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Obsessive-Compulsive Disorder and Chromosome 2 Duplication (2q14.2-q21.1)

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The exact etiopathogenesis of obsessive-compulsive disorder (OCD) remains unknown. Genetic inputs are involved in the new era of psychiatry, allowing a better understanding of the mechanisms of psychiatric disorders.[1] Although environmental factors are involved, several genetic abnormalities have been associated with the disorder.[2]

Case Report

Here we report the first case of chromosome 2 duplication (2q14.2-q21.1) in a 29-year-old woman with OCD. Supplementary Material Topic 1 provides the biological significance of the genetic finding and how rare it is, and Topic 4 lists the genes found at the chromosome 2 duplication 2q14.2-q21.1. The patient was observed for the first time by the authors at the age of 29 after her admission to the emergency department due to suicidal ideation, sadness, and cleaning compulsions. The symptoms had several weeks duration and had increased in intensity in the 20 days before the admission. She also reported feeling anxious and having intrusive thoughts of fear of contamination. She was spending 4 to 5 hours a day cleaning all her personal belongings, such as coins, bills, cell phone, laptop, and dishes with subsequent wounds on both her hands and forearms. She would hoard large sums of newspapers, magazines, and leftover food in her dresser. Typical behavior of kleptomania was also described, such as stealing chocolates, gum, and magazines from the local supermarket. There were no changes in the flow, form, or possession of thoughts or evidence of perceptual changes.

The physical examination showed facial dimorphism, overweight (body mass index of 26 kg/m^2), and the skin lesions previously described. Table 1 summarizes her medical history, including the diagnoses of congenital adrenal hyperplasia (CAH), mild intellectual disability, and depressive symptoms. The psychiatric symptoms of CAH are shown in Supplementary Material Topic 2.

The standard diagnostic tests were unremarkable. She was then admitted to the psychiatric ward and treated with paroxetine (40 mg once/d), valproic acid (500 mg twice/d), and diazepam (5 mg twice/d).

During hospitalization, she adapted her cleaning rituals and hoarding of the materials she had in her room, like slippers and personal hygiene products. These symptoms were experienced as very distressing. On the 11th day of admission, risperidone (4 mg once/d) was added to better control her intrusive thoughts and compulsions. On the 14th day, her mood was euthymic, she had no suicidal ideation, and her obsessive-compulsive symptoms were moderately improved (diminished frequency and duration and no associated distress). She was discharged on the 17th day. During follow-up, she maintained antidepressant therapy and benzodiazepines but had periods of poor treatment adherence to antipsychotic medication. In those periods, her obsessive-compulsive symptoms would aggravate but remit after the reintroduction of the antipsychotic. To promote treatment adherence, she enrolled in a psychoeducation program and subsequently was treated with a long-acting injectable antipsychotic (palmitate of paliperidone 100 mg monthly) (more details on parenteral antipsychotics as an augmentation treatment for OCD are provided in Supplementary Material Topic 3) and was admitted to the psychiatry day hospital, wherein she participates in psychotherapy, psychoeducation, and cognitive stimulation concurrently with psychiatric consultations. Currently, 2 years after her admission, she remains symptom free with no relapses.

Discussion

In short, the patient suffers from OCD, mild hoarding behavior, and, occasionally, some kleptomania impulses. Genetic testing was requested by her endocrinologist at the age of 24 years to study the genotype of her CAH, which showed a duplication of chromosome 2 long arm, between 2q14.2-q21.1, comprising 50 genes and cytochrome P450 21A2 (Supplementary Material Topic 1), the latter being considered the cause of her congenital adrenal hyperplasia. The possible association of CAH with OCD was considered by the authors to be less probable. Genetic abnormalities comprising the 2q14.2–21.1 gene are rare. There is a lack of information regarding the association of these genetic

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Table 1. The Patient's Medical History From First Diagnosis Until the Current Episode

