 Chronic Intestinal Pseudo-Obstruction (CIPO) is characterized by a severe impairment of gut motility, mimicking a mechanical sub-obclusion in the absence of anatomical causes of gut obstruction. The severity of the clinical presentation, often associated with disabling digestive symptoms between sub-occlusive episodes, contributes to poor quality of life and increased mortality. Most CIPO patients are sporadic, although X-linked, autosomal dominant, and autosomal recessive forms have been reported. We previously mapped a predisposing locus in a large consanguineous family segregating an autosomal recessive form of CIPO. In the affected family members, the major clinical feature was represented by CIPO, in addition to megaduodenum, long-segment Barrett oesophagus, and cardiac abnormalities of variable severity (OMIM 611376; Mungan syndrome). Here we report the identification of the mutation underlying CIPO at this locus and its functional characterization in vitro and in vivo.

**Methods**

Whole Exome Sequencing (WES) analysis was performed using the genomic DNA of affected individuals IV-9 and IV-11. In vivo morpholo assays on D. rerio animal models (zebrafish) were performed using Rad21 Morpholinos (MO) and analyzing Runx1 by RNA in situ analysis and enteric neurons by HuC/D immunostaining. Immunohistochemistry was performed on paraffin-embedded adult human gut tissues. Fluorescent cell count was performed with the ImageJ software (http://rsbweb.nih.gov/ij); chi-square tests were calculated using the dedicated option from GraphPad calculator package.

**Results and Discussion**

We found that APOB48, the gut-specific isoform, was markedly increased in the homozygous RAD21 mutant patient’s serum compared to controls. Western blotting analysis showing APOB48 expression in the patient carrying the homozygous RAD21 mutation, compared to control sera. We observed the same results in sera from a subset of well characterized sporadic CIPO patients, negative for RAD21 mutations, also showed a consistently elevated APOB48 as compared to either healthy controls.

**Conclusions**

We provide in vitro and in vivo evidences that the novel RAD21 mutation p.622 Ala>Thr is associated to a syndromic form of CIPO. The identification of RAD21 as predisposing gene to this disease and the discovery of the deranged pathways altered by this mutation might prove relevant for other idiopathic forms of CIPO, in order to understand the pathogenesis of such severe condition. Future research will help elucidating the factors contributing to a specific APOB48 overexpression and its clinical value in the management of CIPO patients.