PSYCHOPATHOLOGICAL PHENOTYPE AND POSSIBLE TREATMENT STRATEGIES IN PATIENTS WITH PHELAN-McDERMID SYNDROME

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Prof. Dr. Willem M.A. Verhoeven

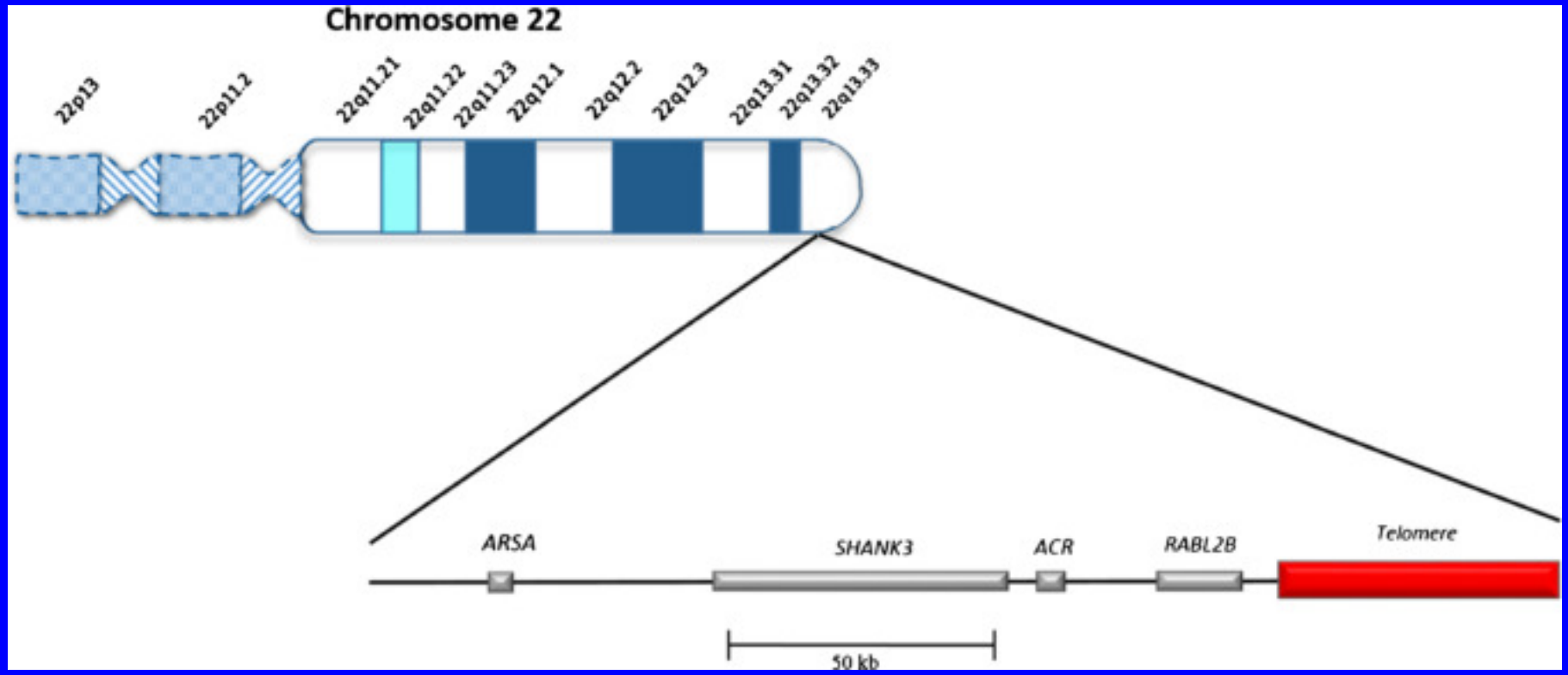
1. Former Head at the Centre of Excellence for Neuropsychiatry and Director Residency Training, Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands
2. Emeritus Professor of Psychopharmacotherapy, Department of Psychiatry, Erasmus University Rotterdam, The Netherlands
3. Present function: consultant neuropsychiatrist for institutes for people with intellectual disabilities and psychiatric hospitals (diagnostic, pharmacological and genetic issues)

GENETIC ETIOLOGY OF PHELAN-McDERMID SYNDROME

1. Deletions or other genetic variants on distal 22q encompassing the *SHANK3* gene (simple deletion, unbalanced translocation, ring chromosome or other chromosomal rearrangement)

2. Mutation in *SHANK3* gene (a distal gene in 22q13.33)

Schematic representation of the short (p) and long (q) arms of chromosome 22, along with mapped areas of particular interest. The genes located in area 22q13.3 (ARSA, **SHANK3**, ACR and RABL2B) are represented in a linear fashion, along with their respective sizes.



