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DOI:

[10.1016/j.ejmg.2017.12.005](https://doi.org/10.1016/j.ejmg.2017.12.005)

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*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Larson, FV, Arrand, JR, Tantam, D, Jones, PB & Holland, AJ 2017, 'Copy number variants in people with autism spectrum disorders and co-morbid psychosis', *European Journal of Medical Genetics*.  
<https://doi.org/10.1016/j.ejmg.2017.12.005>

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DOI: 10.1016/j.ejmg.2017.12.005

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# Accepted Manuscript

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PII: S1769-7212(17)30429-9

DOI: [10.1016/j.ejmg.2017.12.005](https://doi.org/10.1016/j.ejmg.2017.12.005)

Reference: EJMG 3391

To appear in: *European Journal of Medical Genetics*

Received Date: 10 July 2017

Revised Date: 27 October 2017

Accepted Date: 4 December 2017

Please cite this article as: F.V. Larson, J.R. Arrand, D. Tantam, P.B. Jones, A.J. Holland, Copy number variants in people with autism spectrum disorders and co-morbid psychosis, *European Journal of Medical Genetics* (2018), doi: 10.1016/j.ejmg.2017.12.005.

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Word count: 3339

Tables: 2

Figures: 0

Supplements: 3

**Title:** Copy number variants in people with autism spectrum disorders and co-morbid psychosis

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**Key words:** autism; psychosis; co-morbidity; copy number variants

**Abstract**

The genetic association between autism spectrum disorder (ASD) and psychotic disorders such as schizophrenia is complicated and mirrors the clinical overlap between these conditions to some degree. However, no studies to date have examined the genetics of individuals dually diagnosed with both ASD and psychosis. In this study, we present findings of copy number variants (CNVs) from a study of 116 well-characterised individuals with this dual diagnosis. DNA was extracted and arrayed using the Affymetrix CytoScan HD 2.8M array or the Affymetrix Cytogenetics arrays and compared with existing samples from the Database of Genomic Variants and the Simons Simplex Collection of CNVs from individuals with ASD and their families. Twenty-seven novel CNVs  $\geq 20$ k base pairs were identified in the sample, most occurring in only a single individual, although two were found in two female participants. Forty-nine rare CNVs ( $<1.5\%$  rate in general population) were also found at significantly higher frequencies than expected. The findings may provide evidence for areas of further study in the understanding of the development of both ASD and psychosis due to the number of affected genetic regions that have not previously been linked to these conditions.

**Introduction**

Schizophrenia, psychotic bipolar disorder, and atypical psychoses all occur in people with autism spectrum disorder (ASD) (Larson et al., 2017). Psychosis and ASD have a complex historical relationship that has lumped them into one disorder and then split them again over time. Bender (1953) argued that any distinction between the two was false and that schizophrenia and ASD were manifestations of the same diathesis. This view has been argued more recently with regard to overlapping cognitive profiles such as impaired theory of mind and schizotypal traits (de Lacy and King, 2013; Hommer and Swedo, 2015). A number of

individuals with psychosis, particularly schizophrenia, meet criteria for ASD (Hallerback et al., 2012; Lugnegård et al., 2014). Prevalence of psychosis in ASD populations, while difficult to establish, has been found to be higher than 25% in one study (Mouridsen et al., 2008) and is generally found to be elevated across studies in this area. However, the overlap is difficult to investigate epidemiologically because any condition affecting social interaction will have a different impact in early childhood when relationships and personality are forming than in later childhood or adolescence when relationships and social identity are much more established. Indeed, differences in social interaction throughout childhood have been described in longitudinal studies of children who will, as adults, develop schizophrenia (Jones et al., 1994).

As phenotypic differences cannot resolve the question of whether there is a common ASD/psychosis diathesis, the next step is to consider genetic overlap. This genetic overlap remains poorly understood however. Some models suggest that 20-75% of genetic variance is shared by ASD and schizophrenia, and that shared by ASD and bipolar disorder is 20-60% (Rzhetsky et al., 2007), but no single site has been identified and the modelling cannot predict which elements of the genome are shared or what form the variance will take (e.g. structural or functional variation). Work carried out by the Cross-Disorder Group of the Psychiatric Genomics Consortium on functional variants (single nucleotide polymorphisms; SNPs) has begun to identify specific shared variation (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). It seems likely that the shared risk conferred by SNPs is due to rare variants of large effect, rather than common variants of cumulative effect (Boyle et al., 2017).

