Pitt–Hopkins syndrome (PTHS) is characterized by intellectual disability, distinctive facial characteristics, breathing abnormalities, and repetitive behaviours. It is caused by genetic deletions/mutations resulting in TCF4 haploinsufficiency. To date, some 66 patients with confirmed TCF4 changes have been studied worldwide, mainly investigating somatic and genetic aspects.

Early descriptions of PTHS in individuals with intellectual disability emphasized an abnormal breathing pattern, distinctive facial features, and postnatal microcephaly. Further definition of the PTHS phenotype in later publications included severe developmental delays in motor and speech development, episodic diurnal hyperventilation with apnoea, and frequent motor stereotypies. Impairments in all participants were beyond what would be expected for cognitive abilities, fitting a classification of ASD.

METHOD
Participants
The parents of 10 individuals with PTHS were recruited through the Dutch PTHS Family Association. The association knows of 21 individuals with PTHS; participation in the study was determined on the basis of the distance between the family residence and the research centre, and the availability of family residence and the research centre, and the availability of family residence and the research centre.
the family within the time-frame of the study. The study group consisted of four females and six males residing in the Netherlands and Belgium; seven were born between 1998 and 2008, and three between 1987 and 1991. All had a molecularly confirmed TCF4 mutation. All parents gave written informed consent, and the central Medical Ethical Review Committee (Mental Health) gave permission to perform the study.

**Test Instruments**

All participants were examined by the same child psychiatrist (JvB) and neuropsychologists (PJv, MF). The child psychiatrist is experienced in assessing individuals with autism and other developmental disabilities. In-person interviews with parents were used to assess past and current development, and functioning for the domains communication, (adaptive) behaviour, and social–emotional development. Parents were invited to provide further information through a standardized questionnaire assessing emotional and behavioural problems.

### Bayley Scales of Infant Development (BSID-II)

Mental and motor functioning was assessed using the Dutch version of the Bayley Scales of Infant Development, 2nd edition (BSID-II), with Dutch norms, for developmental ages between 0 and 48 months. The BSID-II is considered a reliable and valid instrument. The raw scores on the motor and mental scales were converted into age-equivalents to determine level of motor and mental functioning.

### Autism Diagnostic Interview – Revised

In addition to an in-person psychiatric examination of all participants by an experienced child psychiatrist, one or both parents of eight children were interviewed using the Autism Diagnostic Interview-Revised (ADI-R), the parents of two participants could not be interviewed for practical reasons. The ADI-R is considered a reliable and valid instrument. The ADI-R is a semi-structured diagnostic interview designed to elicit developmental information, a history focused on autism-specific criteria, and information on actual behaviour as manifested in the child’s daily life. The instrument carries the risk of overclassification of autism when used in the assessment of individuals whose mental age-equivalent is less than 24 months. The severity of intellectual disability associated with PTHS demands that ADI-R results should be interpreted with great caution, but we considered the ADI-R a useful tool to establish a developmental history, collect data on current behaviours, and supplement the in-person psychiatric and psychological assessments of the participants. Indeed the ADI-R has previously been used with individuals functioning below a mental age of 24 months, as there is a dearth of adequate instruments available for individuals with intellectual disability and possible comorbid ASD.

### Vineland Adaptive Behaviour Scales

The Vineland Adaptive Behaviour Scales – Survey Form (VABS) was used to assess personal and social self-sufficiency. The VABS measures the level of adaptive functioning with regard to communication, daily living skills, and socialization. These measures provide an overall adaptive composite score, allowing for a classification in adaptive levels. The VABS has good psychometric properties. Decile scores were also determined. These scores are likelihood assertions concerning the level of cognitive functioning based on a Dutch sample of children between the ages 5 years and 18 years with an IQ <70.

### Developmental Behaviour Checklist

The Developmental Behaviour Checklist-Primary Carer (DBC-P) for the children and the Developmental Behaviour Checklist for Adults (DBC-A) for those above 18 years were used to assess behavioural and emotional problems. The DBC-P is a 96-item checklist specifically developed to assess a broad range of behavioural and emotional problems in individuals with intellectual disability. Parents rate items on a three-point scale. The DBC-P is considered reliable and has been validated in a large sample of Dutch children with intellectual disability. The DBC-A is a 107-item instrument with similar properties but suited for adults. The questionnaire is completed by someone who knows the person well. The DBC-A has acceptable reliability, good validity, and satisfactory psychometric properties.

**RESULTS**

The results of the present clinical study include narrative descriptions of individual child psychiatric assessments and clinical observations of interaction, communication and behaviour. These are presented in the Appendix SI (supporting information published online), while summarized findings from clinical assessments, measurements of cognitive and adaptive functioning, assessments of past and current development, and assessments of behavioural and emotional problems are described here.