Adapted from: Costales & Kolevzon. Neurotherapeutics 12: 620-630, 2015

Main clinical characteristics of Phelan-McDermid syndrome

- neonatal hypotonia
- recurrent upper airway infections
- *absence of major dysmorphisms*
- developmental delay / highly variable intellectual disability
- *impaired to absent speech and expressive language*
- *increased sensitivity to sensory stimuli*
- sleep disturbances
- *symptoms from the autism spectrum*
- *decreased perspiration / high pain treshold*
- hypothyroidism / lymphoedema
- epileptic manifestations
- congenital cardiac and urogenital anomalies
- structural cerebral abnormalities (e.g. cerebellar vermis hypoplasia)
- regression (loss of acquired skills), permanently or for extended period and often triggered by seizures or infections
- *atypical bipolar disorder ± catatonic features*

Overview of 24 adult patients with Phelan-McDermid syndrome (cumulative prospective study)

Etiology

***de novo* deletion:**
18 patients (f=11; m=7); in two caused by unbalanced translocation and in two brothers by germline mosaicism in the mother [could not be proven]

***de novo* mutation:**
6 patients (f=4; m=2); in two sisters caused by mosaicism in the mother

Overview of the deletion size in 18 patients with Phelan-McDermid syndrome *

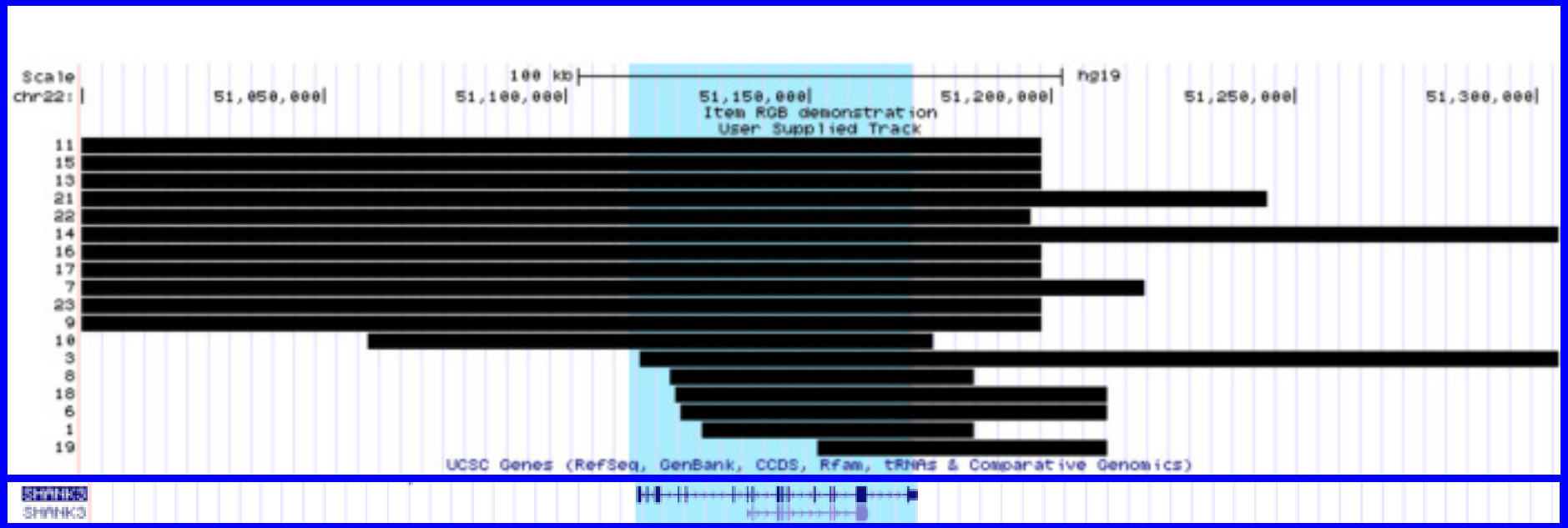


*Figure composed by Dr. Nicole de Leeuw, Department of Human Genetics, Radboudumc, Nijmegen

Characteristics of 24 patients with Phelan-McDermid syndrome - 1

Age range: 16-52 years (+ one 76-year-old female)

