Abstract Preview

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De novo alterations in *KLF7* are a novel cause of intellectual disability, psychiatric and neuromuscular issues

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The *KLF7* gene (MIM 604865) encodes the Krüppel-like factor 7 (KLF7), a transcriptional activator belonging to the KLF family with roles in several developmental processes including apoptosis, cell proliferation, differentiation and energy metabolism. Mouse and *in vitro* studies implicate *KLF7* in neurogenesis (axon guidance in hippocampus, olfactory bulbs and cortex), differentiation and quiescence, and demonstrate high expression in skeletal muscle. *KLF7* is also a candidate gene for the 2q33.3-q34 deletion phenotype in patients with Autism Spectrum Disorder (ASD) and Rett-like features, microcephaly, hypotonia, psychomotor retardation and mild dysmorphic features. Here we report three unrelated affected individuals with *de novo* missense alterations in *KLF7* detected by Diagnostic Exome Sequencing (DES). The first individual was 2 years old at the time of evaluation with hypotonia, gross motor delay, mild language and cognitive delay, swallowing issues, mildly elevated creatine kinase levels and later ASD. DES identified a *de novo KLF7* c.410C>T (p.T137M) alteration predicted by *in silico* methods to be a part of the F-box motif (137-TPPSSP-142), involved in protein-protein interactions and ubiquitin-mediated proteolysis, an important part of cell cycle progression. The second individual is 15 years old and reported to have intellectual disability (ID), tonus dysregulation, motor dyspraxia, coordination issues and is described as anxious and shy. She was previously reported to have neonatal feeding issues and hypertonia. DES revealed a *de novo KLF7* c.415C>T (p.P139S) alteration, also part of the F-box motif and located two amino acids away from the alteration identified in the first individual. The third individual is 16 years old and reported to have severe ID, ADD/anxiety and self-injuring behavior, feeding difficulties, decreased tone in upper extremities and increased tone in lower extremities. DES identified a *de novo KLF7* c.790G>A (p.D264N) alteration located in the zinc finger-containing DNA binding domain shown to bind to the minimal enhancer of the *NTRK1* gene (MIM 191315) encoding a receptor for nerve growth factor. These findings suggest a phenotype for individuals with *KLF7* alterations including developmental delay/ID, abnormal muscle tone, feeding/swallowing issues, psychiatric features and neuromuscular issues. Additional patients with *KLF7* alterations are needed to delineate the phenotypic spectrum and make genotype-phenotype correlations.

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