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A novel 3q29 deletion associated with autism, intellectual disability, psychiatric disorders and obesity.

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ABSTRACT

Copy number variation (CNV) has been associated with a variety of neuropsychiatric disorders, including intellectual disability/developmental delay (ID/DD), autism spectrum disorder (ASD), and schizophrenia (SCZ). Often, individuals carrying the same pathogenic CNV display high clinical variability. By array-CGH analysis, we identified a novel familial 3q29 deletion (1.36 Mb), centromeric to the 3q29 deletion region, which manifests with variable expressivity. The deletion was identified in a three years old girl diagnosed with ID/DD and autism and segregated in six family members, all affected by severe psychiatric disorders including schizophrenia, major depression, anxiety disorder and personality disorder. All individuals carrying the deletion were overweight or obese, and anomalies compatible with optic atrophy were observed in three out of four cases examined.

Amongst the ten genes encompassed by the deletion, the haploinsufficiency of Optic Atrophy 1 (*OPA1*), associated with autosomal dominant optic atrophy, is likely responsible for the ophthalmological anomalies. We hypothesize that the haploinsufficiency of ATPase type 13A4 (*ATP13A4*) and/or Hairy/Enhancer of Split *Drosophila* homolog 1 (*HES1*) contribute to the neuropsychiatric phenotype, while *HES1* deletion might underlie the overweight/obesity.

In conclusion, we propose a novel contiguous gene syndrome due to a proximal 3q29 deletion variably associated with autism, ID/DD, psychiatric traits and overweight/obesity.

INTRODUCTION

Copy number variation (CNV) is a common form of genetic variation in the human genome (Zarrei et al. 2015) and presents as a continuous spectrum from population polymorphisms to severe Mendelian conditions (Sebat et al. 2004; Zarrei et al. 2015). Variable expressivity is a common finding amongst patients sharing a pathogenic CNV, and deletions or duplications of a given region may be associated with distinct or mirror phenotypes (Jacquemont et al. 2011; Weischenfeldt et al. 2013). Recently, an increased burden of large (>500 kb), rare (<1%) CNVs has been identified in an array of neuropsychiatric disorders (Sullivan et al. 2012). The most frequently detected are 22q11 deletions, and deletions/duplications at 1q21, 15q11, and 15q13 (International Schizophrenia 2008; Kirov et al. 2009a; Stefansson et al. 2008). More recently, 17q12 deletions (Moreno-De-Luca et al. 2010), 3q29 deletions/duplications (Levinson et al. 2011; Mulle et al. 2010) and 16p11 deletions/duplications (McCarthy et al. 2009) have been identified.

Several neuropsychiatric phenotypes are associated with CNV, including bipolar disorder, (Green et al. 2015; Malhotra et al. 2011), schizophrenia (SCZ) (International Schizophrenia 2008; Kirov et al. 2012; Malhotra et al. 2011; Stefansson et al. 2008) and autism spectrum disorder (ASD) (Levy et al. 2011; Marshall et al. 2008; Pinto et al. 2014; Pinto et al. 2010; Sanders et al. 2011; Sebat et al. 2007). In particular, *de novo* CNVs have a high burden on the genetic risk for these disorders (Malhotra et al. 2011; Pinto et al. 2010; Sanders et al. 2011; Xu et al. 2008). Most of the pathogenic variants span many genes, but smaller variants are emerging and are pinpointing specific genes, for example Neurexin 1 (Kirov et al. 2009b; Pinto et al. 2010; Rujescu et al. 2009).

Some CNVs found in SCZ and bipolar disorder are also detected in individuals affected by neurodevelopmental disorders, such as Intellectual Disability/Developmental Delay (ID/DD), ASD, Attention Deficit Hyperactivity Disorder (ADHD) and epilepsy. For example, the "chromosome 3q29 deletion syndrome" (MIM609424), discovered in a cohort of patients with ID/DD and minor facial dysmorphisms, was later associated with ASD, bipolar disorder and depression/anxiety

(Quintero-Rivera et al. 2010). The genes and molecular pathways shared between these conditions are supporting the concept that psychiatric disorders have also a neurodevelopmental origin.

Here, we report a four-generation family segregating a 3q29 deletion proximal to the known 3q29 deletion/duplication syndrome, which presents with a variable neuropsychiatric phenotype including ASD, ID and SCZ, obesity and frequent ophthalmological disturbances.

