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Copy Number Variants for Schizophrenia and Related Psychotic Disorders in Oceanic Palau: Risk and Transmission in Extended Pedigrees

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Abstract

Background—We report on copy number variants (CNVs) found in Palauan subjects ascertained for schizophrenia and related psychotic disorders in extended pedigrees in Palau. We compare CNVs found in this Oceanic population to those seen in other samples, typically of European ancestry. Assessing CNVs in Palauan extended pedigrees yields insight into the evolution of risk CNVs, such as how they arise, are transmitted, and are lost from populations by stochastic or selective processes, none of which is easily measured from case-control samples.

Methods—DNA samples from 197 subjects affected with schizophrenia and related psychotic disorders, 185 of their relatives, and 159 controls were successfully characterized for CNVs using Affymetrix Genomewide Human SNP Array 5.0.

Results—CNVs thought to be associated with risk for schizophrenia and related disorders also occur in affected individuals in Palau, specifically 15q11.2 and 1q21.1 deletions, partial duplication of *IL1RAPL1* (Xp21.3), and chromosome X duplications (Klinefelter's syndrome). Partial duplication within *A2BP1* appears to convey an 8-fold increased risk in males (95% CI,

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FINANCIAL DISCLOSURE

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0.8–84.4) but not females (OR=0.4, 95% CI, 0.03–4.9). Affected-only linkage analysis using this variant yields a LOD score of 3.5.

Conclusions—This study reveals CNVs that confer risk to schizophrenia and related psychotic disorders in Palau, most of which have been previously observed in samples of European ancestry. Only a few of these CNVs show evidence that they have existed for many generations, consistent with risk variants diminishing reproductive success.

Keywords

Schizophrenia; Psychotic disorders; Copy Number Variants (CNVs); *A2BP1*; *ILIRAPLI*; Palau

INTRODUCTION

Schizophrenia, like so many psychiatric disorders, shows a puzzling pattern of complex inheritance that has complicated efforts to discover susceptibility genes. Recently several inherited and de novo copy number variants (CNVs) have been shown to be a replicable source of risk for schizophrenia and related psychotic disorders. These CNVs are rare and account for only a small portion of risk. Still, by implicating genes and biological pathways, they could yield a deeper understanding of the genetic etiology of psychotic disorders.

One risk CNV, deletion of the 22q11.2 – the velocardiofacial syndrome or VCFS region (OMIM #192430) – has long been known (1). The VCFS region covers many genes in a 1.5 to 3 Mb region. Those with a VCFS deletion appear to have at least a twenty fold increased lifetime risk of a psychotic disorder, principally schizophrenia. A recently-identified and confirmed region is a roughly 1.5 Mb region of 1q21.1 (2–5). Typically risk is associated with deletion of the region and the many genes therein. Another is duplication/deletion of 15q11.2, between breakpoints one and two of the Prader-Willi/Angelman syndrome region (2, 4). Other genomic regions associated with schizophrenia, autism, and other psychiatric phenotypes are 3q29, 16p11.2, and 17q12 (6–14). Somewhat less support is available for several other genomic regions, including 15q13.3, 16p13.1, and 17p12 (3, 4, 16–18), but they too are likely risk loci. None of these CNV risk regions appear specific to schizophrenia or even psychosis. In fact myriad phenotypes are associated with deletions and sometimes duplications in these regions, including intellectual disability, autism, and attention deficit hyperactivity disorder (ADHD) (6, 8, 10, 12, 13, 18,19).

We use data from the Palauan population to determine if previously-identified risk CNVs also affect risk in Palau (20–24). The nation of Palau is an archipelago of islands in the South Pacific. Geographically isolated, it is situated about 550 miles east of the Philippines. Its nearest neighbor is Yap, approximately 400 miles northeast. Evidence suggests the population of Palau was founded by East Asians and developed over approximately 2,000 years in relative isolation until two centuries ago. Because most studies of psychosis involve samples of European ancestry, analysis of CNVs in a sample from Palau allows us to seek similarities and differences across ancestries. In addition, nearly complete ascertainment of Palauan subjects affected by schizophrenia, most of whom fall in extended pedigrees, could shed some light on the evolution of risk CNVs, specifically the process of how these CNVs arise in the population, whether they are transmitted through generations, and their loss from the population by stochastic or selective processes. Case-control analyses tell us little about the evolutionary processes affecting this kind of variation. Data from extended pedigrees in Oceanic Palau could fill some of this gap.

