THE PRIMARY CARE COMPANION
FOR CNS DISORDERS

Supplementary Material

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

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DOI Number: https://doi.org/10.4088/PCC.20cr02884

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/)

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

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.

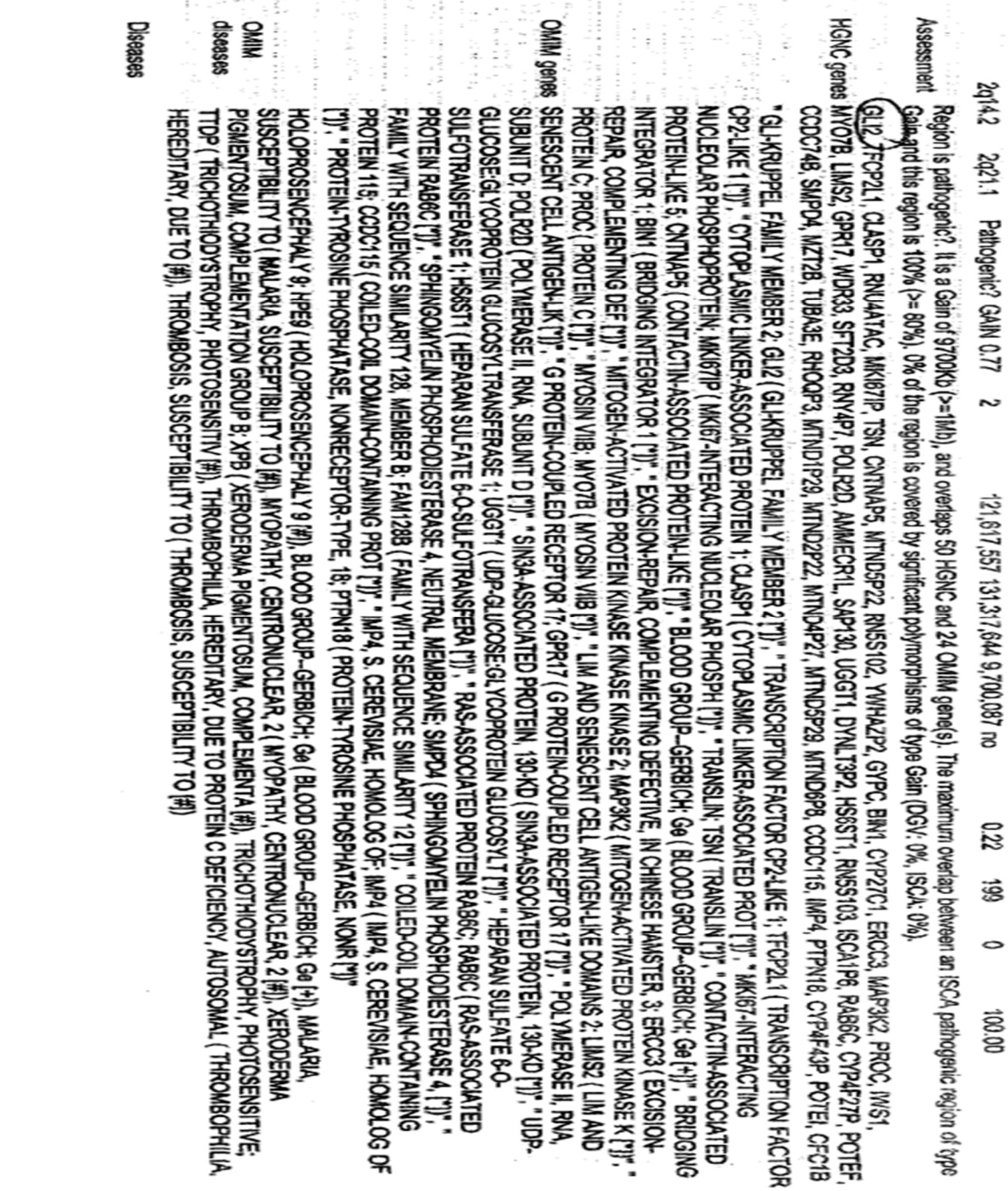
Merke, Deborah P., and Richard J. Auchus. 2020. 'Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency'. *The New England Journal of Medicine* 383 (13): 1248–61. https://doi.org/10.1056/NEJMra1909786.

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

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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Sales M, and Silva-dos-Santos A. Obsessive-Compulsive Disorder (OCD) and Chromosome 2 duplication (2q14.2-q21.1): a case report; Supplementary Material.