

Abstract
The Congenital Disorders of Glycosylation (CDG) are an expanding group of genetic disorders which encompass a spectrum of glycosylation defects of protein and lipids, including N- & O-linked defects and among the latter are the muscular dystroglycanopathies (MD). Initial screening of CDG is usually based on the investigation of the glycoproteins transferrin, and/or apolipoprotein CIII. These biomarkers do not always detect complex or subtle defects present in older patients, therefore there is a need to investigate additional glycoproteins in some cases. We describe a sensitive 2D-Differential Gel Electrophoresis (DIGE) method that provides a global analysis of the serum glycoproteome. Patient samples from PMM2-CDG (n = 5), CDG-II (n = 7), MD and known complex N- & O-linked glycosylation defects (n = 3) were analysed by 2D DIGE. Using this technique we demonstrated characteristic changes in mass and charge in PMM2-CDG and in charge in CDG-II for α1-antitrypsin, α1-antichymotrypsin, α2-HS-glycoprotein, ceruloplasmin, and α1-acid glycoproteins 1&2. Analysis of the samples with known N- & O-linked defects identified a lower molecular weight glycoform of C1-esterase inhibitor that was not observed in the N-linked glycosylation disorders indicating the change is likely due to affected O-glycosylation. In addition, we could identify abnormal serum glycoproteins in LARGE and B3GALNT2-deficient muscular dystrophies. The results demonstrate that the glycoform pattern is varied for some CDG patients not all glycoproteins are consistently affected and analysis of more than one protein in complex cases is warranted. 2D DIGE is an ideal method to investigate the global glycoproteome and is a potentially powerful tool and secondary test for aiding the complex diagnosis and sub classification of CDG. The technique has further potential in monitoring patients for future treatment strategies. In an era of shifting emphasis from gel- to mass-spectral based proteomics techniques, we demonstrate that 2D-DIGE remains a powerful method for studying global changes in post-translational modifications of proteins.

**KEYWORDS:** 2D DIGE, 2-dimensional differential gel expression; C1-esterase inhibitor; CDG, Congenital Disorders of Glycosylation; COG, conserved oligomeric golgi; Congenital Disorders of Glycosylation; Dystroglycanopathies, 2D DIGE; Glycoproteome; IEF, isoelectric focusing; MD, muscular dystrophy; MW, molecular weight; TFN, transferrin; α1-Antitrypsin

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