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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

High-resolution chromosomal microarray analysis for copy-number variations in high-functioning autism reveals large aberration typical for intellectual disability

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Abstract

Copy-number variants (CNVs), in particular rare, small and large ones (< 1% frequency) and those encompassing brain-related genes, have been shown to be associated with neurodevelopmental disorders like autism spectrum disorders (ASDs), attention deficit hyperactivity disorder (ADHD), and intellectual disability (ID). However, the vast majority of CNV findings lack specificity with respect to autistic or developmental-delay phenotypes. Therefore, the aim of the study was to investigate the size and frequency of CNVs in high-functioning ASD (HFA) without ID compared with a random population sample and with published findings in ASD and ID. To investigate the role of CNVs for the "core symptoms" of high-functioning autism, we included in the present exploratory study only patients with HFA without ID. The aim was to test whether HFA have similar large rare (> 1 Mb) CNVs as reported in ASD and ID. We performed high-resolution chromosomal microarray analysis in 108 children and adolescents with HFA without ID. There was no significant difference in the overall number of rare CNVs compared to 124 random population samples. However, patients with HFA carried significantly more frequently CNVs containing brain-related genes. Surprisingly, six HFA patients carried very large CNVs known to be typically present in ID. Our findings provide new evidence that not only small, but also large CNVs affecting several key genes contribute to the genetic etiology/risk of HFA without affecting their intellectual ability.

Keywords Autism spectrum disorder · High-functioning autism · Copy-number variation · Intellectual disability

Abbreviations

ADAD2	Adenosine deaminase domain containing 2
ADCY9	Adenylate cyclase 8
ADHD	Attention deficit hyperactivity disorder
AHI1	Abelson helper integration site 1
ARL13B	ADP-ribosylation factor-like 13B
ARL6	ADP-riboylation factor-like 6
ASAP1	ArfGAP with SH3 domain, ankyrin repeat, and PH domain 1
ASD	Autism spectrum disorder
BBS	Bardet–Biedl syndrome
BRD1	Bromodomain-containing protein 1
CBCL	Child behavior checklist
CC2D2A	Coiled-coil and C2 domain containing 2A
Celsr1	Cadherin, EGF LAG seven-pass G-type receptor 1
CEP290	Centrosomal protein 290
ChAS	Chromosome analysis suite
CMA	Chromosomal microarray analysis
CNS	Central nervous system
CNV	Copy-number variant
COL22A1	Collagen, Type XXII, alpha 1
CRYBG3	Crystallin beta-gamma domain containing 3
DD	Developmental delay

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DGV	Database of genomic variants
DHFRL1	Dihydrofolate reductase-like 1
DNA	Deoxyribonucleic acid
EPHA6	EPH Receptor A6
FAM135B	C8orfK32, family with sequence similarity 135 member B
FAM19A5	Family sequence similarity 19
FARP2	FERM, RhoGEF, and pleckstrin domain-containing protein
GABRR3	Gamma-aminobutyric acid (GABA) A receptor, Rho 3
GRAMD4	GRAM domain containing 4
GWAS	Genome-wide association study
HDAC4	Histone deacetylase 4
HDLBP	High-density lipoprotein binding protein
HFA	High-functioning autism
ID	Intellectual disability
INPP5E	Inositol polyphosphate-5-phosphatase E
IQ	Intelligence quotient
Kb	Kilobyte
KCNG4	Potassium voltage-gated channel subfamily KQT member 4
KCNQ3	Potassium channel, voltage-gated KQT-like subfamily Q, member 3
KHDRBS3	KH domain containing, RNA binding, signal transduction associated 3
LOC150935	Uncharacterized LOC150935
MAPK8IP2	Mitogen-activated protein kinase 8 interacting protein 2
Mb	Megabyte
MINA	MYC-induced nuclear antigen
NPHP1	Nephrocystin-1
NRXN1	Neurexin-1-alpha
NSUN3	NOP2/sun domain family, member 3
OCD	Obsessive-compulsive disorder
PASK	Proline-alanine-rich STE2 0-related kinase
PLXNB2	Plexin B2
PROS1	Protein S
PTCHD1	Patched domain containing 1
RPGRIP1L	Retinitis pigmentosa GTPase regulator interacting protein 1 like
SCO2	SCO2 cytochrome c oxidase assembly
SCQ	Social communication questionnaire
SHANK2	SH3 and multiple ankyrin repeat domains protein 2
SHANK3	SH3 and multiple ankyrin repeat domains protein 3
STX19	Syntaxin 19
TBC1D22A	TBC1 domain family, member 22A
TMEM67/MKS3	Transmembrane protein-67
TTLL8	Tubulin tyrosine ligase-like family member 8
TUBGCP6	Tubulin, gamma complex associated protein 6
TYMP	Thymidine phosphorylase
VSTM4	V-Set and Transmembrane Domain Containing 4
WBCR	Williams–Beuren critical region
WBS	Williams–Beuren syndrome

Background

Autism spectrum disorder (ASD) is a neurodevelopmental disorder behaviorally defined by the deficits in reciprocal social interaction and communication as well as presence of restricted and repetitive behaviors. In the DSM-5 and in recent conceptualizations, these two behavioral dimensions represent the core defining features of ASD. Furthermore, frequently associated dimensions, such as language and intellectual disability (ID), contribute significantly to the heterogeneity of ASD phenotype. Individuals with ASD vary greatly in cognitive development, ranging from above average to ID. Multiple family and twin studies with concordance rates for ASD ranging up to 90% in monozygotic twins and up to 10% in dizygotic twins, respectively, showed the major role of heritability in the etiology of ASD (Hallmayer et al. 2011; Rosenberg et al. 2009; Tick et al. 2016; Colvert et al. 2015; Frazier et al. 2014; Sandin et al. 2014). However, the exact genetic mechanisms are not yet completely understood and identifying those genes is challenging (Freitag et al. 2010). In earlier studies, including case–control association, linkage- and genome-wide association studies chromosome regions including 2q (Consortium 2001; Vorstman et al. 2005), 5p (Vorstman et al. 2005; Wang et al. 2009), 7q (Consortium 2001; Chiocchetti et al. 2015), 11q (Vorstman et al. 2005), 15q (Marshall et al. 2008; Depienne et al. 2009), 16p (Consortium 2001; Marshall et al. 2008; Fernandez et al. 2009), and 16q (Vorstman et al. 2005; Wassink et al. 2008) showed significant association to autism (Yingjun et al. 2017).

