NOONAN SYNDROME WITH MULTIPLE LENTIGINES: INSIGHTS INTO HYPERTROPHY AND HYPERCONTRACTILITY

Sarah Clay, DVM
Stacey Leach, DVM, DACVIM (Cardiology), Thesis Supervisor

ABSTRACT

Noonan Syndrome with Multiple Lentigines (NSML) is a rare genetic disease resulting in a phenotype with specific features, most importantly left ventricular cardiac hypertrophy. The majority of NSML cases result from mutations in \textit{PTPN11}, the gene encoding the non-receptor tyrosine phosphatase Shp-2. NSML shares similar phenotypic features with familial sarcomeric forms of hypertrophic cardiomyopathy (HCM) including hypertrophy, hypercontractility, arrhythmias, and risk of sudden death.

By evaluating the underlying mechanisms of hypertrophy in a transgenic mouse model of NSML, which in humans results in a particularly aggressive form of cardiac hypertrophy (Q510E), we sought to critically evaluate the hypertrophy seen with NSML in hopes that mechanistic understanding of the disease can lead to early diagnosis and intervention for NSML and HCM patients. We hypothesized that NSML hearts demonstrate early hypercontractility secondary to an expanded contractile apparatus due to increased transcription of mRNA and subsequent translation into protein. Additionally, we hypothesized that Q510E mutants demonstrate increased PKA activity relative to non-transgenic littermates, which further augments hypercontractility. The results show that transgenic mouse hearts have increased sarcomere density when compared with nontransgenic littermates. mRNA expression is not increased, suggesting Shp-2 may be important for sarcomere regulation and turnover. PKA activity is not a contributing factor to hypercontractility.