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Association of structural and numerical anomalies of chromosome 22 in a patient with syndromic intellectual disability

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ABSTRACT

Array comparative genomic hybridization (aCGH) is now widely adopted as a first-tier clinical diagnostic test for patients with developmental delay (DD)/intellectual disability (ID), autism spectrum disorders, and multiple congenital anomalies. Nevertheless, classic karyotyping still has its impact in diagnosing genetic diseases, particularly mosaic cases.

We report on a 30 year old patient with syndromic intellectual disability, a 22q13.2 microdeletion and mosaic trisomy 22. The patient had the following clinical features: intrauterine growth retardation at birth, hypotonia, cryptorchidism, facial asymmetry, enophthalmus, mild prognathism, bifid uvula, hypoplastic upper limb phalanges, DD including speech delay, and ID. Whole genome aCGH showed a *de novo* 1 Mb interstitial heterozygous deletion in 22q13.2, confirmed by fluorescence in situ hybridization in all cells examined. Moreover, 18% cells had an extra chromosome 22 suggesting a trisomy 22 mosaicism.

Almost all 22q13 deletions published so far have been terminal deletions with variable sizes (100 kb to over 9 Mb). Very few cases of interstitial 22q13.2 deletions were reported. In its mosaic form, trisomy 22 is compatible with life, and there are about 20 reports in the literature. It has a variable clinical presentation: growth restriction, dysmorphic features, cardiovascular abnormalities, hemihyperplasia, genitourinary tract anomalies and ID. Neurodevelopmental outcome ranges from normal to severe DD. The patient presents clinical features that are common to both the interstitial 22q13 deletion and the mosaic trisomy 22; characteristics related to the interstitial deletion alone and others explained solely by the mosaic trisomy.

Our case points out the role of conventional cytogenetic tools in mosaic cases that could be missed by microarray technology. We therefore suggest the combination of both conventional and molecular karyotyping in the investigation of certain genetic diseases.

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1. Introduction

Developmental delay/Intellectual disability (DD/ID) affects about 2–3% of the general population (Shinawi and Cheung, 2008). We use the term syndromic intellectual disability when it is associated to a certain clinical phenotype, to dysmorphic features and/or multiple congenital anomalies (MCA). It is reported that up to half the identified causes of DD/ID are due to a genetic etiology ranging from chromosomal aneuploidies and genetic rearrangements to monogenic disorders (Srour and Shevell, 2014). Array comparative genomic hybridization (aCGH) is now widely adopted as a first-tier diagnostic test in the investigation of isolated as well as syndromic ID (Vulto-van Silfhout et al., 2013). The available platforms have improved tremendously and increased their technical sensitivities in such a way that they henceforth offer a diagnostic yield as high as 20% (Vulto-van Silfhout et al., 2013). Nevertheless, classic karyotyping still has its impact in diagnosing genetic diseases, particularly mosaic imbalances. In this report, we present a patient with syndromic intellectual disability and two genetic anomalies on chromosome 22, one structural and one numerical.

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2. Clinical report

We present a 30-year old male patient with syndromic intellectual disability. His parents are healthy and not consanguineous and he has a younger, healthy sister. The pregnancy leading to his birth was uneventful. He was born at week 41 of gestational age by caesarean section. Height and weight were below the third percentile although no restriction of growth has been noticed during pregnancy; head circumference was normal. The neonatal period was unremarkable and he caught up his growth delay (reaching target height as an adult) and head circumference remained normal. He had repeated upper respiratory tract infections, and at the age of 4 years he suffered from an acute otitis complicated by a meningitis after which he lost his hearing. He has not experienced any regression. He underwent surgery during childhood for cryptorchidism. He has no heart defect, no kidney malformation or lymphedema and no seizure disorder. He had hydrocephalus probably related to meningitis on computerized tomography scan of the brain, and no evidence of malformation. Concerning his developmental milestones, he exhibited hypotonia and delays in sitting up but walked at 18 months of life. Language was delayed. He had learning troubles in school which necessitated a special education. He is a young adult man with persistent intellectual disability, delayed fine motor skills and severe speech impairment (he speaks very few words and uses sign language). He has optic neuropathy and severe hearing loss. He demonstrates dysmorphic features (Fig. 1): facial palcy, bifid uvula, enophthalmus, marked supra-orbital ridges, mild prognathism and his upper limb phalanges are hyposplatic. He is shy and solitary, he has inappropriate laughs and a tendency to stereotyped behavior but no obvious autistic behaviors, no aggression, and he does not have sleep disturbances.