The role of rare large and small copy-number variations (CNVs) as susceptibility loci in common and complex genetic diseases has been intensively investigated (Pinto et al. 2010; Kaminsky et al. 2011), and large CNVs have been detected in about 10% of patients with ASD (Shishido et al. 2014). It was described in an extensive genome-wide associations study (GWAS) that individuals with ASD carry a significant higher general burden of rare CNVs (1.19 fold), especially affecting loci and genes previously detected in ASD and/or ID (1.69 fold) (Pinto et al. 2010).

Results from Marshall and Scherer (2012) showed that some CNVs are pleiotropic and cause different clinical

presentations (Marshall and Scherer 2012). The authors assume that a CNV at a particular locus may affect intelligence quotient (IQ) in individuals with ASD and, e.g., inflexible behavior in obsessive–compulsive disorder (OCD) patients at the same time. Additionally, rare and common variants in genes seem to be associated with synaptic plasticity (Zoghbi 2003) and brain connectivity (Vissers et al. 2012), and are linked to ASD. Moreover, another study showed that rare and large CNVs have been observed in both ASD and ID. However, these variants lack specificity towards ASD in contrast to developmental delay (DD) presentations (Girirajan et al. 2013). Girirajan and colleagues found that as the size of deletions increases, the non-verbal IQ decreased with no further impact on autism severity (Girirajan et al. 2013). In another study, the authors (Girirajan et al. 2011) reported that the frequency of large CNVs (> 1 Mb) was significantly higher in ID-associated phenotypes compared to autism phenotypes. They also concluded that large CNV burden was positively correlated with the ID severity. At the same time, the increase in CNV burden was modest when comparing autistic participants without ID with controls.

Here, we concentrated on a special population of ASD representing the core defining features of ASD including patients with high-functioning autism (HFA) only. HFA is characterized by features like those of Asperger syndrome and autism; however, the patients are cognitively "high functioning" (Chiang et al. 2014). Although there are currently no explicit diagnostic criteria for HFA, the definition is commonly used for autistic children with an IQ above 65–70 (Gillberg 1998). In the DSM-5, these patients are characterized by the specifier "without intellectual impairment" (American Psychiatric Association 2013).

Granted that former studies showed larger CNVs to be mainly associated with ID, we tested whether the frequency of large CNVs in HFA patients will be lower, as well as to investigate the frequency of rare deletions or duplications comparing to controls.

Up to date, there is no CNV analysis in HFA patients exclusively. Schaaf et al. (2011) sequenced several genes known to cause "syndromic autism" and other cognitive disorders only in an ASD population in general by traditional Sanger method and pyrosequencing.

The present work is, to our knowledge, the first genome-wide CNV analysis in a rigorous phenotyped cohort of patients with HFA using high-resolution chromosomal microarray analysis (CMA). By narrowing the broader phenotype spectrum of ASD, this cohort represents the core defining features of ASD without ID; we aimed to increase the knowledge on the pathophysiology and symptomatology of ASD.

Methods

Study sample: children and adolescents with HFA

108 children and adolescents with HFA were recruited at the Departments of Child and Adolescent Psychiatry and Psychotherapy, University Hospitals of Psychiatry Zurich, Switzerland and of the University of Würzburg, Germany.

All HFA patients fulfilled the diagnostic criteria for ASD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association 2013) and for pervasive developmental disorder according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (Dilling et al. 1996).

The diagnosis was confirmed using either the Autism Diagnosis Observation Schedule (ADOS) (Rühl et al. 2004; Lord et al. 2012) or using Autism Diagnosis Interview-Revised (ADI-R) (Bölte et al. 2006; Lord et al. 1994). In 74 patients, SCQ (Rutter et al. 2007; Bölte and Poustka 2006) was additionally available. According to the HFA definition (Gillberg 1998), the inclusion criterion, which we adopted, was an IQ of at least 70 in standardized IQ tests (see below). The choice of different IQ tests was influenced by individual clinical necessities. The following tests were used: Wechsler Intelligence Scale for Children (Petermann and Petermann 2010), Wechsler Intelligence Scale for Adults (Wechsler 1981), Kaufman Assessment Battery for Children (Kaufman et al. 2009), Culture Fair Intelligence Test (Weiss 2006), or the Snijders–Oomen Non-Verbal Intelligence Test 5.5–17 (Tellegen et al. 2003). Patients underwent a psychiatric investigation conducted by a psychologist supervised by a senior or experienced child and adolescent psychiatrist, and were additionally screened for other psychopathologies as described previously (Werling et al. 2015; Nyffeler et al. 2014). The following parameters have been used: Child Behavior Checklist (Döpfner et al. 1998) and the German ADHD rating scale, FBB-HKS (Döpfner and Lehmkuhl 2000). The self-reported ethnicity was Caucasian origin for all subjects.

Exclusion criteria: neurological disorders including epilepsy or known genetic diseases linked to autism and ID (IQ < 70) and other severe psychiatric disorders such as psychosis and affective disorders (major depression and mania). The genetic data of the parents of the included patients were not available for analysis.

