Supplementary Online Content

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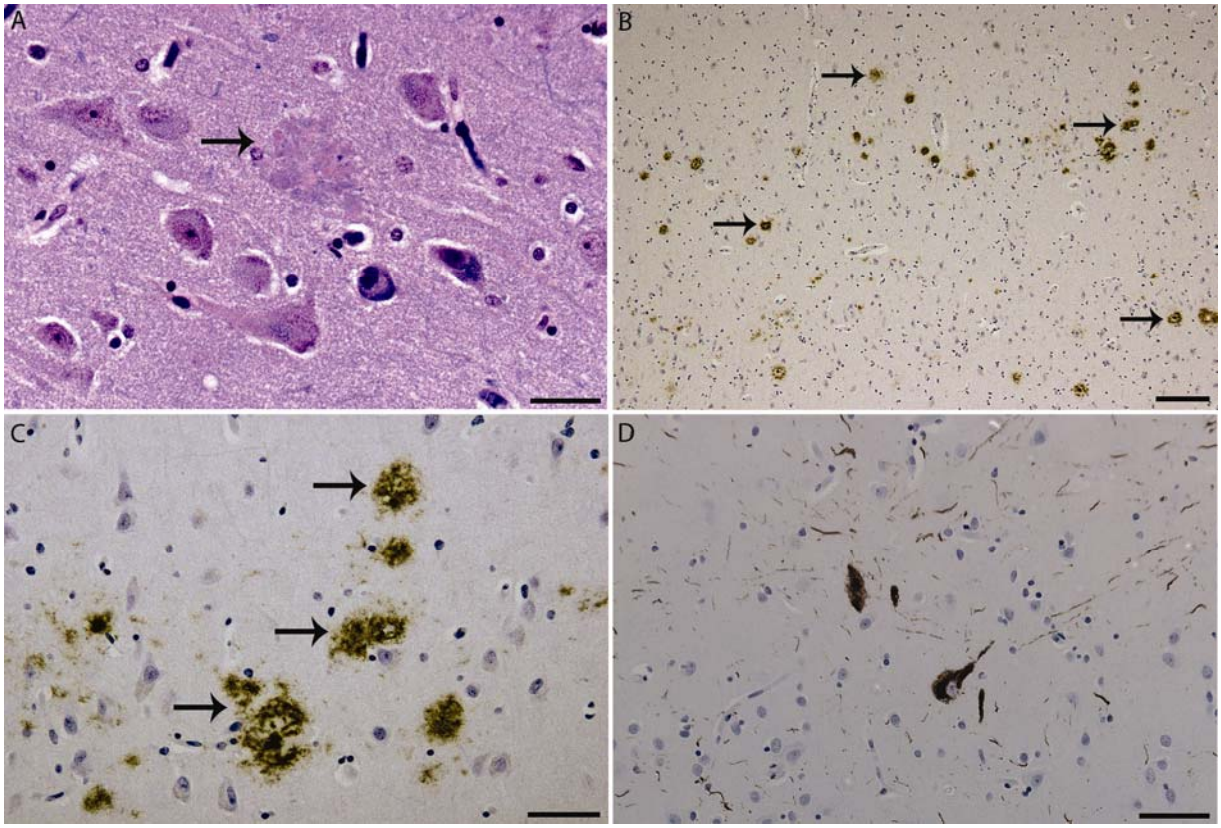
This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. Clinical and demographic features of adults with 22q11.2 deletions and early-onset Parkinson disease

	Case 1	**Case 2**	**Case 3**	**Case 4**
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian
Age at death (y)	56	58	61	Living
Sex	Female	Male	Male	Male
Post-mortem interval (h)	11	60	6	N/A[a]
Brain weight (g)	1260	1130	1350	N/A[a]
Features of 22q11.2DS				
Intellect[b]	Borderline to mild ID	Average	Average	Borderline to mild ID
Schizophrenia Age at onset	Yes 17 y	Yes 22 y	No	Yes 22 y
Seizures	Single (age 52 y)	No	No	Multiple (age at onset 28 y)
Hypocalcemia	Yes	Yes	Yes	Yes
Hypothyroidism[c]	No	Yes	No	Yes
Congenital heart defects	No	Tetralogy of Fallot	No	No

[a]N/A, living patient
[b]ID, intellectual disability
[c]Treated with thyroxine

eFigure 1. Other neurodegenerative pathology in Case 1. A) The amygdala contained frequent amyloid plaques visible with H&E staining (arrow). B, C) The parahippocampal gyrus showed moderate numbers of diffuse and neuritic plaques immunopositive for β-amyloid (arrows). D) The superior frontal gyrus contained tau-positive neurofibrillary tangles (brown). Scale bars = 50 μm in A, D; 300 μm in B; 100 μm in C.



