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2015

#### **document version**

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#### **citation for published version (APA)**

Bugiani, M. (2015). *Comparing and contrasting white matter disorders: a neuropathological approach to pathophysiology*.

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## **Comparing and contrasting white matter disorders: a neuropathological approach to pathophysiology**

Genetic white matter disorders are inherited disorders characterized by selective involvement of the white matter of the brain. They cause abnormalities of myelin, a cell membrane specialization of oligodendrocytes allowing rapid signal propagation along axons. Most genetic white matter disorders are progressive, many are fatal and few can be cured. Deeper insight in their disease mechanisms is essential to find better treatment and, if possible, cure.

Genetic white matter disorders vary considerably regarding the underlying gene defects. Only few mutated genes encode myelin proteins. Many genetic white matter disorders are caused by mutations that do not affect myelin components, or even affect proteins considered to be specifically expressed in cells other than oligodendrocytes. Hypotheses based on such prior knowledge may infer an unjustified bias in the search for disease mechanisms. It is therefore important to revise old concepts and definitions and develop an unbiased methodological approach to achieve further, truly new insights.

This thesis applied a cellular pathology perspective to the neuropathological evaluation of genetic white matter disorders in order to categorize the major neuropathological findings in individual diseases and identify common pathomechanisms driving white matter dysfunction and degeneration. To this purpose, the neuropathology of selected genetic white matter disorders of different aetiology was compared and contrasted. Some of the diseases described are novel conditions. When available, the hypotheses formulated for human diseases were verified and further investigated on their animal models. The information derived from this alternative approach was integrated into a novel classification of genetic white matter disorders.