From evolutionary relics to diabetic mellitus sentinels: a Mendelian randomization study of endogenous retrovirus group V member 1

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Human endogenous retroviruses (HERVs) are retroviral elements that have integrated into the human genome during evolution and have various effects on human health and disease. Diabetic mellitus (DM) is a common metabolic disorder that affects millions of people worldwide. The causal relationship between HERVs and DM is unclear and controversial. In the present study, we used Mendelian randomization (MR) to infer the causal effect of HERV group V member 1 envelope polyprotein (HERVV-1 Env) expression on three types of DM: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM). We found that HERVV-1 Env expression had a significant protective effect on T1DM and GDM, albeit not on T2DM. The reverse MR analysis showed that the three subtypes of DM did not affect HERVV-1 Env expression. Our findings illuminate the intricate relationship between HERVV-1 Env expression and varying DM subtypes, highlighting distinct underlying mechanisms. This pioneering study into the potential causal ties between HERVs family members and DM onset offers a new perspective on the significance of HERVs in human health and pathology.

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and placental tissue[2]. Additionally, activation of HERVs in human embryos and placental cells can express an envelope protein known as suppressyn, which curtails the infectivity of mammalian D retroviruses by competing for the alanine–serine–cysteine transporter 2 (ASCT2) recept[3]. However, not all HERVs activities are beneficial certain products expressed from specific HERVs families can provoke antiviral immune responses, which might escalate into chronic inflammation and autoimmunity, resulting in potential damage to tissues and organs[4,5]. Emerging research also underscores the involvement of HERVs in processes like human cellular senescence[6] HERVs have been implicated in a range of diseases, including Alzheimer's disease[7], amyotrophic lateral sclerosis[8], and various cancers[9,10], illustrating their potential impact on human health. However, the extensive diversity of HERVs families and the variability among different populations have left many aspects of HERVs influence on other diseases relatively unexplored. Consequently, there is a pressing need for more in-depth studies to clarify the involvement of HERVs in the pathogenesis of various diseases, as well as to understand the effects on HERVs expression and functionality during disease progression. The present study is vital for uncovering disease mechanisms and could greatly advance HERVs studies, potentially leading to new treat