METHODS AND MATERIALS

Subjects

Through an ongoing study of schizophrenia in Palau (20–24), with pedigree information for almost 1,000 subjects tracing beyond maternal and paternal grandparents, nearly complete ascertainment of individuals affected with schizophrenia and related psychotic disorders and their first-degree relatives has been achieved. Because individuals in this small isolated population are often if not always related at some level, selecting control subjects present a challenge. We selected individuals as controls if they had no history of psychiatric treatment and were no closer than third-degree relatives of cases. For this study, blood samples from 573 subjects were genotyped including all affected subjects, a sample of relatives of an affected (ROA), and control subjects. There were 208 (36.3%) affected individuals, with 125 having a diagnosis of schizophrenia (60%), 36 schizoaffective (17%), 20 bipolar disorder (10%), and 27 psychotic disorders not otherwise specified (13%); 365 (63.7%) were unaffected by any of these disorders, 191 ROA and 174 controls (Figure S1 in Supplement 1).

Potentially affected individuals, identified by medical records and/or referral by a family member, were interviewed by an experienced clinician (WB, MMW) working with a Palauan mental health professional (JT) using a modified version of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version or SADS-L (25). Subjects were interviewed in their language of preference; if it was Belauan, JT translated. The SADS-L interviews were followed by a detailed review of hospital psychiatric medical records, which document in English inpatient and outpatient visits and thus describe symptoms and treatment over the course of illness, often providing in-depth longitudinal diagnostic data. The SADS-L interview data and medical records were used to reach a DSM-IV based Best Estimate Final Diagnosis (26). Research protocols and procedures were approved by institutional review boards (IRBs) at each of the sites in the US and the Republic of Palau. All subjects provided written informed consent to participate after receiving a full explanation of the study in both English and Palauan.

Copy Number Variation analyses

CNVs were called for 573 Palauan subjects using the genotype image intensities from Affymetrix Genomewide Human SNP Array 5.0 and two different calling algorithms: Birdseye of the Birdsuite package (27) and PennCNV (28). Genotype-based gender was supplied for calling CNVs on X. We evaluated nominal gender based on the level of heterozygosity on chromosome X after excluding SNPs in the pseudo-autosomal region (Figure S2 in Supplement 1). There were 5 (0.87%) discrepancies between the genotype-based gender and the pedigree information based on the assumption that all males would have <1% heterozygosity on the X-linked portion of chromosome X. Where a sample swap was suspected, an attempt to redraw a DNA sample from the subjects was made to resolve the discrepancy. CNVs were called only when covered by 20 or more SNPs or monomorphic markers (henceforth collectively called ‘probes’). Rare CNVs were defined as CNVs called by both Birdsuite and PennCNV that occurred in $\leq 1\%$ of the Palauan chromosomes. Based on the distribution of rare CNVs per sample, we declared a subject to have excessive number of rare CNVs if more than 10 were called from that subject’s DNA; samples with excessive number were excluded (Figure S3 in Supplement 1). Of the 541 remaining samples [267 males (M), 274 females (F)], 197 (36.4%, 128 M: 69 F) were affected, 185 (34.2%, 62 M: 123 F) were ROA, and 159 (29.4%, 77 M: 82 F) were controls. Within this sample, the average count of rare CNVs per sample is 0.68; the average size of a rare CNV is .67 Mb; and an average rare CNV is called using 68 probes.

Risk CNVs were identified using the following criteria: 1) associated with increased risk in this sample; or 2) occur in genes of relevance to schizophrenia and related disorders, typically identified in studies of samples of European ancestry. We consider these risk CNVs to be validated if they are called by both Birdsuite and PennCNV algorithms and if they segregate in families. If a risk CNV is called by at least one algorithm in a subject and the subject is an obligate carrier or a first-degree relative of a subject carrying the CNV, we consider that CNV to be validated also. The association of these CNVs with affection status is assessed by the odds ratio (OR). When there is a zero cell (undefined or infinity OR), we used the Yates correction, which adds 0.5 to all of the cells of a contingency table. Given the relatively small sample size of this study, we do not expect the association of these CNVs with diagnosis to be statistically significant.

