SIGNIFICANCE STATEMENT

Magnesium (Mg^{2+}) is essential for many enzymatic reactions involved in energy metabolism, and abnormal Mg^{2+} levels are associated with diabetes and metabolic disorders. The genetic factors regulating Mg^{2+} homeostasis are poorly characterized. Using genome-wide association studies (GWAS) in European populations, we discovered two loci significantly associated with urinary Mg^{2+}: the *TRPM6* gene coding for a Mg^{2+} channel and the *ARL15* gene, which is linked to lipid levels, type 2 diabetes and cardiovascular disease. We find that ARL15 influences Mg^{2+} reabsorption through regulation of TRPM6, suggesting a genetic mechanism for the association of urinary Mg^{2+} excretion with metabolic phenotypes. These findings suggest that gene-diet interactions may contribute to the link between Mg^{2+} homeostasis and metabolic disorders in the general population.