eAppendix. Clinical case reports of adults with 22q11.2 deletions and early-onset PD

***Case 1*:** This 56 year old Caucasian woman had onset of psychosis at age 17 years, at which time she was hospitalized with symptoms meeting DSM-IV criteria for schizophrenia. The illness had a chronic course. Despite good compliance to antipsychotic treatments and the addition of paroxetine and low dose lorazepam, auditory hallucinations and multiple delusions persisted. Second generation antipsychotics (e.g., olanzapine) were tried but weight gain prompted a return to first generation antipsychotics (haloperidol, up to 6 mg) and risperidone (up to 4 mg) with anticholinergic medications (procyclidine or benztropine) for the extrapyramidal side effects. Tremors and muscle stiffness were initially attributed to side effects of antipsychotic medications. Stooped posture was present from at least age 40 years and gradually worsening bradykinesia began at age 45 years. A psychiatrist noted bilateral tremor of the hands and forearms as well as pronounced jaw tremor of unknown duration at age 52 years. Despite reducing antipsychotic medications, discontinuing paroxetine, and reducing caffeine intake, bilateral (left greater than right) pill-rolling tremors, bradykinesia, slurred speech, cogwheel rigidity, stooped posture, shuffling gait and problems with balance worsened. Occasional incontinence was also noted. There was rapid deterioration over several weeks at age 55, with severe tremors and akinesia that prompted hospitalization. Low dose risperidone and benztropine had been discontinued just prior to admission. A consultant neurologist diagnosed PD and started levodopa-carbidopa with rapid symptomatic response. At 100/25 mg TID levodopa-carbidopa, motor symptoms were significantly improved and mobility restored. Risperidone (0.5 mg) was subsequently restarted and levodopa-carbidopa reduced to BID because of auditory hallucinations. Some worsening of tremor and bradykinesia prompted the addition of benztropine (1 mg BID). The patient was discharged after several weeks and her last year was noted as the best in over a decade in terms of functioning and quality of life, despite some residual tremor, balance and speech problems, and mild psychotic symptoms.

Other history of note included a single generalized tonic-clonic seizure at age 52 years attributed to a respiratory tract infection and/or antipsychotic medications, although was also documented as hypocalcemic. CT scans and MRI scan revealed no intracranial abnormalities. An EEG showed epileptiform discharges intermittently from the left temporal region; a jaw tremor was also noted. A previous EEG at age 17 years had shown paroxysmal dysrhythmia of the fronto-central region.

***Case 2*:** This 58 year old Caucasian man met DSM-IV criteria for schizophrenia with an onset of psychosis at age 22 years. The illness had a chronic course but was managed fairly well with multiple first and second generation antipsychotics over his lifetime. He began feeling off-balance and stumbling when walking at approximately age 48 and presented with proximal muscle weakness at age 53 years. A consultant neurologist (AEL) diagnosed PD at age 54 years and began carbidopa-levidopa treatment (100/25 mg). A brain MRI at age 56 showed a few nonspecific foci of increased T2 signal intensity in hemispheric white matter compatible with microangiopathic change, as well as generalized enlargement of the cortical sulci. At age 57 years, bilateral (left greater than right) hand tremor was mild to moderate and intermittent. He sometimes had leg tremor. Schizophrenia was well-controlled with quetiapine (350 mg, increased to 375 mg following worsened psychotic symptoms). An EEG was normal. At age 58 years, proximal muscle weakness and akinesia had worsened. His speech became more slurred and there was significant drooling. He began to show severe and constant left hand and jaw tremors. Beginning about age 57 years, there was some gradual decline of memory and increasing emotional lability. Quetiapine had been increased to 400 mg following a relapse of some psychotic and depressive symptoms of schizophrenia, which may have contributed to the increased severity of his motor symptoms. As a result, his antipsychotic medication was going to be switched to clozapine. The patient received only two test doses of clozapine, however, over a two day period (total 18.75 mg) two days before death. Cause of death was secondary to cardiovascular failure and unrelated to clozapine initiation.

***Case 3*:** Additional details have been previously reported on this case.[1] This Caucasian man developed bradykinesia, bilateral tremors, mild difficulties with balance, and incoordination in his hands at age 43 y. He also had occasional stuttering and slurring of speech, and a lack of facial expression. He was diagnosed with PD at age 44 y by a neurologist and responded well to levodopa-carbidopa for several years. He had no history of psychiatric illness. Within a year of diagnosis with PD, he began to exhibit symptoms of depression and anxiety including feelings of worthlessness, social withdrawal, and altered eating and sleeping habits. He noted episodes of uncontrollable episodes of laughing and crying. His motor symptoms stabilized for several years then progressively worsened despite increases in his medications. He experienced akinestic rigid episodes and developed more severe gait difficulties, losing his balance at times. An MRI at age 53 y showed non-specific bright foci in hemispheric white matter and cavum velum interpositum. He began gambling at age 54 y, which was controlled with counselling. At

