Cases With Only Variants Classified as VUSs

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Patient PPC-2 was a 32-year-old male diagnosed with schizophrenia, disorganized type with a chronic course. The first episode of psychosis occurred at age 15. The patient completed an 11th grade education. WAIS-III-R testing revealed a VIQ of 75, PIQ of 79, and FSIQ of 75. The patient was noted to have an elongated face and pectus excavatum. Medical history was only notable for psychogenic polydipsia. MRI revealed fronto-parietal white matter foci; cerebral and cerebellar atrophy; cavum septum pellucidum; asymmetric prominence of the lateral ventricles; pointing and prominence of the 4th ventricle. Palatal assessment revealed a submucous cleft palate. We identified a 343 Kb duplication on the long arm of chromosome 22 (22q13.22), containing *FLJ44385* and *C22orf34*. These genes are not known to be associated to the phenotype.

Patient PPC-11 was a 40-year-old male who had his first psychotic episode at age 18 and subsequently received a diagnosis of undifferentiated schizophrenia with a chronic course of illness. The patient was also diagnosed with intellectual disability as a child and attended special education classes. WAIS-III-R testing revealed a VIQ of 68, PIQ of 65, and FSIQ of 64. Dysmorphic features include a sloping forehead; protruding supra-orbital ridges; square nasal root with a bulbar nose and wide nasal tip; short philtrum; retrognathia; malar flatness and a short and broad sternum. Palatal assessment revealed a submucous cleft palate. We identified a 2.11 Mb duplication on the short arm of chromosome 16 (16p12.3) containing *NPIPA7, NPIPA8, PKD1P6-NPIPP1, NOMO2, RPS15A, ARL6IP1* (associated with autosomal recessive spastic paraplegia (1), *SMG, TMC7, COQ7* (associated with autosomal recessive coenzyme Q10 deficiency (2)), *ITPRIPL2, SYT17, TMC5, GDC1, CCP110, C16ORF62, IQCK, GPRC5B,* and *GRP139*.

Patient PPC-15 was a 42-year-old female with a diagnosis of undifferentiated schizophrenia with a chronic course and with prolonged hospitalization (>20 years). WAIS-III-R testing revealed a VIQ of 61, PIQ of 69, and FSIQ of 61. The patient only completed a 9th grade education and was never able to work due to her mental illness. The patient was noted to have a high nasal root protrusion and kyphosis. Medical history is notable for psychogenic polydipsia with hyponatremia and a history of seizures secondary to hyponatremia. MRI revealed asymmetric prominence of lateral ventricles; prominent left Sylvian fissure; prominence of cerebrospinal fluid (CSF) space adjacent to superior parietal lobule. Palatal assessment did not reveal any abnormalities. We identified a 237 Kb duplication on the short arm of chromosome 4 (4p16.3-16.2) containing *STX18* responsible for intracellular transport (3) and *STX18-AS*.

Patient PPC-16 was a 48-year-old male diagnosed with paranoid schizophrenia with a chronic, unremitting course. The patient's first episode of psychosis occurred at the age of 18. The patient graduated high school, after which he joined the U.S. Navy but was discharged 9 months after enrollment due to a first-episode psychosis. The patient reportedly had normal developmental milestones and his medical history is notable for mitral valve prolapse with mitral regurgitation, status post repair and seizures that have occurred exclusively in the context of treatment with clozapine. The patient is noted to have narrow orbital fissures, retrognathia, protruding supra-orbital ridges and pectus excavatum. Neuropsychological testing was not done since the patient was not willing to participate. Palatal assessment was not performed. We identified a 499 Kb duplication on the long arm of chromosome 6 (6q26) containing *PARKIN* which is associated with autosomal recessive early-onset Parkinson's disease (4) and *PACRG* which is the PARKIN-coregulated gene (5).