There is also emerging evidence of shared structural variation in schizophrenia and ASD, in the form of copy number variants (CNVs), regions of DNA that are either duplicated one or more times, or where one or both copies are missing (Crespi and Crofts, 2012).

However, there do seem to be fundamental differences between the CNVs observed in the separate populations. For example, CNVs seem to be much more penetrant in ASD cases versus schizophrenia cases (Kirov et al., 2014). It has also been argued that there are sites where the nature of the CNV (gain or loss) dictates the disorder that emerges (Crespi and Crofts, 2012), although there has been no work conducted to assess whether these different structural variations result in different functional outcomes.

Genetic studies to date have focused on individuals with *either* ASD *or* psychosis, commonly dividing the latter into schizophreniform and affective variants. There is also evidence of sites with linkage to both conditions (chromosome 22q11.2, chromosome 15q11-q13 (see Vorstman (2006) for a discussion) that would logically suggest shared susceptibility and increased risk of co-morbidity. A recent study of 22q11.2 deletion, however, found that the CNV did not necessarily give rise to the development of both conditions in a longitudinal study (Fiksinski et al., 2017). This highlights the possibility of other factors (genetic or environmental) that links to the development of a disorder and further research is needed in this area. There are no previously published studies examining the genetics of individuals dually diagnosed with ASD and co-morbid psychosis. In the current study, we present an analysis of CNVs affecting 116 people with dual diagnosis of ASD and psychosis (affective, schizophrenic, and atypical - for a full clinical description of this cohort, please see Larson et al. (2017)). By studying individuals dually affected, we hope to further clarify the nature of the genetic relationship between the two conditions. The research was premised upon the prediction that rare CNVs (present in less than 1% of a general population sample listed on the Database of Genomic Variants [DGV]) would play a role in the aetiology of co-occurring ASD and psychosis. In particular, we predicted that CNVs overlapping chromosome 15q11-q13, a region associated with Prader-Willi Syndrome (a neurodevelopmental disorder characterised by high rates of psychosis (Soni et al., 2008)) and ASD would be implicated in

those dually diagnosed with ASD and psychosis. In addition, we hypothesised that key genes that have been identified as aetiologically important to both ASD and psychosis separately would be more often affected by rare CNVs in people who have both conditions than in people in the general population or those with ASD only. We also examine the role that CNVs overlapping other genes identified as important to ASD or psychosis separately in people with ASD and co-morbid psychosis.

## **Materials and Methods**

This study took place between January 2011 and April 2014. It was approved by the Norfolk Research Ethics Committee in the United Kingdom (UK). All participants either gave informed consent, or, where they were found to lack capacity to consent following UK guidelines, a consultee was identified to advise on their behalf. People who lacked capacity to consent were only included when they had regular blood tests as part of their clinical care and a sample could be obtained as part of this for genetic study.

### *Recruitment and participants*

Participants were recruited from clinical services in the public and independent sectors in the UK, as well as from charities and an Asperger's syndrome social networking website. Presence of both ASD and psychosis were confirmed using standardized methods. For a full description of the clinical characteristics and methods of ascertainment, please see Larson et al. (2017). A total of 116 individuals with a confirmed dual diagnosis of ASD and psychosis were recruited for this study. While this is a comparatively small number of participants in the field of psychiatric research, the thorough characterisation of the sample and their relative rarity make this sample unique.

*Genetic testing and CNV calling*

DNA was extracted from whole blood samples and tested for quality. DNA was arrayed on either the Affymetrix CytoScan HD 2.8M array or the Affymetrix Cytogenetics array (Affymetrix, Santa Clara, CA, USA). Affymetrix ceased production of the CytoScan array after the study had started, necessitating the change. Comparisons were made with data available from the Simon's Simplex Collection (SSC) of people with ASD (N=1124), arrayed on the Illumina Human1M array (for full details of the methods used, see (Sanders et al., 2011)). This group will be referred to as ASD-No Psychosis (ASD-NP). ASD-NP samples had been genotyped using the Illumina Human1M array and screened for rare CNVs prior to the data being made available to use for comparison.