Control samples

The data of 124 chorionic villi samples of presumably healthy donors from Switzerland of Caucasian origin (76

males and 48 females, $chi^2 = 17.98$, $p < 0.0001$ compared to the HFA patients) were assessed as previously described (Grünblatt et al. 2017). These chorionic villi samples were collected from pregnant women who decided to have invasive prenatal diagnosis due to advanced maternal age or due to parental wish. They were analyzed in the same manner on the Cytoscan HD Array as the patient samples.

Ethics approval

All procedures were performed with the written informed consent of the parents of all participants and the study was approved by the local ethics committees of the Canton of Zurich (Switzerland, E-36/2009), and of Würzburg (Germany, study numbers 8/06 and 227/09), respectively.

DNA extraction and chromosomal microarray analysis (CMA)

Genomic DNA was extracted from whole blood (EDTA tubes) with the desalting Proteinase K methodology (Miller et al. 1988) in 33 patients and from saliva in 75 patients (Oragene DNA, DNA Genotek Inc., Ontario, Canada) following the manufacturer's protocol. DNA was analyzed with the Cytoscan HD Array (containing about 750,000 genotype-able SNPs and 1.9 million non-polymorphic probes) (Affymetrix Inc., Santa Clara, CA, USA) at a genome-wide resolution of 50 kb for both duplications and deletions. Array hybridization was performed according to the manufacturer's protocol. Data were analyzed with Chromosome Analysis Suite (ChAS) software (Affymetrix) for changes of relative intensities. The CNV analyses were based on build 32.1. Genomic coordinates are based on GRCh37/hg19. To exclude common benign CNVs, we used a reference set of 820 in-house controls and 1038 Affymetrix controls in combination with the Database of Genomic Variants (DGV) from the Centre for Applied Genomics (February 2009, hg19). The results derived from the Chromosomal microarray analysis are very stable (Asadollahi et al. 2014). Cases and controls were treated in separate batches and case DNA was extracted from different sources (saliva and blood).

Rare CNVs were defined as aberration in coding sequences of genes that were absent in our in-house and Affymetrix primary control cohort, as well as not found to be reported in the DGV (http://projects.tcag.ca/variation/). The DECIPHER (https://decipher.sanger.ac.uk/) database was used to search for similar rare CNVs found in the current studied sample that occur also in other patients from DECIPHER to compare their phenotypes (last search 19th June 2019).

Brain-related CNVs were defined prior to the analysis if at least one of the genes within CNVs had central nervous system (CNS) expression or link demonstrated in the databases such as GO (Ashburner et al. 2000), Gene Expression Omnibus (GEO) (Edgar et al. 2002), the Genotype-Tissue Expression (GTEx) database (GTEx Consortium 2013), and the Human Protein Atlas database (Uhlen et al. 2015) (see Supplementary Table S1).

Statistical analysis

Frequency analysis was conducted using Chi-square test and Fisher's exact test. For continuous measures, the Mann–Whitney *U* test was used.

Statistical analysis was performed with SPSS v.21 (IBM) and StatView v.5.0 (SAS Inst.). The level of significance was $\alpha = 0.05$.

Results and discussion

Sample

One hundred and eight patients with HFA, 93 males and 15 females, have been enrolled in the study (12 patients with "childhood autism", 37 with "atypical autism, and 59 with "Asperger syndrome"). The male-to-female ratio of 6.2 is representative for HFA, since the most widely reported male–female ratio for autism prevalence is 4–5.1, however, higher at the high-functioning end (Lai et al. 2015). The mean age ± SD of the patients at investigation was 11.29 ± 3.3 years. Only patients with an IQ of at least 70 in standardized IQ tests were included (IQ range 70–145) (For further details, see Table 1).

Fifty-seven of 108 HFA patients had an additional psychiatric disorder, most often ADHD (38.0%), followed by developmental disorders (21.3%, e.g., specific developmental disorders of scholastic skills, of motor function or mixed specific developmental disorders or phonological disorder) and OCD (3.7%) (for details, see Supplementary Table S2). Thirty-three of the patients received medication (methylphenidate; $n = 26$) for the treatment of the ADHD symptomatology. For more details about demographic data, see Table 1.

Frequency of rare CNVs in HFA

We detected small and large rare CNVs (mean size = 640.29 kb, SD 1399.17; range 52–8600 kb) in 42 of 108 patients with HFA (38.9%; Supplementary Table S1). There was no significant difference in the overall number of rare CNVs in the HFA sample compared to the control population ($n = 39$, 31.5%; mean size 273.85 kb, SD 234.04; range 50–1027 kb; $chi^2 = 1.4$, $p = 0.24$ for details on control population see (Grünblatt et al. 2017)). There was no significant difference in the number of rare deletions between

Table 1 Demographic data of the HFA sample

	HFA, $n=108$
Primary diagnosis	
F84.0, Childhood autism	12 (11.1%)
F84.1, Atypical autism	36 (33.3%)
F84.5, Asperger syndrome	60 (55.6%)
Sex	
Male (% total)	93 (86.1%)
Female (% total)	15 (13.9%)
Ratio (M/F)	6.2
Age	
Range	5–18 years
Mean age standard deviation	11.29 years, SD 3.3
Medication intake	
No medication	75 (69.4%)
Methylphenidate	24 (22.2%)
Dexmethylphenidate	1 (0.9%)
Amphetamine	2 (1.9%)
Atomoxetine	1 (0.9%)
Pipamperone	1 (0.9%)
Risperidone	2 (1.9%)
Methylphenidate and Risperidone	2 (1.9%)
IQ	
SON-R, *n*=	77
SON-R, range	79-140
SON-R, mean (SD)	107.8 (SD 15.97)
CFT-1, *n*=	68
CFT-1, range	70-145
CFT-1, mean (SD)	105.63 (SD 13.73)
WISC, *n*=	10
WISC, range	78-129
WISC, mean (SD)	101.2 (SD 17.40)
K-ABC, *n*=	2
K-ABC, range	115-118
K-ABC, mean (SD)	116.50 (SD 2.12)

HFA high-functioning autism, *M* male, *F* female, *SON-R* Snijders-Oomen Non-Verbal Intelligence Test Revised, *CFT-1* Culture Fair Test, *WISC* Wechsler Intelligence Scale, *K-ABC* Kaufman Assessment Battery For Children, *SD* standard deviation

HFA ($n=21$, 19.1%) and control population ($n=15$, 12.1%; $chi^2=2.601$, $p=0.27$).

