

TREATMENT CONTINGENT UPON ETIOLOGY:
TWO ADULT FEMALE PATIENTS WITH MILD INTELLECTUAL DISABILITY
AND A CAUSATIVE COPY NUMBER VARIATION

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Abstract

Objective: While modern genetic techniques have substantially increased the knowledge regarding causes of intellectual disabilities and related neuropsychiatric disorders, a marked time-lag can be noticed with respect to its implementation in common psychiatric practice. Given the relatively strong emphasis on diagnostic classification to the disadvantage of phenomenological and etiopathophysiological factors, the application of etiology-based treatment strategies may be seriously hindered. This a fortiori holds for patients with mild intellectual disability in the absence of salient dysmorphic features or congenital anomalies.

Method: The present paper illustrates this by means of two adult female patients with mild intellectual disability and late onset of symptoms from the mood and cognitive spectra.

Results and conclusions: In both patients microarray analysis disclosed *de novo* copy number variations, being a 2.05 Mb mosaic interstitial deletion in 7p21.1p15.3 in patient A and a 1.48 Mb interstitial duplication in 17q12 in patient B. These findings led to an appropriate diagnosis and gave direction to a significant change in treatment that resulted in an improvement of general functioning.

Key words: CNV, 7p21.1p15.3, 17q12, neuropsychiatry, cognition, etiological diagnosis

Declaration of interest: none

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Introduction

Over the past decades, the introduction of modern genetic techniques like genomic microarray and whole exome sequencing has led to the discovery of several *de novo* copy number variations (CNV) and mutations providing support for their causative nature in developmental delay and intellectual disability (Vissers et al. 2010, de Ligt et al. 2012, Gilissen et al. 2014, Athanasakis et al. 2014, Martinez et al. 2017). Because of the substantially high prevalence of challenging behaviours in neuropsychiatric patients, whether or not associated with intellectual disability, the application of these techniques is of vital importance for the understanding of the disease and its etiology-guided treatment (Vulto-van Silfhout et al. 2013,

McRae et al. 2017).

Since current psychiatric consultation is increasingly restricted to the inventory of symptoms as categorised in diagnostic classification systems, in this process, often, the detailed analysis of course and history including neurocognitive and social-emotional development is neglected. In this way, the importance of a psychiatric diagnosis can be easily overestimated which, in turn, may cloud important etiological factors and increase the risk of erroneous treatment decisions (Verhoeven and Egger 2014).

In this paper, two adult female patients with mild intellectual disability are described who, for the first time, developed psychiatric and cognitive symptoms around the start of their third decade.

Clinical reports

Patient A is a 39-year-old female, prematurely born from non-consanguineous parents with a birth weight of 1,380g. Apart from diabetes mellitus type II and cardiovascular problems in her mother's family, there is no load with intellectual disability or neuropsychiatric diseases. She had one older brother who died at the age of 15 years in a serious traffic accident. When the patient was two years old she nearly drowned. Developmental milestones were all delayed and the patient tended to avoid social contact. After having followed special education, she completed domestic science school after which she was employed for unskilled working activities. Over subsequent years, the patient developed, contingent upon environmental demands, periods with pseudo-hallucinatory auditory experiences, anxieties, irritability and lowering of mood as well as inactivity and withdrawal behaviours. At the age of 23 years, she had a first contact with social psychiatry services and four years later she was hospitalized for a short period. A diagnosis of depression was made and treatment with citalopram was started, later in combination with quetiapine. Thereafter, she moved to a sheltered home facility and continued her work.

The patient was referred by her general practitioner to the specialized outpatient department for neuropsychiatry for re-evaluation of mood complaints in the context of her delayed development.

