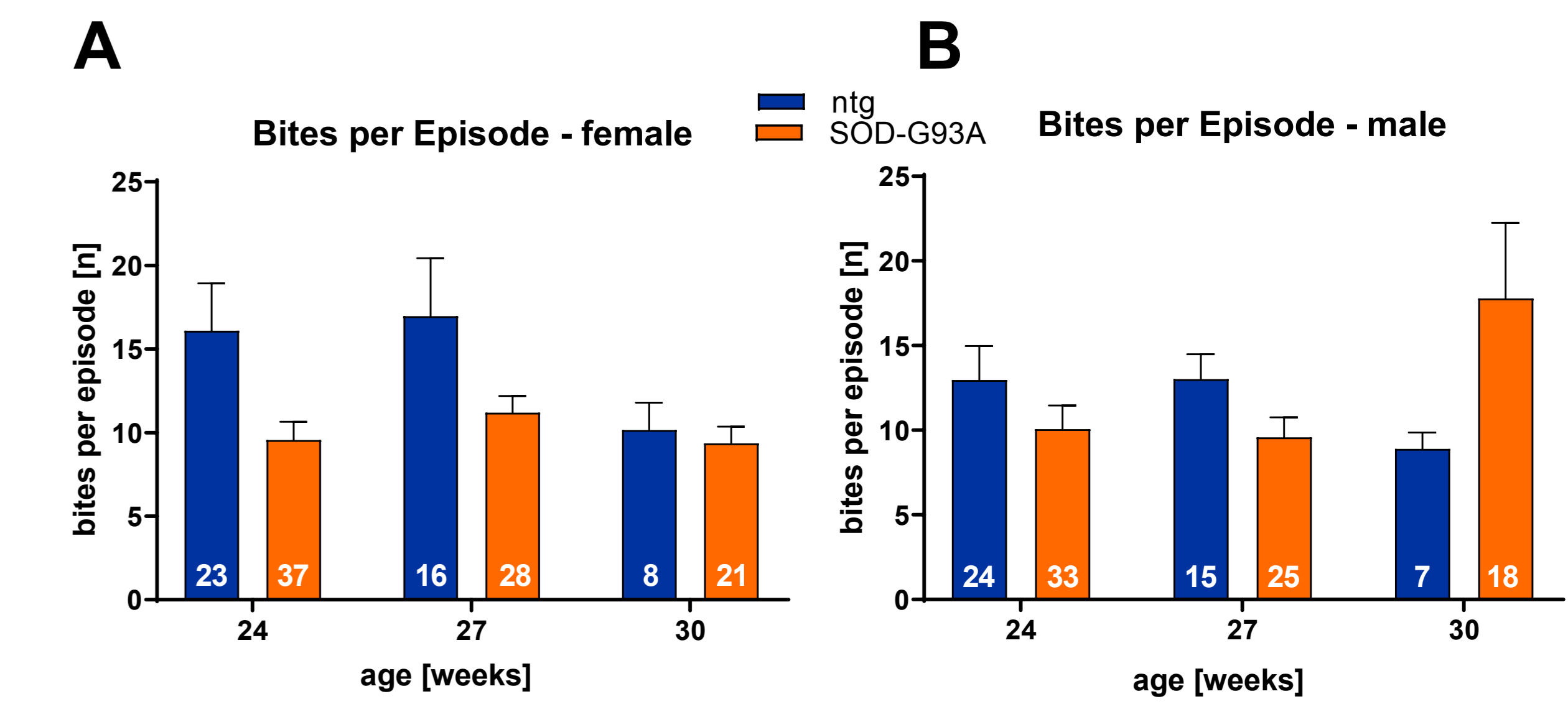


Figure 3. Pasta gnawing: Mean number of bites per chewing episode of female (A) and male (B) SOD1-G93A mice. 24 and 27 week old female SOD1-G93A mice exhibit slightly less bites per episode than age-matched non-transgenic littermates, although differences were not significant. Mean \pm SEM. Mixed-effects analysis with Bonferroni's *post hoc* test.