Although there were no significant group differences overall, interestingly, some of the patients with HFA were carriers of unexpected large CNVs, both deletions (cases A114: 2200 kb; A039: 4200 kb; A044: 8600 kb; A10W: 4300 kb) and duplications (cases A40W: 1600 kb; A044: 1600 kb; A092: 1400 kb) in known disease loci (summary in Table 2). In the control group, only one control proband carried a large duplication of unknown significance (0.8%, M40756 1027 kb), while all others carried rather small CNVs (see details on control population in (Grünblatt et al. 2017). Furthermore, there was a significant difference in the number of HFA carrying rare CNVs' spanning genes involved in synaptic and brain-related processes ($n=28$, 25.4%), compared to controls ($n=16$, 12.9%; $chi^2=6.02$, $p=0.014$). This last finding is in line with previous studies on rare CNV, showing that in particularly patients with ASD carry CNVs spanning brain-related gene regions (Belmonte et al. 2004; Gilman et al. 2011).

As the present sample size is rather small, we cannot rule out that the negative results are due to statistical power to detect difference between HFA and controls. However, the current aims of the study were to see whether patients with HFA carry large rare CNVs, as well as large rare CNVs similar to those found previously in patients with ASD with ID or ID alone.

HFA carrying large rare CNVs (> 1 Mb) frequently described in ID

Strikingly, we found in six of our HFA patients very large rare CNVs (> 1 Mb) typically described in ID patients (Phelan and McDermid 2011; Mefford et al. 2012). Therefore, we focused on the medical history and the phenotypical details of each patient (Table 2) and discussed the findings in view of the current literature.

"Patient A10W"

The patient was a 14.9-year-old boy suffering from childhood autism (F84.0; IQ = 115) without any comorbidity. At the time of investigation, he took risperidone for aggressive and impulsive behavior.

We detected a 4.3-Mb large deletion in 22q13.31 (hg19 chr22:46885024–51183767), encompassing 50 genes in total, 31 OMIM-Gene, 11 of which involved in synaptic or brain-related pathways (details see Table 2). According to DECIPHER, overlapping CNVs (hg19 chr22:46885024–51183767) were found in 271 individuals (female $n=119$, male $n=110$; $n=42$ with unknown sex). The ratio between ASD males and females in DECIPHER was 1.6 (female $n=11$, male $n=18$; $n=8$ with unknown sex). Several patients have been reported with this deletion, and the clinical characterization of 22q13 deletion syndrome, known as Phelan–McDermid syndrome (PMS), is well established (Phelan and McDermid 2012). It is a contiguous genetic disorder on the terminal long arm of chromosome 22. These patients show neurological or neurodevelopmental deficits, and 50% of the patients show additionally autism or autistic-like behavior (Phelan and McDermid 2012). To our knowledge, HFA has not been described in patients with Phelan–McDermid syndrome up to now.

Table 2 Large (> 1 Mb) rare CNVs typical for intellectual disability (ID) and/or developmental disorders (DD), discovered in pediatric high-functioning autism (HFA) patients