After ruling out Fragile X Syndrome, aCGH was prescribed to investigate the patient's syndromic intellectual disability. Whole genome oligonucleotide microarray 105 K (Agilent® Technologies) was performed on DNA from blood leucocytes using a dye-swap strategy and analysed with the Workbench® software (adm2 method). The microarray showed a *de novo* 1 Mb interstitial deletion in chromosomal region 22q13.2 (positions 41,864,255–42,865,320 by the GRCh37, hg 19 version) (Fig. 2). Fluorescence in situ hybridization FISH on cultured blood leukocytes using an in-house probe BAC RP11-101F24 with the α-satellite 14/22 D14Z1/D22Z1 Cytocell® probe confirmed the microdeletion in all cells of the patient and excluded its inheritance from his parents. Moreover, 18% of the cells examined had three signals with the α-satellite probe in addition to the 22q13.2 deletion (Fig. 3A). R-banded karyotype (Fig. 3B) was done and revealed a trisomy 22 mosaicism. FISH using the DiGeorge/VCFS TUPLE 1 and 22q13.3 Deletion Syndrome Probe Combination (Cytocell®) further confirmed the mosaic trisomy 22. The patient's karyotype was designated as follows according to ISCN nomenclature:

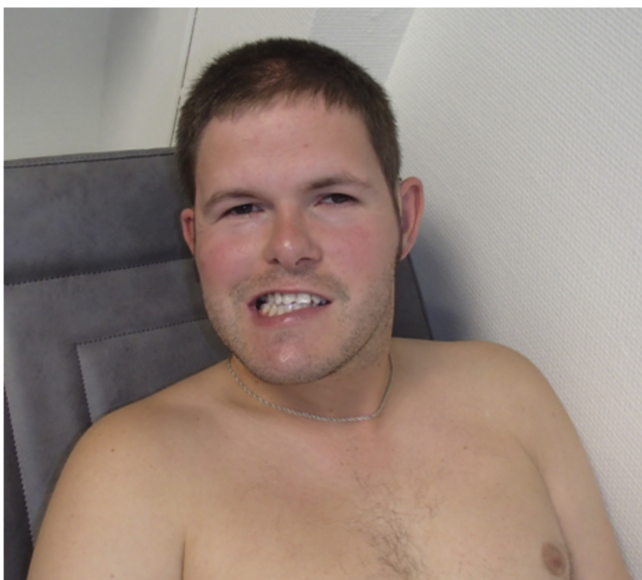

Fig. 1. Photograph of the patient at adult age. Patient has a facial asymmetry due to facial palsy, prominent supraorbital ridges, enophtalmia, proganathism, high arched palate, bifid uvula, and thin upper lip.

mos 46,XY.ish del(22)(q13.2q13.2)(RP11-101F24-)[123]dn/
47,XY,+22.ish del(22)(q13.2q13.2)(RP11-101F24-)[27]dn

Array CGH was performed on DNA extracted from salivary cells using the Oragen-DNA® kit and the 22q13.2 deletion was present in the saliva as well. Of note, a deletion is represented by an absolute $\log_2$ ratio of 1. A $\log_2$ ratio of 0.77 was measured in the blood (Fig. 3C, left), mimicking a mosaic deletion. This was in fact due to the hidden mosaic trisomy of an extra, not-deleted, chromosome 22. In contrast, in salivary DNA, the $\log_2$ ratio was almost equal to 1 (Fig. 3C, right), advocating that the trisomic cell line was not significantly present in the salivary tissue.

In an attempt to understand the mechanism behind the presence of two anomalies -one structural and another numerical- on the same chromosome, microsatellite genotyping was performed on the patient and his parents. Fig. 3D shows an informative microsatellite marker localized to the chromosomal region 22q13.2. The patient's remaining allele in the deleted area was inherited from his father. The *de novo* microdeletion was thus considered to be of maternal origin. None of the markers distributed outside the deletion region on the chromosome 22 were informative within the limits of the technique. Therefore the parental origin of the mosaic trisomy could not be determined.

3. Discussion

The aCGH detected a *de novo* 1 Mb deletion in the 22q13.2 region. The deleted area contains about 20 genes, 3 of which are OMIM genes: *TNFRSF13C* has a role in immune cells survival and regulation (Thompson et al., 2001), *NAGA* codes for a glycoside hydrolase (Sakuraba et al., 2004), and *CYP2D6* is a cytochrome involved in the metabolism of endogenous and exogenous molecules (Gaedigk, 2013). The vast majority of deletions involving the 22q13 regions are terminal deletions with variable sizes: 100 kb–9.2 Mb (Sarasua et al., 2011), and up to 600 patients have been reported to date (Phelan and McDermid, 2012). The 22q13 deletion syndrome, also known as the Pheland-McDermid syndrome, is characterized by neonatal hypotonia, normal growth, global developmental delay, autistic behavior, absent or severely delayed speech and mild dysmorphic features (Phelan, 2008). *SHANK3* was suggested to be the candidate gene responsible for the neurological features of this syndrome (Wilson et al., 2003). The patient described here has an interstitial 22q13 deletion that does not involve the *SHANK3* gene. To the best of our knowledge, there have been four reports of patients harboring this kind of deletion, with a total of thirteen patients (Disciglio et al., 2014; Romain et al., 1990; Simenson et al., 2014; Wilson et al., 2008). Wislon et al. postulated that patients with deletions proximal to *SHANK3* might have a mild phenotype masked by the terminal deletion of *SHANK3*. Common features of patients with interstitial 22q13 deletion not involving *SHANK3* gene are developmental delay, absent or severely delayed speech, minor dysmorphic features and hypotonia. The

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