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Gitelman syndrome

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telman syndrome (OMIM 263800) is an autosomal recessive salt-losing renal tubulopathy aracterized by hypokalemic metabolic alkalosis in conjunction with hypomagnesemia and pocalciuria. With an estimated prevalence of 1 to 10 per 40.000, and a heterozygote rrier frequency of 1% in the Caucasian population, Gitelman syndrome is one of the ost frequent inherited renal tubular disorders. In Asia, the disease is probably even ore prevalent with a heterozygote carrier frequency up to 3%. The Gitelman syndrome enotype can be observed from the age of 6 years, but in most instances the diagnosis is ade during adulthood. The phenotype is extremely variable; the most common mptoms seen in more than 50% of cases are salt craving, muscle weakness, tetany, tigue, dizziness, nocturia, palpitations, paresthesia, thirst, polydipsia, and low blood essure. Other prominent symptoms, seen in 20-50% of cases are fainting, polyuria, thralgia, chondrocalcinosis, prolonged QT, and febrile episodes. Remarkably, some tients are completely asymptomatic and in these patients the disease is detected rtuitously. There are a few case reports of Gitelman syndrome presenting already before years of age. The Gitelman syndrome phenotype is in most cases caused by bi-allelic ss-of-function mutations in the solute carrier family12, member 3 gene, *SLC12A3*, which codes the thiazide-sensitive NaCl cotransporter (NCC) in the distal convoluted tubule CT) of the nephron. A minority (3-5%) of Gitelman syndrome patients has bi-allelic ss-of-function mutations in *CLCNKB*, encoding the chloride channel subunit b (ClC-Kb). th mutations in NCC as well as in ClC-Kb lead to disruption of NaCl reabsorption in the CT, resulting in increased sodium delivery to the collecting duct and mild volume ntraction. Hypovolemia will, via stimulation of the renin-angiotensin-aldosterone system, crease sodium reabsorption in the collecting duct, maintaining sodium homeostasis at e expense of increased secretion of potassium and hydrogen ions, and an attendant pokalemia and metabolic alkalosis. Enhanced passive Ca^{2+} reabsorption in the proximal bule and reduced abundance of the epithelial Mg^{2+} channel TRPM6, located in the DCT, e suggested to explain the hypocalciuria and hypomagnesemia, respectively.

my presentation, I will update you on the genetics of Gitelman syndrome. At present, ore than 500 different disease-causing mutations in *SLC12A3* have been reported. Of ese mutations several are common in Asia: p.Arg642Cys, p.Leu858His, and Thr60Met. I will also discuss the differential diagnosis of Gitelman syndrome and how netic testing can help in differentiating Gitelman syndrome from phenocopies. I will aborate on studies that try to explain the high phenotypic variability of Gitelman ndrome and I will explain why Gitelman syndrome cannot be considered a benign bulopathy. Finally, I will review the current management, further therapeutic options and e long-term prognosis of Gitelman syndrome.