Level of intellectual disability

mild/moderate: n=5

moderate: n=5

moderate/severe: n=4

severe: n=6

profound: n=4

Language development

limited reciprocal conversation: n=3

sentences or 2-3 word phrases: n=11

single or no functional words: n=10

Characteristics of 24 patients with Phelan-McDermid syndrome – 2

Pre-existent behavioural concerns*

Mood lability / depression	n=19
Psychotic symptoms	n=4
Catatonic symptoms	n=5
ADHD-like symptoms	n=16
OCD-like symptoms	n=5
Regression	n=4

*several patients with more than one behavioural concern

Characteristics of 24 patients with Phelan-McDermid syndrome - 3

-History of challenging behaviours: nearly all
-Sleep disturbances: n=8
-Genuine epileptic seizures: n=2
-Secondary epileptic seizures: n=2
(meningeoma / malignant hypertension with ischaemic infarct in infancy)
-Lymphoedema: n=3
-Hypothyriodism: n=1
-Congenital renal anomalies: n=2
-MRI brain adulthood (only in 12): cerebellar vermis hypoplasia and/or enlarged ventricles/cerebral atrophy: n=6; other 9 without abnormalities
-Regression: n=4 (age start: ± 40 years; so far only in deletion patients)

Characteristics of 24 patients with Phelan-McDermid syndrome - 4

Previous psychiatric diagnoses*

Autism spectrum disorder: n=19

Attention Deficit Hyperactivity Disorder: n=1

Depression: n=10

Psychosis: n=7 (with catatonic features: n=4)

Bipolar disorder: n=3

*in some patients more than one psychiatric diagnosis

Previous pharmacological treatment**

Variety of antipsychotics and antidepressants or combination: nearly all

Mood stabilizing agents: n=11

Psychostimulants: n=1

Clonidine: n=1

**duration of treatment mostly to short and dose adjustment not based on plasmaconcentration

Actual psychiatric diagnoses in 24 patients with Phelan-McDermid syndrome*

Atypical bipolar disorder:	n=17 (71%)
Autism spectrum disorder:	n=7
Schizoaffective disorder:	n=1
Recurrent catatonic features:	n=4
Obsessive compulsive disorder:	n=1
No psychiatric diagnosis:	n=2

P.M. In some patients more than one psychiatric diagnosis

*Diagnoses actualized in interdisciplinary consultation meetings and, in the presence of the parents or primary caregivers, followed by treatment advices.

Treatment advice in 24 patients with Phelan-McDermid syndrome

Mood stabilizing agents

-Valproic acid: n=11 (600 up to 2100 mg daily; dose adjustment according to clinical response and/or plasma concentration)

-Carbamazepine: n=1 (600 mg)

-Lithium carbonate: n=6 (500-1200 mg daily; dose adjustment according to clinical response and/or plasma level)

-ECT: none

Antipsychotics

Quetiapine: n=6 (500-1200 mg daily)

Olanzapine: n=4 (2,5-15 mg daily)

Contextual measures only

n= 6

P.M. In almost all patients combination of psychotropics and contextual measures

Treatment effects in 24 patients with Phelan-McDermid syndrome

In 60% of patients with a diagnosis of atypical bipolar disorder gradual stabilization of mood and behaviour after start of treatment with mood stabilizing agent (mostly valproic acid) in combination with atypical antipsychotic (10 patients).

In case of comorbid catatonic features (n=5), remission in all patients either spontaneously or after treatment with lorazepam ± low dose olanzapine.

Contextual measures (avoiding overestimation and excessive environmental stimuli) crucial in maintaining remission of psychiatric symptoms.

Course of disease, treatment efficacy and general functioning interdisciplinary monitored (interval 3, 6 or 12 months) for a period varying from 1 to 5 years.

In case of slowly progressive regression (n=4), no effect of psychopharmacological interventions. In those patients, adjusting contextual factors at the level of performance in terms of daily activities and cognitive functions.

