Background and Aims: We recently identified a single nucleotide polymorphism (Rs 1800574) in the DNA binding domain of transcription factor Hepatocyte Nuclear Factor 1 alpha (HNF1A) of early-onset colorectal cancer patients. The conservative missense mutation changes an alanine to a valine at residue 98. The HNF1A^{A98V} variant is a loss-of-function (LOF) mutation, exhibiting reduced DNA binding affinity and avidity in gel shift assays. In *Hnf1a*^{A98V} transgenic mice generated using Crisper/Cas9 technology, we demonstrated that this mutation led to the development of colon polyps at 6 mos, but only when heterozygous (*Hnf1a*$^{A98V/+}$) and homozygous (*Hnf1a*$^{A98V/A98V}$) mice were placed on a high-fat diet (HFD). Mutations at this locus are also associated with diabetes and dyslipidemia in humans. Incidentally, the *Hnf1a*^{A98V} transgenic mice on HFD also developed liver tumor at 14 mos. Therefore, we hypothesize that this LOF mutation contributes to metabolic dysfunction-associated steatotic liver disease (MASLD), and ultimately hepatocellular carcinoma (HCC). **Methods**: Glucose homeostasis (glucose tolerance test), insulin sensitivity (insulin tolerance test) and liver triglyceride levels were quantified. Liver function/damage was assessed by serum ALT. The severity of hepatic steatosis, fibrosis and inflammation was determined by H&E staining and immunohistochemistry. Changes in the transcriptome mediated by elevated fat and loss of HNF1A function was determined by bulk RNA-Seq and confirmed by qPCR, and western blots. **Results**: Within 6 mos of a HFD, glucose and insulin levels were elevated in mice heterozygous and homozygous for the *Hnf1A*^{A98V} mutations consistent with development of the metabolic syndrome. Moreover, these mice also developed MASLD and showed elevated liver triglyceride and ALT levels. Using the picrosirius red stain, their livers showed higher fibrosis in the mutant

mice on the HFD. There were no changes in these parameters in mice on normal chow or WT mice on the HFD, demonstrating that this LOF mutation was sufficient to induce changes but only in the presence of a fatty meal. Genes related to protein folding (HSPs), fatty acid oxidation (FABPs) and inflammation (STAT3), were differentially expressed especially in the homozygous group on the HFD. By 14 mos, 3.7% *Hnf1a*$^{A98V/A98V}$ mice developed MASLD related tumors on normal chow, while none of the WT or heterozygous mice developed tumors. By contrast, on the HFD, 13.3% of the heterozygous and 27.5% of the homozygous *Hnf1a*^{A98V} mice developed tumors. In addition, 10.5% of the WT mice on the HFD developed liver tumors at 14 mos. Histology confirmed the tumors as HCC and were AFP positive. **Conclusion**: A seemingly benign LOF HNF1A missense mutation in the DNA binding domain predisposes mice and possibly human subjects to MASLD and HCC but mainly in the presence of a HFD. These results suggest that diet can influence gene function.