At examination, a female obese patient was seen with large ears and lobules, deep set eyes and columella below alae nasi, but no major dysmorphisms. Height, weight and head circumference were 174cm (+0.5 SD), 124kg (>>+2 SD) and 55.5cm (0 SD), respectively. Neuropsychiatric and somatic/neurological examination disclosed a tendency to referential thinking, but no signs of major depression or other abnormal findings. Haematological and biochemical parameters including FT4 were all within normal range. Extensive neuropsychological testing revealed mild intellectual disability (WAIS-IV Total IQ: 54) with lowered verbal comprehension and working memory, the latter attenuating particularly verbal learning capacities. Social cognitive functioning, including Theory of Mind, was undisturbed albeit with diminished (facial) expression of heightened stress levels. This configuration of cognitive and neuropsychiatric characteristics enhances the risk for overestimation presenting with reactive depressive signs.

Subsequent genome wide analysis on DNA from peripheral blood using a CytoScanHD array platform (Affymetrix, Santa Clara, CA, USA) demonstrated a *de novo* interstitial deletion of 2.05 Mb in 7p21.1p15.3 (arr[hg19] 7p21.1p15.3(20,788,314-22,837,872)x1~2 dn). The deletion, comprising 12 genes, appeared to be present in ~50% of the cells (cross validated and confirmed in DNA from buccal swab cells) and was considered to be implicated in the developmental problems (Figure 1).

Because no diagnosis of major depression could be established and since the use of quetiapine for many years had resulted in marked obesity, the patient was advised to taper off gradually both citalopram (40mg daily) and quetiapine (300mg daily), guided by her own general practitioner. Instead, a very structured living and working environment avoiding unpredictable events was recommended in order to avoid social interaction bound overestimation.

Patient B is a 46-year-old female who was referred for the first time, aged 36 years, to the specialized outpatient department for neuropsychiatry by the

regional institute for social-pedagogic services, primarily for evaluation of her cognitive and social-emotional functioning. She was born from non-consanguineous parents after an uncomplicated pregnancy and has two older healthy brothers. There was no family load with intellectual disabilities or neuropsychiatric diseases. Her history showed a slight delay of all milestones. After having completed primary school, the patient followed special education until the age of 20 years. Over subsequent years she was employed at a sheltered home facility while staying at her parents' home. Sixteen years later, while considering to leave her parental home, she was examined for the first time. A healthy woman was seen with a height, weight and head circumference of 155cm, 70kg and 49cm, respectively. Apart from relatively small hands, no dysmorphisms were noticed. Psychiatric examination disclosed an anxious and dependent attitude with lack of social initiative without, however, any signs of major psychiatric symptoms. Neuropsychological assessment disclosed mild intellectual disability (WAIS-III Total, Verbal and Performal IQ: 51, 48 and 61, respectively) with enhanced distractibility and lowered speed of information processing. Cytogenetic analysis revealed no abnormalities and Fragile-X syndrome was excluded. Social supportive therapy was advised without the need for neuropsychiatric follow-up. However, five years later, after her mother had deceased, she was referred to a neurologist because of persistent attention and memory problems. Apart from some minor periventricular white matter lesions (detected with MRI scanning), no neurological abnormalities were found and psychotherapeutic interventions were started.

The patient was referred again because of suspected gradual decline of neurocognitive functioning as well as complaints about increased anxiety levels. Intellectual capacities were similar to the former measurement (WAIS-IV Total, Verbal and Performal IQ: 53, 51 and 72, respectively). As to neurocognition, performance levels were generally comparable to those found ten years before except for speed of information processing and executive functioning which were both lowered. In addition, some indication for socio-emotional impairment was found. Apart from minor signs of distress, psychiatric symptoms could not be ascertained. MRI scanning of the brain revealed no changes as compared to six years before and was considered normal. Genome wide CytoScan HD array analysis showed a paternally inherited 205 kb gain in 22q11.1 and a *de novo*, interstitial duplication of 1.48 Mb in 17q12 encompassing 24 genes (arr[hg19]17q12(34,823,616-36,307,774)x3 dn,22q11.1(17,624,770-17,831,814)x3 pat; Figure 2). The duplication in 17q12 is a known recurrent microduplication that is associated with the so-called 17q12 duplication syndrome (OMIM #614526) which is predominantly characterized by mild to moderate intellectual disability.

