

Parkinson's Disease in a Patient with 22q11.2 Deletion Syndrome: The Relevance of Detecting Mosaicisms by Means of Cell-By-Cell Evaluation Techniques

Perandones C^{1*}, Farini VL², Pellene LA³, Sáenz Farret M³, Cuevas SM³, Micheli FE³ and Radrizzani M²

¹Scientific and Technological Coordination Unit of the ANLIS Directorate, National Administration of Laboratories and Institutes of Health, Argentina

²Laboratory of Neuro and Molecular Cytogenetic (CONICET), School of Sciences and Technology, CESyMA, National University of San Martín, Buenos Aires, Argentina

³Parkinson's Disease and Movement Disorders Program, Hospital de Clínicas, University of Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina

Abstract

We report the case of a male patient from an Ashkenazi Jewish ethnic group with a history of midline defects (congenital heart disease, high-arched palate and bifid uvula). At the age of 46 years, he came to our center complaining of resting tremor, and a neurological examination concluded Parkinson's disease. As a part of his approach, genetic evaluation was performed. Fluorescence in-situ hybridization (FISH) confirmed a mosaicism of a 22q deletion in 24% of the analyzed blood cells. Also, immunohistochemical studies were performed on samples from the minor salivary glands using a SNCA antibody. Intense SNCA immunoreactive profiles were obtained for cells from the salivary glands of the patient. This is, to our knowledge, the first description of the association of a mosaicism of a 22q11.2 microdeletion syndrome with Parkinson's disease.

Our findings suggest that, before excluding the involvement of the 22q11.2 deletion in the etiology of early-onset PD cases, the spectrum of evaluations should be extended to include more sensitive FISH analysis and immunohistochemical studies. The pathogenesis of early-onset PD in patients with 22q11.2 deletion syndrome remains unknown but, if elucidated, it may contribute to understanding the etiology of PD and ultimately to prevention and treatment strategies.

Keywords: Parkinson disease; Tremor; Immunoreactive

Introduction

The 22q11.2 deletion syndrome (22qDS), also known as Di George Syndrome or Velocardiofacial Syndrome (VCFS), is a common genetic disorder. It results from an autosomal dominant microdeletion on the long (q) arm of chromosome 22 which occurs de novo in approximately 90% of cases and is inherited in approximately 5–10% [1].

Prevalence of 22qDS is approximately 1 in 4000 live births [2]. The phenotypic presentation of VCFS is extensive and shows substantial variability across individuals [3]. The hallmark features of the syndrome are characteristic facial appearance, velopharyngeal insufficiency, conotruncal heart disease, parathyroid and immune dysfunction, developmental delays and learning difficulties [4].

Early-onset Parkinson disease (PD) refers to patients presenting with onset before the 50 years [5]. In this group, the probability of an inherited form is increased. Known genetic mutations account for 4% to 16% of early-onset PD cases [6,7] including LRRK2, PARK2, SNCA, PARK7, and PINK1 [8].

Case Report

We report the case of a 46-year-old male patient from an Ashkenazi Jewish ethnic group. He had a history of preterm birth at 7 months because of premature rupture of membranes. He was diagnosed with congenital heart disease (interventricular communication and subaortic stenosis) which was corrected surgically; he was also diagnosed with congenital left deafness and right hearing loss, high-arched palate and bifid uvula.

In his medical family history, his maternal grandfather had been evaluated because of psychiatric symptoms without a definitive diagnosis. His great-uncle in his maternal line was diagnosed with Parkinson's disease at the age of 70, while his second cousin in his maternal line suffered from mental retardation and congenital deafness.

Regarding his past medical history, he experienced seizures at 6 years in the context of fever. At the age of 10, he presented gum bleeding and after hematological evaluation he was diagnosed with Von Willebrand disease.

Because of psychomotor retardation, his academic performance was poor; he attended a special school. During adulthood, he was diagnosed with hepatitis C related to transfusions performed for cardiac surgery (subaortic stenosis); he was treated with pegylated interferon and ribavirin. He had no history of antipsychotic medication use or other dopamine blockers.

At the age of 46, he was brought by her mother complaining of left arm tremor, which presented mainly at rest. Because of his cognitive deficits and movement disorder, a previous physician had considered a diagnosis of Wilson's disease. In anamnesis, he denied the presence of pre-motor signs; a subsequent otolaryngological evaluation, however, revealed severe olfactory alteration in an olfactometry tests.