MATERIALS AND METHODS

Patients and genomic DNA extraction

Clinical information from all patients involved in the study was collected by experienced psychiatrists and clinical geneticists. Informed consent was obtained from patients or their legal representative. Genomic DNA was extracted from peripheral blood using the QIAamp DSP DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. DNA quality was assessed using NanoDrop 1000 Spectrophotometer (ThermoScientific, Wilmington, DE, U.S.A.).

Molecular analyses

Array-CGH was performed using a 44K whole-genome oligonucleotide microarray following the manufacturer's protocol (Agilent Technologies, Santa Clara, California, USA). Briefly, 500 ng of genomic DNA was digested with *AluI* and *RsaI* and labelled with cyanine 3-dUTP (proband) cyanine 5-dUTP (control subject). Pooled DNAs were denatured and hybridized on the macroarray for 24 hours at 65°C. Slides were washed and scanned using a G2565BA scanner, and analyzed using Agilent CGH Analytics software ver. 4.0.81 (Agilent Technologies Inc.) with the statistical algorithm ADM-2 and a sensitivity threshold of 6.0. Significant copy number changes were identified by at least three consecutive aberrant probes. The pathogenicity of the CNVs identified by array-CGH was evaluated based on the findings in the Database of Genomic Variants (DGV, http://projects.tcag.ca/variation), the ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/) and the

Database of Chromosomal Imbalance and Phenotype in Humans using Ensemble Resources (DECIPHER, https://decipher.sanger.ac.uk/application/).

Real-time quantitative PCR was performed to confirm array-CGH data. We designed a set of primers and probes specific for exon 30 of *OPA1* gene (ref seq NM_130837) using the Roche Diagnostics Universal probe Library software (http://www.universalprobelibrary.com). Amplification was performed in a total volume of 20 µl containing 2X TaqMan Universal PCR Master mix (P/N 4324018, Life Technologies, CA, USA), 1X RNaseP assay (20X, VIC dye), 0.2 µM of forward (5'- cgttaggctttctgttaatagtggt – 3') and reverse (5'- tgtcataatccggtggctct – 3') primers and 0.1 µM UPL probe #2. Each sample was run in triplicate using the following protocol: 2 min at 50°C, 10 min at 95°C, followed by 40 cycles 15 sec 95°C and 1 min 60°C. The PCR was performed on a 7500 fast apparatus (Life Technologies). The copy number was calculated using the comparative delta Ct method.

RESULTS

Clinical description

The proband was a 3 year old girl referred to the Pediatrics Genetic Unit for severe DD and ASD. Pregnancy was reported as normal, except for a positive Wald test; fetal karyotype performed on chorionic villus sampling was normal (46,XX). She was born by spontaneous delivery at term; birth weight was 3,120 gr (25^{th} centile), length 50 cm (50^{th} centile), OFC 35 cm (75^{th} centile), and APGAR scores 9/10. She suffered from gastroesophageal reflux and milk protein intolerance since the first months of life. She reached motor milestones within expected range (independent walking 14 months). She was initially referred to the Neuropsychiatric Service for language delay at the age of 30 months. After further evaluation with ADOS, CARS and Vineland Adaptive Behavior scales, the patient was diagnosed with severe autism accompanied with cognitive delay (ADOS module 1: communication score 9, reciprocal social interaction score 12; CARS score 39; Vineland Adaptive Behavior scale: age-equivalent score 20 months *versus* chronological age of 4 years). Brain MRI,

EEG, tonal audiometry, standard karyotype and FRAXA testing were all normal. On clinical examination, she showed no evident facial dysmorphisms and a normal growth pattern (weight 14 kg, 50th centile, height 95 cm, 50th centile, OFC 48.5 cm, 25th centile). Cardiological exams and thyroid function were normal. The patient was included in a protocol for clinical follow-up, and we performed array-CGH analysis (see molecular data below).

At the last clinical evaluation (9-year old), she showed severe cognitive delay (Griffith scale total quotient = 34), motor stereotypies and bruxism; language was absent and she communicated by Augmentative and Alternative Communication. She also showed infantile obesity (weight 53 kg, height 138 cm, BMI 27.8) with *acanthosis nigricans* on the neck and armpits. Parents reported selective eating with no hyperphagia, constipation, nocturnal awakenings and occasional self-injuries.