We examined the segregation of risk CNVs in families by determining the relationships and haplotype sharing among CNV carriers. Relationships in this Oceanic population are complex and sometimes unknown, although most relationships fifth degree or less can be inferred by analysis of numerous independent genotypes, and most are known from pedigrees. We examined the genetic-based estimates of relationships by using tag SNPs, which were chosen as SNPs with no Mendelian errors, no missingness, and minor allele frequency of > 0.05 in controls. We then sub-selected SNPs that are 25 kb apart, yielding 59,627 SNPs and used Hclust (29, 30) to select 6,860 SNPs that had a pairwise correlation of $r^2 \leq 0.2$. Pairwise identity-by-descent (IBD) relationships for *all* pairs of samples were estimated using maximum likelihood. Genetic relationships were computed as $p(\text{IBD}2) + 0.5 p(\text{IBD}1)$ where $p(\text{IBD}1)$ and $p(\text{IBD}2)$ are the probabilities that two individuals share one and two alleles, respectively, IBD. Allele sharing among subjects was also examined to identify samples of non-Palauan ancestry. None were identified as having a distinct ancestry, as might be predicted by recent European admixture, although two individuals were born in Yap.

To complement estimated relationships, we also evaluated haplotype sharing in the CNV region amongst all CNV carriers (31). Extended haplotype-sharing, teamed with sharing in risk CNV, is clear evidence that the CNV is inherited IBD from a common ancestor. One hundred SNPs around the CNV, 50 SNPs from each side, were phased using Beagle 3.0.1 (32). If fewer than 50 SNPs were available, all available SNPs were used.

RESULTS

CNV analysis

We detected a substantial set of CNVs in the Palau sample, some of which confer risk to schizophrenia and related disorders, namely, CNVs in the *1q21.1*, *15q11.2*, *16p13.2*, and *Xp21.3* regions (Table 1). A 2.8Mb deletion on chromosome *1q21.1* was observed in one male subject affected with schizophrenia. Deletions of *1q21.1* spanning 1.35–2.19Mb have been previously reported in schizophrenia (2, 3, 5), autism, mental retardation, and other behavioral abnormalities (OMIM #612474).

A deletion in the *15q11.2* (2, 4, 5, 33) region, between breakpoints 1 and 2 of the Prader-Willi/Angelman syndrome region (34) and covering the genes *TUBGCP5*, *CYFIP1*, *NIPA2*, and *NIPA1*, occurred in two full-sibs (one affected and one unaffected), their paternal affected half-sib, and their unaffected father, as well as an unrelated unaffected female (Tables S1 & S2 in Supplement 1). All relationships were confirmed using genetic-based estimates of relationships. The deletion seems to affect risk (OR=4.1; 95% CI, 0.36–45.6) and is clearly incompletely penetrant. As expected, all deletion carriers related through their carrier father share an extended haplotype identical-by-descent (Table S3 in Supplement 1).

However, the unrelated female with the *15q11.2* deletion does not carry that haplotype, consistent with this CNV arising at least twice in this population.

An intronic duplication at *16p13.2* within *A2BP1* (32–40) appears to convey risk in males (OR=8.2, 95% CI, 0.8–84.4) but not females (OR=0.4, 95% CI, 0.03–4.9). There were 6 males carrying the duplication, all affected, whereas none of the females carrying the duplication were affected (Table S4 in Supplement 1). Pedigree relationships and genetic-based estimates of relationships show that this CNV is inherited (Figure 1, Table 2). All females with the CNV are either mothers or full siblings to an affected individual, except for one subject who is an adolescent and is not yet through the age of risk for developing schizophrenia and related disorders. Haplotype sharing also demonstrates that this CNV is inherited IBD (Table 3). To evaluate how the IBD-sharing translated into linkage, we performed an affected-only linkage analysis with the set of carriers and their close relatives. We assumed the CNV was rare and inherited IBD. Some individuals did not have clear pedigree relationships, but were genetically inferred to be related. We constructed a simple pedigree consistent with the genetically-inferred relationships that also fit with the known pedigrees (Figure S4 in Supplement 1). We then computed a LOD score using this pedigree and an affected-only model in which the probability of being affected was extremely small (0.0001) and the probability of being affected given the subject carries the CNV is 0.49. For this model and pedigree, a LOD score of 3.5 results.