Age, y	Diagnosis	Clinical Manifestations	Complementary Diagnostic Tests	Treatment
4	Congenital adrenal hyperplasia; mild intellectual disability			
15	Left eye retinal detachment followed by major depressive disorder	Loss of visual acuity (unknown percentage) and depressive humor		Started follow-up in psychiatry
24		Depressive humor with transient periods of marked irritability and regular outbursts of rage and aggression	A genetic test using array-CGH showed 2q14.2-q21.1 duplication comprising 50 genes and mutation of cytochrome P450 21A2	Paroxetine, valproic acid
27	Obsessive-compulsive disorder	Obsessive thoughts and compulsions related to fear of contamination		Paroxetine, benzodiazepines, aripiprazole, with moderate response

abnormalities with major psychiatric disorders. Nevertheless, there is a report of 2 siblings with 2q trisomy (2q11.2→ q21.1) who both had mild mental retardation and psychosis.[3] The atypicality of this case is based on OCD associated with a very rare genetic alteration (chromosome 2 duplication [2q14.2-q21.1]), which has not yet been reported. There are no other reported associations, to the best of our knowledge, between the presented duplication and OCD in the literature. Regarding the medication, in addition to the antidepressant treatment, the patient was also treated with antipsychotics to achieve remission.

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Supplementary material follows this article.

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THE PRIMARY CARE COMPANION
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Supplementary Material

Article Title: Obsessive-Compulsive Disorder and Chromosome 2 Duplication (2q14.2-q21.1)

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List of Supplementary Material for the article

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Topic 1. The biological significance of the current genetic finding and how rare is it.

According to our patient clinical file, a Microarray analysis of the DNA sample was performed using a Bluegnome ISCA 60K Oligo Cytochip, at Liverpool Women's NHS Foundation Trust that showed a duplication of chromosome 2 encompassing 199 probes located within the long arm at the 2q14.2-q21.1. This duplication is estimated to be between 9.70Mb (bp:121617557-131317644) and 9.74 Mb (bp:121611176-131360914) in size using the BlueFuse database. Information indicated that this is a known duplication detected via karyotype analysis and reported as 46, XX, dup(2)(q13q21). Array analysis has therefore characterised the size and position of the duplication and redefined the breakpoints to 2q14.2 and 2q21.1. There are 50HGNC genes within the duplicated region, of which 24 are OMIM referenced (for more details, please consult **Supplementary Material, Topic 4: List of genes found in the duplication region**). One gene, GLI2, is partially overlapped at the proximal end of the duplication. There are no other cases with a similar duplication detected at Liverpool Women's NHS Foundation Trust*. Pure duplications of the proximal region of chromosome 2 are rare, with very few reported cases in the literature, and therefore a specific 2q duplication syndrome has not yet been defined. There appear to be no reports in the literature describing the exact imbalance as seen in this patient, and there are no patients referenced on the Decipher database either. However, one patient was noted to have a 9.9Mb duplication at 2q14.3-q21.3, which overlapped our region of interest. This patient is noted to have neuroradiological abnormalities, mental retardation/developmental delay, seizures, hypotonia and abdomen anomalies.

*The genetic test was performed at Liverpool Women's NHS Foundation Trust (https://www.liverpoolwomens.nhs.uk/)

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Considering that pure duplications of the proximal region of chromosome 2 are rare, very few reported cases are found in the literature. Therefore a specific 2q duplication syndrome has not yet been defined. There are, until now, no reports in the literature describing the exact imbalance as was seen in our patient.

Regarding the CYP21A2 mutation, causing congenital adrenal hyperplasia and deficiency of function of 21-hydroxylase, the most recent data has stated that alterations in the hypothalamic-pituitary–adrenal axis might contribute to psychiatric illness vulnerability, mainly mood disorders, but no correlation with OCD was yet described (**Supplementary Material Topic 2. Psychiatric and brain aspects of congenital adrenal hyperplasia (CAH), Table 1**).

Topic 2. Psychiatric and brain aspects of congenital adrenal hyperplasia (CAH)

According to a recent literature review on the clinical manifestation and treatment of CAH (Merke and Auchus 2020) although psychiatric manifestations can occur, there are no specific reports of comorbid Obsessive-Compulsive Disorder with CAH.

Table 1 of this supplementary material shows the main psychiatric manifestations of CAH.