All reported complaints about cognitive functioning and recurrent anxieties could be emanated from an enhanced susceptibility to context-related socio-emotional overestimation. Therefore, a more structured environmental approach was recommended with periodic re-evaluation of cognitive functioning. No further psychopharmacological or psychosocial interventions were indicated.

Discussion

In this paper, two adult female patients with mild

Figure 1. A. Array plot of chromosome 7 of patient A with a de novo, mosaic, interstitial deletion of 2.05 Mb in 7p21.1p15.3. The single horizontal line represents the probe signal values, with $n=2$ for a normal copy number. The genotype information is represented below this single line by the so-called B-Allele Frequency, with three combinations possible in case of $n=2$ (AA, BA or BB) and two combinations for $n=1$ (A or B), if there is a deletion. In case of a mosaic loss there will be a mixture of cells with and without loss of the 7p21.1p15.3 allele resulting in four possible combinations (BB, BA, AB or AA). The plot in blue shows the array findings in DNA from buccal swab cells and the plot in pink the array findings in DNA from peripheral blood. B. Screen shot of the UCSC genome browser (<https://genome.ucsc.edu>) of the aberrant 7p21.1p15.3 region encompassing 12 protein-coding genes. The probe coverage on the CytoScanHD array platform and the presence of repeat sequences are indicated in the lower part of the figure

