A gastrointestinal origin of iron-deficiency anemia in the Jervell and Lange-Nielsen Syndrome?

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Background: The *KCNQ1*-encoded voltage-gated potassium channel regulates (**Figure 1**):

- cardiac repolarization
  (dysfunction = arrhythmia propensity)
- inner ear endolymph flow
  (dysfunction = congenital hearing loss)
- gastric acid secretion
  (dysfunction = ? *gastric hypertrophy/dysplasia suggested*)

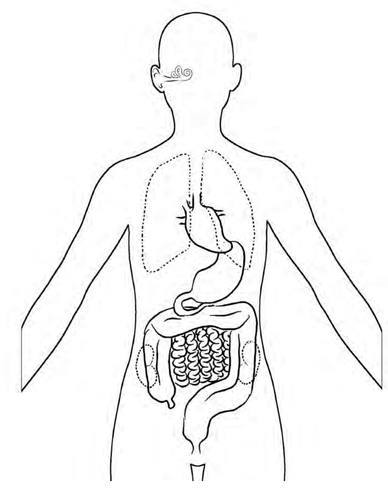

Figure 1. Locales where *KCNQ1* K+ channels contribute to physiological function

Conclusions

We propose that JLNS phenotypically includes gastrointestinal symptoms/signs and secondary iron-deficiency anemia, due to hypochlorhydria on the basis of *KCNQ1* mutations.

Clinical monitoring with regards to developing anemia and hypergastrinemia should be considered in JLNS

Aim: To investigate the occurrence of extra-cardiac symptoms and/or signs in the recessive long QT -Jervell and Lange-Nielsen syndrome (JLNS), where several cases of severe unexplained anemia have been reported.

Methods: All Swedish JLNS cases with double *KCNQ1* mutations (n=14) were investigated by medical record review, a personal semi-structured interview, and were offered laboratory testing for iron-deficiency anemia and gastrointestinal markers.

Results: All included cases had a clinical JLNS diagnosis (congenital hearing loss and a prolonged QTc 587±69 ms)

Extra-cardiac clinical findings:

- previous iron-deficiency anemia (12/14)
- current signs of anemia (9/12)
  (i.e. < Hb for age, ± < plasma-Fe or iron-substitution)
- gastrointestinal symptoms (13/14)
  (i.e. pains, diarrhoea, malabsorption etc.)

Elevated levels of gastrin (7/9 cases), pepsinogen (6/7 cases), and fecal calprotectin (9/9 cases) were present (**Table 1**).

A significant correlation between gastrin levels >60 pmol/L and concurrent iron-deficiency and/or anemia was revealed (p=0.039).

Table 1. Relation between current anemia and gastrointestinal markers in 10 JLNS cases

Cases F/M	*KCNQ1* mutations amino acid change	Current anemia status	Gastrin pmol/L NV<60	Pepsinogen µg/L NV<130	Calprotectin mg/kg NV<50
1 F†	M159/ R518X	< Fe, borderline Hb	**418**	**802**	**599**
3 F†	M159/ R518X	< Fe, borderline Hb	**218**	**892**	**77**
4 M†	Q530X/ R518X	< Fe and < Hb			**121-308**
5 F†	R518X‡	Fe N and Hb N	51	**179**	**156**
6 M†	S349W/ R518X	< Fe and < Hb	**449**		**469-641**
7 F	R518X‡	Fe N and Hb N	22		
10 F	R518X/ Q530X	< Fe and Hb N	**66**	**138**	**220**
11 M	S227del/ R518X	Fe N and Hb N	**92**	121	**291**
12 F	Y111C‡	Fe- substitution	**783-811**	**237**	**188**

Abbreviations: F- female, M- male, NV- normal values, Fe- plasma iron, Hb- hemoglobin count (< low for age, N-normal), †Pediatric cases, ‡Homozygous mutation-carriers

Previous endoscopy (n=5) had revealed no case of celiac- or inflammatory bowel disease but in three cases where biopsies were taken mucosal hyperplasia/dysplasia was seen (**Figure 2.**).

