two-fold increased risk of dying from ALS compared to never smokers during the follow-up period. Diet, heavy metal exposure, previous trauma, occupation and education have been investigated by others, with contradictory results. A high relative risk (6.5) for ALS has recently been reported in Italian football players compared with the general population, possibly due to intense physical activity. In ALS, an abnormally elevated LDL/HDL ratio has recently been shown to increase survival of ALS patients and an association has been reported between ALS and paraoxonases (PONs). Furthermore, gene expression studies in autopsy ALS cases have shown an up-regulation of cholesterol 25 hydroxylase, a key regulator of lipid metabolism. Smoke from cigarettes contains a number of toxins known to induce oxidative stress which may also be a risk factor for ALS. Exhaled cigarette smoke has also been shown to contain formaldehyde, a substance generated from saccharides used as tobacco ingredients inducing lipid peroxidation in humans. Recently occupational exposure to formaldehyde has been associated to increased ALS mortality. It has recently been shown that bulbar signs and advanced age among subjects with spinal onset are indicators of poor prognosis while El Escorial category at entry does not predict survival. Among subjects with spinal onset of the disease, a trend for a better survivorship of subjects with UMN signs has been noted; younger age, longer interval onset to diagnosis, and clinical features with predominance of upper motor signs are predictive of longer survival.

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Muscular dystrophy and cardiomyopathy rescue in bio14.6 hamster following single or double aav treatments


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Limb-girdle muscular dystrophies 2C-2D-2E-2F are a distinct subgroup of muscle disorders also known as “sarcoglycanopathies”. They have often a childhood onset and represent among the most severe forms of LGMD, occasionally associated with cardiomyopathy. They result from mutations in any of the four sarcoglycan genes (alpha, beta, gamma, delta) at the dystrophin-associated complex. When one sarcoglycan is absent, the other sarcoglycans are displaced and degraded, since the stability of the complex is impaired. The BIO14.6 hamster is a widely studied model because of its lethal and well-documented course, due to a spontaneous deletion of delta-sarcoglycan gene promoter and first exon. Disease stages are uniform within BIO14.6 strain due to the homogeneous genetic background. The muscle disease is progressive and average lifespan is shortened to 10-13 months, because heart dilation progresses to heart failure. Based on the ability of adeno-associated viral (AAV) vectors to transduce all body muscles following systemic administration, we delivered human delta-sarcoglycan cDNA into male BIO14.6 hamsters by testing different ages of injection, routes of administration and AAV serotypes. We measured the following parameters at different times after the treatment: i) degree and distribution of human delta-sarcoglycan re-expression; ii) re-expression of the other components of the sarcoglycan complex; iii) muscle pathology; iv) cardiac and skeletal muscle function. Body-wide restoration of delta-SG expression was associated with functional reconstitution of the sarcoglycan complex and with significant lowering of centralized nuclei and fibrosis. Motor ability and cardiac functions were completely rescued. Lifespan was extended up to 22 months with sustained delta-SG expression, when we used serotype 2/8 in combination with serotype 2/1.