Code	Sex	Age (years)	ICD-10	IQ Score	ADOS	ADI-R A/B/C/D	CNV size (kb)	chromosomal location (hg19)	Deletion/ Duplication	Genes within CNV	DECIPHER (overlapping findings, last date 19.06.2019)	Evidence in literature for the link with ID /DD
A114	male	9	F84.1	87[1]	9	8/8/2/2	2200	chr2 2q37.2: 240633456-242783384	Deletion	LOC150935, MIR4786, NDUFA10, **OR6B2**, PRR21, **OR6B3**, MYEOV2, **OTOS**, GPC1, PP14571, MIR149, ANKMY1, DUSP28, RNPEPL1, **CAPN10**, GPR35, AQP12B, AQP12A, KIF1A, AGXT, C2orf54, LOC200772, SNED1, MTERFD2, PASK, PPP1R7, ANO7, HDLBP, **SEPT2**, **FARP2**, **STK25**, BOK-AS1, BOK, THAP4, **ATG4B**, DTYMK, ING5, D2HGDH, GAL3ST2, NEU4	https://decipher.sanger.ac.uk/search?q=2%3A240633456-242783384#consented-patients/results 113 individuals: 73 deletions/ 40 duplications 50 reported with ID or/and DD	Doherty and Lacbawan 1993; Felder et al. 2009; Imitola et al. 2015; Deviilard et al. 2010; Leroy et al. 2013
A039	male	16	F84.1	106[1]	2	14/6/1/0	4200	chr3 3q11.1-q11.2: 93519464-97738323	Deletion	PROS1, ARL13B, STX19, DHFRL1, NSUN3, LOC255025, EPHA6, **ARL6**, CRYBG3, MINA, **GABRR3**	https://decipher.sanger.ac.uk/search?q=3%3A93519464-97738323#consented-patients/results 25 individuals: 9 deletions/ 15 duplications/ 1 duplication/ triplication 15 reported with ID or/ and DD	Guo et al 2017; Uzunova et al. 2016
							96	chr16q24.1:84 223309-84319789	Deletion	ADAD2, **KCNG4**	https://decipher.sanger.ac.uk/search?q=16%3A84223309-84319789#consented-patients/results 36 individuals: 19 deletions/ 15 duplications/ 1 duplication/triplication 18 reported with ID or/ and DD	--
A40W	male	15	F84.1	78[2]	14	23/18/7/4	1600	chr7 7q11.23: 72659674-74245599	Duplication	GTF2IRD2P1, NSUN5, TRIM50, FKBP6, **FZD9**, BAZ1B, BCL7B, TBL2, MLXIPL, VPS37D, DNAJC30, WBSCR22, **STX1A**, MIR4284, ABHD11-AS1, ABHD11, CLDN3, CLDN4, WBSCR27, WBSCR28, ELN, **LIMK1**, EIF4H, MIR590, LAT2, RFC2, **CLIP2**, GTF2IRD1, GTF2I, NCF1, GTF2IRD2	https://decipher.sanger.ac.uk/search?q=7%3A72659674-74245599#consented-patients/results 210 individuals: 103 deletions/ 105 duplications/ 2 triplications 92 reported with ID or/ and DD	Pober 2010; Berg et al.; Van der Aa et al. 2009; Sanders et al. 2011; Somerville et al. 2005; Depienne et al. 2009
A044	male	10	F84.5	87[1]	6	12/12/6/3	8600	chr8 8q24.21-q24.3: 131409413-140043304	Deletion	ASAP1, **ADCY8**, EFR3A, OC90, HHLA1, **KCNQ3**, HPYR1, LRRC6, TMEM71, PHF20L1, **TG**, SLA, WISP1, **NDRG1**, ST3GAL1, ZFAT, ZFAT-AS1, MIR30B, MIR30D, LOC286094, KHDRBS3, FAM135B, COL22A1	https://decipher.sanger.ac.uk/search?q=8%3A131409413-140043304#consented-patients/results 75 individuals: 18 deletions/ 45 duplications/ 2 triplications 41 reported with ID or/ and DD	Verheij et al. 2009; Lowe et al. 2015; Rauch et al. 2012; Curry et al. 2008.
							1600	chr16 16p13.11: 14899277-16494783	Duplication	**ABCC6P2**, NOMO1, MIR3179-1, MIR3179-3, MIR3179-2, MIR3180-1, MIR3180-3, MIR3180-2, NPIP, **PDXDC1**, **NTAN1**, RRN3, MIR3180-4, MPV17L, C16orf45, KIAA0430, **NDE1**, MIR484, **MYH11**, FOPNL, ABCC1, **ABCC6**, NOMO3, PKD1P1	https://decipher.sanger.ac.uk/search?q=16%3A14899277-16494783#consented-patients/results 443 individuals: 158 deletions/ 274 duplications/ 3 triplications/ 1 amplification 125 reported with ID or/ and DD	Nagamani et al. 2011; Fujitani et al. 2017; Hannes et al. 2009; Ramalingam et al. 2011; Allach El Khattabi et al. 2018
A092	male	10	F84.5	124[1]	6	n.a.	1400	chr16 16p13.11: 14927356-16328781	Duplication	MPV17L, C16orf45, KIAA0430, **NDE1**, MIR484, **MYH11**, FOPNL, ABCC1, **ABCC6**, NOMO3, NOMO1, MIR3179-1, MIR3179-3, MIR3179-2, MIR3180-1, MIR3180-3, MIR3180-2, NPIP, **PDXDC1**, **NTAN1**, RRN3, MIR3180-4	https://decipher.sanger.ac.uk/search?q=16%3A14927356-16328781#consented-patients/results 437 individuals: 158 deletions/ 275 duplications/ 3 triplications/ 1 amplification 162 reported with ID or/ and DD	Nagamani et al. 2011; Fujitani et al. 2017; Ramalingam et al. 2011; Hannes et al. 2009; Allach El Khattabi et al. 2018
A10W	male	14	F84.0	115[3]	15	16/18/11/5	4300	chr22 22q13.31-q13.33: 46885024-51197838	Deletion	**CELSR1**, GRAMD4, CERK, TBC1D22A, LOC339685, FLJ46257, MIR3201, FAM19A5, LOC284933, MIR4535, LOC100128946, C22orf34, BRD1, LOC90834, ZBED4, ALG12, CRELD2, PIM3*, IL17REL, MLC1, **MOV10L1**, **PANX2**, TRABD, SELO, **TUBGCP6**, HDAC10, **MAPK12**, **MAPK11**, **PLXNB2**, FAM116B, PPP6R2, SBF1, ADM2, MIOX, LMF2, NCAPH2, SCO2, **TYMP**, ODF3B, KLHDC7B, SYCE3, CPT1B, CHKB-CPT1B, CHKB, LOC100144603, **MAPK8IP2**, **ARSA**, **SHANK3**, ACR, RPL23AP82	https://decipher.sanger.ac.uk/search?q=22%3A46885024-51197838#consented-patients/results 271 individuals: 181 deletions/ 86 duplications/ 1 triplication/ 4 amplifications 153 reported with ID or/ and DD	Phelan and McDermid 2012; Leblond et al. 2014; Slavotinek et al. 1997; Bonaglia et al. 2011; Harony-Nicolas et al 2015.

n.a. not available, – not relevant, *ID* intellectual disability, *DD*, developmental disorder. Bold brain/synapse related genes according to gene ontology, Gene Expression Omnibus (GEO), Genotype-Tissue Expression (GTEx) database and the human Protein Atlas database; Red, same gene and regions. [1]SON-R, [2]WISC-IV, [3]K-ABC, [4]WISC-III, [5]WAIS-R, [6]CFT-1, * in patient A49W (see Suppl. Table S1)

Although the size of the deletion in patients with PMS can vary, the critical region includes a deletion of *SHANK3*, encoding for a scaffold protein in the postsynaptic densities of excitatory synapses (Phelan and McDermid 2012). This gene is known to be involved in the functionality of post-synaptic structures of the CNS (Egger et al. 2016). Leblond et al. (2014) claimed *SHANK* mutations for about 1% of patients with ASD with a specific distribution in terms of the cognitive impairment: *SHANK1* were not significantly present in males with normal IQ; *SHANK2* were also not significantly detectable and only in patients with mild ID. However, *SHANK3* was significantly observable, but in cases with moderate to profound ID. Due to *SHANK3´s* frequency and impact, the authors advised to screen for mutations in clinical practice in individuals with ASD and ID.

