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*Research Letter*

# Molecular Order in Mucolipidosis II and III Nomenclature

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**To the Editor:**

The Second International Conference on Glycoprotein and Related Storage Diseases was held on July 26–27, 2007 in Ann Arbor, Michigan. It was organized by the group known as the International Advocate for Glycoprotein Storage Diseases. Progress reports on pathogenesis, molecular genetics, and therapy were presented by clinicians and scientists active in the field of these rare lysosomal disorders. We present a proposal initiated at the meeting, regarding the nomenclature of mucolipidosis (ML) II and ML III. The proposed naming system incorporates the recently acquired knowledge of the molecular etiology of these conditions.

ML II (I-cell disease, OMIM # 252500) [Leroy et al., 1971] and ML III (pseudo-Hurler polydystrophy, OMIM # 252600) [Maroteaux and Lamy, 1966] are considered to be allelic disorders due to deficient UDP-N-acetylglucosamine: lysosomal hydrolase *N*-acetyl-1-phosphotransferase (IUBMB # 2.7.8.17) [Hasilik et al., 1981; Reitman et al., 1981], commonly termed UDP-GlcNAc 1-phosphotransferase (GlcNAc-PT). The enzyme catalyzes the initial step in the synthesis of the mannose 6-phosphate (M6P) recognition marker that is crucial for targeting nascent hydrolases to lysosomes [Kaplan et al., 1977; Hasilik and Neufeld, 1980]. Because its function is failing in ML II and ML III patients, the lysosomal enzymes lack the M6P marker and cannot bind to M6P receptors. The acid hydrolases cannot enter lysosomes and are released instead into the intercellular space and body fluids. Intracellular inclusions, identified as swollen lysosomes filled with undigested macrocompounds, are seen in ML II and ML III patients. Excessive urinary excretion of oligosaccharides is observed consistently in both disorders, and ML II and ML III have been grouped among the oligosaccharidoses, also termed glycoproteinoses. Complete loss of GlcNAc-PT activity causes the clinically severe ML II, which is apparent from early infancy or even prenatally. Residual enzyme activity is detected in patients with ML III, with onset of symptoms in childhood and slower progression.

The GlcNAc-PT has been purified and characterized as a hexameric ($\alpha 2\beta 2\gamma 2$) protein, a 540-KDa complex of disulfide linked homodimers [Bao et al., 1996]. Both the $\alpha$ and the $\beta$ subunits are encoded as a single $\alpha\beta$ polypeptide by the *GNPTAB* gene comprising 21 exons and assigned to chromosome 12q23.3 [Kudo et al., 2005; Tiede et al., 2005]. The subunits acquire molecular maturity following post-translational proteolysis of the initial gene product and encompass the catalytic center in the GlcNAc-PT enzyme complex. Mutations in the *GNPTAB* gene (OMIM # 607840) cause ML II and ML IIIA [Paik et al., 2005; Tiede et al., 2005; Kudo et al., 2006; Cathey

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TABLE I. Revised Classification of Mucolipidosis II and III

| | Current nomenclature | Proposed nomenclature |
|---|---|---|
| I-cell disease | ML II | ML II alpha/beta |
| Pseudo–Hurler polydystrophy | ML IIIA | ML III alpha/beta |
| ML III variant | ML IIIC | ML III gamma |

et al., 2007]. Mutations in the *GNPTG* gene (OMIM # 607838) that encodes the γ subunit of the GlcNAc-PT protein complex were first identified in a large Druze family in the Middle-East with a variant form of ML III, termed ML IIIC (OMIM # 252605). *GNPTG* is located at chromosome 16p13.3 [Raas-Rothschild et al., 2000]. The original designations ML III "A" and ML III "C" refer to the results of in vitro complementation studies in heterokaryons obtained by fusion of fibroblast strains derived from ML II and ML III patients with fibroblasts derived from other ML patients or from individuals with other lysosomal storage diseases with single enzyme deficiencies [Honey et al., 1982; Shows et al., 1982]. These experiments ultimately identified the three complementation groups A, B, and C. All ML II patients were assigned to group A. Group B was the label assigned to only a single cell strain that showed complementation with all other strains. The clinical characterization of the patient designated group B was never completed. No published patients have subsequently been assigned to the B complementation group. ML III patients were considered to belong to either complementation group A or C. Because the molecular characterization of the ML III patients proved to be congruent with the earlier complementation results, the designations, ML II, ML IIIA, and ML IIIC were adopted [OMIM, 2007].

It is now appreciated that all ML II patients and the larger group of ML III patients (ML IIIA) are either homozygotes or compound heterozygotes for mutations in the *GNPTAB* gene. The location of the mutations within the α subunit or the β subunit appears to be of less importance in determining the phenotype than the nature of the mutations themselves [Cathey et al., 2007]. The second, smaller group of patients with ML III (ML IIIC) are homozygotes or compound heterozygotes for mutations in the *GNPTG* gene [Raas-Rothschild et al., 2000]. Although the complementation studies led to accurate predictions that these conditions are caused by different genes, the designations A and C can now be replaced by more descriptive terms. The proposed changes are summarized in Table I.

These name changes have been prompted by the knowledge of the molecular causes of these rare disorders. The reclassification is relevant to clinicians and patients, as *GNPTG* (gamma) mutations appear to predict a milder phenotype and better prognosis than do *GNPTAB* (alpha/beta) mutations. As clinicians and scientists with special interest in ML II and ML III, we believe that this new nosology succinctly summarizes our understating of the clinical, biochemical, and now, molecular, heterogeneity of ML II and III.

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