







# Is a heterozygous missense variant in *SGSH* the cause of a syndromic form of congenital amastia in an Original Braunvieh calf?

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## Funding information

This research was partially funded by Swiss National Science Foundation, grant number 172911.

## BACKGROUND

Congenital amastia is a rare developmental disorder characterised by the complete absence of the mammary gland and teats (Huppert & Zidenberg, 2008). It occurs as an isolated anomaly or as a syndromic form (Mareti et al., 2021). Only a few syndromic forms of amastia are known in humans (OMIM 129510, OMIM 207780, OMIM 173800, OMIM 181270). Both autosomal dominant and recessive inheritance have been described for syndromic forms of amastia, but only for a few the molecular causes have been identified. To date, no case of congenital amastia in domestic animals has been reported.

## ANALYSIS

A 5-days-old female purebred Original Braunvieh female calf was referred owing to a congenital absence of teats and cleft palate. Gross pathology revealed the entire absence of the udder including teats, complete palatoschisis affecting both soft and hard palate, hepatomegaly, corneal opacity and an open vulva (Figure S1). Whole genome sequencing (WGS) was performed using genomic DNA obtained from ear tissue from the calf. Reads were mapped to the ARS-UCD1.2 assembly

(Rosen et al., 2020), resulting in an average read depth of 14.7×. The WGS data were evaluated as previously described (Jacinto et al., 2021). Variant filtering did not reveal any private homozygous protein-changing variants present in the genome of the affected calf, making a possible recessive inheritance unlikely. Assuming that a spontaneous mutation affecting a protein-coding gene is the cause, filtering for private heterozygous coding variants present in the calf's genome allowed the identification of six variants with a predicted moderate or high impact (Table S1). These variants were confirmed as true by visual inspection with the INTEGRATIVE GENOMES VIEWER software (Robinson et al., 2017). These variants were absent from a total of 5365 controls and a single variant affects *SGSH*, a putative candidate gene for the observed congenital anomaly. This heterozygous variant at chr19:52427490C>T represents a missense variant in *SGSH* exon 4 (NM\_001102189.2: c.425C>T) (Figure S2). We suspected that the identified variant in *SGSH* either occurred post-zygotically in the developing embryo or was inherited from a mosaic parent. Unfortunately, no biological samples were available from the parents. The encoded amino acid of *SGSH* is predicted to be altered at codon 142 (NP\_001095659.2: p.Thr142Met) located in the *N*-sulphoglucosamine sulphohydrolase domain. The substitution of threonine to methionine affects an amino acid that is highly conserved in all species (Figure S2)

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and has been predicted to be harmful using three different tools (Provean,  $-4.729$ ; PhD-SNP, 50%; SIFT, 79%).

## COMMENTS

The affected gene *SGSH* encodes an enzyme, *N*-sulphoglucosamine sulphohydrolase, which catalyses a step in lysosomal heparan sulphate degradation that plays an important role in glycosaminoglycan and heparan sulphate proteoglycan degradation processes (Muschol et al., 2004). In humans (OMIM 252900), mice (MGI1350341) and dogs (OMIA 001309-9615) pathogenic variants in *SGSH* cause mucopolysaccharidosis III, a recessively inherited lysosomal storage disease that occurs owing to impaired degradation of heparan sulphate (Esposito et al., 2000). Affected individuals may have a variety of abnormalities including mental retardation, abnormal neurocranium and vertebrae, abnormal cardiac morphology, hepatomegaly, splenomegaly, corneal opacity, diarrhoea and respiratory infections (Bhaumik et al., 1999; Valstar et al., 2008). The calf reported herein had palatoschisis, hepatomegaly and corneal opacity (Figure S1). Unfortunately it was not possible to evaluate the central nervous system. However, given the rarity, *in silico* effect prediction and known function of *SGSH*, the identified missense variant might be considered as a possible cause for the observed congenital anomaly, although this gene has not been associated with syndromic forms of amastia in mammals, including humans. However, the possible role of *SGSH* in the origin of mammary gland developmental defects needs to be confirmed in future research.

