In an effort to better mimic human disease in animal models, our team has created a number of porcine models for rare neuropediatric disease. In this talk, we will highlight these various models, including pigs that model CLN2- and CLN3-Batten disease and Ataxia Telangiectasia, and delve more deeply into findings from our most recent model of neurofibromatosis type 1 (NF1). Loss of the NF1 tumor suppressor gene results in this more common human diseases of the nervous system. Children and adults with NF1 suffer from pathologies ranging from benign and malignant tumors to cognitive deficits, seizures, growth abnormalities and migraines. The NF1 gene encodes neurofibromin, a Ras-GTPase activating protein (Ras-GAP) whose mutation in NF1 patients results in hyperactivated Ras signaling. Existing genetically modified NF1 mutant mice effectively mimic individual aspects of NF1, but none comprehensively models the disease. Here, we describe the first large animal, porcine model of NF1 bearing a mutation in the endogenous NF1 gene (exon 42 deletion) orthologous to one found in NF1 patients. NF1+/ex42del heterozygous pigs phenocopy the wide range of manifestations seen in humans with NF1, including café au lait spots, neurofibromas, auxillary freckling, and neurological defects in learning and memory. Molecular analyses verified reduced neurofibromin expression in porcine NF1+/ex42del cells, as well as hyperactivation of Ras, as measured by increased expression of its downstream effectors, phosphorylated ERK1/2 and the checkpoint regulators, p53 and p21. Thus, these NF1+/ex42del mutant pigs successfully recapitulate the human disease and provide a unique, much needed tool to advance NF1 research and treatment.