A general physical examination showed the presence of hypernasal speech, short stature and bifid uvula.

***Corresponding author:** Claudia Perandones, Scientific and Technological Coordination Unit of the ANLIS Directorate, National Administration of Laboratories and Institutes of Health, Dr. Carlos G. Malbran, Argentina, Tel: (54 11) 4303-1807/11; E-mail: claudia.perandones@gmail.com

Received October 31, 2015; **Accepted** November 28, 2015; **Published** November 31, 2015

Citation: Perandones C, Farini VL, Pellene LA, Sáenz Farret M, Cuevas SM, et al. (2015) Parkinson's Disease in a Patient with 22q11.2 Deletion Syndrome: The Relevance of Detecting Mosaicisms by Means of Cell-By-Cell Evaluation Techniques. Single Cell Biol 4: 123. doi:[10.4172/2168-9431.1000123](https://doi.org/10.4172/2168-9431.1000123)

Copyright: © 2015 Perandones C, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

On neurological examination, the patient was found inattentive. In cranial nerves, ocular motility was preserved, there was left eighth nerve deafness and hypoacusia in the right; motor examination showed hypophonia and hypomimia, marked bradikinesia in both arms, bilateral cogwheel rigidity and resting tremor in his upper extremities, predominating in the left arm. He also had postural and intention tremor, predominating in the left arm. We concluded PD and calculated UPDRS at that moment was 40 points. Additional investigations included ophthalmologic examination, which was negative for Kayser-Fleischer ring, and otolaryngological evaluation, which showed severe alteration on olfactometry.

He was started on ropinirole with modest clinical motor response, and a subsequent challenge with levodopa turned out positive, so we progressively titrated up the dose. While being on this dopamine agonist, he developed behaviors such as ordering objects, closing doors and cleaning the floor, compatible with punding, which were not problematic. He also developed insomnia, irritability, emotional lability, fear of being alone and disorganized conduct; therefore, quetiapine and clonazepam were added. During the following weeks, it was necessary to add levodopa and as the compulsive behavior worsened, ropinirole was tapered slowly without improvement. The department of psychiatry considered it necessary to add carbamazepine and promethazine, but the latter worsened the parkinsonian symptoms. Promethazine was then discontinued, with improvement of the motor aspect. Later levodopa was titrated up, with good clinical motor response.

Results

Blood count

(January 2012) Hemoglobin 14.7, mean corpuscular volume 85, hematocrit 44.0, erythrocytes 5.17, leukocytes 5.0, lymphocytes 40%, monocytes 10%, neutrophils 44%, eosinophils 5%, platelets 203 000.

Hemostatic evaluation

(December 2014): aPTT 37 sec., factor VIII 110%, Ristocetin cofactor 170%, Von Willebrand Factor 110%.

Platelet function

(December 2014): Bleeding time 5.0 minutes, in vivo platelet adhesiveness 30%.

(January 2012) Liver function tests: Alkaline phosphatase 63, total bilirubin 0.7 mg/dl, indirect bilirubin 0.4 mg/dl, direct bilirubin 0.3 mg/dl, aspartate aminotransferase 25 U/l, alanine aminotransferase 21 U/l, gamma-glutamyl transpeptidase 25 U/l, total proteins 7.4 g/dl.

(January 2012) Ceruloplasmin: 42 mg/dl. Urine copper: 24 ug/24 h.

(January 2012) Electrophoretic proteinogram: Total protein 7.4 g/dl, albumin 4.0 g/dl, alpha 1 globulin 0.28 g/dl, alpha 2 globulin 0.63 g/dl, beta globulin 0.86 g/dl, gamma globulin 1.63 g/dl.

(January 2012) Ionogram: Na 139 mEq, K 4.0 mEq, urea 43 mg/dl, creatinine 0.7 mg/dl. TSH 1.45, Total T3 1.28, Total T4 7.6.

Imaging studies

Brain MRI showed cortical atrophy. There was no evidence of metal deposits. Heart Doppler: Mild to moderate aortic insufficiency, normal left ventricular function, subaortic septal hypertrophy.

