Innovative models to explore hepatic involvement in Prader-Willi syndrome.

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Frontiers in Endocrinology 17, 2026.

Prader-Willi syndrome (PWS; MIM# 176270) is a rare neurodevelopmental disorder characterized by clinical manifestations across multiple body systems. PWS represents an atypical form of obesity-associated metabolic disease in which extreme adiposity coexists with a comparatively attenuated risk of insulin resistance and hepatic complications. The genetic basis of PWS leads to impaired lipid storage and oxidation capacity in adipocytes, with downstream consequences for hepatic lipid burden. Systemic lipidomic and metabolomic profiling further supports the existence of a distinct metabolic signature in PWS, showing consistent qualitative alterations in circulating phospholipids that may, in turn, influence hepatic lipid export and the risk of steatosis. Hepatic involvement in PWS seems to be shaped by intrinsic alterations in lipid handling and endocrine signaling rather than by adiposity. Finally, metabolic dysfunction-associated steatotic liver disease (MASLD) remains less prevalent in PWS. Among the currently available models derived from induced pluripotent stem cells (iPSCs), hepatocyte-like cells (HLCs) and iPSC-derived organoids, have emerged as valuable tools for investigating rare genetic liver disorders and as powerful strategies to dissect tissue-specificmechanisms underlying PWS phenotype, because they bridge the gap between molecular epigenetic mechanisms and organism-level metabolic phenotypes in PWS. Their ability to capture patient-specific epigenetic regulation and tissue-specific metabolic dysfunction positions them as indispensable tools for advancing both mechanistic understanding and therapeutic development in PWS.