# Complex movement disorder in a patient with heterozygous YY1 mutation (Gabriele-de Vries syndrome)

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# Abstract

*YY1* mutations cause Gabriele-de Vries syndrome, a recently described condition involving cognitive impairment, facial dysmorphism and intrauterine growth restriction. Movement disorders were reported in 5/10 cases of the original series, but no detailed description was provided.

Here we present a 21-year-old woman with a mild intellectual deficit, facial dysmorphism and a complex movement disorder including an action tremor, cerebellar ataxia, dystonia, and partial ocular apraxia as the presenting and most striking feature. Whole-exome sequencing revealed a novel heterozygous *de novo* mutation in *YY1* [NM: 003403.4 (YY1): c.907T>C; p.(Cys303Arg)], classified as pathogenic according to the ACMG guidelines.

# Manuscript

## Introduction

A mutation leading to haploinsufficiency of the *YY1* gene has been identified in an individual with unexplained syndromic intellectual disability[Vissers et al., 2010]. *De novo* mutations of *YY1* (n=10) or small deletions encompassing *YY1* (n=13) were reported in 23 individuals with a phenotype encompassing cognitive impairment, behavioral alterations, intrauterine growth restriction, feeding problems, and in some cases various congenital malformations[Gabriele et al., 2017]. This condition, initially labeled as “YY1 syndrome”, was subsequently renamed “Gabriele-de Vries syndrome” in the OMIM database. One further case has been published since the original report[Morales-Rosado et al., 2018], leading to a total of 14 patients in the Human Disease Genes websites series [<https://humandiseasegenes.nl/yy1/>].

*YY1* encodes a 414-amino acid zinc-finger transcription factor with known roles in both direct repression and activation of gene expression, cofactor recruitment to transcriptional regions, and possibly aiding chromatin remodeling[Cromer et al., 2015; Lee et al., 2004]. Other reported functions include activation of peripheral myelination[He et al., 2010]and regulation of T-cell cytokine gene expressive and the allergic immune response[Guo et al., 2008]. It is expressed in a variety of tissues and is well conserved across species. Complete loss of *YY1* in mice results in early embryonic demise, whereas heterozygous mice display growth retardation, neurulation defects and brain abnormalities, supporting a haploinsufficiency-driven model of disease[He and Casaccia-Bonnefil, 2008].

In the original series of 10 cases with *de novo* mutations, five patients presented with a movement disorder: three had dystonia, one tremor, and one a waddling gait. However, the clinical description of the movement disorder phenotype in this syndrome remains very sparse, the emphasis of previous descriptions having been on developmental problems and dysmorphism. Here we report a 21-year-old woman with a *YY1* missense variant in whom a severe, complex movement disorder was the most striking feature.

## Case report

Our proband is the second child of a healthy non-consanguineous Portuguese couple. Family history is unremarkable, including one healthy older brother. Following a normal pregnancy, she was born at 39 weeks’ gestation by vaginal delivery with a birth weight of 2580g (3rd centile), length of 47cm (10th centile) and head circumference of 33.5cm (10th-50th centile). She was mildly hypotonic and experienced some feeding difficulties in the first year of life as well as repeated pulmonary infections. Early developmental milestones were described as normal with walking at the age of 11 months, first words at 12 months and sphincter control at three years, but a possible psychomotor delay was noted at age 30 months by her daycare educators. She had left divergent strabismus that was surgically corrected at age four. Attention deficit hyperactivity disorder was diagnosed and she was temporarily medicated with risperidone and methylphenidate.

She started elementary school aged seven: psychometric evaluation at that age revealed a delay of approximately two years in cognitive abilities. She received special educational support and successfully learned to read and write.

An action tremor first developed at five years of age, initially in the upper extremities, left more than right, before becoming generalized. It became gradually more severe and is now the patient’s major cause of disability.

By the age of 10 years, the patient had lost her ability to write legibly and to complete activities of daily living such as feeding herself. Speech and gait problems also occurred, but there was no cognitive regression. At the age of 10, neurological examination showed resting, postural and kinetic tremor, myoclonic jerks involving the left arm, and static ataxia with normal muscular tone.

After completing compulsory schooling, she lived at home without further education or employment. Now aged 21 years, she remains dependent for activities such as feeding and fastening clothing. She cannot write and her speech is unclear but she is able to use a keyboard. She can still walk unassisted.