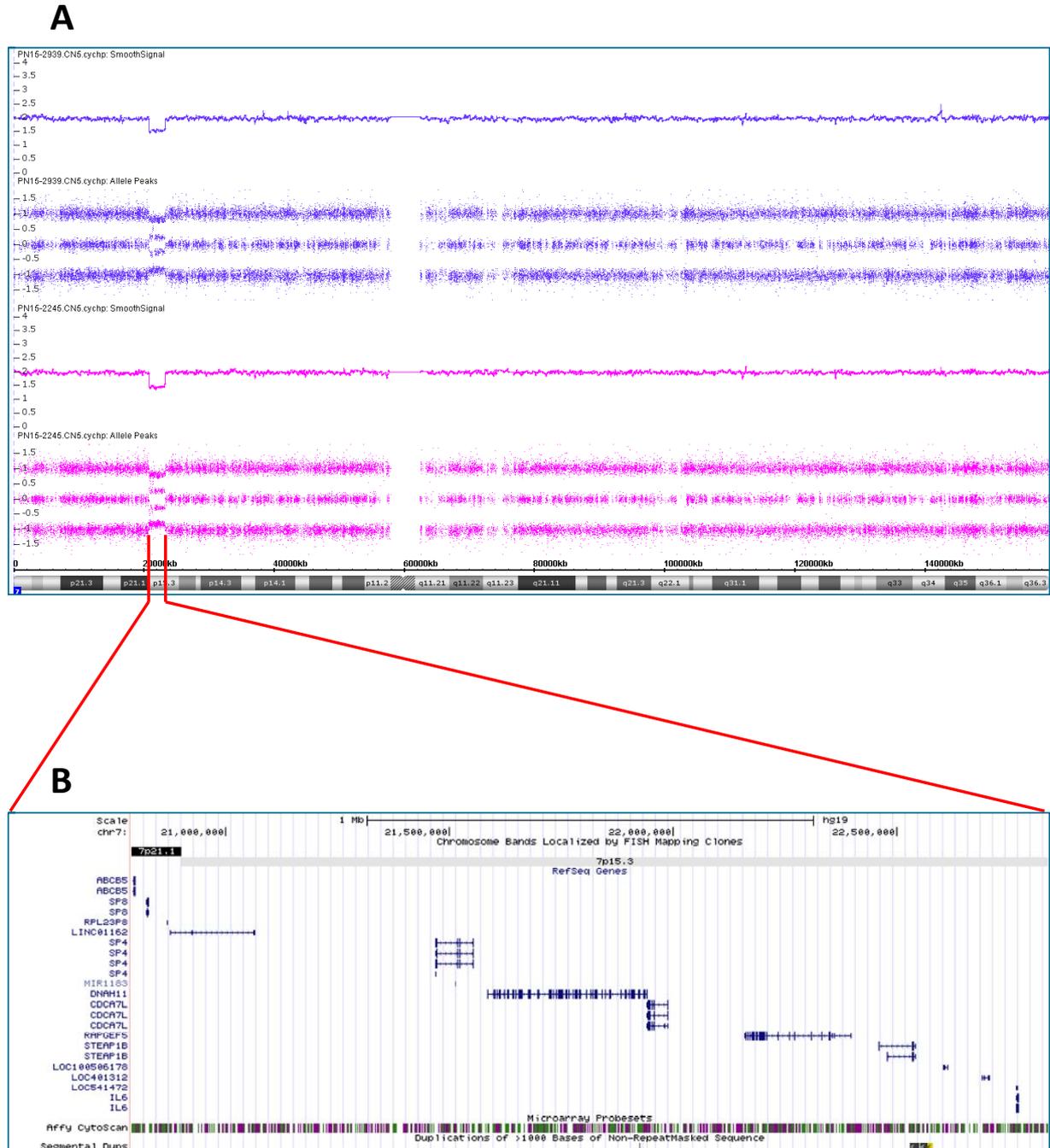
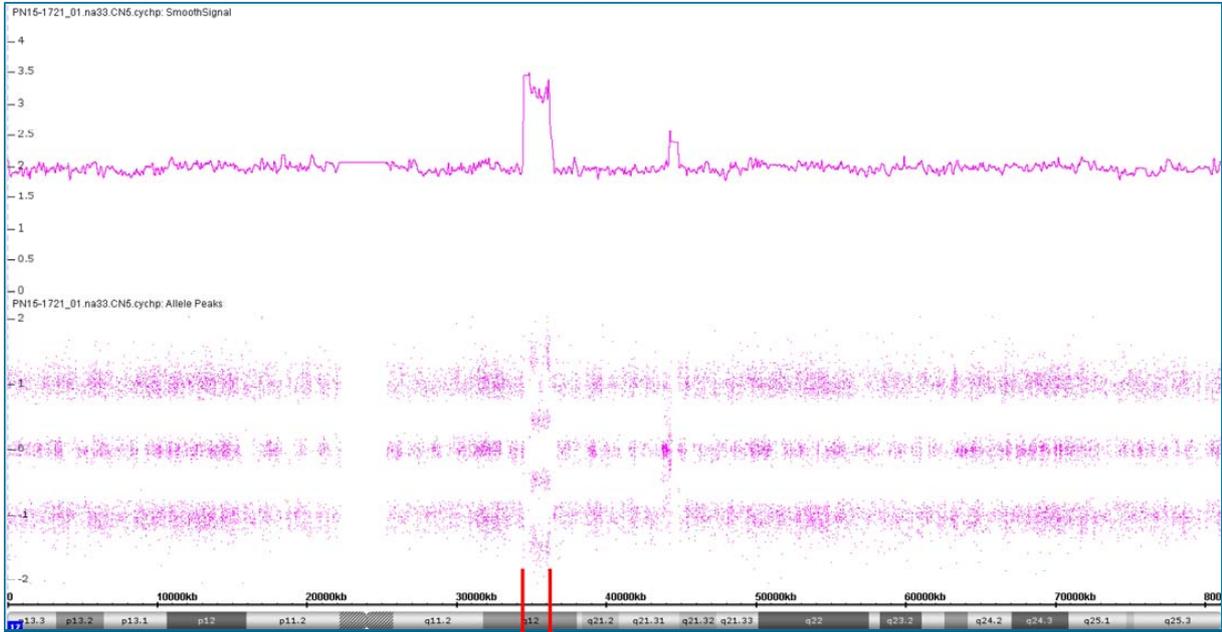