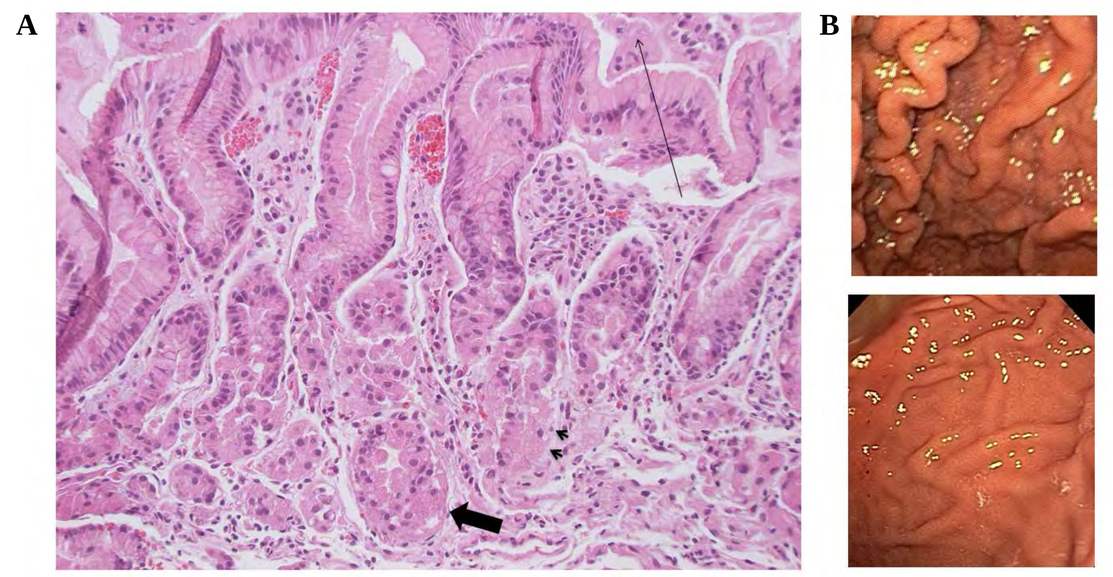

Figure 2. **A**. Biopsy from the fundic mucosa of Case 6 (20X objective magnification). A deranged parietal cell histology is evident including hyperplasia (bold arrow), but also degeneration of parietal cells (arrow heads). In addition, a slight increase in chronic inflammatory cells is noted in the lamina propria. An increased amount of exfoliated parietal cells is seen at the luminal border (thin arrow).
B. Endoscopic photographic image from Case 6 (above) revealing hypertrophic rugal folds in the corpral and antral part of the stomach. Below: corresponding image from a healthy control.

Our hypothesis regarding how JLNS genotype could result in the observed symptoms and signs is presented in **Figure 3**.

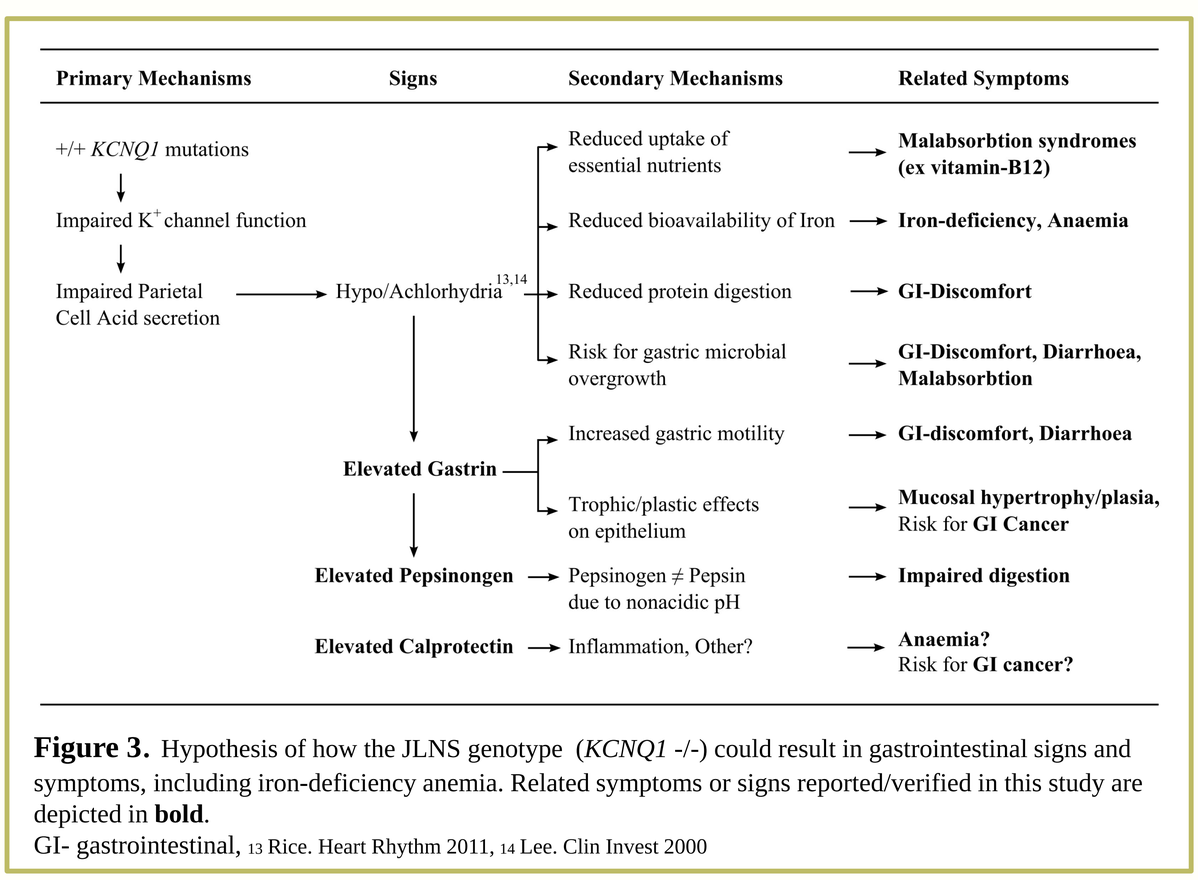

Figure 3. Hypothesis of how the JLNS genotype (*KCNQ1* -/-) could result in gastrointestinal signs and symptoms, including iron-deficiency anemia. Related symptoms or signs reported/verified in this study are depicted in **bold**.
GI- gastrointestinal, 13 Rice. Heart Rhythm 2011, 14 Lee. Clin Invest 2000

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