At *Xp21.3* (41–47), we find a partial duplication of the gene encoding interleukin 1 receptor accessory protein-like 1, *ILIRAPL1* (OR=1.6, 95% CI, 0.3–7.7). While sex-specific effects of CNVs on chromosome X is the expectation, it is curious that females rather than males with the *ILIRAPL1* duplication appear to be at higher risk (Table 1). Notably, however, 5 out of the 6 unaffected female carriers were first-degree relative of an affected. The *ILIRAPL1* CNV is inherited based on identified and genetic relationships (Figure S5 & Tables S5 & S6 in Supplement 1) and IBD on the basis of haplotype sharing (Table S7 in Supplement 1). Aside from parent-offspring pairs, most other relationships are distant. Intriguingly on the proximal side of the duplication we find clusters of SNPs with evidence that they are heterozygous in males, suggesting that after the duplication event there was a recombination that disrupted a portion of the duplication. This region (between rs5943613 and rs4893560) has been identified as a recombination hotspot (<http://mathgen.stats.ox.ac.uk/Recombination.html>).

Three male subjects, 2 affected and 1 unaffected, were identified to have Klinefelter's syndrome (KS; 47, XXY). None of these subjects were related and none of their parents were genotyped. However, they are most likely to be *de novo* events as KS is associated with male hypogonadism and infertility (48). Notably, XXY was only called by PennCNV, which is not completely surprising because most algorithms have diminished accuracy of calling CNVs on chromosome X. However, XXY was confirmed based on the rate of heterozygosity on the X-linked SNPs, which was similar to that of females and by previous unreported results for genotyping of Short Tandem Repeats (STRs) by the Center for Inherited Disease Research (CIDR) (20–23). CIDR results also reveal Y markers consistent with an intact Y chromosome, thereby confirming KS.

We also detected several CNVs for which the risk ratio of affected to unaffected individuals is not large but they involved genes in neuronal-developmental pathways that have been previously reported to affect the risk for schizophrenia or related disorders, including autism. We report these CNVs (Table S8 in Supplement 1) and all other rare CNVs (<1%) called by Birdsuite and PennCNV (Table S9 in Supplement 1). *GRM7* is among the CNVs that have been previously reported in schizophrenia (49). We find a large duplication in one affected subject on *17p12*, a region that falls between Potocki-Lupski syndrome (PLS,

OMIM#610883) and Charcot-Marie-Tooth Type 1A (CMT1A, OMIM#118220). We also find another large duplication on 19p13.3 in one subject affected with schizophrenia and another with mild mental retardation, a duplication that was previously reported in schizophrenia (50).

DISCUSSION

In this population, we identify several CNVs that are associated with increased risk of schizophrenia and related psychotic disorders, similar to those detected in populations of European ancestry. We report CNVs in the *1q21.1* and *15q11.2*, which are confirmed regions of risk for schizophrenia (2–5). We also add to the existing evidence of the importance of CNVs in *16p13.2* and *Xp21.3* involving *A2BP1* and *IL1RAPL1* genes, respectively, in the risk for schizophrenia and related disorders. Most of these CNVs (except for *1q21.1*) are inherited and have incomplete penetrance, the latter consistent with studies reporting these deletions and duplications in unaffected individuals (51, 52).

This study has limitations. Our sample size of affected and unaffected subjects lacks power to detect statistically significant associations between CNVs and case-control status. The complex relationships amongst individuals in this Oceanic population allows the evaluation of the transmission of CNVs, which a strength of this study; however, it poses a limitation in the choice of controls. We include controls who are no less than third degree relatives to cases because relationships among case and control subjects are inevitable. Indeed, relationships amongst controls are also certain. Another limitation is that controls and relatives of an unaffected were not administered the SADS-Lifetime. While the absence of psychiatric disorders has been confirmed through medical records without a full psychiatric interview, it does not preclude milder and subsyndromal diagnoses for which medical care may not have been sought.

A duplication affecting *A2BP1* is associated with an 8-fold increased risk in males but not in females. *A2BP1* codes for a brain-expressed RNA binding or splicing factor involved in neurological function. *A2BP1* binds with ataxin-2 (53), which is the product of the gene causing spinocerebellar ataxia 2, a neurological disease that can express psychosis as one of its symptoms (54). Reduced mRNA expression in lymphocytes was found in an autistic patient with a deletion of the first exon of *A2BP1* (35). Duplications and deletions disrupting *A2BP1* are reported in schizophrenia (36), attention deficit hyperactivity disorder (37), epilepsy, and mental retardation (38). *A2BP1* is also reported as a candidate gene for bipolar disorder (39, 40). This duplication has been present in Palau for many generations because all carriers show evidence of haplotype-sharing and genetic relationship to other carriers, with some of the related carriers separated by many generations.

