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Consensus recommendations on counselling in Phelan-McDermid syndrome, with special attention to recurrence risk and to ring chromosome 22

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ABSTRACT

This paper focuses on genetic counselling in Phelan-McDermid syndrome (PMS), a rare neurodevelopmental disorder caused by a deletion 22q13.3 or a pathogenic variant in *SHANK3*. It is one of a series of papers written by the European PMS consortium as a consensus guideline. We reviewed the available literature based on pre-set questions to formulate recommendations on counselling, diagnostic work-up and surveillance for tumours related to ring chromosome 22. All recommendations were approved by the consortium, which consists of professionals and patient representatives, using a voting procedure. PMS can only rarely be diagnosed based solely on clinical features and requires confirmation via genetic testing. In most cases, the family will be referred to a clinical geneticist for counselling after the genetic diagnosis has been made. Family members will be investigated and, if indicated, the chance of recurrence discussed with them. Most individuals with PMS have a *de novo* deletion or a pathogenic variant of *SHANK3*. The 22q13.3 deletion can be a simple deletion, a ring chromosome 22, or the result of a parental balanced chromosomal anomaly, influencing the risk of recurrence. Individuals with a ring chromosome 22 have an increased risk of *NF2*-related schwannomatosis (formerly neurofibromatosis type 2) and atypical teratoid rhabdoid tumours, which are associated with the tumour-suppressor genes *NF2* and *SMARCB1,* respectively, and both genes are located on chromosome 22. The prevalence of PMS due to a ring chromosome 22 is estimated to be 10–20%. The risk of developing a tumour in an individual with a ring chromosome 22 can be calculated as 2–4%. However, those individuals who do develop tumours often have multiple. We recommend referring all individuals with PMS and their parents to a clinical geneticist or a comparably experienced medical specialist for genetic counselling, further genetic testing, follow-up and discussion of prenatal diagnostic testing in subsequent pregnancies. We also recommend karyotyping to diagnose or exclude a ring chromosome 22 in individuals with a deletion 22q13.3 detected by molecular tests. If a ring chromosome 22 is found, we recommend discussing personalised follow-up for *NF2*-related tumours and specifically cerebral imaging between the age of 14 and 16 years.

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1. Introduction

This paper was written by the European Phelan-McDermid syndrome (PMS) consortium and is one of the series of papers that form the European consensus guideline for PMS (van Ravenswaaij-Arts et al., 2023; this issue). The present paper focuses on genetic counselling in PMS, with special attention given to the increased risk for brain tumours in individuals with PMS due to a ring chromosome 22. The guideline and this paper focus on *SHANK3*-related PMS, defined as a deletion 22q13.3 including *SHANK3* or a pathogenic variant of *SHANK3*, but the findings and guidelines may in part also apply to *SHANK3*-unrelated PMS (Phelan et al., 2022).

PMS (OMIM *606232) is a rare neurodevelopmental disorder mainly characterised by neonatal hypotonia, developmental delay, intellectual disability, absent or severely delayed speech, minor dysmorphic features and autism spectrum disorder or autistic-like behaviour, as described in the literature review by Schön et al. (2023, this issue). PMS can be caused by a deletion 22q13.3 or a pathogenic variant in *SHANK3* (Phelan et al., 2005; reviewed in Vitrac et al., 2023, this issue). Most individuals with PMS are diagnosed using chromosomal microarray analysis or by whole exome sequencing (WES) or whole genome sequencing (WGS).

Various medical specialists can be involved in the PMS diagnostic process, including (neuro-)paediatricians, intellectual disability physicians and clinical geneticists, assisted on occasion by other medical professionals. PMS is typically not diagnosed based on clinical features alone, and the diagnosis requires genetic testing. A diagnosis of *SHANK3*-related PMS is established in an individual with neurodevelopmental disease and a heterozygous deletion at chromosome 22q13.3 involving at least part of *SHANK3* (OMIM *606230) or a heterozygous pathogenic variant in *SHANK3*. However, there is some debate about the definition of PMS (Schön et al., 2023, this issue; Goodspeed et al., 2020; Phelan et al., 2022) because a minority of patients has a 22q13 deletion that does not involve *SHANK3*.

A PMS diagnosis has consequences for not only the individual with PMS (Schön et al., 2023, this issue) but possibly also for family members. It is the expertise of the clinical geneticist and/or cytogeneticist to determine whether there is an indication for genetic testing of family members and the method of this investigation. In addition, the clinical geneticist can explain the variability of the phenotype, including the physical, developmental and behavioural aspects, the (limited) relationship between genotype and phenotype, the natural history of the syndrome and available reproductive options.