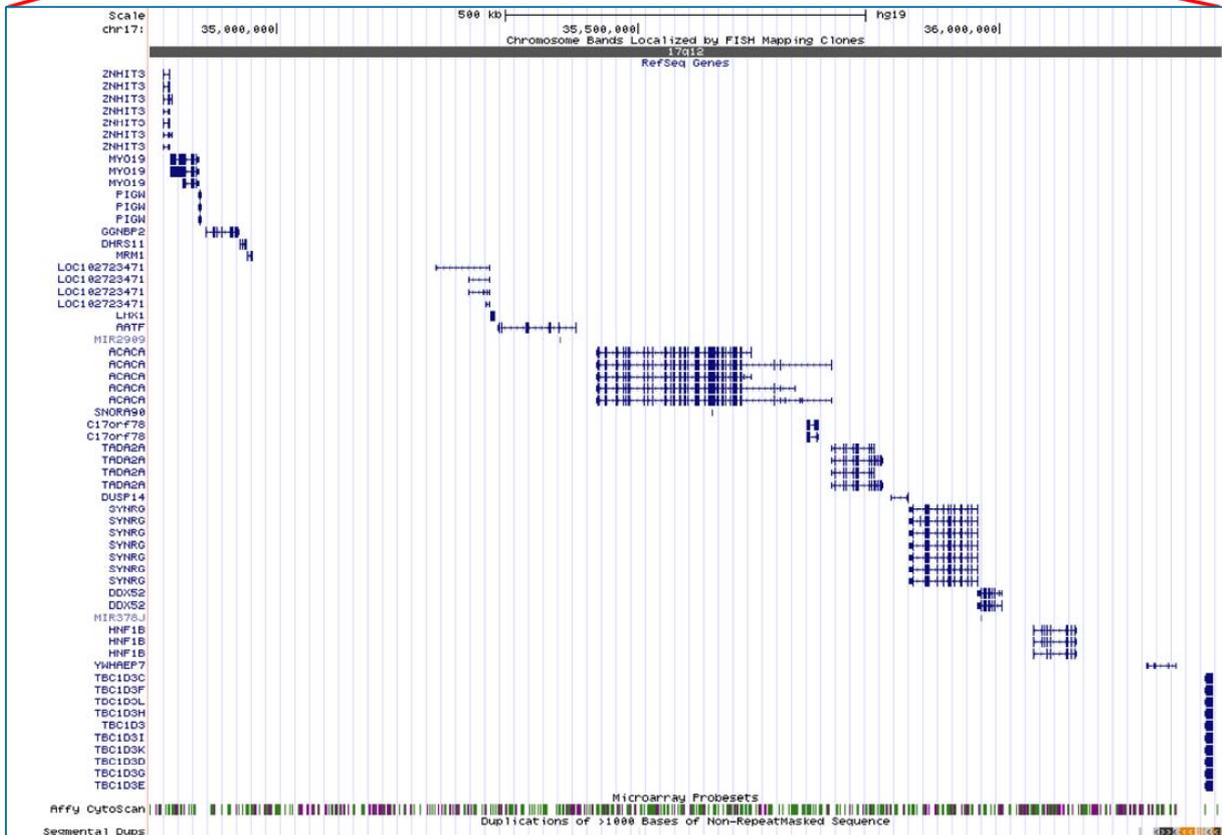