Family history was remarkable for psychiatric and ophthalmologic disorders (Figure 1 and table I). Two maternal aunts and a brother of the maternal grandmother were institutionalized for schizophrenia (III-4 undifferentiated schizophrenia, III-5 paranoid schizophrenia, II-3 schizoaffective disorder). The mother (subject III-6) had experienced an episode of major depression and suffered from anxiety disorder. Anxiety disorder was reported also for the great-grandmother (subject I-2). Formal neuropsychiatric evaluation indicated ASD, social anxiety and borderline personality disorder in subject III-1, and dysthymia, avoidant personality disorder and microcephaly in subject II-2. Learning disabilities were reported for patients II-3 and III-4 and both had not completed the lower secondary school.

Evaluation of non-carriers (subjects III-2 and III-3) indicated no cognitive or psychiatric disorder. Another consistent phenotype was overweight/obesity, which was present in all carriers of the deletion but not in non-carriers (Table I).

Since the deletion spans *OPA1*, a gene associated with an autosomal dominant syndromic form of optic atrophy (MIM#165500) (see molecular data below), we performed a formal ophthalmologic

and audiological examination in four subjects (II-2, III-1, III-6 and IV-2). Given the profound behavioral disturbances of proband (IV-2), we were able to assess solely the auditory brainstem response (ABR) and *fundus oculi* and both were normal. The three remaining subjects underwent a complete ophthalmological evaluation, including visual acuity, visual field testing with Humphrey Field Analyzer (HFA), Visual Evoked Cortical Potentials (VECPs), contrast sensitivity, retinal Optical Coherence Tomography (OCT), analysis of optic nerve with the Glaucoma Diagnosis instrument (scanning laser polarimeter; GDx) and OCT nerve fiber layer, Cup-to-Disc (CD) ratio. We detected in all patients an optic disc pallor involving the temporal area with cup to disc ratio > 0.5, a feature observed in 50% of patients with dominant optic atrophy (Votruba et al. 2003), and associated with OCT nerve fiber layer borderline to lower than normal in II-2 and III-6. Audiometry measures were normal in all subjects (II-2, III-1 and III-6).

Molecular analyses

Array-CGH analysis identified a 1.36 Mb deletion on chromosome 3q29 (position 193,046,853-194,407,385, assembly GRCh17/hg19) encompassing 10 RefSeq coding-genes: *ATP13A4*, *OPA1*, *HES1*, *CPN2*, *GP5*, *LRRC15*, *ATP13A3*, *TMEM44*, *FAM34A* and *LSG1*. To validate the deletion identified by array-CGH, we performed real-time qPCR in all available subjects of the family (Fig. 1B). The deletion was inherited from the mother (III-6), and was present in the maternal uncle (III-1), two maternal aunts (III-4), the maternal grandmother (II-2), and her brother (II-3).

Using the online databases (ClinVar, Database of Genomic Variants, DECIPHER, Ecauruca and PubMed), we found other cases with syndromic ID/DD that overlap with the deleted region we identified: six large deletions (two from DECIPHER, each of 9 Mb: 256994 and 4430, and four from ClinVar: nssv577933, nssv577935, nssv582956 and nssv1494859) and fifteen large duplications (two from DECIPHER: 252539, 249410, and thirteen from ClinVar: nssv584484, nssv578943, nssv578945, nssv578946, nssv578949, nssv578951, nssv578952, nssv578953, nssv578954, nssv578955, nssv582491, nssv1494856 and nssv1494861).

DISCUSSION

The 3q29 microdeletion syndrome is a recurrent subtelomeric 1.3-1.6 Mb deletion, which encompasses more than 20 protein-coding genes (Willatt et al. 2005). Its variable clinical manifestations include intellectual deficit and/or learning disabilities with speech delay and mild dysmorphic features (Cox and Butler 2015; Digilio et al. 2009; Willatt et al. 2005). This deletion and its duplication counterpart belong to a growing group of CNVs associated both with psychiatric disorders and ID/DD. Indeed, a recent meta-analysis showed a 41.1-fold increased risk for SCZ, showing that the 3q29 deletion may be the single largest risk factor for SCZ, exceeding even the 22q11.2 deletion (Mulle 2015). Three genes, *FBXO45* (MIM 609112), *DLG1* (MIM 601014), and *PAK2* (MIM 605022), have been proposed as causative of the psychiatric manifestations, because they play putative roles in synaptic transmission (Quintero-Rivera et al. 2010).