2. Methods

This paper, as part of the European consensus guideline for PMS, follows the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II), an international tool for evaluating the quality and reporting of guidelines (Brouwers et al., 2010).

No PMS-specific literature emerged in a search on counselling and the chance of recurrence. Therefore, we widened the search to include papers that describe causes of recurrence in PMS and performed a citation search from these papers. For ring chromosome 22, a literature search was performed using the following keywords: ("Phelan-McDermid syndrome" OR "22q13 deletion syndrome" OR "ring chromosome 22") AND ("Neurofibromatosis type 2" OR "NF2" OR "NF2-associated tumours/tumours" OR "SMARCB1 tumours/tumours" OR "atypical teratoid rhabdoid tumour/tumour" OR "brain tumor/tumour"). Articles were included if they described cases of individuals with a ring chromosome 22 and the above-mentioned tumours. The reference lists of the included papers were also hand-searched for additional candidate papers. The aim of the literature search was to answer the following questions:

- If a deletion 22q13.3 has been detected by molecular genetic methods, what is the frequency of ring chromosome formation as a cause?
- What are the prevalence and characteristics (age at presentation, nature of initial signs and symptoms, type of tumours, number of tumours, etc.) of *NF2*-related tumours in individuals with a ring chromosome 22?
- What are the prevalence and characteristics (age at presentation, nature of initial signs and symptoms, type of tumours, number of tumours, etc.) of *SMARCB1*-related tumours in individuals with a ring chromosome 22?
- What is the best surveillance scheme for early detection of tumours in individuals with PMS due to a ring chromosome 22?

Based on this literature review, recommendations for clinical practice were developed and discussed. The formulation of the recommendations took into account the extent to which scientific evidence was available. Feedback on the full text and recommendations was provided by consortium members, including the patient representatives. In June 2022, the final text was thoroughly discussed during a consensus meeting of the consortium. The recommendations were adjusted accordingly and were only accepted if, after a voting procedure, a consensus was reached. To ensure the reliability of the recommendations, all members had the right to vote (van Ravenswaaij-Arts et al., 2023; this issue).

3. Review of the literature

3.1. Referral to a clinical geneticist

In most countries, referral for genetic counselling will be to a clinical geneticist, but this task will be directed to other specialists with similar experience in genetic counselling in some countries. The scope of the clinical geneticist covers providing explanations, often for rare and complex genetic and congenital disorders (Table 1). This explanation includes the physical, developmental, and behavioural aspects of the phenotype and its expected variation; the natural history of the syndrome; the underlying cause (genotype) and its effect on the phenotype; the probability of recurrence and which investigations are needed to determine this; and the possibilities for prenatal diagnosis and other reproductive options (Patch and Middleton, 2018; Schupmann et al., 2020).

Discussing the effect of the genotype on the phenotype and the likelihood of recurrence is particularly important for a diagnosis of PMS. PMS is typically caused by a deletion of chromosome 22q13.3 including *SHANK3* or a heterozygous pathogenic variant in *SHANK3* (Phelan et al., 2005; reviewed in Vitrac et al., 2023, this issue). The deletion can result from a pure (isolated) deletion, both terminal and interstitial (Luciani et al., 2003), but can also result from a ring chromosome 22, an unbalanced translocation (Bonaglia et al., 2011; Tabet et al., 2017), or a more complex chromosome rearrangement including a terminal 22q deletion. This means that genetic studies are important for establishing genotype-phenotype correlation and recurrence risk. The effects of the

Table 1
Conclusions from the literature on genetic counselling in PMS.

Following a PMS diagnosis, referral to a clinical geneticist (or a medical specialist with similar experience) is always indicated for counselling, especially for the estimation of the probability of recurrence for family members, and to advise them on the care the individual with PMS needs, depending on the clinical picture.
Following diagnosis of a terminal 22q13.3 deletion using microarray analysis, it is important to initiate additional genetic studies (karyotyping or metaphase FISH studies) concerning a ring chromosome 22 because of its effect on the phenotype.
PMS may be the result of a mis-segregation of a parental balanced chromosome aberration involving 22q13, or of a mosaic deletion 22q13.3 or pathogenic *SHANK3* variant in one of the parents, leading to an increased chance of recurrence.

genotype on the phenotype are discussed in detail by Schön et al. (2023, this issue) and those for ring chromosome 22 in the present paper.