### Clinical Assessments

These showed that without exception, all participants made repetitive hand and/or finger movements (e.g. flapping, twisting, waving or flicking hands and/or fingers repetitively). Nine participants repetitively fiddled with toys or other items by spinning, twiddling, banging, tapping, twisting, or flicking them repeatedly and showed a fascination with a specific object or part of the object. Six participants enjoyed playing repetitively with the same toy, listening to the same music, or watching the same video/DVD repeatedly. Examinations further showed that nine of the participants were non-verbal or produced very few words, while breathing abnormalities were present in six and ranged from overbreathing and breath-holding spells to gasping or sighing. Aggression
towards self is present in five participants and towards others in four. Most participants exhibited an amiable demeanour, but also showed high levels of self-absorption and difficulties in engaging socially. The parents of five participants noted difficulties when changes in the routine occurred. None of the participants would become upset at minor changes in the home or to objects, none insisted on wearing the same clothes or arranged toys in rows or patterns. These behaviours have not been reported in previous publications.

**Bayley Scales of Infant Development (BSID-II)**
The scores for mental age and motor development as measured using the BSID-II are shown in Figure 1. As participants had severe intellectual disability and a chronological age above the norms of the BSID-II, only age-equivalent scores are shown and no standard scores. The chronological age of the participants lies between 32 and 289 months and the developmental age between 3.5 months and 15 months for the mental scale and between 4 months and 19 months for the motor scale. With the exception of one young child, all participants performed better on the motor scale than on the mental scale.

**Autism Diagnostic Interview – Revised (ADI-R)**
Participants 2 and 5 were not measured. The ADI-R items scores on the three domains, social skills and play, communication (verbal and non-verbal), and behavioural abnormalities, showed the following results.

Participants exhibited the highest scores, well above the cut-off level, on the domain of social interactions and play. Eight participants scored at or above the cut-off level on both the social and communication domains. Participants 6 and 10 did not score above the cut-off on the behavioural domain. These ADI-R scores in themselves should not be interpreted as conclusive of autism or indicative of symptom severity, especially as mental age-equivalents in this group were lower than the minimum developmental level described in the ADI-R manual. However, they add to and corroborate other findings.

**Vineland Adaptive Behaviour Scales (VABS)**
VABS results (Fig. 2) were determined with age-equivalent scores. Only the eldest participants performed beyond a developmental age of 20 months. The domains of daily living skills and communication appear to be relative strengths, with weaker functioning in the domain of socialization. It also seems that with increasing age very little progress in adaptive functioning is accomplished.

The decile scores in the present study showed a very profound intellectual disability in seven of eight participants and profound disability in one participant (participant 3). In the case of participants 1 and 2, their young age prevented calculation of a decile score. The three participants older than 18 years (participants 8, 9, and 10) were categorized as category 1 (lowest category), although they fell outside the last age range of 14 to 18 years. However, because they are older and fall within category 1, it is unlikely that we are underestimating their cognitive functioning.

**Developmental Behaviour Checklist (DBC)**
The DBC assessment revealed two participants (participants 6 and 10) with scores above the clinical cut-off level for problem behaviours for age group (Fig. 3). Clinical cut-off scores for the age group below 18 years (46) and for the age group above 18 years (51) are shown in Figure 3 as separate dotted lines. Total problem behaviour in participant 6 was caused by a high score on the Self-Absorbed scale, whereas participant 10 scored highly on the Communication Disturbance and Disruptive Behaviour scales.

All participants had high scores for self-absorption. Five of the seven participants below 18 years scored just above threshold on the DBC Autism Screening Algorithm. This algorithm

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**Figure 1:** Developmental level of mental and motor functioning, measured by the Bayley Scales of Infant Development (BSID), compared with chronological age.
is not available for adults using the Developmental Behaviour Checklist for Adults.

**DISCUSSION**

This is the first study of development, cognition, and behaviour in classic PTHS. The results of this exploratory study show that all participants share (very) profound intellectual disability, severe impairments in social interactions, severe impairments in communication and language, and highly frequent, intense stereotyped behaviour consisting primarily of repetitive hand and finger flapping/twisting and/or rocking. Table I compares frequently reported features of TCP4 deletions and mutations with our findings in the present study.

We have previously assessed cognition, behavioural phenotype, and autism in Marshall–Smith syndrome (MSS), a very rare entity characterized by failure to thrive, developmental delay, abnormal bone maturation, and a characteristic face. In comparison with the MSS study with a similar methodology, the findings in the present study indicate that in classic PTHS the behavioural phenotype is clearly similar to behaviours seen in ASD. This can be noted not only in the difficulties in engaging and communicating with others, but also in the much higher occurrence and level of severity of repetitive motor stereotypies, repetitive play and fascination with specific objects, and difficulties with changes in daily activities or routines. The motor stereotypies in our study are also more prevalent than reported in several genetic studies of PTHS (see Table I), suggesting that these behaviours may be less recognized as a distinct characteristic of PTHS.

