Reviewer’s report

Title: Mutation screening of ASMT, the last enzyme of the melatonin pathway, in a large sample of patients with Intellectual Disability

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Reviewer: Derek Morris

Reviewer’s report:

Pagan and colleagues investigate the potential contribution of genetic mutations in the melatonin pathway to ID risk by screening the ASMT gene for rare coding or functional mutations in a sample of 361 ID cases and 440 controls. The authors set out a reasonable hypothesis for investigating this gene in an ID sample. The authors do not succeed in identifying a significant excess of rare mutations in cases versus controls, but do report that the activity of ASMT is reduced in case mutation carriers compared to controls.

Comments

1. It is not definitively stated in the methods section that all case samples are male. Is this the case? If yes, and because the control sample is part female, the authors should comment on whether this introduces any bias into the study.

2. ASMT activity in cell lines: the authors compare case mutation carriers to controls. Do any of the 31 controls carry functional mutations? Is it possible to compare either case versus control mutation carriers, or case mutation carriers versus case non-mutation carriers to explore this finding further? Is it possible that the reduced ASMT activity in the case mutation carriers is in fact not due to the mutation but due to some other element of the ID pathophysiology?

3. Methods, Subjects section – there are references to “A1” and “A2” – please correct.

4. Have the new mutations been deposited in dbSNP?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.