Supplementary Material, Table 1. Psychiatric and brain aspects of congenital adrenal hyperplasia (CAH) according to sex and disease´s subtype

Classic CAH	
Male	Female
Increase prevalence of: - Anxiety - Depression - Alcohol misuse - Personality disorders - Suicidality	Increased prevalence of - Adjustment disorders - Aggressive behavior Improved spatial navigation skills Different pattern of amygdala activation
Severe null genotype of CAH Some reports of substance abuse and attention deficit-hyperactivity disorder in both sex	

However, it should be noted that Charmandari and collaborators (Charmandari et al. 2004) assessed psychological features of patients with CAH compared to healthy subjects. They did not find any statistically significant specific diagnose category, although a lower 24-h urinary free cortisol excretion and an increased ACTH response to ovine CRH stimulation was associated with a predisposition to obsessive-compulsive behavior, novelty seeking, reward dependence, and harm avoidance.

Charmandari, Evangelia, Deborah P. Merke, Paulo J. Negro, et al 2004. ‘Endocrinologic and Psychologic Evaluation of 21-Hydroxylase Deficiency Carriers and Matched Normal Subjects: Evidence for Physical

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and/or Psychologic Vulnerability to Stress'. *The Journal of Clinical Endocrinology and Metabolism* 89 (5): 2228–36. https://doi.org/10.1210/jc.2003-031322.

Merke, Deborah P., and Richard J. Auchus. 2020. 'Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency'. *The New England Journal of Medicine* 383 (13): 1248–61. https://doi.org/10.1056/NEJMra1909786.

Topic 3. Parenteral antipsychotics as an augmentation treatment for OCD

There is a lack of randomized control trials regarding the use of parenteral antipsychotics in OCD. According to the guidelines of the National Institute of Care and Health Excellence ((NICE) [1], augmentation therapy with antipsychotic medication is a valid option if the patient has not responded to treatment with SSRI. Since risperidone was introduced earlier in the clinical practice and was one of the first second-generation antipsychotics to be studied as augmentation therapy for OCD, there are much more studies about this drug than paliperidone (used in our patient). However, we have chosen paliperidone because it is reported to be associated with less adverse metabolic effects, lower risk of hyperprolactinemia and fewer drug interactions than risperidone. Parenteral antipsychotic, in this case, was proposed to target better compliance with the treatment since the patient had several periods of non-adherence to the medication.

[1]https://www.nice.org.uk/guidance/CG31/chapter/1-Guidance#steps-35-treatment-options-for-people-with-ocd-or-bdd - topic 1.5.4.7 - last accessed 23-03-2021