this time, his rigidity, tremors, and slurred speech were under good control with levodopa-carbidopa (100/25 mg, 8 tablets for 6 equal doses; also ropinirole, 5 mg four times a day; entacapone 200 mg tid; and domperidone 10 mg, 7 tablets for 5 equal doses) although would reoccur as medication wore off before next dose. He continued to deteriorate and decline in response to antiparkinsonian medications, moving to a nursing home at age 58. Symptoms of depression and anxiety worsened with poor response to antidepressants. Urinary retention and incontinence developed. He was treated for delusions and agitation with olanzapine (5 mg). He remained in the nursing home for almost 3 years, with gradual wasting because of feeding difficulties, and died of pneumonia at age 61.

***Case 4*:** This 48 year old Caucasian man began showing signs of schizophrenia at age 17, including delusions and disorientation, and was diagnosed with schizophrenia at age 20. The illness had an intermittent but severe course. He had numerous generalized seizures associated with antipsychotic medication (ages 28, 33, 37, 42, 43, 46, and 47 years) and was treated with various anticonvulsant medications. After responding poorly to a series of first and second generation antipsychotics, the patient began on clozapine at age 33. He began exhibiting slurred speech and stuttering at the age of 34. At age 39, the mother reported right-sided leg and arm weakness and rigidity and dragging of the right leg while walking. The right-sided weakness became so severe by the following year that he lost right-handed dominance for eating. At age 40, clozapine was reduced from 250 mg to 125 mg in an attempt to reduce excessive drooling. His stiffness worsened and was felt to be Parkinsonian; he responded well to benztropine (2 mg bid). Choreoathetoid movements of his head and tongue were noted. His affect was downcast and aggressive and he was treated with electroconvulsive therapy. Clozapine was reduced to 75 mg and benztropine was apparently not maintained. Later in the year, he demonstrated poor gag reflex and difficult swallowing. His speech became unintelligible and he had a lack of facial expression. He deteriorated to a catatonic state and exhibited urinary incontinence. Clozapine and then risperidone (2 mg) were completely discontinued at age 41 because of his movement problems. He began to require the use of a geri-chair due to balance problems. Following worsening of his stiffness, benztropine (2 mg tid) and levodopa-carbidopa (100/25 mg 2 tid) were started. He responded well to the antiparkinsonian treatments and clozapine was restarted. Bowel incontinence began at age 42. Clozapine was again discontinued, following a seizure at age 43. At age 44, his freezing episodes showed worsening. At attempt to taper the patient off of benztropine, levodopa-carbidopa, and lorazepam worsened his symptoms, leading to right-sided rigidity and affective changes. He showed a positive response to the addition of pramipexole (0.75 mg tid). He was diagnosed with depression and anxiety. A neurologist noted his parkinsonian symptoms but felt that the patient did not have typical PD due to a lack of “rigidity and hypokinesia”. At age 45, he was spending hours frozen in one position, was unable to keep himself from falling, and had difficulty controlling his body. He showed some deterioration of intellectual capacity. Stiff Man Syndrome was suspected by a neurologist and a trial of diazepam conducted without benefit. Entacapone was added to help control motor symptoms (200 mg). At age 46, a psychiatrist suggested that his symptoms and history were consistent with severe PD, including tremors, affective flattening, flexed posture, difficulty initiating gait, a tendency to fall, and hypersalivation. Freezing episodes became more frequent and prolonged and prevented voluntary movement. He was unable to swallow oral medications and regurgitated his food. At age 48, his antiparkinonsian medications included levodopa-carbidopa (100/25 mg, 3/4 tablets, 5 times a day) with 200 mg entacapone with each dose in addition to pramipexole 1.5 mg tid. He showed dramatic levodopa-carpodopa dose-related motor fluctuations, ranging from being completely immobilized in the Off state and able to walk, speak, and feed himself during the On state. He was not on any antipsychotic medication. He was recently seen by one of the authors, a movement disorders neurologist (AEL), and the diagnosis of PD was confirmed at age 48.

Other history of note for this patient includes a breech forceps delivery. An EEG at 46 y was normal. Brain MRI was normal at age 41 and showed nonspecific white matter lesions at age 47. At age 38, an EMG and CT scan of the craniocervical junction was normal. A head CT scan showed cavum septum pellucidum but was otherwise normal. A cervical and lumbar spine x-ray revealed the absence of a portion of the odontoid process and bifid spinous process at C1.

eReference

1. Zaleski C, Bassett AS, Tam K, Shugar AL, Chow EW, McPherson E. The co-occurrence of early onset Parkinson disease and 22q11.2 deletion syndrome. *Am J Med Genet A.* 2009; 149A(3):525-528.