CHANGES IN TRANSGENE COPY NUMBER IN A hSOD1\textsuperscript{G93A} ALS RAT MODEL

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the progressive dysfunction and death of motor neurons. The specific etiology of ALS is unknown, but 20% of the familial cases of the disease carry mutations in the gene encoding superoxide dismutase 1 (hSOD1). Transgenic animals overexpressing the G93A mutation of hSOD1 reproduces the pathology and symptoms of ALS patients constituting a useful animal model of the disease. We have been working with the hSOD1\textsuperscript{G93A} ALS rat model (Taconic) and detected some animals showing a decelerated disease progression. This phenotype arose spontaneously in our colony of hSOD1\textsuperscript{G93A} rat. Changes in transgene copy number, although rare in mouse, can sometimes occur and it has been reported to modify disease progression in a G93A SOD1 mouse model of ALS. To evaluate this occurrence in our rat colony, changes in transgene copy number were evaluated using real time qPCR coupled with measurements of parameters of disease onset and survival. The results showed that a drop in transgene copy number of approximately 60% led to a strong delay in disease onset (from 127 ± 10 to 202 ± 32 days) and extended survival (from 137 ± 9 to 324 ± 25 days). On the other hand, differences in copy number around 30% did not correlate with changes in disease onset and survival. In conclusion, transgenic hSOD1\textsuperscript{G93A} rats are an interesting tool for studying the etiology of ALS and therapeutic approaches; however it is imperative that the animals are monitored for copy number, especially with the breeder males. Animals showing a decrease in transgene copy number higher than 30% should not be used as breeding animals, unless a new colony of rats with slow disease development is warranted for research purposes.

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