Prevalence of the Amish, Hutterite, and Mennonite Variants in Maple Syrup Urine Disease Brazilian Patients

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Introduction
Maple syrup urine disease (MSUD) is caused by biallelic pathogenic variants in one of the genes related to the alpha-keto acid dehydrogenase complex (BCKDHA, BCKDHB, DBT, DLD, and PPM1K), and has common variants in Hutterites (c.595_596delAG, BCKDHB gene), and Mennonites (c.1312T>A, BCKDHA gene). The Mennonites arrived at South Brazil in 1930. The worldwide distribution of the c.595_596delAG variant are shown in Figure 1.

Aims
To access the prevalence of the Anabaptist-related MSUD variants in Brazilian MSUD patients.

Methods
Review of the genotype bank of the 40 unrelated Brazilian MSUD patients analysed by the Brazilian MSUD Network. Published (8, 9) and unpublished data were retrieved. Among them, 22 had variants in BCKDHB, 11 in BCKDHA, and 7 in DBT.
Results

- Published: 21
- Classic MSUD: 39
- Consanguinity rate: 7/40
- Anabaptist ancestry: 0/40

Most common variants in all patients
- p.Pro200Ter in BCKDHB, 6/80
- p.Ala248CysfsTer10 in BCKDHA, 4/80
- p.Glu148Ter in DBT, 4/80

- c.595_596delAG
  - 5 patients
  - South Brazil: 1
  - North Brazil: 1
  - Unknown: 3
  - Homozygous: 1

- c.1312T>A
  - Not found

Discussion

As expected, BCKDHB was the most frequent gene associated with MSUD in Brazil. The variant c.595_596delAG is related to a founder effect in the Hutterites and the most frequent found in our cohort. However, this variant is also reported in other populations such as Spanish, Austrian, Portuguese, and Brazilian. Hutterites originated in a part of Austria, moved to several Europe regions and USA. The gnomAD frequency for this variant is 0.0000283. It is located in a repetitive region (AGAG), being a hotspot for replication errors.

Conclusion

The origin of the variant c.595_596delAG in Brazil, is probably heterogeneous. The variant c.1312T>A is much rarer in the worldwide population, which justifies its absence in Brazilian patients.

Support
References

1 – Mroch, et al. (2014). PMID: 24791375