Associations between dystrophin genotype and ambulatory outcomes in DMD: implications for trials of genotype-targeted therapies

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Clinical trials of genotype-specific treatments in DMD traditionally compare treated patients to controls with the same dystrophin genotype. This avoids confounding due to genotype effects on outcomes but also shrinks the pool of eligible controls. To evaluate suitability of genotypically unmatched controls in DMD, we quantified genotype effects on 1-year changes in North Star Ambulatory Assessment total score (NSAA) across data sources. Data were analyzed from over 1,500 patient-years of follow-up (>700 patients) from six real-world/natural history data sources (UZ Leuven, PRO-DMD-01 study (shared by CureDuchenne), iMDEX study, North Star UK network, Cincinnati Children's Hospital Medical Center, and DMD Italian Group), with genotypes classified as amenable to skipping exons 44, 45, 51 or 53, other skippable, nonsense, and other mutations. Associations between genotype and NSAA change were studied in each data source with and without adjustment for baseline function, steroid use, age, height, weight and BMI, and meta-analyzed. The pooled estimate of skip 51 versus other skippable mutations on 1-year NSAA change was -0.9 units (95% CI: (-3.2, 1.4) without adjustment and -1.3 units (-2.3, -0.4) with adjustment. Adjusted effects for skip 53 (-1.0 (-2.0, 0.1)), skip 44 (0.3 (-0.5, 1.1)) and skip 45 (0.3 (-1.2, 1.9)) were similar in magnitude. Effect sizes were smaller than clinically important differences in NSAA, and were precisely estimated with standard errors < 2 units, suggesting likely viability of genotypically unmatched controls for studies up to 12 months in duration. Power and sample size of trial designs incorporating genotypically unmatched controls will be explored.