Surprisingly, our patient does not show any of the described symptom characteristics of PMS except for ASD, and although our patient carries a large deletion in

this region including the *SHANK3* gene, no intellectual impairment was detected. Since we analyzed only one tissue (i.e., blood) in our patient, we cannot exclude that the observed aberration is present in mosaic or even absent in other tissues. Nevertheless, another study investigated 32 patients with PMS, with ascertained *SHANK3* deficiency (Soorya et al. 2013). 84% of the aforementioned cases met the diagnostic criteria for ASD and 75% for autistic disorder, indicating that this syndrome is one of the more highly penetrant causes of ASD. Since most of the patients (77%) exhibited severe to profound ID this study provides additional evidence on the severity of intellectual, motor, and speech impairments seen in *SHANK3* mutations (Soorya et al. 2013).

Some other genes on the occurred large CNV deletions in patient A10W are discussed: The *FAM19A5* (family sequence similarity 19) gene is expressed in the brain and is possibly related to neuropsychological features, like autistic behavior or general DD (Guilherme et al. 2014). The study by van der Zwaag identified *BRD1* (Bromodomain-containing protein 1) gene in 22q13.33 region as a plausible novel autism candidate gene within the CNV region (van der Zwaag et al. 2009). A study by Prasad et al. (2012) discovered rare variants on the *TYMP* (thymidine phosphorylase) gene, which is also located in chromosome 22q13.33 and it associated with ASD. However, no intelligence description of these ASD patients has been provided. Finally, *PLXNB2* (Plexin B2) and *MAPK8IP2* genes (Mitogen-Activated Protein Kinase 1), both located on 22q13.33, are considered strong candidates for cerebellar phenotypes (Aldinger et al. 2013).

Interestingly, both in patient A10W and in patient A49W, an 8-year-old girl diagnosed with childhood autism (F84.0 according to ICD-10), the gene *PIM3* was deleted. *PIM3,* a proto-oncogene with serine/threonine kinase activity, is located on 22q13.33 and is about 775 kb proximal to the *SHANK3* gene. *PIM3* participates amongst others in the regulation of the circadian rhythm (Mitz et al. 2018). This could possibly explain sleep disturbances often seen in ASD patients. However, currently, no literature is available describing *PIM3* association with ASD or ID.

"Patient A039"

The patient was a 16-year-old boy suffering from atypical autism (F84.1; IQ = 106) without any comorbidity or medication at the time of study participation.

The patient was found to carry a 4.2 Mb large deletion in 3q11.1–q11.2 (hg19 chr3:93519464–97738323) involving 11 genes, 5 OMIM genes. Two genes encompassing the deletion are brain-related genes (Table 2). Furthermore, the patient was carrier of a small 96-kb deletion on 16q24.1 (hg19 chr16:84223309–84319789) encompassing the genes *ADAD2* (Adenosine Deaminase Domain Containing 2) and the brain expressed *KCNG4* (Table 2).

According to DECIPHER, there were 25 and 36 individuals carrying overlapping CNVs (hg19 chr3:93519464–97738323 and hg19 chr16:84223309–4319789, respectively), amongst them 17/20 male, 4/14 female and 4/2 individuals of unknown sex, respectively. There were more female individuals detected with ID or DD (0/9 females, 5/6 males). In contrast, there were only male individuals detected with autistic symptoms (2/3 males, no females). Despite the heterozygote deletion in the current patient, the gene *ARL13B,* also known in Joubert syndrome, an autosomal recessive disorder with partial or complete agenesis of the vermis and characterized by neurological and phenotypical symptoms and ID, could be of interest. Recently, loss of ciliary GTPas Arl13b in interneurons showed impairment in interneuronal morphology as synaptic connectivity leading to altered excitatory/inhibitory activity balance (Guo et al. 2017). Indeed, the excitatory/inhibitory imbalance has been postulated to be one of the mechanisms involved in ASD (Uzunova et al. 2016); therefore, this gene might be linked to the phenotype of our patient.

"Patient A40W"

The patient was a 15.3-year-old male adolescent presenting with atypical autism (F84.1; IQ = 78) with a hyperkinetic conduct disorder (F90.1). He was treated with methylphenidate.

We detected a 1.6-Mb duplication on 7q11.23 (hg19 chr7:72659674–74245599), encompassing 31 genes in total, 24 OMIM genes. Four genes are brain-related (Table 2). The duplication encompasses the Williams–Beuren syndrome (WBS) region, a well-described microdeletion syndrome (Pober 2010b). In contrast, the clinical phenotype caused by the reciprocal duplication is less documented and only few studies to date report duplication of the WBS region (WBCR) (Berg et al. 2007). According to DECIPHER database, 210 individuals were reported to carry overlapping CNVs (hg19 chr7:72659674–74245599), in which 80 were females and 119 were males ($n = 11$ unknown sex). Only seven conferred autistic behavior with more males individuals (male $n = 5$, female $n = 2$), while 92 conferred with ID/DD (male $n = 53$, female $n = 36$, $n = 3$ unknown sex).