Genetic studies

FISH analysis: FISH (Fluorescent In-Situ Hybridization) was

conducted using probes that had been labeled with fluorescent oligonucleotides by means of nick translation. BACs corresponding to the control telomeric region -RP11-976a21 were label with FITC or the RP5-882j5 deleted region 22q11.2 and RP5-925j7 labeled with rhodamine. FISH analysis confirmed a 22q deletion in 24% of the evaluated blood cells (Figure 1).

Immunohistochemistry of salivary glands

Immunohistochemical studies were performed on samples from the minor salivary glands using the rabbit anti-alpha synuclein antibody () and developed with secondary antibody (sc-7011-r #-synuclein (C-20)-R and 30 sc-2004 and g anti-rabbit IgG-HRP, Santa Cruz, Intl., Ca. USA). Intense SNCA immunoreactive profiles were obtained (Figure 2).

Discussion

Although 22qDS is acknowledged as the most common autosomal deletion syndrome, the reported prevalence is lower than could be expected (1 in 4000 live births) [2]. This may reflect the lack of clinical detection in individuals with mild symptoms and/or incomplete penetrance.

The presence of PD in this syndrome has been recently reported. This underreporting may be due to confusion with parkinsonian symptoms associated with antipsychotic medication prescribed for the common psychiatric/behavioral features of the 22q11.2 deletion. This was the case of Krahn et al.; they reported parkinsonian symptoms for the first time in a patient with schizophrenia and chromosome 22 microdeletion. However, the use of antipsychotic medication predated the development of the parkinsonism [9].

It was Zaleski et al. who showed a consistent association of 22q11.2 deletion syndrome and PD in two patients. In these cases, the association was clear because antipsychotic medication did not complicate the diagnosis [10].

Possible evidence linking velocardiofacial syndrome with a synucleinopathy comes from a previous study, where the authors confirmed that substantially more children with 22q11 deletion syndrome (68%) as compared with neurotypical control subjects (13%) had University of Pennsylvania Smell Identification Test scores

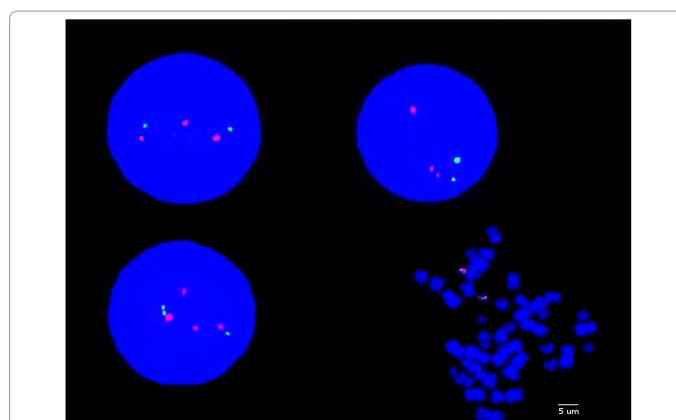


Figure 1: FISH analysis for 22q deletion syndrome. FISH analysis was performed on interphase chromosomes using the following probes: The figure shows the overlapping of the fluorescent marks on the DAPI-labeled DNA (blue). The loss of one of the red signals indicates the microdeletion. The green mark shows the centromere of chromosome 22. The bottom left interphase shows a normal nucleus and a metaphase with the microdeletion in one of its chromosomes 22 [17].