Recent physical examination identified the following findings (See Supplemental Video 1). She was extremely slim, almost cachectic: weight 47kg (10th centile), height 167cm (75th centile), head circumference 56cm (75th centile), body mass index 16.8. There was facial dysmorphism with a long asymmetric face, broad high forehead, mandibular prognathism and malar flattening with a short philtrum. Ears were small, nose long with a full nasal tip, palate high arched, upper lip indented shaped like a Gingko leaf and thick lower lip (Picture 1). Hands and feet showed no unusual features.

She was alert, cooperated well, and was able to follow instructions given in Portuguese. There was no aphasia but marked adductor-type laryngeal dystonia, making her speech difficult to understand.

Examination of ocular motility was hampered by her postural head tremor, but showed unsteady fixation and lack of smooth pursuit, especially towards the left, because of numerous saccadic intrusions. Reflex saccades were hypometric (gain 0.88, normal range 0.94-0.98) with prolonged initiation time (236ms, normal range 156-207ms) but their velocity was normal, and neither head-thrusts nor blinks preceding saccades were present. Optokinetic nystagmus was present horizontally but somewhat weaker towards the left and absent vertically. We noted frequent anticipatory saccades and saccadic intrusions (both square-wave jerks and saccadic oscillations), visible both at rest and when reaching the landing point.

Strength was full throughout the body, deep tendon reflexes were normal and symmetrical, and sensory examination, including vibration and position sense, was unremarkable. Muscular tone was reduced in all four limbs. A marked action tremor, both postural and kinetic with an intentional component, was present throughout the body, especially in the left arm. Generalized dystonia was apparent, especially affecting the neck and left hand, associated with a kyphotic posture and valgus knees. Cerebellar features were present including gait and stance ataxia.

There was no dysphagia on formal assessment of swallowing, but sticky foods tended to remain glued to the palate. Neuropsychological assessment confirmed normal object recognition and understanding of language, but memory and executive function were hard to assess, due to the difficulties with speech and writing.

Extensive clinical investigations were non-diagnostic, including karyotype, CGH (comparative genomic hybridization) array, testing of the *FMR1, SLC2A1*, and *POLG1/2* genes, mitochondrial DNA sequencing, muscle biopsy and extensive neurometabolic testing including thyroid hormones, acanthocytes, ceruloplasmin, alpha-fetoprotein, vitamin assays (B1, 2, 3, 6, 7, 9, 12, D, E) and liver and renal function. Video EEG at age 12 and nerve conduction studies were normal. Ophthalmological assessment ruled out telangiectasia and retinal abnormalities. MRI brain scan at eight years old was within normal limits: repeat scan at 20 years noted a slightly small cerebellum, but no definite atrophy.

Several pharmacological treatments were tried without benefit, including phenazepam, clonazepam, topiramate, lamotrigine and levodopa. An alcohol challenge did not ameliorate the symptoms. The anticholinergic biperiden gave mild but consistent improvement at a very low dose of 1mg/day but led to blurred vision and headaches at 8mg/day. Blurred vision resolved at 4mg/day but headaches persisted, so the drug was eventually tapered off.

## Methods

Informed consent for genetic testing and for publication, including video with recognizable face, was obtained from the patient and her parents.

### Whole exome sequencing with subsequent targeted bioinformatics analysis

The patient’s exome was captured using the Agilent SureSelect QXT Human All Exon V7 kit and sequenced on a NextSeq500 instrument (Illumina). Read mapping and variant calling were performed using BWA 0.7.13, Picard 2.2.1, GATK HaplotypeCaller 3.7 and annotated with ANNOVAR 2017-07-17 and UCSC RefSeq (refGene) downloaded on 2018-08-10. The variants were searched in various databases including dbSNP151, gnomAD 2.1, ClinVar 2018 and HGMD 2016. Pathogenicity prediction scores were obtained for missense variants using SIFT, PolyPhen, MutationTaster and CADD. Splicing effect alterations were assessed using dbscSNV. We analyzed a total of 1868 genes involved in developmental delays, dystonia, hereditary ataxia and cerebellar anomalies. Genetic workup was carried out independently in two different laboratories (London and Geneva).

## Results

### Genetics

Our patient was found to carry a novel missense variant in the *YY1* gene (NM\_003403.4): c.907T>C, p.(Cys303Arg) in exon 4. Segregation analysis showed that this variant occurred *de novo* in our patient. It is absent from the gnomAD database and also from ClinVar, LOVD and HGMD. The amino acid change was predicted as pathogenic by all algorithms used. The variant is located in the distal part of the gene where most of the pathogenic variants have been described[Gabriele et al., 2017], in a zinc-finger domain. According to the ACMG guidelines[Richards et al., 2015], we classified the p.(Cys303Arg) variant as pathogenic. Both laboratories discovered and confirmed the same mutation in the present patient.