Rota Rod

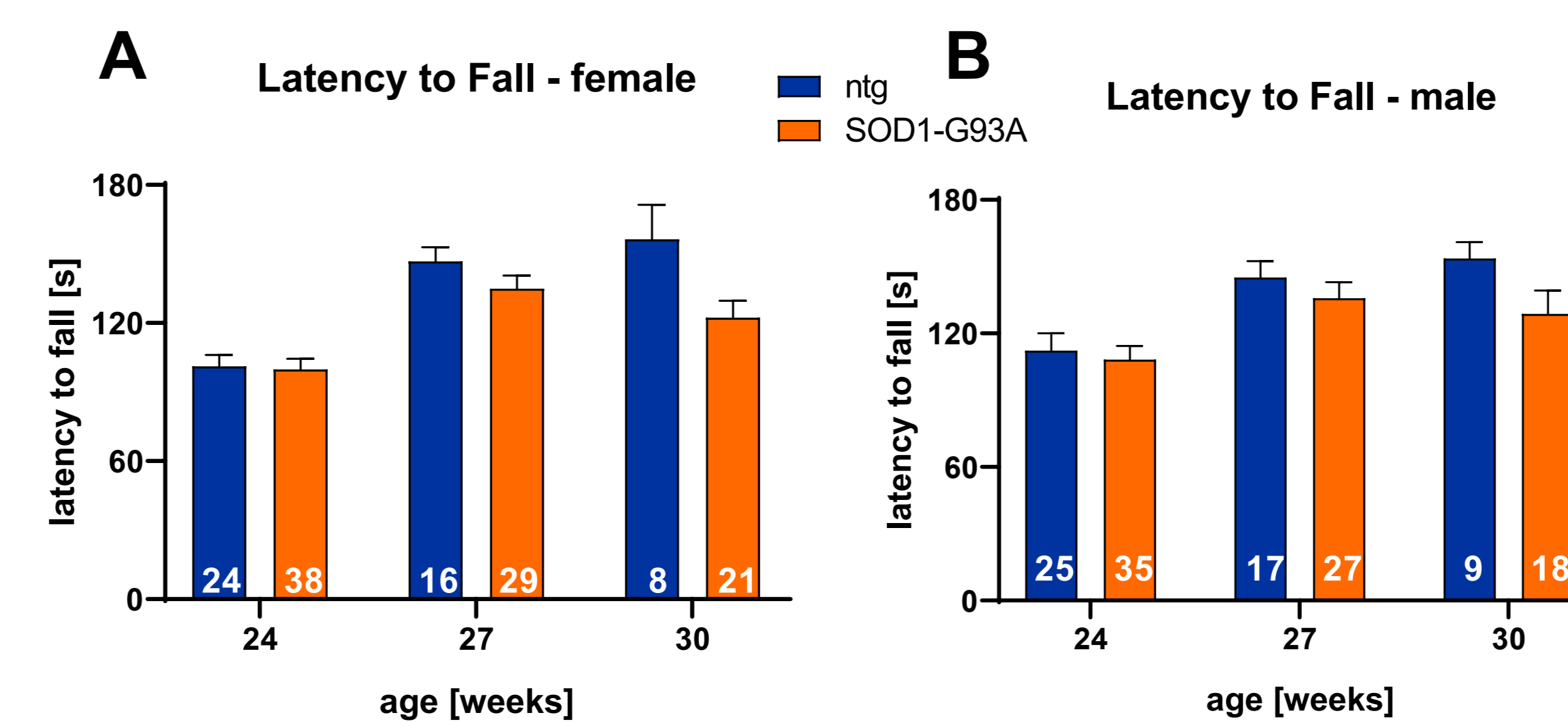


Figure 4. Rota Rod: Mean latency to fall off the rod of female (A) and male (B) SOD1-G93A mice at the age of 24, 27 and 30 weeks. 30 week old female and male SOD1-G93A mice fall off the rod quicker while crossing the beam than age-matched non transgenic littermates, although differences were not significant. Mean \pm SEM. Mixed-effects analysis with Bonferroni's *post hoc* test.

