Burden of Rare Coding Variants in the 22q11.2 Deletion Region is Associated with Educational Attainment and Schizophrenia Risk in Two General Population Cohorts

***Elemi Breetvelt*[1]**, *Karel Smit*[2], *Jessica van Setten*[2], *Loes Olde Loohuis*[3], *Roel Ophoff*[3], *René Kahn*[2,4], *Jacob Vorstman*[5]

Institution(s): *Centre for Addiction and Mental Health and Toronto General Hospital, University Health Network, Toronto, ON, Canada* [1], *University Medical Center Utrecht, Utrecht, The Netherlands* [2], *UCLA, Los Angeles, CA, USA*[3], *the Icahn School of Medicine at Mount Sinai, New York, NY* [4], *The Hospital for Sick Children, Toronto, ON, Canada* [5]

Background: The 22q11.2 deletion is associated with a high risk for schizophrenia and intellectual impairment. We have previously presented our preliminary findings indicating that rare single nucleotide coding variants (SNVs) within the 22q11.2 region can also exert relevant phenotypic effects. We analyzed putative functional exonic variants in 22q11.2 to calculate their cumulative impact on educational attainment in a large population sample. A steep decline in the level of educational attainment occurred at a burden of four or more SNVs. Here, we will report on our completed study, which encompasses testing of the identified SNVs in a second, independent schizophrenia case-control cohort. **Methods:** We tested the risk genotype - i.e. four or more putatively coding SNVs (MAF<5) in 22q11.2 – identified in the first sample in an independent schizophrenia case-control sample (n= 1933), using the same strategy. To this end, we determined in each individual the number of SNVs in the minimal critical region of 22q11.2 (i.e. flanked by low copy repeats A and B). Data were obtained with the Illumina HumanExome Beadchip v1.1. Post-hoc, we explored which SNVs were contributing. **Results:** We observed that the same burden was significantly associated with an increased risk for schizophrenia (8 schizophrenia cases vs 1 control; OR=8.54; p-value = 0.02). We found that in 7 of the 9 individuals with an increased burden, the same 3 SNVs were present within the Homo sapiens clathrin, heavy chain-like 1 gene (CLTCL1). Of note, association of this CLTCL1 haplotype did not reach statistical significance when considered independently (18 in the schizophrenia versus 10 in the control group; OR=1.93; p-value = 0.13), i.e. outside the context of the defined burden of four or more SNVs in 22q11.2. **Conclusions:** An increased burden of rare coding SNVs in 22q11.2 is associated with lower educational attainment and an increased risk for schizophrenia. These findings have several tentative implications. First, they suggest that in a genomic region where pathogenic structural variants recurrently arise, SNVs can, cumulatively, also confer a relevant phenotypic impact. Second, they contribute to the empirical basis of the hypothesized genetic link between schizophrenia and cognition. Lastly, post-hoc results suggest the involvement of CLTCL1 in cognition and schizophrenia in individuals without 22q11DS and that the effect of this haplotype may be contingent upon the presence of additional modifier gene variation.