**Effects of Copy Number Variants in Schizophrenia on Longitudinal Psychosocial Functioning**

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**Abstract**

Individual illness severity may be measured by the degree of psychosocial functioning. We studied whether the presence of one or more copy number variants (CNVs) is associated with the level of psychosocial impairment measured by the Global Assessment of Functioning (GAF; DSM-IV Axis V) scale in a sample of individuals with DSM-V schizophrenia (SZ). The GAF score measured the overall functioning level of an individual from 1 (lowest) to 100 (highest). Using a genome-wide, high-quality CNV dataset, we assessed whether CNVs are related to GAF values collected for three points in time over the individual course of disease: before illness onset, the "worst ever" (during an illness episode) and the current (in remission) GAF score. Investigating GAF values adjusted for phenotypic predictors, our analysis revealed a trend towards lower psychosocial functioning at the "worst ever" GAF in individuals possessing one or more CNVs compared to individuals without CNVs. An exploratory analysis of CNVs present in the study sample found a protective effect on the current GAF score for a duplication on chromosome 10p26.3.

**Introduction**

Psychosocial impairment, common to all mental disorders, is especially pronounced in SZ. CNVs have been shown to affect vulnerability to disease (e.g. Szatmari et al., 2014) and certain CNVs previously linked to SZ have been shown to affect cognition and GAF scores also in individuals without SZ (Stefans et al., 2014). Therefore, we hypothesized CNV load to contribute to the degree of psychosocial impairment also within SZ individuals. To investigate this issue, we studied a sample of 52 women for whom the levels of psychosocial functioning at multiple points in time over the course of the disorder had been characterized.

**Methods**

CNV data

We took advantage of a large (n=1,637) existing genome-wide CNV data set of patients with a DSM-V diagnosis of schizophrenia or schizoaffective disorder (Priebe et al., 2013) to identify deletions and duplications. For the purpose of this study, we excluded all regions reported by Levinson et al. (2011), as these are prone to false-positives (e.g. telomeric regions).

CNV data were used to study participants in our study sample. The Genotypephenotype association study (GPAS) platform was used to construct and assess CNVs. CNVs were selected based on the following criteria: 1. detection by PennCNV (Wang et al., 2007) and QuantiSNP (Coeilers et al, 2007) software, 2. ≥30 covered SNPs, 3. confidence value/log Bayes Factor ≥30 and 4. overlapping with RefSeq genes. We provided detailed information on detection and quality control is provided elsewhere (Degenhardt et al., 2012). CNVs were classified according to the location and type of CNVs.

**Results**

Table 1 displays descriptive data of our sample and raw GAF scores. Analyses using Wilcoxon tests revealed a trend towards lower psychosocial functioning at the "worst ever" GAF in patients with larger CNVs (≥30 SNPs; Figure 1). All other measures of psychosocial functioning were not affected by the CNVs analyzed. The non-parametric longitudinal test did not detect any effect of CNVs on GAF values either.

**Exploratory analysis of CNVs present in our study sample**

Regarding specific CNVs (see Table 2), Wilcox non-parametric rank tests to compare psychosocial functioning between patients carrying one or more CNVs with patients carrying no CNVs. We also looked for possible longitudinal effects of CNVs on the longitudinal non-parametric test (LNPT; Malzahn et al., 2010). Furthermore, we explored the effects of CNVs in specific chromosomal regions on GAF scores. We investigated all CNVs present in at least three individuals in our sample and, independently, also assessed CNV regions previously associated with SZ (Rees et al., 2014).

**Figure 1.** The presence of one or more CNVs is associated with lower psychosocial functioning at the “worst ever” GAF (adjusted for duration of illness and sex) in SZ patients. Horizontal lines show medians of adjusted GAF scores.

**Discussion**

This is the first analysis relating CNVs to psychosocial functioning. We provide tentative evidence for an effect of CNVs on psychosocial functioning within SZ patients. In line with their effect in non-diseased individuals (Stefansson et al., 2014), CNVs appear to have negative influence on psychosocial functioning also within SZ patients. The analysis of specific CNVs present in our study sample found suggestive evidence for a protective effect of a duplication in a region containing the genes SCART1 (non-coding RNA), CYP2E1 and SCY1 (noncoding RNA). This implicates non-coding RNA, possibly via an effect on transcription, drug metabolism and/or molecules involved in melatonin in the pathway between genetics and psychosocial functioning. Due to the small sample size, investigation in a larger independent sample is warranted to confirm our at best nominally significant results. Also, while the use of high-quality CNVs may be required to avoid false-positive findings, this approach may also have impeded the detection of true effects. Also, we only focused on large CNVs whereas effects of smaller CNVs remain to be investigated.

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**Conflict of Interest**

There are no conflicts of interest.