Analysis of genes implicated in Alzheimer's disease pathogenesis using *Danio Rerio* as a model organism

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Contents

List of Publications

Alzheimer Disease: Amyloidogenesis, the presenilins and animal models. Review paper.

Morgan Newman, Ian Musgrave and Michael Lardelli

Biochimica et Biophysica Acta 1772 (2007) 285-297.

Interference with splicing of Presenilin transcripts has potent dominant negative effects on Presenilin activity.

Svanhild Nornes, Morgan Newman, Giuseppe Verdile, Simon Wells, Cristi L. Stoick-Cooper, Ben Tucker, Inna Frederich-Sleptsova, Ralph Martins and Michael Lardelli

Human Molecular Genetics, 2008, Vol17, No3 402-4122.2.

Altering presenilin gene activity in zebrafish embryos causes changes in expression of genes with proposed functions in Alzheimer Disease pathogenesis.

Morgan Newman, Ben Tucker, Svanhild Nornes and Michael Lardelli

Journal of Alzhiemer's Disease, 2008, Accepted Manuscript.

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Abstract

Alzheimer's disease (AD) is the most prevalent form of dementia. There is considerable evidence that AD is caused by accumulating amyloid beta peptides in the brain, as a result of amyloid precursor protein (APP) cleavage by secretase enzymes. The presenilin proteins are central to the gamma-secretase cleavage of the intramembrane domain of APP. Aberrant splicing and point mutations in the human presenilin genes, *PSEN1* and *PSEN2*, have been linked to familial forms of AD, through aberrant APP cleavage resulting in irregular amyloid beta formation. Paper 1 gives a review of the literature on AD research and how animal models are used to elucidate mechanisms of AD pathogenesis. The zebrafish model is used in this thesis to investigate genes with potential relevance to AD initiation and pathogenesis. Paper 2 demonstrates that low-level aberrant splicing of exon 8 in *psen1* transcripts in zebrafish embryos produces potent dominant negative effects that increased *psen1* transcription, cause a dramatic hydrocephalus phenotype, decreased pigmentation and other developmental defects. Similar effects are also observed after low-level interference with splicing of exon 8 in *psen2* transcripts. In paper 3, a microarray analysis was performed to analyse global gene expression changes to illuminate the molecular aetiology of the phenotypic effects described in paper 2. Of the 100 genes that showed greatest dysregulation after *psen1* or *psen2* manipulation, 12 genes were common to both treatments. Five of these have known function and showed increased expression. C*yclin* G1 (*ccng1)* was of particular interest as the human CCNG1 protein shows increased immunoreactivity in the cytoplasm of neurons in human AD brains. Phylogenetic and conserved synteny analysis confirmed the orthology of zebrafish *ccng1* with human *CCNG1*. Expression of zebrafish *ccng1* in developing embryos at 24 hours post fertilization (hpf) was

observed in the eye, tectum and somites. Decreased Ccng1 expression does not lead to any developmental defects and also cannot rescue the hydrocephalus or pigmentation phenotypes of embryos with aberrant splicing of *psen1* exon 8. An analysis of zebrafish *ccng1* function in paper 4 (thesis chapter in the form of a manuscript) indicates that truncation of Ccng1 appears to cause developmental defects in the brain, notochord and somites, however, it does not decrease the level of normal *ccng1* transcript. The *CCNG1* paralogue, *Cyclin G2*, (*CCNG2),* is also expressed in zebrafiish (*ccng2*). Decreasing the expression of Ccng2 results in similar effects on embryo development as truncating Ccng1. Therefore, the truncated forms of Ccng1 potentially interfere with Ccng2 function in a dominant negative manner.