Mutually exclusive *VPS13B* isoforms in skeletal muscle: implications for Cohen syndrome

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VPS13B (COH1) encodes a large Golgi-associated protein involved in Golgi integrity, lipid transport and membrane trafficking. *VPS13B* deficiency causes Cohen Syndrome (CS), a rare autosomal recessive disorder characterized by neurodevelopmental impairment, retinopathy, neutropenia, systemic hypotonia and joint hypermobility. *VPS13B* gene comprises 62 exons and undergoes alternative splicing, generating several transcript isoforms. Mutually exclusive splicing of exons 28b and 28 generates full-length isoforms 1 and 5, respectively.
GTEx transcriptomic analysis indicates that isoform 1 is broadly expressed, whereas isoform 5 is enriched in brain, retina and skeletal muscle. We characterized *VPS13B* isoforms in human *vastus lateralis* muscle, CS fibroblasts, and compared them with mouse muscle and differentiating C2C12 cells.
Competitive PCR and RT-qPCR demonstrated abundant isoform 5 expression in human skeletal muscle, whereas it was barely detectable in control and CS fibroblasts. An additional transcript containing both exons 28b and 28 was mainly detected in CS fibroblasts. This aberrant transcript is predicted to disrupt the open reading frame, generating a premature termination codon and potentially undergoing Nonsense-Mediated mRNA Decay (NMD) or production of truncated *VPS13B* protein. Unexpectedly, only isoform 1 was detected in mouse muscle and C2C12 cells during differentiation. Sequence alignment revealed a 7-bp deletion in mouse exon 28, introducing premature stop codons and preventing production of a full-length human isoform 5. Multispecies alignment showed that exon 28 is highly conserved across vertebrates, indicating that mouse, and possibly rat, are evolutionary exceptions.
These findings reveal tissue- and species-specific regulation of *VPS13B* alternative splicing and establish a foundation for studying the functional roles of its isoforms during human myogenic differentiation and their potential contribution to muscle involvement in Cohen Syndrome.