Example of male patient aged 38 with regression

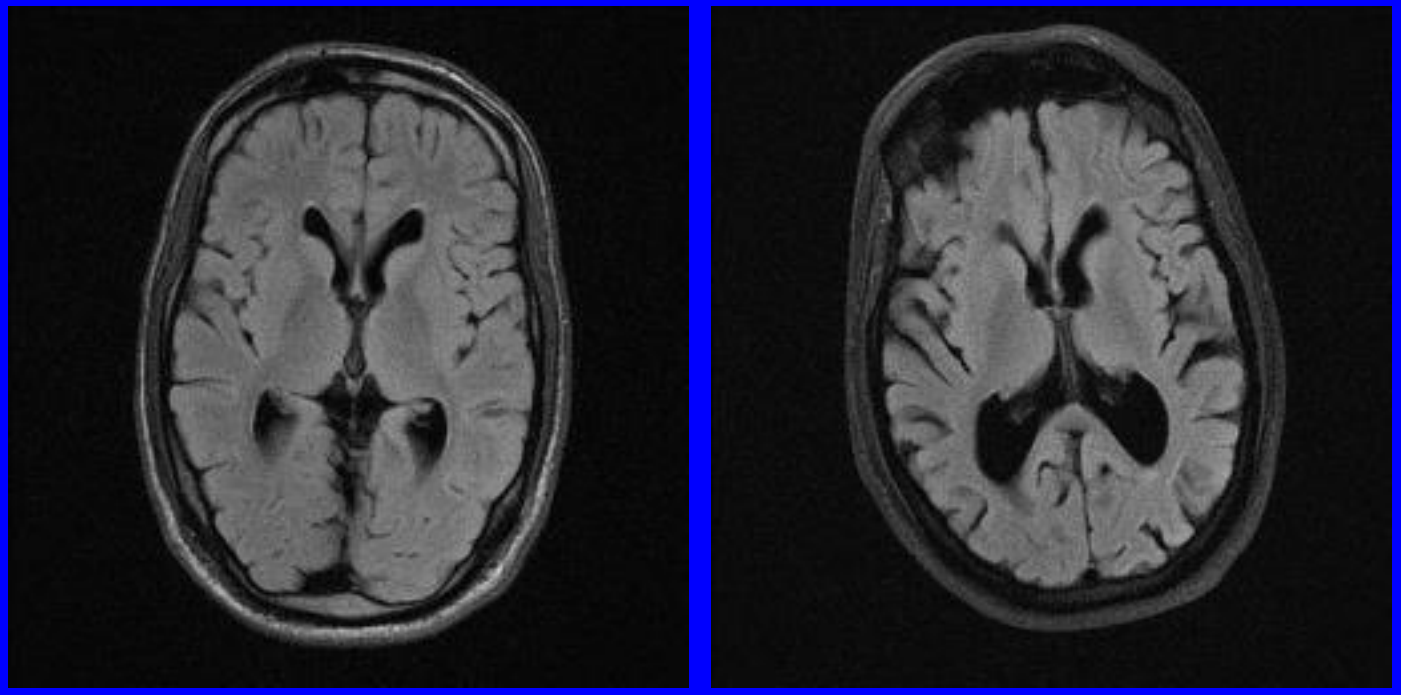
(published as patient 2 in Neuropsychiatr Dis Treat 8: 175-179, 2012)

Since about 3 years gradual decline of daily activities and cognitive as well as motor functioning despite adequate treatment with valproic acid and quetiapine together with adjustment of contextual parameters.

At present, dementia-like syndrome and apathy symptoms (lack of motivation, interest and initative).

Advise: discontinuation of all psychotropics and renewed referral to clinical geneticist (additional disorder?).

MRI brain of male patient aged 38 with progressive regression



Development of generalized cerebral atrophy
between 2011 en 2018 seen on T2* images

Conclusions about psychopathological phenotype and treatment approaches in 24 patients with genetically proven Phelan-McDermid syndrome -A

1. The psychopathological phenotype is characterized by atypical bipolar disorder.

2. Catatonic symptoms (n=5) resolve either spontaneously or after introduction of olanzapine ± temporarily lorazepam.

3. The preferred pharmacological treatment strategy comprises a mood stabilizing agent (valproic acid or, if possible, lithium carbonate), combined with an atypical antipsychotic (quetiapine or olanzapine).

Conclusions about psychopathological phenotype and treatment approaches in 24 patients with genetically proven Phelan-McDermid syndrome -B

4. In general, any psychopharmacological intervention should be accompanied by adaptation of contextual parameters.

5. Start psychotropics always slowly and in low dose, preferably after pharmacogenetic analysis (CYP2D6 and CYP2C19) and under regular control of plasma concentration and metabolic parameters.

6. The efficacy of treatment interventions of any kind should be monitored periodically in multidisciplinary consensus meetings.

Concluding Remarks

1. Phelan-McDermid syndrome may be underrecognized because of the absence of major dysmorphic features and unfamiliarity with genetic disorders in general psychiatric practice.

2. In case of normal array analysis, exome sequencing is warranted to detect *SHANK3* mutation.

3. It can be expected that with regular use of exome sequencing a diagnosis of Phelan-McDermid syndrome will be established more frequently.

4. If technically possible, MRI brain scanning should always be performed and repeated in case of suspected regression.