CNVs in the ASD-P group were called using the SNP-FASST2 Segmentation algorithm in the Nexus Copy Number 7 software (BioDiscovery, Hawthorne, CA, USA), with a significance threshold of  $1 \times 10^{-8}$ . CNVs were also called using Affymetrix Chromosome Analysis Suite, (ChAS) using the inbuilt proprietary algorithm with default settings. CNVs are presented here if there was an area of overlap between calls from both algorithms – only the area of overlap defined by both algorithms with a minimum of five markers forms the reported CNVs in this study. A minimum size of 20kbp for calls was selected to enhance reliability of calls and also identify events likely to be rare, based on finding that the most common CNVs are smaller than 10kbp (McCarroll et al., 2008). Although this size is somewhat arbitrary, we consider it to strike a balance between screening out common genetic “noise” and not excluding the majority of CNVs of interest to this study. CNVs were compared with results listed on the DGV (up to October 2017) and included in this study if they were rare (reported in less than 1.5% of the population studied in the DGV) or unique (not reported on the DGV).



Additionally, a list of key genes previously implicated in ASD and/or psychosis was generated for targeted search in our results, using the AutWorks database (<http://autworks.hms.harvard.edu/>) (Nelson et al., 2012), and forms Supplement 1. The list was generated using the following disease terms in the database: “bipolar disorder”, “schizophrenia” and “psychotic disorders”. CNVs overlapping these genes were considered potentially relevant to ASD and/or psychosis.

All comparison reported between groups remained significant after correction using the Benjamini-Hochberg/False-Discovery Rate (FDR) method.

## Results

### *Overall CNV Rates*

The median number of CNVs larger than 20kbp present in individuals in the ASD-P group was 15 (range: 0-107). Two individuals did not carry a single confirmed CNV of larger than 20kbp.

### *Unique CNVs*

Twenty-seven CNVs larger than 20kbp that occurred in the ASD-P group were unique, meaning that they were unreported on the DGV and also unreported in the ASD-NP data. Most of these CNVs were only present in a single member of the ASD-P group and contained no genes from the AutWorks database search. Only one unique CNV contained a gene that appeared on the list of key genes generated from the Autworks database. This was a 22kbp gain affecting chromosome 6p21.32 and contained *SYNGAP1*, a gene with a known link to autism (Berryer et al., 2013). It occurred in a participant with normal-range IQ. Two participants shared two unique CNVs (details are presented in Table 1 below, including brief clinical information). Both of these cases had a similar total number of CNVs detected (22 and 28).

**Table 1.** This table shows a unique CNV not previously reported in the literature identified in two participants in the ASD-P group and not in the ASD-NP group. A brief clinical description is given of the cases.

Chr	Size (bp)	CNV Type	Gene(s)	Clinical information
<b>6p21.32</b>	40,180	Gain	<i>COL11A2, RXRB, SLC39A7, HSD17B8</i>	Both participants with this gain were female, with normal range IQ, psychosis onset in early 20s, atypical psychosis with a strong affective component.
<b>20</b>	24,010	Gain	<i>CDH4</i>	

Unique CNVs present in only a single member of the cohort are presented in Supplement 2, also including brief clinical information. Notably, one of these was a duplication of the Prader-Willi Syndrome critical region of chromosome 15q.

#### *Rare CNVs*

In addition to unique CNVs, we also investigated the occurrence of rare CNVs (<1.5% frequency in large general population samples) in the ASD-P group. We found a number of rare CNVs (N=34) that were also present in cases and their families in the ASD-NP data set, suggesting primarily an association with ASD, rather than specifically the comorbidity with psychosis. However, many rare CNVs were not found in the ASD-NP data and were significantly more frequently found in the ASD-P group than in the general population (N=49). Of these, only a small number contained genes previously identified as of interest to ASD or psychosis. Table 2 summarises rare CNVs found in more than one individual in the ASD-P group (n=18), giving the FDR-corrected *p*-value of the difference between the rate in the ASD-P group and rate found in the general population sample with the most frequent occurrence of this CNV reported on the DGV. Supplement 3 shows rare CNVs present in a single ASD-P participant along with Fisher's exact comparison with the highest reported frequency of this variant in the DGV.

**Table 2. Table showing the frequency of rare CNVs not found in the ASD-NP group.** *P*-values are shown for Fisher's exact testing comparing rates of the CNV in the ASD-P cohort and general population data available on the Database of Genomic Variants. Pseudogenes are included if they were overlapped by a CNV that also overlapped a gene.