We identified a 1.36 Mb deletion centromeric to this region, and showed that is also associated with ASD, ID/DD, psychiatric traits with variable expressivity, as well as with overweight/obesity. Similar to the 3q29 microdeletion syndrome, the familial deletion we identified manifests with heterogeneity in the neuropsychiatric phenotype. The rearrangement segregated from the mother, affected by anxiety disorder and major depression, and was present in five additional family members, all displaying psychiatric disturbances, such as schizophrenia, anxiety and personality disorders. The father and three other members of the maternal family did not show psychiatric traits and did not carry the deletion. Two carriers of the deletion were diagnosed with ASD: the child proband (IV-2) and an adult (III-1). The observation that the adult ASD patient has borderline personality disorder and social anxiety in comorbidity) raises the intriguing possibility that the 3q29 deletion might undergo a phenotypic transition during development, as documented for patients with the 22q11.2 deletion syndrome (Swillen and McDonald-McGinn 2015). Longitudinal follow-up of the proband will help elucidating the developmental trajectory of the 3q29 proximal deletion.

An alternative hypothesis is variable intra-familial expressivity. A shared basis for SCZ and ASD has been suggest almost half a century ago (Ornitz 1969), and is supported by similar neuropsychological profiles (e.g., Theory of mind and mirror neuron function deficits) (Baron-Cohen et al. 1985; Enticott et al. 2008; Lysaker et al. 2011; Rizzolatti and Craighero 2004; Rizzolatti and Fabbri-Destro 2010), alterations in brain cytoarchitecture al organization (e.g., proliferation, migration and lamination defects) (de Lacy and King 2013), neuroimaging patterns (Avino and Hutsler 2010; Baribeau and Anagnostou 2013; Cauda et al. 2014; Cauda et al. 2011; Cheung et al. 2010; Eastwood and Harrison 2003; Mueller et al. 2012; Venkataraman et al. 2012; Walterfang et al. 2008), and genetic overlap (Cross-Disorder Group of the Psychiatric Genomics et al. 2013; De Rubeis et al. 2014; Fromer et al. 2014). SCZ and high functioning ASD show a high degree of clinical convergence, particularly in SCZ cases with negative symptoms, and differential diagnosis requires experienced skills (Keller 2015; Luciano et al. 2014; Spek et al. 2010). Mild neurological signs in Asperger's syndrome are not different from early-onset psychosis (Mayoral et al. 2010) and an overlap of autistic and schizotypal traits in adolescence has been described (Barneveld et al. 2011). Both may share cognitive impairment, and motor symptoms, including catatonia (Nylander et al. 2013). Some autistic subjects develop a clinical course indistinguishable from SCZ in adolescence and, on the other hand, childhood onset schizophrenia is preceded by and comorbid with ASD in 30%-50% of cases (Rapoport et al. 2009). Anxiety disorders are also frequent in ASD (Mazefsky et al. 2008). Finally, genes with *de novo* mutations in SCZ overlap with those mutated in ASD (De Rubeis et al. 2014; Fromer et al. 2014) and ASD and SCZ share risk genes important brain development and physiology, e.g., *SHANK3* (Bozdagi et al. 2010; Kozol et al. 2015), *SCN2A* (Gazina et al. 2015; Hu et al. 2009), *NRXN1* (Sudhof 2008), and *RELN* (D'Arcangelo et al. 1995).

The 3q29 proximal deletion syndrome here described may link the phenotypic psychotic dimension (schizophrenic spectrum disorder), the avoidant dimension (anxiety, social phobia, avoidant personality) and ASD.

Among the genes spanned by the deletion, only *OPA1* mutations cause a Mendelian disorder, the autosomal dominant optic atrophy type 1, and its haploinsufficiency explains the typical profile with bilateral symmetrical thinning around the optic disc, most pronounced in the temporal quadrant (Hudson et al. 2008), observed in the 3q29 proximal deletion carriers. This feature is consistent with the retinal ganglion cell atrophy typical for *OPA1* deletion, and it co-occurred with abnormal contrast sensitivity indicative of optic nerve dysfunction. The visual field, another index of optic nerve dysfunction, did not have extensive damage.

