Reviewer's report

Title: Detection of large deletions in the LDL receptor gene with quantitative PCR methods

Version: 1 Date: 28 February 2005

Reviewer: Joep C. Defesche

Reviewer's report:

General
The manuscript by Damgaard et al. is from a group, well-established and renowned in the molecular genetics of Familial Hypercholesterolemia. In their study they validate the new MLPA technology for the detection of of major gene rearrangements in the LDL-receptor gene. Following a sound and solid line of investigation, they first test the sensitivity of MLPA in patients with a characterised deletion of exon 5, in comparison to the established method of real-time PCR. Subsequently, MLPA is tested in a group of clinically diagnosed, but molecularly undetermined FH patients, and new large gene rearrangements are found indeed. Additionally they re-evaluate the value of a diagnostic paradigm issued by the Dutch Lipid Clinic Network Group. The manuscript is well-written, to-the-point and straightforward. For investigators in this field, this study is of high interest and fills a knowlegde gap that momentarily exists.

-----------------------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
NONE

-----------------------------------------------------------------------------------------------

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

This reviewer is somewhat puzzled by the numbers used throughout the manuscript. The the abstract the authors state that major gene rearrangements occur in about 5% of FH patients with LDL-receptor mutations, a frequency also reported by other researchers. Again in the abstract they report the finding of 5 deletions in 318 patients, a frequency of 1.6%. In the results section on page 8, they report that 4 plus one mutations were detected in 37 plus one patients (5/39=15%). Lastly, in the discussion on page 10, a frequency of 3.1% (5/197) is presented. In all likelihood the patient groups of 318, 39 and 197 patients respectively are defined differently, but this should be described more clearly.

Furthermore, this reviewer wonders how the size of the newly identified mutations presented in table 3 was determined.

-----------------------------------------------------------------------------------------------

Discretionary Revisions (which the author can choose to ignore)
NONE

-----------------------------------------------------------------------------------------------

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
'I declare that I have no competing interests'