## Discussion

Gabriele et al. have reported 10 individuals with *de novo* mutations in the *YY1* gene[Gabriele et al., 2017]. Four out of the 10 individuals carry truncating variants (stop or frameshift mutations) but the 6 other mutations are missense changes located in the various zinc-finger domains of the protein. The 13 cases reported with deletions are less informative, as large deletions may encompass other genes. More recently, Morales-Rosado et al. also reported a female patient with a *de novo* truncating mutation[Morales-Rosado et al., 2018]. We have identified a novel *de novo* missense variant, c.907T>C, p.(Cys303Arg), in the *YY1* gene, which is also located in a zinc-finger domain.

The original description of the “Gabriele-de Vries syndrome” fits our patient well: she has all the key features of facial dysmorphism, mild intellectual disability and infant feeding difficulties. The most striking feature in our proband, however, is her severe progressive movement disorder, which combines dystonic and cerebellar features and complex oculomotor disturbances. Five of the original 10 reported patients had movement disorders and interestingly four of these were older than 10 years, while all the five patients in whom no movement disorder was found were less than 10 years old. This suggests that the lifetime incidence of movement disorder could be high, as the younger members of the original cohort might not yet have had time to manifest it.

Hypotonia, likely representing a cerebellar problem, was mentioned in 3 out of 10 cases, pointing to cerebellar dysfunction as a prominent feature of the movement disorders phenotype seen in Gabriele-de Vries syndrome. Action tremor, both postural and kinetic with an intentional component, was the most striking and debilitating feature in our proband; it was mentioned only once in their 10 cases (the individual aged 39 years) but its nature was not specified. Oculomotor apraxia has not previously been reported in Gabriele-de Vries syndrome. Questionable atrophy of the cerebellum may reflect the cerebellar syndrome seen in our patient.

Interestingly, a recent paper reports that *THAP1* mutations (resulting in DYT-THAP1, previously known as DYT6, a primary dystonia with typical onset in adolescents or young adults, characterized by segmental, predominantly cranio-cervical dystonia with dysarthria, dysphonia and dysphagia, or predominantly upper limb dystonia) reduce the DNA occupancy of *YY1*[Yellajoshyula et al., 2017]. It was suggested that *THAP1* loss affects *YY1*-related genes through occupancy at shared loci, not by altering the expression of *YY1*. It is tempting to hypothesize that *YY1* mutations also have a negative effect on the transcription of *THAP1*, which could possibly explain the dystonia found both in our patient and in the older patients reported in the original series.

## Conclusion

Movement disorders including action tremor, ataxia, dystonia and ocular apraxia can be a major feature of disease related to *YY1* mutations. When faced with complex movement disorders in an individual with suggestive facial dysmorphism and mild to moderate intellectual disability, *YY1* mutations need to be considered. In young children, however, the movement disorder may yet appear.

# Video legend

First segment shows the patient in her teenage hood. Her severe action tremor makes self-feeding almost impossible. Second segment shows the patient aged 21 years. Laryngeal dystonia is evident on speech. At rest, generalized irregular tremor is seen. Dystonic posturing of the fingers is observed on arm extension. Tremor is exacerbated on reaching but there is no true past-pointing. Severe action tremor prevents writing. On walking, dystonic posture and gait ataxia are seen.

# Picture 1

Picture of the patient at the age of 21 years-old.

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# Authors' Roles

1) Research project: A. Conception, B. Organization, C. Execution.

2) Statistical Analysis: not applicable.

3) Manuscript: A. Writing of the first draft, B. Review and Critique.

MC: 1A, 1B, 1C, 3A

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SS: 1A, 1B, 1C, 3B

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MG: 1A, 1B, 1C, 3A

SL: 1C, 3A

SF: 1B, 3B

AM: 1B, 1C, 3B

AZ: 1C, 3A

ED: 1C, 3B

RO: 1A, 1B, 1C, 3B

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# Conflict of interest

The manuscript has not been previously published and is not under review at any other journal. No other related work is under submission elsewhere. All authors of the paper have participated to the study, revised the manuscript and approved the final version of the manuscript. There is no ghost writer. There is no financial or any other type of conflict of interest related to the manuscript.

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