Higher levels of repetitive motor behaviours may be explained by the lower levels of adaptive and cognitive skills found in our participants, or may be part of a phenotype of
ASD, especially when occurring together with other behaviours such as impairments in social interaction and communication, repetitive play, fascination with specific objects, and insistence on daily routines, such as was the case in our sample. Severity of intellectual disability is considered a risk factor for difficulties in communication and social interactions, sometimes resulting in behavioural problems. Previous publications have emphasized the increased vulnerability to comorbid psychopathology to which individuals with developmental disability are prone. Comorbidities associated with intellectual disability include a high prevalence of epilepsy and behavioural, psychiatric, and sensory disorders. Higher prevalence and severity of comorbid disorders is closely related to lower levels of intellectual functioning. In addition, when intellectual disability is highly prevalent in one specific diagnostic group, clinician expectation of an individual’s developmental potential may be biased. This fact, combined with the lack of suitable instruments for measuring severe intellectual disability and associated behavioural problems, may prevent more thorough evaluations of cognitive and adaptive functioning in both clinical and research settings. In the study of genetic syndromes, differentiating between deficits related to intellectual disability with severe developmental delay and deficits related to autism remains difficult.

Phenotypic overlap with comparable impairments in social communication in autism, and in intellectual disability and schizophrenia may be caused by impaired filtering and information processing at brain level, and by atypical responsiveness to social and learning environments at behavioural level. Communication, social interaction, and learning in humans is determined by speech and language abilities, by the capacity to imitate and to understand the intent of the other person, and by non-verbal expressions such as eye gaze, joint attention, facial expressions, gestures, and postures. Language plays an important role in understanding social interactions, which is part of social cognition. Social cognition, in turn, is necessary to acquire language, and it includes the capacity to follow the other person’s gaze to objects of interest, imitate, and understand the meaning of another person. In our sample of individuals we found very low levels of cognitive ability and many behaviours similar to autism, such as severe impairments in communication and language, difficulties in social engagement, fascinations with specific objects, and very frequent and intense motor stereotypies. In contrast with this is the fact that we also found that nine out of 10 of the participants had a happy temperament, as was previously reported in studies of classic PTHS. However, we found that this seemed to be more indicative of a mostly contented state and did not necessarily indicate intent to interact socially. We concluded that ASD, of varying severity, may be part of the phenotype of classic PTHS.

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Many studies have shown that although a particular genetic variation may be the same, the behavioural outcome is not necessarily completely predictable. Behaviour will also be influenced by interactions within social and learning environments and by reactions from that environment to the individual’s tempera-
strength, external features, and neuropsychological deficits. Studying phenotypes of rare and ultra-rare genetic syndromes associated with severe intellectual disability has made it clear that, although individual outcomes may arise from genetic differences, the expression of genes affecting structure, development and function of the brain is also influenced by the interplay between genes, learning, and social context, and too much emphasis on biological determinants should be avoided.43,44

Strengths and limitations of the present clinical study
The major strengths of our study are that participants constituted a diagnostically homogeneous group with a diagnosis of PTHS caused by TCF4 alterations, that all participants were directly assessed through individual psychiatric examinations and a robust, comprehensive battery of tests, and that they had a wide (chronological) age distribution, which allowed assessments from toddlerhood to young adulthood. Nonetheless, the following limitations of the study also need to be considered. First, our sample of 10 participants is relatively small, although it could be considered substantial in light of the rarity of the syndrome. Second, the lack of suitable instruments to measure cognitive functioning directly in individuals with severe intellectual disability required an a priori judgement of approximate cognitive level through clinical psychiatric assessment. In our study, all participants scored within developmental levels that could be measured by our instrument of first choice (Bayley Scales), and the use of another instrument was not necessary. Similarly, it should be noted that use of the ADI-R to assess individuals whose mental age-equivalent is below a developmental level of 24 months carries the risk of over-classification of autism. However, in this study the results of the ADI-R were used to add to other data collected through individual psychiatric assessments, informant reports, and individualized standardized testing. Third, potential confounders include the facts that recruitment of potential participants was constrained by geography (distance between family residence and research centre) and by availability of families within the time-frame of the study.

Conclusion
This first exploratory study of cognition and behaviour in classic PTHS shows (very) profound intellectual disability, severe impairments in communication and language with difficulties in engaging socially, fascinations with specific objects, and very frequent and intense motor stereotypes. We conclude that the quality and intensity of social, communication and behavioural difficulties in our sample are beyond what would be expected for individuals with a very low cognitive level and therefore cannot be readily explained by it. Thus, we conclude that ASD may be part of the phenotype of classic PTHS, albeit presenting in varying degrees of severity.

Changes in TCF4 in PTHS have been implicated in neurodevelopmental outcomes of intellectual disability, epilepsy, autism, and schizophrenia, though their precise impact on the development and function of neuronal networks is still unclear. Understanding the neurodevelopmental phenotype in classic PTHS may be useful for the understanding of other disorders that share some of the same behavioural, cognitive, and possibly genetic features. Continued studies of rare genetic disorders will eventually, through longitudinal data, allow for improved recognition of shared aetiologies and comorbid conditions. They will increase our understanding of significant contributions from social and learning environments, shed more light on individual and group-level developmental trajectories and on changes over time, and suggest possibilities to improve outcomes.

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We would like to thank the Dutch Pitt–Hopkins Syndrome Family Association and the participants and their families for making this study possible.

Online material/supporting information
Additional material and supporting information may be found online.

Appendix S1: Narrative descriptions of individual psychiatric assessments, and clinical observations of interaction and behaviour.

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References
