

## Abstract

Meckel-Gruber syndrome is a severe autosomal, recessively inherited disorder characterized by bilateral renal cystic dysplasia, developmental defects of the central nervous system (most commonly occipital encephalocele), hepatic ductal dysplasia and cysts and polydactyly. MKS is genetically heterogeneous, with three loci mapped: MKS1, 17q21-24 (ref. 4); MKS2, 11q13 (ref. 5) and MKS3 (ref. 6). We have refined MKS3 mapping to a 12.67-Mb interval (8q21.13-q22.1) that is syntenic to the Wpk locus in rat, which is a model with polycystic kidney disease, agenesis of the corpus callosum and hydrocephalus. Positional cloning of the Wpk gene suggested a MKS3 candidate gene, TMEM67, for which we identified pathogenic mutations for five MKS3-linked consanguineous families. MKS3 is a previously uncharacterized, evolutionarily conserved gene that is expressed at moderate levels in fetal brain, liver and kidney but has widespread, low levels of expression. It encodes a 995-amino acid seven-transmembrane receptor protein of unknown function that we have called meckelin.