The sex difference we found for duplications in *A2BP1* is intriguing given the well-known sex differences in the age at onset and clinical features of schizophrenia (55, 56). Also notable in this regard are potential regulatory pathways whereby sex hormones could regulate *A2BP1*. *A2BP1* has a predicted binding site for the microRNA has-mir-21 (57) and other evidence suggests has-mir-21 is regulated by androgen and estrogen receptors (58, 59). This raises the possibility that *A2BP1* signaling may mediate sex effects in the expression of psychosis. However, given our small sample size, further studies are needed to confirm the sex difference in *A2BP1* duplications.

IL1RAPL1 encodes for a protein that is a member of the Interleukin 1 receptor family and is highly expressed in postnatal brain structures involved in hippocampal memory. *IL1RAPL1* plays a role in the regulation of neurite outgrowth and exocytosis and in the down-regulation of calcium channels. The *IL1RAPL1* consists of 10 coding exons. A loss of function results

in a truncated protein that is unable to control neurite out-growth in hippocampal neurons (41). Males with deletions and mutations of *ILIRAPLI* exhibit a range of neurological disorders such as X-linked mental retardation (MR), autism, and cognitive impairments (OMIM #300206; #300143) (41–47) whereas females are not necessarily affected. Duplicated genes on chromosome X often show sexually dimorphic expression due to skewed X inactivation; in females, a duplicated or disrupted gene is often silenced by the X inactivation mechanism. Thus, females with an X-linked abnormality can develop normally. Contrary to expectation for the Palauan sample, females with *ILIRAPLI* duplications are affected more than would be expected by chance. Selective or incomplete inactivation of the X chromosome could explain the diversity of the phenotype in females, consistent with several studies reporting some X-linked genes escaping X-inactivation in the Xp21.3-p22.1 boundary (60, 61). Because the CNV duplicates two exons of *ILIRAPLI*, it is likely that it alters the conformation of the resulting protein, thereby functioning as a mutation. However, it is also possible that the duplicated exons are not transcribed or translated and therefore does not alter gene function.

We identified three subjects with Klinefelter's Syndrome in this sample. This represents an increased prevalence of KS in Palau (3 per 268 males) as compared to the expected prevalence of 1 per 500 males or higher (62). The risk for KS is known to increase with increased maternal age in maternally-derived cases and recent studies show increased risk with increased paternal age (63–65). Subjects with KS present with a variety of clinical features including developmental delays and behavioral problems (66). An increased prevalence of psychotic disorders and increased levels of schizophrenia-spectrum pathology in KS patients have been previously reported (67, 68).

Deletion of a 300Kb region in *15q11.2*, between breakpoints 1 and 2 of the Prader-Willi/Angelman syndrome region (33) has previously been reported as a risk region for schizophrenia in samples of European ancestry (2, 4, 5). The deletion is found in one nuclear family and an unrelated individual and therefore has arisen at least twice in Palau. Yet the deletion appears rare because it is not found in our study's controls. Like results from populations of European ancestry, our results suggest deletions convey modest risk for schizophrenia.

We identified one affected male with a deletion on 1q21.1. Deletions on 1q21.1 have been consistently implicated for schizophrenia (2–5), as well as developmental delay, intellectual disability, behavioral abnormalities, autism, nonspecific dysmorphic features, and congenital abnormalities (OMIM #612474). Because his parents were deceased, inherited or a *de novo* status could not be established. Still, because this CNV is not found in any other individual, is not present in his affected sibling, and because of the high penetrance of this deletion, it is very likely a *de novo* mutation, consistent with observations in populations of European ancestry (2–5).

This study reveals several CNVs that confer risk to schizophrenia and related psychotic disorders in Palau. These CNVs have been previously reported in samples of European ancestry. These findings suggest that rare *de novo* and inherited CNVs account for a proportion of the risk to these disorders regardless of ancestry. However, most of these CNVs have incomplete penetrance. A few of these CNVs show evidence that they have existed in Palau for many generations, while others show no such evidence. It is interesting to note that the CNVs showing some evidence of extended longevity in the population are also those that show (*A2BPI*) or should show (*ILIRAPLI*) sex-dependent risk. In theory this would expose the variant to natural selection, as a result of reduced reproductive success typically associated with schizophrenia, in a sex-differential manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Nominal pedigree relationships between subjects carrying a duplication in *A2BP1*. Subjects in red are affected; triangle symbol represents unknown gender. Subjects with OC are obligate carriers who were not genotyped to confirm their carrier status. The pedigree section linking 2034, 22554, 22532, and 60038 was inferred from genetic-based estimates of the relationships. Genetic-based estimates uncover additional distant relationships between CNV carriers (Table 2).

