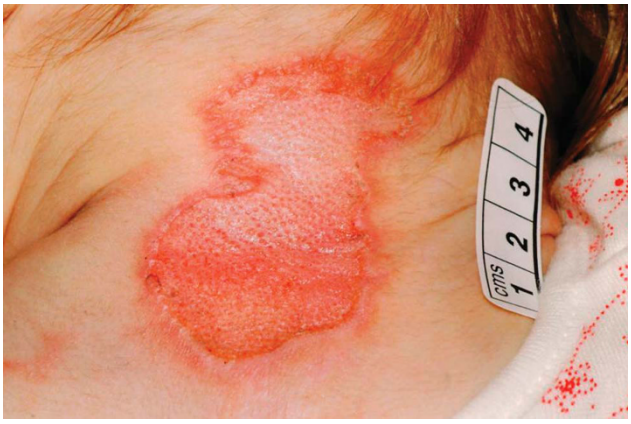

Figure 1 Neck of case 3 with the SCN11A/$Na_V1.9$ mutation p.L811P at the age of 1 year 5 months. A large contiguous healing region is shown. This was caused by the child scratching, mostly while awake. This area was excoriated for 6 months due to intense itching for which hyperhidrosis was a significant contributory factor.

CONFLICT OF INTEREST

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Connexin 26 variant carriers have a better gastrointestinal health: is this the heterozygote advantage?

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Connexin 26 (GJB2) is one of the major factors in human deafness worldwide. On average 1/1000 children is born deaf and the most common GJB2 variant (c.35delG) causes ~40% of cases in Southern Europe. Carriers' frequency for different loss-of-function GJB2 mutations is very high worldwide (up to 3%),[1] suggesting a heterozygous advantage for a global condition or a founder effect.[2] In this light, epidermal thickening in GJB2 carriers[3,4] has been proposed as a possible advantage reducing infections and bacterial invasion through skin.[5,6] Moreover, *in vitro* functional studies demonstrated that the loss-of-functional GJB2 expression provides improved protection against gastrointestinal bacterial pathogens.[7] In particular, enteropathogenic *Escherichia coli* and *Shigella flexneri* may induce a strong selective effect, being the most common causes of diarrhoea. Thus, GJB2 carriers might have an increased resistance to gastrointestinal infectious diseases, as already proposed by Simpson *et al.*[7]

To test this hypothesis, a cross-sectional study involving 203 subjects aged 19–65 years (63% women) was carried out. Subjects (170) were wildtype for the *GJB2* gene, whereas 33 carried one or more variants. The information about diarrhoea episodes and frequency, medical history and covariates (sex and age) was collected. People self-reporting diarrhoea episodes at least once a year were set as cases, whereas the remaining ones were controls (all the subject had similar level of education) (Table 1; Figure 1). Subjects affected by pertinent chronic diseases (Crohn's disease, Intestinal bowel disease and so on) were excluded from the study. Fisher's exact test was performed for case/control proportion in relation to genotype, giving a significant result ($P = 0.007$), with an odds ratio (OR) of 3.21 (95% confidence interval (CI): 1.27–9.24). Although our sample was sex and age homogeneous (Wilcoxon test $P > 0.05$), performing the same analysis separated by sex revealed that females mainly contributed to the finding ($P = 0.0016$). In particular, in our data set women had higher incidence of diarrhoea than men (46% and 36% respectively), and for female GJB2 carriers this proportion dropped to 12.5%, with an OR = 8.33 (95% CI: 1.82–78.03). As regards to the reported frequency per die (range: 0–3), linear regression was applied,

Table 1 Summary of the analysed sample

GJB2 sequence[a]	*No. of subjects*	*Diarrhoea no.; yes/no*
Wildtype +/+	170	79/91
c.35delG/c.290_291insA	1	0/1
c.35delG/+	24	4/20
c.35delG/c.109G>A	1	0/1
c.478G>A/+	2	0/2
c.380G>A/+	1	1/0
c.457G>A/+	1	0/1
c.269T>C/+	1	0/1
c.35delG/c.35delG	2	1/1

[a]Accession version: NM_004004.1.

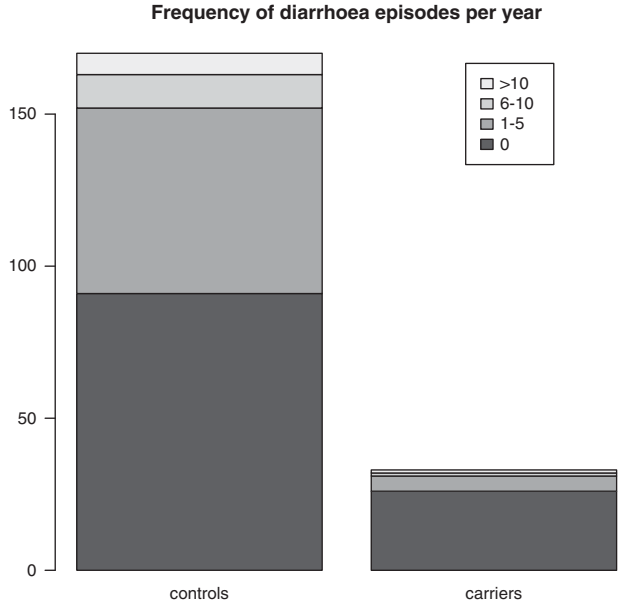

Figure 1 Frequency of diarrhoea episodes per year. The figure shows a bar plot of reported frequencies of diarrhoea episodes per year by cases and controls separately.

including covariates, and a significant effect for genotype was detected ($P = 0.006/0.017$ for females/total sample) indicating lower diarrhoea frequency for GJB2 carriers.

In conclusion, present clinical results provide new insights on GJB2 heterozygote advantage, further suggesting that it might consist in an increased resistance to gastrointestinal infections as already demonstrated by *in vitro* studies. Future research activities should be carried out to further confirm the present finding (eg, increasing the sample size) and to investigate whether GJB2 carriers have a different gut microbiota composition.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Data collection was done by AF, LM and MDP; study design by DV, PG and BD; data analysis by DV; and writing by DV and PG.

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Reply to 'The 'extremely ancient' chromosome that isn't' by Elhaik *et al*

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Recently, Elhaik *et al*[1] criticized several aspects of an analysis in which Mendez *et al*[2] estimate the time to the most recent common ancestor (TMRCA) for the Y chromosome tree incorporating a newly identified basal branch called A00. Elhaik *et al* asserted that Mendez *et al* derived an inflated estimate of the TMRCA by applying incorrect assumptions and approximations, numerical miscalculations, and data manipulation. In particular they focused on (1) the method used to estimate the Y chromosome mutation rate, (2) the relative lengths of sequences that should be compared in order to estimate branch lengths in a tree, and (3) the implications of the Y chromosome TMRCA estimates reported by Mendez *et al* for human evolution. Here we show that these criticisms result from a misunderstanding of population genetic theory, as well as a misrepresentation of the methodology of Mendez *et al.* However, before addressing the various arguments put forward by Elhaik *et al*, we comment on conceptual and theoretical issues surrounding the significance of the Y chromosome TMRCA.