In regard to the duplication syndrome, different studies detected children with speech delay including autistic symptoms (Berg et al. 2007b; Van der Aa et al. 2009; Sanders et al. 2011) or without autistic symptoms (Torniero et al. 2007) as well as cognitive dysfunction ranging from ID to normal cognitive abilities (Somerville et al. 2005) or general DD (Depienne et al. 2009). Interestingly, WBS is characterized mostly by a highly social and empathic personality

(Pober 2010a), which contrasts the autistic symptoms observed in the patients with duplications. Our patient fits well into the described phenotypic spectrum of HFA with the autistic presentation and absent cognitive impairment.

"Patient A092"

The patient, a 10-year-old boy, was diagnosed with Asperger syndrome (F84.5; IQ = 124) without any comorbidity, but showed some ADHD symptoms without fulfilling the full diagnosis for ADHD. The patient did not take any medication.

We detected a 1.4-Mb large duplication in 16p13.11 (hg19 chr16:14927356–16328781), encompassing 22 genes in total, 10 OMIM genes. Five were brain-related (Table 2). According to DECIPHER, 437 individuals carry overlapping CNVs, in which 39 individuals with autistic symptoms were found (male $n = 24$, female $n = 10$, $n = 2$ known sex), while ID/DD consisted of 62 females and 85 males ($n = 11$ unknown sex).

Various studies showed that deletions within chr16p13.11 are associated with a variety of neuropsychiatric disorders such as DD and behavioral abnormalities, like ADHD and ASD (Nagamani et al. 2011; Fujitani et al. 2017). Ramalingam and colleagues (Ramalingam et al. 2011) detected duplications within chr16p13.11 in patients with ID and autistic symptoms. In another study, patients with duplications in this region were found with clinical features including difficulties with social interactions, which were comparable with autistic symptoms (Nagamani et al. 2011). Duplication in this region has also been previously described in patients with speech delay and learning difficulties (Hannes et al. 2009).

Interestingly, we found in our patient the same duplication with similar location (chromosome 16p13.11) as Gazzeloone et al. reported in a pediatric patient who suffered from OCD (Gazzellone et al. 2016). However, the duplication in his study was smaller (783 kb) than in our patient. This locus has been associated with neurocognitive disorders like autism and OCD (Gazzellone et al. 2016). Despite our rather small study sample, we found another patient (A044) with overlapping duplication as found in A092 (Table 2). The clinical manifestations of our two patients associated with 16p13.11 duplications are in agreement with the clinical description in previous studies and suggests pathogenicity in the context of ASD (Allach El Khattabi et al. 2018).

"Patient A044"

The 10-year-old boy was diagnosed with Asperger syndrome (F84.5; IQ = 87; details Table 2) with a comorbid OCD and congenital hypothyroidism at the time of investigation. The patient was medicated with methylphenidate and levothyroxine.

Beside a 1.6-Mb duplication on chr16p13.11 (hg19 chr16:14899277–16494783), very similar to the one observed in the patient A092 and discussed above, we detected an additional 8.6-Mb large deletion on 8q24.21–q24.3 (hg19 chr8:131409413–140033208), encompassing 23 genes in total and 14 OMIM genes. Four genes are brain-related.

A case report with a similar deletion described a patient with multiple congenital malformations, mental delay, and seizures (Verheij et al. 2009). According to DECIPHER, 75 individuals were found to have overlapping gene variants similar to hg19 chr8:131409413–140033208 (34 males, 28 females, 13 of unknown sex). There was a predominance of males showing autistic behavior (males $n = 5$; females $n = 0$), or ID or DD (males $n = 13$; females $n = 7$).

A recent genome-wide study performed a quantitative linkage analysis to the autism endophenotype (social responsiveness) and identified two loci on chromosome 8 (Lowe et al. 2015). They detected a peak SNP on chr8q24.22, where *ASAP1* is located. Interestingly, this gene is deleted in our patient as well. Another gene, the *KCNQ3* (Potassium Channel, Voltage-Gated KQT-Like Subfamily Q, Member 3), a brain-related gene, was deleted in our patient A044. In the study by Rauch and colleagues (2012), aberrations involving *KCNQ3* in a few families with ID were reported (Rauch et al. 2012). Moreover, this gene was found to be involved in epilepsy (Miceli et al. 1993). Interestingly, our patient had once a seizure at the age of 12 months that did not reoccur since (till age 15). Curry et al. illustrated two unrelated patients with ID and large homozygous deletions (> 150 kb). One patient with ID showed a deletion in 8q24.2 (Curry et al. 2008). Furthermore, *FAM135B* and *COL22A1* (Tsang et al. 2013), present in the deleted region of our patient, were identified as candidate genes for ASD in some studies, but were not investigated particularly in HFA patients up to now.

"Patient A114"

The patient is a 9-year-old boy presenting with atypical autism (F84; IQ = 87) with comorbid ADHD (F90.0) medicated with methylphenidate, comorbid transient tic disorder (F95.0), and a combined reading and spelling disorder (F81.0).

We detected a 2.2-Mb deletion on 2q37.2 (hg19 chr2:240633456-242783384), encompassing 40 genes in total and 23 OMIM genes. Eight genes were brain-related (Table 2). According to the DECIPHER, 113 individuals conferred with gene variations at the same position as hg19 chr2:240633456-242783384 (male $n = 46$, female $n = 52$, $n = 15$ unknown sex). Nine had autism (male $n = 2$, female $n = 3$, $n = 4$ unknown sex), while 50 conferred ID/DD with

ratio of 0.7 between sexes (male $n=18$, female $n=27$, $n=5$ unknown sex).

This deleted region encompasses the 2q37 deletion syndrome characterized by hypotonia, mild-to-severe ID, DD, and other facial or physical abnormalities and sometimes kidney tumor (Wilms tumor) (Doherty and Lacbawan 1993). The study by Felder et al. (2009) described a patient with 2q37 deletion syndrome (features of Albright Hereditary Osteodystrophy). The deleted region included the following genes *FARP2, HDLBP,* and *PASK* (Felder et al. 2009) (which were deleted in our patient, too), whose expression analyses performed on lymphoblastoid cell lines showed a considerably downregulation. They hypothesized that haploinsufficiency of these genes are possibly responsible for the patient's phenotype (Felder et al. 2009). In our patient, all three genes were affected in the deletion that could explain ASD.