Chr	Size (bp)	CNV Type	Gene(s)	Frequency ASD-P	FDR-corrected <i>p</i> -values †
<b>1p36.33</b>	51,504	Loss	<i>AGRN, RNF223, C1orf159</i>	2/116	0.007
<b>2q11.2</b>	112,727	Gain	<i>ANKRD36</i>	8/116	0.002
<b>2q14.2</b>	29,204	Gain	<i>GLI2</i>	3/116	0.002
<b>2q21.1</b>	27,568	Gain	<i>ANKRD36B</i>	4/116	0.003
<b>6p11.2</b>	20,932	Gain	<i>PRIM2</i>	2/116	<0.001
<b>7p22.1</b>	25,295	Gain	<i>CCZ1, RSPH10B2, RSPH10B</i>	2/116	0.001
<b>10p12.33</b>	156,336	Gain	<i>MRC1, TMEM236, MIR511-1, MIR511-2</i>	2/116	0.02
<b>10q11.22</b>	24,049	Gain	<i>LOC643650</i>	9/116	<0.001
<b>10q22.3</b>	43,022	Gain	<i>ZMIZ1</i>	3/116	<0.001
<b>10q23.2</b>	94,341	Gain	<i>FAM35A</i>	2/116	0.02
<b>11q11</b>	41,984	Gain	<i>TRIM51</i>	2/116	0.001
<b>11q14.1</b>	31,919	Loss	<i>DLG2</i>	2/116	0.01
<b>15q11.2</b>	106,346	Gain	<i>PWRN2</i>	3/116	0.003
<b>16p13.3</b>	57,904	Loss	<i>RAB40C, WFIKK1, C16orf13, FAM195A, WDR90, RHOT2, RHBDL1</i>	7/116	<0.001
<b>16p11.2</b>	876,949	Gain	<i>SLC6A10P, TP53TG3B, TP53TG3, LOC390705</i>	4/116	<0.001
<b>16q22.1</b>	155,025	Gain	<i>PDXDC2P, MIR1972-2, MIR1972-1, PDPR</i>	2/116	0.02
<b>19p13.2</b>	61,990	Loss	<i>EMR4P, FLJ25758</i>	2/116	0.01

## Discussion

There are a number of limitations to the work presented here that should be addressed. The small sample size is unusual for genetic research, particularly in the era of cross-border collaboration such as that demonstrated by the Psychiatric Genomics Consortium, who can boast sample sizes in the tens of thousands. It is our assertion that people with comorbid psychosis and ASD are special, however, in that it seems reasonable to assume they are particularly genetically affected in order to have not one but two rare conditions. We would also argue that phenotypically, they represent a more well-defined group than the large datasets used in GWAS studies. The fact that any significant results were found given such a relatively small sample size seems to support our assertions.

It was also clearly less than ideal to compare with samples arrayed using different chips and in different labs. However, many studies published in the field rely on being able to use publically available data, and the difficulties surrounding identifying suitable comparison samples should not be underestimated. We felt that the ASD-NP data set was large enough to overcome difficulties with heterogeneity of ASD, and that using the DGV gave robust estimates of rates of CNVs in the general population. By restricting ourselves to what would be considered moderate or large CNVs, we hope to have removed much of the “noise” likely to be generated by different methods, materials, and so on. Smaller CNVs are much more susceptible to differences in array or calling techniques.

Our study has demonstrated, in line with our hypotheses, that there are differences between the CNVs observed in the ASD-P group versus the general population or the ASD-NP group. A number of rare or unique CNVs were present in people with ASD-P. However, we found only limited evidence for the presence of high-confidence CNVs overlapping genes of known interest to the aetiology of ASD, psychosis, or both conditions. This raises the possibility that some of the rare or unique CNVs found in the ASD-P population may be of

interest to those seeking to understand the aetiology of both ASDs and psychosis, perhaps because they are unique indicators of risk of the comorbidity. It is also interesting to note that the majority of the rare and unique CNVs found in the ASD-P group were duplications. Itsara and colleagues (Itsara et al., 2009) reported higher rates of deletions than duplications in CNVs smaller than 100kbp in a general population sample, while the converse was true in our sample. There are several possible reasons why this might be the case. For example it could be as a result of “amplifications” of existing, smaller genetic defects in the parent or parents of individuals with ASD-P, or it could be a hallmark of a different pathological processes to those seen in deletions. Molecular and expression studies would be useful in clarifying this point, although it is known that duplications can have similarly significant effects to deletions (Ionita-Laza et al., 2009).