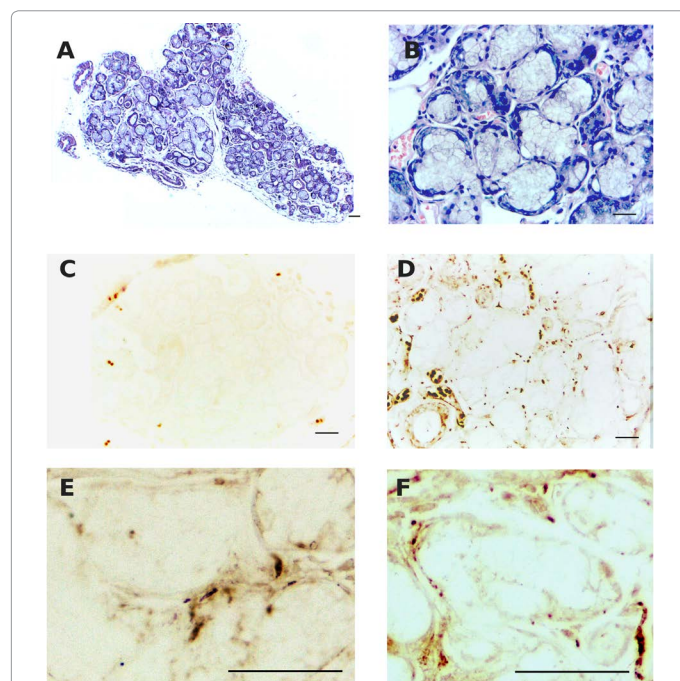


Figure 2: Immunohistochemical analysis of minor salivary glands. The first row shows the staining of the patient's minor salivary gland with Hematoxylin and Eosin at 10 X (A, left) and 400 X (B, right). The second row shows the staining control for the patient's gland, without the addition of the primary antibody at 200 X (C, left) and with the addition of the primary antibody (D, right). Abundant SNCA immunoreactive profiles were detected in the periacinar space. The third row shows (E, left) the image obtained from a patient with alpha-synuclein gene rearrangements. On the right (F), it shows the image obtained from the patient with 22q deletion syndrome at 400 X. Abundant SNCA immunoreactive profiles were detected in the periacinar space. The images were obtained in an optical microscope at 10, 20 and 40 X. The scale bar corresponds to 20 μ m for panels A, B, C and D. The scale bar corresponds to 50 μ m for panels E and F.

≥ 2 SDs below the standardization sample mean. This study lacked histopathological evidence; olfactory dysfunction, however, is typical in synucleinopathies [11].

More recently, the largest cohort of adults with a 22q11.2DS diagnosis was studied. Individuals with this deletion had a significantly elevated occurrence of PD compared with standard population estimates (standardized morbidity ratio = 69.7; 95% CI, 19.0-178.5), which suggests that 22q11.2 deletions represent a novel genetic risk factor for early-onset PD. In this study, the post-mortem analysis of 3 patients with 22q11.2 syndrome associated with PD revealed dopaminergic neuron loss in the midbrain substantia nigra in all three cases. Typical α -synuclein-positive Lewy bodies were present in the expected distribution in 2 cases but absent in the other one [12].

In our patient, we could also detect the presence of α -synuclein immunoreactive aggregates in his salivary glands, which have been shown to accumulate in PD patients and provide further evidence of the neurodegenerative pathology in this genetic syndrome [13].

Possible genes implicated in the pathway of PD and 22q11.2 syndrome include genes contained in the 22q11.2 deletion region, among them one of the best known for its role in dopamine catabolism, the catechol-O-methyl transferase (COMT) gene [12].

Other candidate genes include DGCR8, which encodes a key protein involved in the biogenesis of brain micro-RNA [14], micro-RNA miR-185, predicted to target LRRK2 [15], and SEPT5, which

encodes a protein that interacts with the product of PARK2 [16].

In contrast to previous reports, our patient had a family history of Parkinson's disease. However, it was a second-grade family member, and the onset of the disease was in adulthood.

As there was no previous use of antipsychotics, the diagnosis of Parkinson's disease could be made earlier. In cases where this has happened, the diagnosis has been delayed.

It is important to note that our patient presented symptoms consistent with punding; however, they did not resolve when the dopamine agonist was discontinued, and he still keeps closing doors and ordering objects in our center. Perhaps the psychiatric comorbidity common in this disorder constitutes a risk factor for the persistence of this behavior, or it was just that psychiatric issues were unmasked by dopamine agonists.

For research purposes, genetic analysis of 22q11.2 should be conducted in patients with early-onset PD, or at least in individuals with phenotypic features of this syndrome such as cardiac and palatal defects, learning difficulties and immunodeficiency, among others. To our present knowledge, this is the first description of the association of Parkinson's disease with a mosaicism of a 22q11.2 microdeletion syndrome.

Therefore, this case does not only provide more evidence about the relationship between Parkinson's disease and the 22q11.2 deletion syndrome, but it also highlights the relevance of performing individual cell-by-cell tests like FISH analysis, at least until single-cell sequencing becomes optimized and generally available. The pathogenesis of early-onset PD in patients with 22qDS remains unknown but, if elucidated, it may contribute to understanding the etiology of PD and ultimately to prevention and treatment strategies.