Figure 2. A. Array plot of chromosome 17 of patient B with a de novo, interstitial gain of 1.48 Mb in 17q12. The single horizontal line represents the probe signal values, with $n=2$ for a normal copy number. The genotype information is represented below this single line by the so-called B-Allele Frequency, with three combinations possible in case of $n=2$ (AA, BA or BB), two combinations for $n=1$ (A or B), if there is a deletion, and four combinations in case of a gain, $n=3$ (AAA, AAB, ABB or BBB).
 B. Screen shot of the UCSC genome browser (<https://genome.ucsc.edu>) of the aberrant 17q12 region encompassing 24 protein-coding genes. The probe coverage on the CytoScanHD array platform and the presence of repeat sequences are indicated in the lower part of the figure



B



intellectual disability and relatively adequate social participation are described. In both, *de novo* CNVs were demonstrated to be causatively implicated in their developmental delay. In patient A, a mosaic interstitial deletion in 7p21.1p15.3 was detected while in patient B a 17q12 microduplication was established. In both patients, referral was initiated because of suspected cognitive decline and/or psychiatric symptoms from the affect domain.

With respect to the 7p deletion, no deletions of comparable size have been reported so far. There are only a few patients described in the literature and a mere dozen patients registered in clinical genetic databases such as ECARUCA (www.ecaruca.net) and DECIPHER (<https://decipher.sanger.ac.uk>). However, these concern patients with significantly larger deletions that are associated with severe intellectual disability, marked dysmorphisms and somatic anomalies (Chotai et al. 1994, Shimada et al. 2013).

The 17q12 duplication syndrome is associated with a highly variable degree of intellectual disability and, in most cases, with neurological and somatic disorders, such as seizures and renal abnormalities (Mefford et al. 2007, Nagamani et al. 2010, Caselli et al. 2010, Faguer et al. 2011, Bierhals et al. 2013).

As to patient A, more than 15 years prior to referral, a diagnosis of major depression was made after which she underwent a form of psychotherapy focused on anxious cognitions. In addition, she was treated over a long period of time with psychotropics. The psychotherapeutic intervention did not attenuate her anxious feelings and affective dysregulations and was therefore discontinued. Psychopharmacological treatment lacked any effect and resulted in morbid obesity (BMI: 41). Recurrent complaints about cognitive functioning brought patient B under the attention of a neurologist who did not detect any abnormalities and forwarded her to a psychotherapist to cope with anxieties and feelings of bereavement related to her mother's death. No improvement was achieved, instead, symptoms of distress and memory complaints intensified. In both patients, personalized contextual measures with increased staff involvement resulted in a reduction of complaints and amelioration of behaviour.

In conclusion, as can be inferred from the above, the absence of notable facial dysmorphisms or somatic abnormalities often does not signal the clinician to initiate essential etiological examinations. Likewise, such a presentation may also easily obscure the presence of (mild) intellectual disability which, in turn, evokes psychiatric and neurologic misdiagnoses with a subsequent cascade of unnecessary, ineffective and sometimes harmful treatment programs.

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Patient A and B are included in the ECARUCA database with ID 5204 and 5225, respectively.