## ACKNOWLEDGEMENTS

We thank the Interfaculty Bioinformatics Unit of the University of Bern for providing computational infrastructure. Open access funding provided by Universitat Bern.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The WGS data (sample accession SAMEA8565096) are available at the European Nucleotide Archive ([www.ebi.ac.uk/ena](http://www.ebi.ac.uk/ena)).

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## REFERENCES

- Bhaumik, M., Muller, V.J., Rozaklis, T., Linda, J., Dobrenis, K., Bhattacharyya, R. et al. (1999) A mouse model for mucopolysaccharidosis type III A (Sanfilippo syndrome). *Glycobiology*, 9(12), 1389–1396. Available from: <https://doi.org/10.1093/glyco/b/9.12.1389>
- Esposito, S., Balzano, N., Daniele, A., Villani, G.R., Perkins, K., Weber, B. et al. (2000) Heparan N-sulfatase gene: two novel mutations and transient expression of 15 defects. *Biochimica et Biophysica Acta*, 1501(1), 1–11. Available from: [https://doi.org/10.1016/s0925-4439\(99\)00118-0](https://doi.org/10.1016/s0925-4439(99)00118-0)
- Huppert, J.S. & Zidenberg, N. (2008) Breast disorders in females. In: Slap, G.B. (Ed.) *Adolescent medicine*. Philadelphia, Pennsylvania: Elsevier Inc., pp. 146–151. Available from: <https://doi.org/10.1016/b978-032304073-0.10021-4>
- Jacinto, J.G.P., Häfliger, I.M., Akyürek, E.E., Sacchetto, R., Benazzi, C., Gentile, A. et al. (2021) KCNG1-related syndromic form of congenital neuromuscular channelopathy in a crossbred calf. *Genes*, 12, 1792. Available from: <https://doi.org/10.3390/genes12111792>
- Mareti, E., Vatopoulou, A., Spyropoulou, G.A., Papanastasiou, A., Pratilas, G.C., Liberis, A. et al. (2021) Breast disorders in adolescence: a review of the literature. *Breast Care*, 16(2), 149–155. Available from: <https://doi.org/10.1159/000511924>
- Muschol, N., Storch, S., Ballhausen, D., Beesley, C., Westermann, J.C., Gal, A. et al. (2004) Transport, enzymatic activity, and stability of mutant sulfamidase (SGSH) identified in patients with mucopolysaccharidosis type III A. *Human Mutation*, 23(6), 559–566. Available from: [10.1002/humu.20037](https://doi.org/10.1002/humu.20037)
- Robinson, J.T., Thorvaldsdóttir, H., Wenger, A.M., Zehir, A. & Mesirov, J.P. (2017) Variant review with the integrative genomics viewer. *Cancer Research*, 77(21), e31–e34. Available from: <https://doi.org/10.1158/0008-5472.CAN-17-0337>
- Rosen, B.D., Bickhart, D.M., Schnabel, R.D., Koren, S., Elsik, C.G., Tseng, E. et al. (2020) De novo assembly of the cattle reference genome with single-molecule sequencing. *GigaScience*, 9(3), 1–9. Available from: <https://doi.org/10.1093/gigascience/giaa021>
- Valstar, M.J., Ruijter, G.J., Van Diggelen, O.P., Poorthuis, B.J. & Wijburg, F.A. (2008) Sanfilippo syndrome: a mini-review. *Journal of Inherited Metabolic Disease*, 31(2), 240–252. Available from: <https://doi.org/10.1007/s10545-008-0838-5>

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**How to cite this article:** Jacinto, J.G., Häfliger, I.M., Christen, M., Paris, J.M., Seefried, F.R. & Drögemüller, C. (2022) Is a heterozygous missense variant in *SGSH* the cause of a syndromic form of congenital amastia in an Original Braunvieh calf? *Animal Genetics*, 53, 530–531. Available from: <https://doi.org/10.1111/age.13207>