The neuropsychiatric and cognitive phenotype likely resulted from the haploinsufficiency of *ATP13A4* and/or *HES1*. *ATP13A4* (MIM609556) encodes a cation transporter ATPase of the P5 family and was reported as disrupted by an inversion in a female with specific language impairment having significant deficits in both expressive and receptive language abilities but intact cognitive function (Kwasnicka-Crawford et al. 2005). The inversion was inherited from her father, who was also language delayed (Kwasnicka-Crawford et al. 2005). Our patient is not verbal. The behavioral phenotype of the patient with the inversion is milder that the one we observed: she had delayed expressive and receptive language and exhibited some difficulties in communication and social interaction, but did not show stereotyped behaviors or restricted interests. She was not classified on the autism spectrum. A mutational screening also detected a missense variant (p.Glu646Asp) in 6 out of 32 individuals affected by ASD, although the pathogenicity of this variant remains unclear (Kwasnicka-Crawford et al. 2005). The neuronal functions of ATP13A4 have not been investigated yet, but *ATP13A4* expression in mouse brain increases during neurogenesis suggesting that it might be critical in early neuronal development (Vallipuram et al. 2010; Weingarten et al. 2012). Overexpressing *ATP13A4* in a cell line causes an increase in intracellular calcium, and the

p.Glu646Asp amino acid change identified in subjects with ASD suppresses such affect (Vallipuram et al. 2010). These data suggests that ATP13A4 might regulate calcium homeostasis. Noteworthy, calcium channels and regulators of calcium homeostasis have been repeatedly implicated in ASD, ID and schizophrenia (De Rubeis et al. 2014; Endele et al. 2010; Purcell et al. 2014; Ripke et al. 2013; Splawski et al. 2004). Interestingly, another P5 ATPases is encompassed by the 3q29 deletions we identified (*ATP13A3*), but no evidence supports a role for this gene in ASD or other psychiatric conditions. Recently, a *de novo* 3q29 duplication partially overlapping with the region in the 3q29 proximal deletion in a patient with oculo auriculo vertebral spectrum (OAVS, OMIM 164210) was reported and *ATP13A3* suggested as candidate gene (Guida et al. 2015).

A second gene within the deleted region, Hairy/Enhancer of Split *Drosophila* homolog 1 (*HES1;* MIM*139605), was shown to be involved in neuronal migration, oligodendrocytes maturation, and in cochlear neuroepithelium proliferation (Aujla et al. 2011; Ogata et al. 2011; Tateya et al. 2011). *HES1* has been suggested to be a candidate for ASD by association studies (de Krom et al. 2009; Lasky-Su et al. 2008), and might represent a promising candidate gene for the neuropsychiatric phenotype observed in the family. We speculate that mutations in *ATP13A4 or HES1* may associate with a psychiatric phenotype, suggesting a screening among patients with psychiatric disorders.

Several observations indicate that HES1 plays a complex role in the regulation of metabolism. HES1 is a downstream target of Notch and mediates preadipocytes differentiation in white adipocytes (Bi et al. 2014), indicating that HES1 loss or downregulation might reduce white adipocytes differentiation and thus prevent weight gain. However, decreased hepatic expression of *HES1* underlies hepatic steatosis (Lemke et al. 2008), which is intimately associated with obesity. Furthermore, HES1 regulates the maintenance and differentiation of neuronal progenitors of the hypothalamic arcuate nucleus, which contributes to regulate feeding, energy balance and body size: mice lacking a critical co-factor of Notch and regulator of HES1 have abolished HES1 expression and show increased body weight (Aujla et al. 2013). The latter evidence supports the hypothesis

that the overweight/obesity phenotype associated with the 3q29 proximal deletion might be due to altered development of the arcuate nucleus resulting from HES1 haploinsufficiency.

We cannot exclude that the deletion here described is causing a "position effect", with a mechanism known as enhancer adoption. We recently showed this mechanism may cause a rare neurodegenerative disease, disrupting regulatory boundary elements (Giorgio et al. 2015). Indeed, almost 12% of the deletions reported in Decipher are best explained by enhancer adoption or a combination of enhancer adoption and gene-dosage effects. In analogy, we can take in consideration that the two nearby deletions in 3q29 may share a common genetic mechanism .as recently demonstrated for other copy number variations (Ibn-Salem et al. 2014).

In conclusion, our data suggest a novel contiguous gene syndrome with optic nerve atrophy due to *OPA1* and neuropsychiatric features associated with overweight/obesity associated with *ATP13A4* or/and *HES1*.

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FIGURES LEGENDS

Figure 1. Genealogical tree, qPCR results and the 3q29 deleted region identified. In panel A the pedigree of the family is depicted. Filled symbols indicate affected subjects; a short line above the symbol indicates available genomic DNA, while the arrow indicates the proband. Panel B shows gene quantification (*OPA1*) by real-time PCR on eight members of the family. In panel C the region deleted is reported with the nearby canonical 3q29 deletion defined between *TRFC* and *DLG1* gene (~195.7-197.3 Mb, hg19)(Cox and Butler 2015). Protein-coding genes are indicated as arrows, based on UCSC Genome Browser GRCh37/hg19 human assembly.