Our hypothesis regarding elevated rates of CNVs affecting 15q11-q13 and the 22qDS region was not supported, although we found a single case of each CNV in this cohort. This is surprising, as these are the two highest frequency regions with known associated to both ASD and psychosis. Given this was a small study, it is possible that it was underpowered to detect these CNVs, but it seems odd that other rare or unique CNVs should be represented more frequently. It is possible that individuals with known genetic abnormalities may have participated in the research due to already being involved with clinical genetic services, which could have biased results. This seems unlikely to have had a major impact on the results given the small number of individuals in the UK who have confirmed genetic abnormalities.

It is also interesting that there was such a range of CNV burden across participants, as this is another potential factor that may be relevant to the comorbidity developing. The median number of CNVs larger than 20kbp was 15, but nine participants had at least twice this number, up to a maximum of 107. We do not know, from this study, whether these are de

novo or inherited. We cannot draw any conclusions from the present study what this difference might mean but it is possible that a high rate of CNV simply increases the possibility of hits on multiple genes with differing genetic effects.

Our results indicate that rare and unique CNVs may play a role in the aetiology of co-morbid psychosis and ASD, as well as possibly the overall large CNV burden. Two rare CNVs in the current study contained genes that were already known to be related to ASD, psychosis, or both conditions – *MTNR1A*, *FAT1*, *SYNGAP1*, and *RELN*. *MTNR1A*- and *FAT1*-affecting deletions have been reported previously, linked to ASD (Vona et al., 2014) and a rare variant of *FAT1* has been linked to bi-polar disorder (Belmonte Mahon et al., 2011). Mutations affecting melatonin receptors (of which *MTNR1A* is one) have been found in individuals with ASD, but their impact on ASD risk has been proposed to be minimal due to the frequencies of mutations found in healthy control populations (Chaste et al., 2010). The functional impact of a duplication affecting *MTNR1A* is currently unknown. However, the genes highlighted by our results are generally not currently implicated in any disease process, or are linked to unrelated conditions. We would suggest that this could be due to several factors: 1) the CNVs found may be rare but have a large effect on the brain that increases vulnerability to ASD and psychosis, or 2) they may have no phenotypic impact linked to ASD and/or psychosis. Further evidence is needed to improve understanding of the function of the genes highlighted in the current study. The results suggest a direction for future study for those seeking to understand the genetic basis for co-morbid ASD and psychosis.

Our study is unusual in having very well-characterised participants who have not been previously studied. It is likely that it would be under-powered to find significant CNVs, and so the fact that any CNVs of interest have been identified at all indicates that this is a population with rich genetic variation. In particular, the two female participants with the same CNVs not reported in the general population, are of interest as this hints that, even in

such a small population, common potentially pathological CNVs are present. Our hope is that these results will encourage more research into the overlap between these two conditions, particularly with a view to improving understanding of the risk factors for co-morbidity. This study indicates that there may be particular risk factors that predispose an individual to developing both an ASD and later a psychotic illness, but much of the current conceptualisation regarding the relationship between the conditions has focused on differentiating them. It is only by studying people who are affected by both conditions that a true understanding of the co-morbidity can be reached. Due to complications regarding categorical approaches to the diagnosis of complex conditions such as ASD and psychosis, it is also important to consider that such future study may benefit from classifying individuals on relevant symptom dimensions rather than diagnoses. Genetic study is much better suited to this type of approach, as genetic differences have a cumulative and interactive effect rather than mapping perfectly onto behaviourally defined syndromes. It may be that genetic variation such as that reported in the current study could in future help inform, in a top-down fashion, our diagnosis or understanding of psychiatric conditions.

### **Acknowledgements**

We would like to thank all the participants and their families who took part, the clinicians and others who kindly approached them on our behalf, and Dr Tessa Webb for her involvement with the study.

### **Funding Sources**

This work was supported by a grant from the Baily Thomas Charitable Foundation. The funders had no role in the preparation of this manuscript.

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