References

1. Robin NH (2005) Velo-cardio-facial Syndrome: A Model for Understanding Microdeletion Disorders. *American Journal of Human Genetics* 77: 1129-1130.
2. Bassett AS, McDonald-McGinn DM, Devriendt K, Digilio MC, Goldenberg P, et al. (2011) Practical guidelines for managing patients with 22q11.2 deletion syndrome. *J Pediatr* 159: 332-339.
3. Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, et al. (1997) Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *Journal of medical genetics* 34: 798-804.
4. Bassett AS, Caluseriu O, Weksberg R, Young DA, Chow EW (2007) Catechol-O-methyl transferase and expression of schizophrenia in 73 adults with 22q11 deletion syndrome. *Biol Psychiatry* 61: 1135-1140.
5. Butterfield PG, Valanis BG, Spencer PS, Lindeman CA, Nutt JG (1993) Environmental antecedents of young-onset Parkinson's disease. *Neurology* 43: 1150-1158.
6. Macedo MG, Verbaan D, Fang Y, van Rooden SM, Visser M, et al. (2009) Genotypic and phenotypic characteristics of Dutch patients with early onset Parkinson's disease. *Mov Disord* 24: 196-203.
7. Alcalay RN, Caccappolo E, Mejia-Santana H, Tang MX, Rosado L, et al. (2010) Frequency of known mutations in early-onset Parkinson disease: implication for genetic counseling: the consortium on risk for early onset Parkinson disease study. *Archives of neurology* 67: 1116-1122.
8. Houlden H, Singleton AB (2012) The genetics and neuropathology of Parkinson's disease. *Acta Neuropathol* 124: 325-338.
9. Krahn LE, Maraganore DM, Michels VV (1998) Childhood-onset schizophrenia associated with parkinsonism in a patient with a microdeletion of chromosome 22. *Mayo Clin Proc* 73: 956-959.
10. Zaleski C, Bassett AS, Tam K, Shugar AL, Chow EW, et al. (2009) The co-occurrence of early onset Parkinson disease and 22q11.2 deletion syndrome. *Am J Med Genet A* 149A: 525-528.

11. Sobin C, Kiley-Brabeck K, Dale K, Monk SH, Khuri J, et al. (2006) Olfactory disorder in children with 22q11 deletion syndrome. *Pediatrics* 118: e697-703.
12. Butcher NJ, Kiehl TR, Hazrati LN, Chow EW, Rogaeva E, et al. (2013) Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. *JAMA neurology* 70: 1359-1366.
13. Cersosimo MG, Perandones C, Micheli FE, Raina GB, Beron AM, et al. (2011) Alpha-synuclein immunoreactivity in minor salivary gland biopsies of Parkinson's disease patients. *Movement disorders : official journal of the Movement Disorder Society* 26: 188-1890.
14. Stark KL, Xu B, Bagchi A, Lai WS, Liu H, et al. (2008) Altered brain microRNA biogenesis contributes to phenotypic deficits in a 22q11-deletion mouse model. *Nat Genet* 40: 751-760.
15. Dweep H, Sticht C, Pandey P, Gretz N (2011) miRWalk--database: prediction of possible miRNA binding sites by "walking" the genes of three genomes. *J Biomed Inform* 44: 839-847.
16. Zhang Y, Gao J, Chung KK, Huang H, Dawson VL, et al. (2000) Parkin functions as an E2-dependent ubiquitin- protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1. *Proceedings of the National Academy of Sciences of the United States of America* 97: 13354-13359.
17. Halder A, Jain M, Kabra M, Gupta N (2008) Mosaic 22q11.2 microdeletion syndrome: diagnosis and clinical manifestations of two cases. *Mol Cytogenet* 1: 18.

Citation: Perandones C, Farini VL, Pellene LA, Sáenz Farret M, Cuevas SM, et al. (2015) Parkinson's Disease in a Patient with 22q11.2 Deletion Syndrome: The Relevance of Detecting Mosaicisms by Means of Cell-By-Cell Evaluation Techniques. *Single Cell Biol* 4: 123. doi:[10.4172/2168-9431.1000123](https://doi.org/10.4172/2168-9431.1000123)

OMICS International: Publication Benefits & Features

Unique features:

- Increased global visibility of articles through worldwide distribution and indexing
- Showcasing recent research output in a timely and updated manner
- Special issues on the current trends of scientific research

Special features:

- 700 Open Access Journals
- 50,000 editorial team
- Rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, DOAJ, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsgroup.org/journals/submission/>