Loss-of-function mutations in *ABCA1*, HDL-cholesterol, metabolomic profiling and risk of vascular disease and dementia

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Figure 1 Astrocyte/hepatocyte/enterocyte

HDL-C levels of N1800H/P85L carriers versus noncarriers

Figure 2

Background and Aim: The adenosine triphosphate-binding cassette transporter A1 (ABCA1) is a major cholesterol transporter highly expressed in liver and brain. ABCA1 mediates cholesterol and phospholipid efflux to lipid-poor apolipoproteins, and is essential for the biogenesis of high-density lipoprotein (HDL) cholesterol in the circulation and HDL-like particles in the brain (**Figure 1**). We therefore investigated the impact of two well-known HDL-deficiency loss-of-function mutations in ABCA1 on lipid levels, metabolomic profiles, and on risk of vascular disease and dementia.

Methods: The association between ABCA1 N1800H/P85L and plasma lipid levels, metabolomic profiles, and risk of vascular disease and dementia were tested in 13,000-100,000 individuals from the Copenhagen City Heart Study and the Copenhagen General Population Study.

Figure 3

Figure 4

Results: N1800H/P85L heterozygous carriers versus noncarriers had lower HDL cholesterol levels (**Figure 2**), lower cholesterol/total lipid ratio (**Figure 3**), and higher phospholipid/total lipid ratio in small HDL particles (**Figure 4**). For heterozygous carriers versus noncarriers, multifactorially adjusted hazard ratios (HR) were 0.27 (confidence interval (CI) 0.10-0.72) for ischemic heart disease (IHD), 1.95 (1.27-3.00) for cerebrovascular disease, and 1.60 (0.88-2.90) for dementia (**Figure 5**).

N1800H/P85L carriers and risk of dementia, cerebrovascular and cardiovascular disease

Figure 5

Conclusion: Loss-of-function mutations in ABCA1 were associated with low plasma levels of HDL cholesterol, altered metabolomic profile, and with lower risk of IHD, but with higher risk of cerebrovascular disease and dementia. These differential findings in circulation and brain are in accordance with current knowledge of lipid biology in the two compartments.