Figure 1

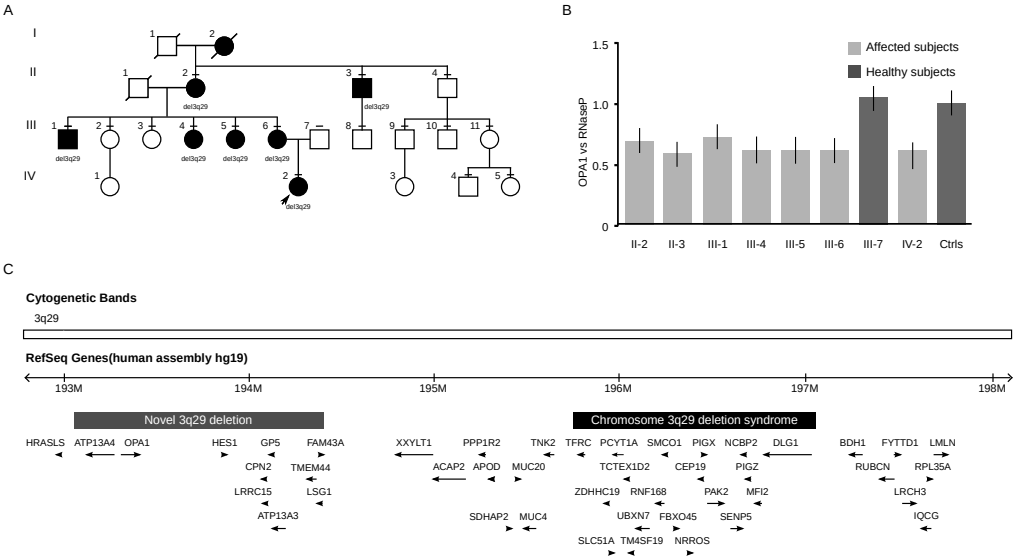
A
I
II
III
IV
del3q29
B
Affected subjects
Healthy subjects
OPA1 vs RNaseP
1.5
1.0
0.5
0
II-2
II-3
III-1
III-4
III-5
III-6
III-7
IV-2
Ctrls
C
Cytogenetic Bands
3q29
RefSeq Genes(human assembly hg19)
193M
194M
195M
196M
197M
198M
Novel 3q29 deletion
Chromosome 3q29 deletion syndrome
HRASLS ATP13A4 OPA1
HES1 GP5 FAM43A
CPN2 TMEM44
LRRC15 LSG1
ATP13A3
XXYLT1 PPP1R2 TNK2
ACAP2 APOD MUC20
SDHAP2 MUC4
TFRC PCYT1A SMCO1 PIGX NCBP2 DLG1
TCTEX1D2 CEP19 PIGZ
ZDHHC19 RNF168 PAK2 MFI2
UBXN7 FBXO45 SENP5
SLC51A TM4SF19 NRROS
BDH1 FYTTD1 LMLN
RUBCN RPL35A
LRCH3
IQCG

Figure 2

Table I. Phenotypic features of patients with 3q29 deletion.

	II-2	**II-3**	**III-1**	**III-4**	**III-5**	**III-6**	**IV-2**
Age[a]	72 yrs.	70 yrs.	38 yrs.	39 yrs.	40 yrs.	48 yrs.	9 yrs.
DD/ID	No	Yes	No	Yes	No	No	Yes
Psychiatric disorder	Dysthymia, Avoidant Personality Disorder	Schizoaffective disorder	ASD, Border-line personality disorder, social anxiety disorder	Undifferentiated schizophrenia	Paranoid schizophrenia	Anxiety disorder, Major depression	Autism
Microcephaly	Yes	No	No	No	Yes	No	No
Optic atrophy	Yes	n.a.	Yes	n.a.	n.a.	Yes	n.a.
Hearing loss	Yes	Yes	No	n.a.	n.a.	No	No
BMI	32 (Obese)	n.a. (Overweight)	29.2 (Overweight)	33.6 (Obese)	30.5 (Obese)	29.4 (Overweight)	27.8 (Overweight)
Other	Bilateral inguinal hernia Uterine fibroma Hypertension	Lumbar scoliosis Hypothyroidism BPCO					Constipation