Table 1

List of CNVs in Palau that appear to confer risk to schizophrenia and related psychotic disorders

Chr band	Gene	Start	End	Dup / Del	Intronic/ Exonic	Affected: ROA: Controls			OR ² (95% CI)		
						Total	Females	Males	Total	Females	Males
1q21.1 ³	<i>Several Genes⁴</i>	143,560,909	146,395,590	Del	Exonic	1:0:0	0:0:0	1:0:0	2.5 (0.2–30.3)	---	1.8 (0.15–22.4)
15q11.2	<i>TUBGCP5, CYFIP1, NIPA2, NIPA1</i>	19,537,067	20,852,161	Del	Exonic	2:3:0	1:2:0	1:1:0	4.1 (0.36–45.6)	3.6 (0.29–44.4)	1.8 (0.15–22.4)
16p13.2	<i>A2BP1</i>	6,581,119	6,645,572	Dup	Intronic	6:6:1	0:4:1	6:2:0	5.0 (0.8–31.6)	0.4 (0.03–4.9)	8.2 (0.8–84.4)
Xp21.3	<i>ILIRAPLI</i>	29,163,088	29,455,307	Dup	Exonic	4:6:2	2:5:1	2:1 ⁵ :1	1.6 (0.3–7.7)	2.4 (0.3–18.8)	1.2 (0.15–9.3)
47, XXY	Klinefelter Syndrome	230,897	154,582,819	Dup	Both	2:0:1	0:0:0	2:0:1	1.2 (0.2–9.2)	---	1.2 (0.2–9.2)

¹ Dup= Duplication, Del=Deletion;

² Odds ratio compares affected individuals to controls. In the case of a zero cell that would lead to undefined or infinity OR, we used the Yates correction, which adds 0.5 to all of the cells of a contingency table;

³ 247/403 copy number probes for Birdsuite and PennCNV, respectively;

⁴ PDE4DIP, SEC22B, NOTCH2NL, HFE2, POLR3GL, ANKRD34A, LIX1L, PEX11B, ITGA10, ANKRD35, NUDT17, POLR3C, ZNF364, CD160, PDZK1, PRKAB2, FMO5, CHD1L, BCL9, ACP6, GJA5, GJA8, GPR89B;

⁵ Subject diagnosed with alcohol abuse.

Table 2Estimated relationship matrix for subjects carrying a duplication in *A2BP1*

	2058	17615	19800	20248	22415	22554	20244	22352	22563	60038	22353	2034	22532
2058	1	0.015	0.01	0.006	0.007	0.092	0.005	0.018	0.005	0.5	0.003	0.038	0.118
17615		1	0	0	0	0.004	0	0.509	0	0.033	0	0.004	0.021
19800			1	0.144	0	0.003	0.498	0	0.008	0.011	0.145	0	0
20248				1	0	0	0.228	0.0002	0	0.006	0.417	0	0
22415					1	0.001	0	0.005	0.506	0	0	0	0.014
22554						1	0.003	0	0.002	0.178	0.001	0.24	0.476
20244							1	0	0	0.005	0.31	0	0
22352								1	0.008	0	0	0.004	0
22563									1	0	0	0.001	0.0001
60038										1	0.002	0.075	0.279
22353											1	0	0.010
2034												1	0.262
22532													1

Table 3Haplotype sharing surrounding the *A2BP1* CNV

Subject	Haplotype
22353	*****/2212121212212****
20248	*****/2212121212212****
20244	*****/2212121212212****
19800	*****/2212121212212****
22532	*****/2212121212212****
22554	*****/22 2 12121212212****
22352	*****/22 2 12121212212****
17615	*+*+*/2212121212212****
60038	*+*+*/2212121212212****
2058	*+*+*/2212121212212****
2034	*+*+*/22 2 12121212212****
22563	^^^^/2212121212212\\+++++
22415	^^^^/2212121212212\\+++++

Haplotypes are ordered in terms of similarity; CNV region is the region between // and \\\; Symbols represent similarity on a stretch of 10 SNPs except in the CNV region where the actual haplotype is presented; Variation in the CNV region is presented in red and bold.