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References

- Athanasakis E, Licastro D, Faletra F, Fabretto A, Dipresa S, Vozi D, Morgan A, d'Adamo AP, Pecile V, Biarnés X, Gasparini P (2013). Next generation sequencing in nonsyndromic intellectual disability: From a negative molecular karyotype to a possible causative mutation. *American Journal of Medical Genetics* 164A, 170-176.
- Bierhals T, Maddukuri SB, Kutsche K, Girisha KM (2013). Expanding the phenotype associated with 17q12 duplication: Case report and review of the literature. *American Journal of Medical Genetics* 161A, 352-359.
- Caselli R, Ballarati L, Selicorni A, Milani D, Maitz S, Valtorta C, Larizza L, Giardino D (2010). A 12.4 Mb duplication of 17q12.2q12 in a patient with psychomotor developmental delay and minor anomalies. *European Journal of Medical Genetics* 53, 325-328.
- Chotai KA, Brueton LA, van Herwerden L, Garrett C, Hinkel GK, Schinzel A, Mueller RF, Speleman F, Winter RM (1994). Six cases of 7p deletion: Clinical, cytogenetic and molecular studies. *American Journal of Medical Genetics* 51, 270-276.
- De Ligt J, Willemsen MH, van Bon BWM, Kleefstra T, Yntema HG, Kroes T, Vulto-van Schelphout AT, Koolen DA, de Vries P, Gilissen C, del Rosario M, Hoischen A, Scheffer H, de Vries BBA, Brunner HG, Veltman JA, Vissers LELM (2012). Diagnostic exome sequencing in persons with severe intellectual disability. *New England Journal of Medicine* 367, 1921-1929.
- Faguer S, Chassaing N, Bandin F, Prouheze C, Arveiler B, Rooryck C, Nogier MB, Chauveau D, Calvas P, Decramer S (2011). A 17q12 chromosomal duplication associated with renal disease and esophageal atresia. *European Journal of Medical Genetics* 54, e437-e440.
- Gilissen C, Hehir-Kwa JY, Tjwan Thung D, van de Vorst M, van Bon BWM, Willemsen MH, Kwint M, Janssen IM, Hoischen A, Schenck A, Leach R, Klein R, Tearle R, Bo T, Pfundt R, Yntema HG, de Vries BBA, Kleefstra T, Brunner HG, Vissers LELM, Veltman J (2014). Genome sequencing identifies major causes of severe intellectual disability. *Nature* 511, 344-347.
- Martinez F, Caro-Llopis A, Roselló M, Oltra S, Mayo S, Monfort S, Orellana C (2017). High diagnostic yield of syndromic intellectual disability by targeted next-generation sequencing. *J Med Genet* 54, 87-92.
- McRae JF, Clayton S, Fitzgerald TW, Kaplanis J, Prigmore E, Rajan D, et al. (2017). Prevalence and architecture of *de novo* mutations in developmental disorders. *Nature* E-pub ahead of print, doi:10.1038/nature21062.
- Mefford H, Clauin S, Sharp AJ, Moller RS, Ullmann R, Kapur R, Pinke D, Cooper GM, Ventura M, Ropers HH, Tommerup N, Eichler EE, Bellanne-Chantelot C (2007). Recurrent reciprocal genomic rearrangements of 17q12 are associated with renal disease, diabetes and epilepsy. *American Journal of Human Genetics* 81, 1057-1069.
- Nagamani SCS, Erez A, Shen J, Li C, Roeder E, Cox S, Karaviti L, Pearson M, Kang SHL, Sahoo T, Lalani SR, Stankiewicz P, Sutton VR, Cheung SW (2010). Clinical spectrum associated with recurrent genomic rearrangements in chromosome 17q12. *European Journal of Human Genetics* 18, 278-284.
- Shimada S, Okamoto N, Nomura S, Fukui M, Shimakawa S, Sangu N, Shimojima K, Osawa M, Yamamoto T (2013). Microdeletions of 5.5 Mb [4q13.2-q13.3] and 4.1 Mb [7p15.3-p21.1] associated with a Saethre-Chotzen-like phenotype, severe intellectual disability and autism. *American Journal of Medical Genetics* 161A, 2078-2083.
- Verhoeven WMA, Egger JIM (2014). Aetiology based diagnosis and treatment selection in intellectually disabled people with challenging behaviours. *Journal of Intellectual Disability Diagnosis and Treatment* 2, 83-93.

Vissers LELM, de Ligt J, Gilissen C, Janssen I, Stehouwer M, de Vries P, van Lier B, Arts P, Wieskamp N, del Rosario M, van Bon BWM, Hoischen A, de Vries BBA, Brunner HG, Veltman JA (2010). A *de novo* paradigm for mental retardation. *Nature Genetics* 42, 1109-1113.

Vulto-van Silfhout AT, Hehir-Kwa JY, van Bon BW, Schuurs-Hoeijmakers JH, Meader S, Hellebrekers CJ, Thoonen IJ, de Brouwer AP, Webber C, Pfundt R, de Leeuw N, de Vries BBA (2013). Clinical significance of *de novo* and inherited copy-number variation. *Human Mutation* 34, 1679-1687.