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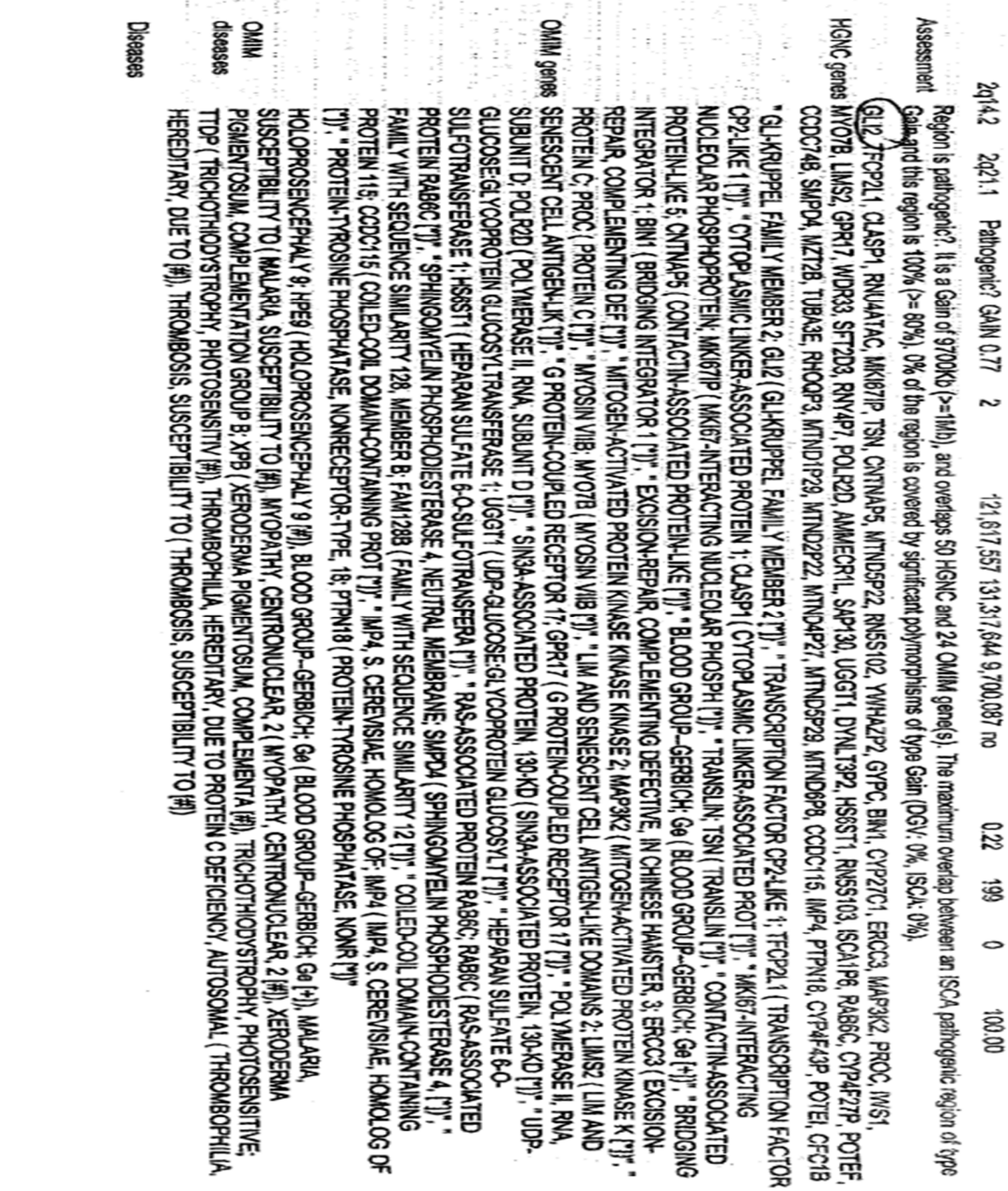
Topic 4. List of genes found at the Chromosome 2 duplication 2q14.2-q21.1)



Region #	Start Cyto	End Cyto	Assessment	Type	Copy #	Chromosome	Start	End	Size (bp)	Main Change	Std Dev	Included	Essential	Non-Included
	2q14.2	2q21.1	Pathogenic?	GAIN	0.77	2		121,617,557	131,317,644	9,700,087	no	0.22	199	0	100.00

Assessment: Region is pathogenic?. It is a Gain of 9700Kb (>=1Mb), and overlaps 50 HGNC and 24 OMIM gene(s). The maximum overlap between an ISCA pathogenic region of type Gain and this region is 100% (>= 80%), 0% of the region is covered by significant polymorphisms of type Gain (DGV: 0%, ISCA: 0%).

HGNC genes: GLI2, FCP2L1, CLASP1, RNU4ATAC, MKI67IP, TSN, CNTNAP5, MTND5P22, RN5S102, YWHAZP2, GYPC, BIN1, CYP27C1, ERCC3, MAP3K2, PROC, IMS1, MYO7B, LIMS2, GPR17, WDR33, SF7203, RNY4P7, POLR2D, AMMECR1L, SAP130, UGGT1, DYNLT3P2, HS6ST1, RN5S103, ISCA1P6, RAB6C, CYP4F27P, POTEF, CCDC74B, SMPD4, MZT2B, TUBA3E, RHOQP3, MTND1P29, MTND2P22, MTND4P27, MTND5P29, MTND6P8, CCDC115, IMP4, PTPN18, CYP4F43P, POTEI, CFC1B