Survival

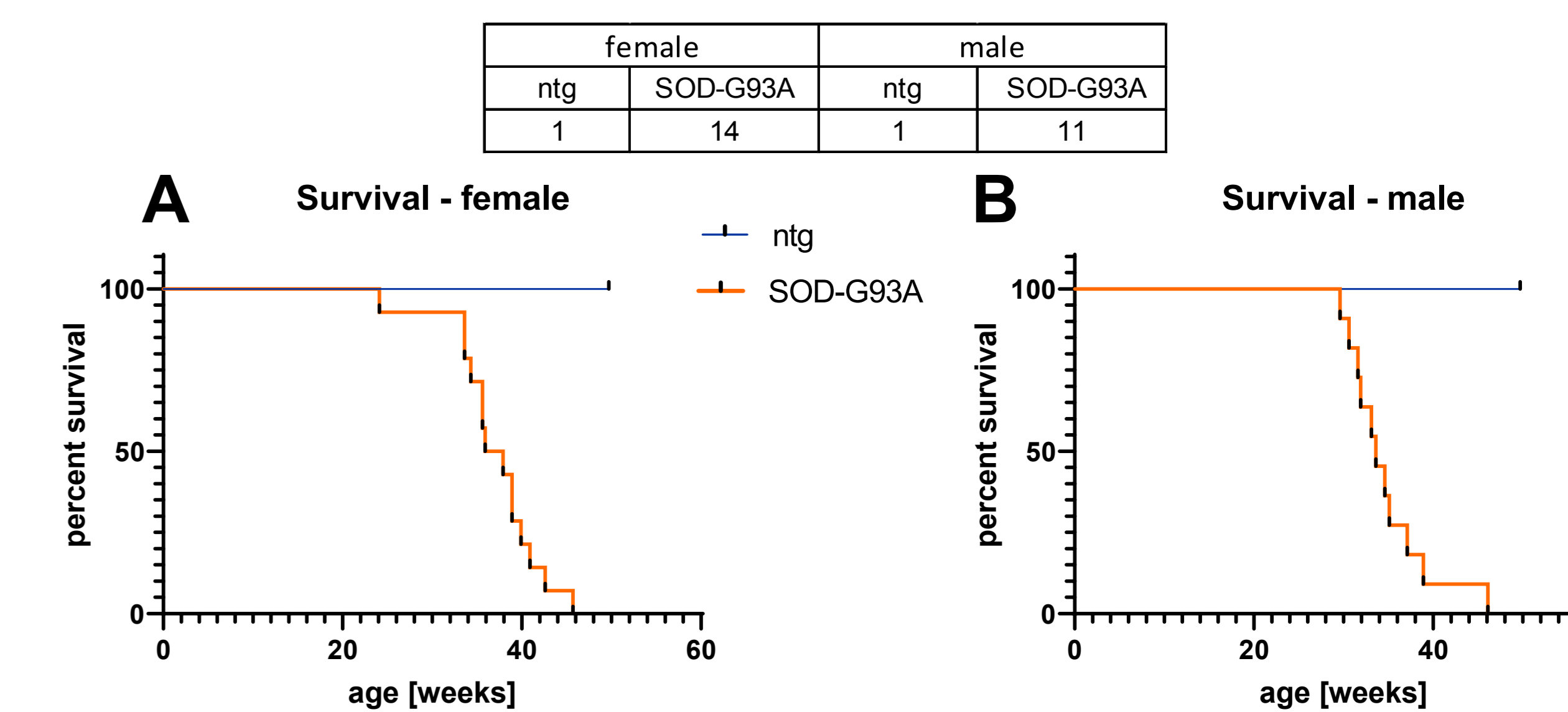


Figure 5. Survival curve: Survival curve of female (A) and male (B) SOD1-G93A mice. Female transgenic mice showed an average survival rate of 36.9 weeks while male transgenic mice survived on average 33.6 weeks.

SUMMARY and CONCLUSION

The slow progressing pathology observed in female SOD1-G93A low copy number mice could provide a more appropriate gender-specific model for studying early-stage disease processes in ALS by having a longer treatment window for testing new therapies.

