NAME OF PRESENTING AUTHOR: Arenella Martina

EMAIL ADDRESS OF PRESENTING AUTHOR: martina.arenella@radboudumc.nl

Autism spectrum disorders and increased brain volume link through a set of mTOR-related genes.

Arenella Martina[1,2,3], Mota, Nina Roth[1,3], Teunissen, Mariel W.A. [1,4], PhD, Brunner, Han G.[1,5,6], Bralten, Janita[1,3] .

[1]Department of Human Genetics, Radboud university medical center, Nijmegen, The Netherlands.

[2]Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, The United Kingdom

[3]Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands

[4]Department of Neurology, Maastricht university medical centre, Maastricht, The Netherlands.

[5]Department of Clinical Genetics, Maastricht University Medical centre, Maastricht, The Netherlands.

[6]GROW School of development and Oncology, and MHENS school of Neuroscience, Maastricht University, the Netherlands

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ABSTRACT:

Large brains are often observed in individuals with autism spectrum disorders (ASDs). Both ASDs and brain volume are highly heritable, and it is unclear if these traits share genetic mechanisms. Genes from the mammalian target of rapamycin (mTOR) pathway influence variability in brain volume, and mutations are found in rare genetic syndromes that include ASD features. We investigated whether variations in mTOR-related genes constitute a genetic link between large brains and ASDs. To test this hypothesis, we first investigated whether macrocephaly and ASDs were enriched in individuals with rare *de-novo* mTOR-related variants in a local cohort (N=2,257) and using publicly available data (N=32,991). We next explored common variant datasets and estimated the genetic correlation between ASDs (N=46,350) and ICV (N=25,974) by LD-score regression. Lastly, we performed gene-set analyses in MAGMA and restricted the ASD-ICV genetic correlation analysis to variants in mTOR-related genes using GNOVA. Both macrocephaly and ASDs are more frequent in individuals carrying rare de-novo mutations in mTOR-related genes compared to carriers of de-novo non -mTOR-related mutations. Although no significant genome-wide correlation between ASD and ICV was present (p=0.81), we show a significant mTOR gene-set association with ASDs (p=0.0029), and a mTOR-stratified positive genetic correlation between ASD and ICV (p=0.027).