Predictive AI-Based Genomic Optimisation of Donor Pig Livers for Human Xenotransplant Compatibility

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The global shortage of donor organs has renewed interest in xenotransplantation, with genetically modified pigs (Sus scrofa domesticus) emerging as potential donors for human liver transplantation. Immune rejection driven by molecular and structural differences between pig and human proteins remains a major barrier, and identifying which pig genes to modify, and how, has traditionally been a complex, manual process. This study developed an integrative bioinformatics and machine learning pipeline to prioritise gene-editing strategies for pig-to-human liver xenotransplantation. Protein sequence comparisons, AlphaFold-derived structural predictions, liver-specific expression data, and immune-related features were combined to classify genes into modification categories. In the first stage, genes were predicted as requiring modification or not; in the second stage, genes were assigned knockout or humanisation strategies. The system successfully prioritised known immunogenic genes, including GGTA1 and CMAH, for knockout and identified conserved, functionally important genes suitable for humanisation or no modification. Model evaluation demonstrated reliable discrimination between edit classes, and feature importance analysis confirmed that biologically meaningful predictors, rather than sequence similarity alone, drove decisions. By integrating biological insight with interpretable machine learning, this approach provides a scalable, transparent tool to guide experimental gene-editing in xenotransplantation, reducing trial-and-error and improving the efficiency of future donor organ optimisation.

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