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## Sequence variants and genotypes among 898 patients with Pompe disease: data from the Pompe Registry

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Pompe disease (PD) is an autosomal recessive disorder caused by deficient lysosomal acid α-glucosidase (GAA). Phenotypic heterogeneity is due to several factors, including different pathogenic variants in the *GAA* gene, which influence disease severity and manifestations. Identification of variants is valuable for confirming diagnosis or carrier status, in newborn screening, and for treatment algorithms (e.g., immunomodulation). We report the frequency and characteristics of sequence variants, including homozygous genotypes, among patients enrolled in the Pompe Registry (sponsored by Sanofi Genzyme), the largest PD database. Genotype information from patient records was evaluated. The Human Genome Variation Society Recommendations were used to standardize nomenclature. The analysis population included patients with the following: ≥1 documented sequence variant; dates of birth, PD diagnosis, and symptom onset; gender; and PD classification (classic-infantile [IOPD]) or late-onset [LOPD]). LOPD was classified further based on symptom-onset age (LOPD <12 years and LOPD ≥12 years). Novel alleles were identified by comparisons with current listings in *GAA* mutation databases. Of 898 Registry patients with evaluable sequence variant information, 150 were classic IOPD and 748 LOPD (207 LOPD <12 years; 541 LOPD ≥12 years). Of 1729 total variants recorded, 91 (5.3%) novel variants were identified. Overall, splice site (37.8%) and missense (31.8%) variants were the most commonly reported. Missense variants were the most common (48.7%) in IOPD patients; splice site variants were the most common (44.6%) in LOPD patients. Among 134 IOPD patients with 2 variants, 45 (33%) were homozygous vs. 25 (3.8%) of 665 LOPD patients. *GAA* sequence data from the Pompe Registry provide valuable information about frequency and distribution of variants among patient populations. They show how such data can be successfully captured in a registry and how collecting data is a means to increase understanding of the phenotypic heterogeneity seen in PD, develop treatment algorithms, and improve genetic counseling.

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