The standard molecular diagnostic tool for detecting point mutations in genes (here: *SHANK3*; if there is a concrete suspicion of PMS) is Sanger sequencing. In cases with less clinically recognisable developmental disorders, genome-wide methods (gene panel analysis, WES or WGS) are currently used as the first tier in clinical practice, when available. When testing by WES, individuals carrying *SHANK3* point mutations may be under-detected as the guanine/cytosine-rich regions in some exons lead to low coverage by WES (Caspar et al., 2018).

3.2. Chance of recurrence and the method of follow-up diagnostics in parents

Most PMS individuals have a *de novo* deletion or pathogenic variant, which means that the chance of recurrence for siblings is effectively very low (Sarasua et al., 2014). However, considering the difficulty of detecting any possible parental mosaicism (Zwanenburg et al., 2018; Wright et al., 2019), prenatal diagnostics should be offered to parents of a child with a *de novo* deletion or pathogenic variant.

In the worldwide parental survey presented elsewhere in this special issue, an unbalanced translocation was detected in 37 of 325 individuals (11%) with a 22q13 deletion (Landlust et al., 2023, this issue). For 29 of these individuals parental results were available, and 13 (45%) were the result of a balanced parental translocation. A mosaic deletion was detected in 1/274 (0.3%) parents and a mosaic *SHANK3* variant was detected in 3/79 (3.7%) parents studied for the deletion or *SHANK3* variant of their child.

The chance of recurrence is increased when one of the parents is a carrier of a balanced chromosomal anomaly in which chromosome 22q13 is involved. Typically, the parental chromosomal anomaly involves a balanced reciprocal translocation (Phelan et al., 2001; Rodríguez et al., 2003; Wilson et al., 2003; Manning et al., 2004), but insertions and pericentric inversions have also been described (Slavotinek et al., 1997; Jafri et al., 2011). The exact chance of recurrence depends on the chromosomal aberration in the parent and cannot be given as a clear percentage but can be as high as 50% in rare cases, depending on the viability of the unbalanced offspring (Gardner et al., 2012, p. 99). The chance of recurrence is also increased when one of the parents has a deletion of chromosome 22q13.3 in mosaic form (Tabolacci et al., 2005; Verhoeven et al., 2012). An increased chance of recurrence (50%) because one parent has a non-mosaic deletion 22q13.3 has only been described twice (Denayer et al., 2012; Tabet et al., 2017).

For evaluating parents, Fluorescent in situ Hybridisation (FISH) is the preferred method because a balanced chromosome anomaly cannot be detected by microarray analysis (Gardner et al., 2012, p. 22). The same FISH should also be performed in the proband to ensure that the deletion can be detected by the probe used (Zwanenburg et al., 2018).

Table 1 summarises the conclusions from the literature on genetic counselling in PMS, specifically regarding referral to a clinical geneticist, diagnostics and chance of recurrence.

3.3. Prevalence of ring chromosome 22 in PMS individuals

The prevalence of a ring chromosome 22 in individuals with PMS is not exactly known. A study by Bonaglia et al. revealed a prevalence of 14% in 44 individuals diagnosed with PMS based on conventional or molecular karyotyping (Bonaglia et al., 2011). Ziats et al. (2020) analysed data from the PMS International Registry and found that 33% (42/129) of PMS individuals with a terminal deletion who were diagnosed by chromosomal microarray and also had karyotyping had a ring chromosome 22. However, more individuals with a ring chromosome 22 will be present, especially in the older patient population, because, prior to the introduction of microarrays, ring chromosomes were easier to detect by karyotyping than were simple small terminal deletions.

A recent international survey based on data reported from 587 parents showed that 377 out of 484 individuals with PMS for whom the genetic cause was known (78%) had a deletion 22q13. For 325 of these 377 the cause of the deletion was known, and 43 (13%) had a ring chromosome (Landlust et al., 2023, this issue). A similar result was found in a study from the developmental synaptopathies consortium: of the 136 individuals with a deletion, 18 had a ring chromosome 22 (13%) (Levy et al., 2022). In a yet unpublished study in the Netherlands, karyotyping of individuals with a terminal deletion 22q13 primarily detected by microarray showed a ring chromosome 22 in 11 out of 47 (23%) individuals (van Ravenswaaij, unpublished). This 23% seems exceptionally high compared to similar studies in Spain and France. Nevado et al. reported a ring chromosome in only 3 out of 77 (4%) patients in whom the deletion 22q13.3 was originally diagnosed by microarray (Suppl. to Nevado et al., 2022). Comparably, Tabet et al. identified that 4 out of 78 (5%) patients with a 22q13 deletion initially identified by microarray had a ring 22 (Tabet et al., 2017). In total, assuming that identical methods were used, this results in a percentage of 9% ring chromosomes when the deletion was detected by microarray as the first-tier test.