Several genes deleted in the patients A114 have been linked to ASD, ID and/or DD. For example, Wheeler et al. claimed that the deleted region contains next to the coding sequence of *HDAC4* two uncharacterized non-coding RNA sequences like *LOC150935* (contained in the deletion our patient carries). They concluded that haploinsufficiency of *HDAC4* does not cause ID in their patients (Wheeler et al. 2014).

In the study by Imitola et al. (2015), the deleted region was identified in a patient fulfilling the criteria for this above-mentioned syndrome with DD. This deletion contains those genes which are also affected in our patient: *DTYMK, SEPT2, THAP4*, *PPP1R7*, and *STK25*, whereas network analysis revealed that *STK25* was associated with neural development (Imitola et al. 2015). Puffenberger et al. (2012) performed an exome sequencing on two children from the Wisconsin sibship and revealed that the *PRR21* variant cannot be causative for the general DD and ASD of these patients (Puffenberger et al. 2012). The case report by Devillard et al. (2010) described a boy with autism and a deletion of the distal breakpoint at 2q37.3. He showed a cognitive delay (IQ 46–50). High-resolution SNP microarray confirmed the deletion of the gene *OTOS* and *C2orf54* located at 2q37.3 (Devillard et al. 2010). Smith et al. (2001) evaluated four genes mapping in the 2q37.2 region, whereas *GPC1* is the most likely candidate gene for autism (Smith et al. 2001). The patient mentioned in Smith's work showed average score in the intelligence test. The study by Leroy and colleagues (2013) described 14 intellectually deficient patients with a 2.6–8.8 Mb large 2q37 deletion (Leroy et al. 2013). Next to the ID, the patient displayed with morphological and behavioral problems like ASD. They identified candidate genes like *ATG4B, PASK, HDLBP,* and *FARP2*, which were detected in our patient, too (Leroy et al. 2013).

Conclusion

Rare large CNVs have emerged as the major pathogenic factors, amongst others for ASD and ID. To find etiologically relevant factors for social interaction and communication deficits together with restricted and repetitive behaviors, the core defining features of ASD - HFA - was assumed to represent a very specific phenotype for these ASD features. Here we present the results of a high-resolution chromosomal microarray CNV analysis of children and adolescents with HFA, often understudied in ASD genetic studies. Previous studies demonstrated large chromosomal aberrations in ASD to be associated with ID.

In the present study, the patients suffered from high-functioning ASD without ID. Surprisingly, we detected in six patients large CNVs, up to now associated with ID and additional features. A limitation of this study is the fact that only one tissue type per patient was analyzed (peripheral blood, or saliva). Therefore, we cannot exclude that the abnormalities observed are in reality mosaics, a feature that might explain the absent of ID and of other malformations in our patients. Another limitation of this study is that no genetic data from the parents were available and it was not possible to assess whether the CNVs are de novo or inherited.

Comparable to other studies conducted in early onset OCD patients (Grünblatt et al. 2017) and HFA (Gilman et al. 2011), in the present investigation, brain-associated CNVs were significantly more often seen in HFA compared to controls and thus confirm the previous findings. Our detailed discussion of the individual findings further illustrates the phenotypes associated with such CNVs and helps to improve genetic counseling in affected families.

In summary, this study suggests that large CNVs can be associated with autistic symptoms seen in HFA. Thus, our results indicate that a large number of structural variants like CNVs might still be unreported in psychiatric disorders in general and especially for HFA.

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Author contributions AW and EG drafted the manuscript, performed literature search and worked on the interpretation of the data. EG participated in the study design and performed the statistical analysis. BO planned and carried out the genetic studies, worked on the interpretation of the data, and revised the manuscript. EB was involved in the clinical design, recruitment and acquisition of clinical data in Zurich. RG was involved in the supervision of the acquisition of the clinical data in Zurich and was involved in the interpretation of data. RT was involved in the clinical acquisition of data in Würzburg and interpretation of data and revised the manuscript. MR was responsible in the clinical acquisition of data in Würzburg. AR was responsible for the CNV study design, the interpretation of the data and revised

the manuscript. SW was responsible for the underlying clinical study design, initiated and created together with AR the CNV study; she was involved in the interpretation of data and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials The data sets generated and/or analyzed during the current study are not publicly available due to limits in consents, but are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest SW has received in the last 5 years royalities from Thieme Hogrefe, Kohlhammer, Springer, Beltz. SW has received lecture honoraria from Opopharma in the last 5 years. Her work was supported in the last 5 years by the Swiss National Science Foundation (SNF), diff. EU FP7s, HSM Hochspezialisierte Medizin of the Kanton Zurich, Switzerland, Bfarm Germany, ZInEP, Hartmann Müller Stiftung, Olga Mayenfisch, and Gertrud Thalmann Fonds. Outside professional activities and interests are declared under the link of the University of Zurich www.uzh.ch/prof/ssl-dir/interessenbindungen/client/web/. AR was supported by the Swiss National Science Foundation, E-rare, and Von Sick foundation. Outside professional activities and interests are declared under the link of the University of Zurich https://www.uzh.ch/prof/ssl-dir/interessenbindungen/client/web/R. The other authors declare no conflict of interest.

Ethical approval and consent to participate All procedures were performed with the written informed consent of the parents of all participants and the study was approved by the local ethics committees of the Canton of Zurich (Switzerland, E-36/2009), and of Würzburg (Germany, study numbers 8/06 and 227/09), respectively.

Consent for publication The aforementioned consent form includes publication consent as well.

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