Patient PPC-18 was a 36-year-old male with a diagnosis of schizoaffective disorder, characterized by a chronic course with continued loss of functional capacity. The patient was first evaluated by a psychiatrist at age 14 for psychotic symptoms and was first hospitalized at age 18. The patient graduated high school and completed 6 months of college after which he dropped out. The patient never worked and has been living in a residential treatment facility. WAIS-III-R testing revealed a VIQ of 92, PIQ of 83, and FSIQ of 90. Medical comorbidity was notable for hypothyroidism, psychogenic polydipsia with hyponatremia, chronic neutropenia, hiatal hernia and obesity. In terms of dysmorphisms, the patient was noted to have a high/protruded nasal root and with flat nasal alae; diminished vermillion of the upper lip, clefted nasal tip as well as mild midline cleft of lower lip; hypoplastic teeth (upper and lower jaw), hyoplastic earlobes, slender, tapered ('carrot-like') fingers. Palatal assessment revealed a high-arched, V-shaped, steepled submucous cleft palate. We identified a 510 Kb duplication on the short arm of chromosome 2 (2p21) containing *SRBD1*. This gene is not known to be associated with the phenotype.

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Patient EMC-1 was a 34-year-old male diagnosed with bipolar II disorder and substance abuse. With a full-scale IQ of 76, he classified as having borderline intellectual functioning. Dysmorphological and physical examination of our patient indicated a high forehead, upslanted palpebral fissures, epicanthic fold, flat philtrum, downturned corners of the mouth, carious dentition, and an asymmetrical and prominent jaw. Furthermore, he had edema of the lower legs and central obesity. The patient had a 238 Kb deletion on the short arm of chromosome 5 (5p13.3), harboring the majority of *WDR70*. The clinical implication of this variant is uncertain. Five patients have been

previously described with 5p13 duplication syndrome which included developmental delay, intellectual disability, congenital abnormalities and facial dysmorphology, however in only one case was *WDR70* in the duplication region (OMIM #613174).

Patient EMC-4 was a 37-year-old male who suffered from PDD-NOS, PTSD, and psychotic disorder NOS. He had mild intellectual disability with a full-scale IQ of 69. Our patient had hypertelorism, broad palpebral fissures, brushy eyebrows, synophrys, a prominent nose tip, narrow upper lip, an edentate upper jaw, and dysplastic helices of the ear. Furthermore, he had increased lordosis and kyphosis, mild pectus excavatum, aberrant scar formation, striae on the upper legs, no hypermobility (i.e., a Beighton Hypermobility Score of 2/9), a slim posture, and a hypotrophic muscular system, with normal body length and skull circumference. Genotyping relevaled a 481 Kb duplication on the short arm of chromosome 7 (7p22.3), containing *FAM20C*. No patients with this duplication are described in the structural variant databases with this duplication. Autosomal recessive loss-of-function mutations of *FAM20C* in this gene cause Raine Syndrome, a rare autosomal recessive form of osteosclerotic bone dysplasia (OMIM #259775). The functional effect of *FAM20C* duplication is unclear. Agiropoulos and colleagues describe a patient with intellectual disability, short stature, microcephaly, and dysmorphic features that was found to have both a chromosome 7 *de novo* terminal deletion and a chromosome 7 terminal duplication which included *FAM20C* (6).

Patient EMC-21 was a 43-year-old male with a diagnosis of autistic disorder, depressive disorder, and OCD. The patient had borderline intellectual functioning, with a full-scale IQ of 82. He was obese, had narrow palpebral fissures, hypoplastic alae nasi, a high palate, long ears, hernia umbilicalis, panniculus, thoracic kyphosis, and had long hands and feet. Body weight was 2 SDs above the mean. We identified a 236 Kb duplication on the long arm of chromosome 5 (5q21.1) containing *FAM174A*. *FAM174A* is abundantly expressed in all organ systems, including the brain.

Patient EMC-30 was a 50-year-old female with a diagnosis of brief psychotic disorder and mild intellectual disability with a full-scale IQ of 64. Our patient had a long hypotonic face, exophthalmos, a full nose tip, a hallux valgus (right>left), and thoracic kyphosis. Genotyping revealed a 1.7Mb deletion on the long arm of chromosome 13 (13q33.3) containing *FAM155A, LIG4, ABHD13, and TNFSF13B*. No patients with a similar loss have been described in the DECIPHER database. Homozygous mutations in *LIG4* are associated with *LIG4* syndrome/Nijmegen breakage syndrome that includes facial dysmorphisms, developmental delay, and immunodeficiency (7).

Supplementary References

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