OMIM genes: "GLI-KRUPPEL FAMILY MEMBER 2; GLI2 (GLI-KRUPPEL FAMILY MEMBER 2 [*1]" ; "TRANSCRIPTION FACTOR CP2-LIKE 1 [*1]" ; "CYTOPLASMIC LINKER-ASSOCIATED PROTEIN 1; CLASP1 (CYTOPLASMIC LINKER-ASSOCIATED PROT [*1]" ; "MKI67-INTERACTING NUCLEOLAR PHOSPHOPROTEIN; MKI67IP (MKI67-INTERACTING NUCLEOLAR PHOSPH [*1]" ; "TRANSLIN; TSN (TRANSLIN [*1]" ; "CONTACTIN-ASSOCIATED PROTEIN-LIKE 5; CNTNAP5 (CONTACTIN-ASSOCIATED PROTEIN-LIKE [*1]" ; "BLOOD GROUP--GERBICH; Ge (BLOOD GROUP--GERBICH; Ge [+1]" ; "BRIDGING INTEGRATOR 1; BIN1 (BRIDGING INTEGRATOR 1 [*1]" ; " EXCISION-REPAIR, COMPLEMENTING DEFECTIVE, IN CHINESE HAMSTER, 3; ERCC3 (EXCISION-REPAIR, COMPLEMENTING DEF [*1]" ; "MITOGEN-ACTIVATED PROTEIN KINASE KINASE 2; MAP3K2 (MITOGEN-ACTIVATED PROTEIN KINASE K [*1]" ; " PROTEIN C; PROC (PROTEIN C [*1]" ; "MYOSIN VIIB; MYO7B (MYOSIN VIIB [*1]" ; "LIM AND SENESCENT CELL ANTIGEN-LIKE DOMAINS 2; LIMS2 (LIM AND SENESCENT CELL ANTIGEN-LIK [*1]" ; " G PROTEIN-COUPLED RECEPTOR 17; GPR17 (G PROTEIN-COUPLED RECEPTOR 17 [*1]" ; " POLYMERASE II, RNA, SUBUNIT D; POLR2D (POLYMERASE II, RNA, SUBUNIT D [*1]" ; " SIN3A-ASSOCIATED PROTEIN, 130-KD (SIN3A-ASSOCIATED PROTEIN, 130-KD [*1]" ; " UDP-GLUCOSE:GLYCOPROTEIN GLUCOSYLTRANSFERASE 1; UGGT1 (UDP-GLUCOSE:GLYCOPROTEIN GLUCOSYLT [*1]" ; " HEPARAN SULFATE 6-O-SULFOTRANSFERASE 1; HS6ST1 (HEPARAN SULFATE 6-O-SULFOTRANSFERA [*1]" ; " RAS-ASSOCIATED PROTEIN RAB6C; RAB6C (RAS-ASSOCIATED PROTEIN RAB6C [*1]" ; " SPHINGOMYELIN PHOSPHODIESTERASE 4, NEUTRAL MEMBRANE; SMPD4 (SPHINGOMYELIN PHOSPHODIESTERASE 4, [*1]" ; " FAMILY WITH SEQUENCE SIMILARITY 128, MEMBER B; FAM128B (FAMILY WITH SEQUENCE SIMILARITY 12 [*1]" ; " COILED-COIL DOMAIN-CONTAINING PROTEIN 115; CCDC115 (COILED-COIL DOMAIN-CONTAINING PROT [*1]" ; " IMP4, S. CEREVISIAE, HOMOLOG OF; IMP4 (IMP4, S. CEREVISIAE, HOMOLOG OF [*1]" ; " PROTEIN-TYROSINE PHOSPHATASE, NONRECEPTOR-TYPE, 18; PTPN18 (PROTEIN-TYROSINE PHOSPHATASE, NONR [*1]"

OMIM diseases: HOLOPROSENCEPHALY 9; HPE9 (HOLOPROSENCEPHALY 9 [#]), BLOOD GROUP--GERBICH; Ge (BLOOD GROUP--GERBICH; Ge [+]), MALARIA, SUSCEPTIBILITY TO (MALARIA, SUSCEPTIBILITY TO [#]), MYOPATHY, CENTRONUCLEAR, 2 (MYOPATHY, CENTRONUCLEAR, 2 [#]), XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP B; XPB (XERODERMA PIGMENTOSUM, COMPLEMENTA [#]), TRICHOTHIODYSTROPHY, PHOTOSENSITIVE; TTDP (TRICHOTHIODYSTROPHY, PHOTOSENSITIV [#]), THROMBOPHILIA, HEREDITARY, DUE TO PROTEIN C DEFICIENCY, AUTOSOMAL (THROMBOPHILIA, HEREDITARY, DUE TO [#]), THROMBOSIS, SUSCEPTIBILITY TO (THROMBOSIS, SUSCEPTIBILITY TO [#])

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