Two new disorders of glycogen metabolism

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Avhandlingen baseras på följande delarbeten:

I. Moslemi AR, Lindberg C, Nilsson J, Tajsharghi H, Andersson B, Oldfors A, Glycogenin-1 deficiency and inactivated priming of glycogen synthesis**.** *N Engl J Med. 2010 Apr 1;362(13):1203-10.*

II. Nilsson J, Halim A, Moslemi AR, Pedersen A, Nilsson J, Larson G, Oldfors A, Molecular pathogenesis of a new glycogenosis caused by a glycogenin-1 mutation. *Biochim Biophys Acta. 2012 Apr;1822(4):493-9.*

III. Nilsson J, Halim A, Larsson E, Moslemi AR, Oldfors A, Larson G, Nilsson J, LC-MS/MS characterization of combined glycogenin-1 and glycogenin-2 enzymatic activities reveals their self-glucosylation preferences. *Biochim Biophys Acta. 2013 Nov. [Epub ahead of print]*.

IV. Nilsson J, Schoser B, Laforet P, Kalev O, Lindberg C, Romero NB, López MD, Akman HO, Wahbi K, Iglseder S, Eggers C, Engel AG, Dimauro S, Oldfors A, Polyglucosan body myopathy caused by defective ubiquitin ligase RBCK1. *Ann Neurol. 2013 Jun 24. [Epub ahead of print]*.

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Two new disorders of glycogen metabolism

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Glycogen is a polymer of glucose and serves as a source of rapidly available energy. Glycogen synthesis is initiated by autoglucosylation of glycogenin. Two glycogenin genes, *GYG1* and *GYG2*, encode the two isoforms glycogenin-1 and -2, respectively. Glycogenin-1 is ubiquitously expressed whereas glycogenin-2 has been described as being expressed mainly in the liver but also in the heart.

This thesis describes two new disorders affecting glycogen turnover. The first disease presented as sudden cardiac arrest due to arrhythmia after exercise in a 27-year-old man. Clinical history revealed minor muscle weakness of the upper extremities. He was found to have a cardiomyopathy with abnormal glycogen storage in the heart and depletion of glycogen in the skeletal muscle. An amino acid substitution was detected from a threonine to a methionine at position 83 of glycogenin-1 that resulted in inactivated autoglucosylation. Detailed studies applying cell-free protein expression, *in vitro* glucosylation, and mass spectrometry (MS) demonstrated abolished Tyr-O-glucosylation, the initial step of the autoglucosylation. Catalytically active glycogenin-1, but not glycogenin-2, could compensate for this defect by inter-molecular glucosylation. Transcriptome and western blot analyses indicated that glycogenin-2 is mainly expressed in liver and adipose tissue and only to a minor degree in cardiac and skeletal muscle. By applying a automated analysis of glycopeptides from MS data of co-expressed glycogenin-1 and -2, we show that glycogenin-1 enhances the glucosylation of glycogenin-2.

The second disease presented as myopathy and cardiomyopathy in 10 patients from eight families. Initial symptoms were leg weakness starting in childhood or adolescence, later followed by generalized muscle weakness and cardiomyopathy. The cardiomyopathy was rapidly progressive, necessitating heart transplantation in several cases. The characteristic morphological features were inclusions of abnormal glycogen, polyglucosan, in approximately 50% of the skeletal muscle fibers that were depleted of normal glycogen. Different truncating and missense mutations were detected in the gene *RBCK1*, coding for an E3 ubiquitin ligase. RBCK1 deficiency appears to be a common type of glycogen storage disease and is to be considered in cases with dilated cardiomyopathy.

In conclusion, we have described two new glycogenoses affecting heart and skeletal muscle and investigated the pathogenesis. The discovery of the genetic background of these novel disease entities is important for correct diagnosis, evaluation of prognosis, genetic counseling and treatment.

Keyword: Glycogen, Glycogenin, Glycogenosis, Glycogen storage disease, Glycosylation, Mass spectrometry.

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