Three heterozygous GAA cases mimicking late-onset Pompe disease

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CONCLUSION

There may be a small cohort of late-onset Pompe disease-like cases in which a symptomatic heterozygosity or digenic/oligogenic inheritance can be considered. Further studies are needed to confirm or contradict this hypothesis.

BACKGROUND

Late-onset Pompe disease (LOPD) is an autosomal-recessive disorder caused by acid alpha-glucosidase (GAA) deficiency. Carriers of one GAA pathogenic variant are considered as asymptomatic. There are several symptomatic cases reported, where only one pathogenic GAA variant has been identified, alone or together with other heterozygous variant(s) related to neuromuscular disease(s). Here, we present three unrelated cases with suspected LOPD carrying one pathogenic GAA variant together with other heterozygous variant(s) related to glycogen storage disease or structural muscle protein.

RESULTS

Our cohort at this moment consists of three unrelated cases: one from Switzerland and two from the Czech Republic from LOPD cohorts. Further families are being recruited.

Case 1
- onset at 14 years
- strong calves myalgia during exercises
- mild proximal weakness of thighs - 4/5 on the Medical Research Council (MRC) scale; muscular atrophy of the calves
- strong myalgias (opioid treatment)
- mild/moderate restriction of respiration capacity
- creatine kinase (CK) mildly elevated to normal

The muscle MRI of the tights was normal; the MRI of the whole body showed swelling and oedema in the paraspinal and thorax muscles.

Case 2
- onset at 54 years
- myalgias, fatigue, difficulty climbing stairs
- brother has a waddling gate
- he is still ambulatory at the age of 57 years
- mild proximal weakness of thighs (3-4/5 MRC) scale
- CK 819 U/L

The muscle MRI of the tights was normal.

Case 3
- onset at 13 years
- muscle cramps in calves, while riding a bike, muscular weakness from 2015
- scapular winging
- still ambulatory without assistance
- progressive shortness of breath
- CK 1140 U/L
- VUS in FHL1 could be related to the symptoms

The muscle MRI of lower extremities – maximum changes in adductors, hamstrings and in M. soleus, the dystrophic changes have patchy pattern.

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ACKNOWLEDGEMENTS

We thank Drs. Matthias Baumgartner, Johannes Hieberle and Marianne Rohrbach for the GAA activity measurement.

The study was supported by the Swiss Foundation for People with Rare Diseases. LM and OP are members of the European Reference Network for Neuromuscular Diseases-Project ID N° 870177.

DISCLOSURES

The authors have no relevant financial or non-financial interests to disclose.

MATERIALS AND METHODS

All three index patients were examined by a neurologist (MM, LM or OP) and underwent whole genome sequencing (WGS; 60x, PCR-free, PE150). The GAA enzyme activity was measured in dried blood spot, leukocytes and/or in fibroblasts (also used for total RNA sequencing, PE75).
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RESULTS

Molecular studies have been performed on the fibroblasts of index patient 1 (case 1).

MOLECULAR STUDIES

In fibroblasts of index patient 1, the activity of GAA was 0.83 nmol/min/mg prot. (normal range (NR) 6.04–17.06 nmol/min/mg prot; 5–14\% NR). In leukocytes, the activity of GAA with acarbose was normal 0.61 nmol/min/mg prot. (NR 0.45–2.45 nmol/min/mg prot), however, quotient ±/− acarbose was reduced (0.24 nmol/min/mg prot., NR 0.45–0.63 nmol/min/mg prot; 38–53\% NR). NR is illustrated as a blue bar and the patient’s value as a red cross.

Index patient 1 (case 1): As shown in Sashimi plot, RNA-Seq from fibroblasts confirmed abnormal transcripts due to c.-32–13T\textgreater G (red arrow) but showed no other splicing defects in GAA.

Cellular modeling:
1) Reprogramming of patient fibroblasts to iPSCs through viral-mediated gene transfer (around 3 months);
2) Differentiating into myoblasts (around 6 months); three clones;
3) Investigating the cell morphology, measuring GAA activity in the patient line (around 4 weeks);
4) Repairing the GAA mutations by means of CRISPR-Cas9.