Thus, although the prevalence of a ring chromosome 22 in patients with a terminal 22q13.3 deletion is reported to vary from 4 to 33%, and taking into account that microarray is now preferred over conventional karyotyping, our cautious estimation is that the prevalence varies from 10 to 20%.

3.4. Ring chromosome 22 and the overall phenotype

Individuals with a 22q13.3 deletion, whether due to a simple terminal deletion or a ring chromosome, share most clinical features because they all lack the part of chromosome 22q13 that includes the *SHANK3* gene (Jeffries et al., 2005). Additionally, 22p deletions that are associated with a ring chromosome 22 do not lead to clinical features. A study by Luciani et al. (2003) showed no difference in phenotype between similar-sized simple deletions 22q13 and ring chromosome 22, apart from overgrowth in the former and growth failure (4 out of 17 individuals) in the latter. It has been hypothesised that a ring chromosome may behave differently during mitosis. Mitotic sister chromatid exchanges can sometimes lead to interlocked or dicentric ring structures and subsequently to aneuploidy resulting in increased cell death and ultimately growth failure. However, given the low rate of growth failure observed in individuals with a ring chromosome 22 (4/17), mitotic instability does not seem to play a major role. Additionally, silencing of genes due to ring formation has been described for chromosome 14 (van Karnebeek et al., 2002), but this effect is not known for ring chromosome 22.

Some ring chromosomes 22 may have a much more complex structure than shown by routine karyotyping or FISH approaches, and these are often associated with more intricate clinical features than those seen in patients with a 22q13.3 terminal deletion on a linear chromosome. In these patients, the microarray analysis can identify a terminal deletion associated with a contiguous proximal duplication concordant with an inverted duplication/deletion 22q (Rossi et al., 2008). Furthermore, the size of the ring chromosome 22 can vary even between cells within the same individual, reflecting the complexity of the mechanisms involved. Lastly, the disruption of the topologically associated domains either because of the duplication/deletion regions or of the ring conformation itself, plays an equally important role in the clinical manifestations (Kurtas et al., 2018). Thus, ring chromosome genotype-phenotype correlations always require further definition of the ring structure using sophisticated molecular approaches for proper comprehension of the mechanisms behind clinical abnormalities. For clinical practice, however, after ring identification through karyotype analysis, only microarray analysis is recommended (if not already performed).

3.5. Ring chromosome 22 and tumour risk

There is an important clinical difference between a simple deletion 22q13 and a ring chromosome 22. People with a ring chromosome 22 have an increased risk of developing tumours related to tumour-suppressor genes located on chromosome 22, especially the *NF2* gene (located at 22q12.2). Therefore, tumours similar to those occurring in *NF2*-related schwannomatosis (NF2; Plotkin et al., 2022) are observed in individuals with a ring chromosome 22 (Denayer et al., 2009; Zirn et al., 2012). Because of ring chromosome instability, cells missing the ring chromosome can be formed, leaving only the normal chromosome 22 in a daughter cell. As a result, only one copy of the *NF2* gene remains in the cells. In the nervous system (spinal cord or brain), such a cell can develop into a histologically benign tumour (schwannoma or meningioma) if a somatic mutation occurs in the remaining *NF2* gene as a second hit. Not all individuals with a ring chromosome 22 will develop symptoms after the second hit, but some can develop epilepsy, deficits, or other neurological problems due to the suppression of normal tissue, e.g. deafness due to (bilateral) vestibular schwannomas. Individuals with a ring chromosome 22 and their caretakers should therefore be aware of the possibility of a histologically benign tumour as the cause for these symptoms or for general deterioration. Affected individuals can then benefit from treatment, for example, drug treatment with bevacizumab or surgery.

The same mechanism may also apply to other tumour-suppressor genes located on chromosome 22. Indeed, this has incidentally been reported for *SMARCB1* (located at 22q11.23, formerly known as *INI1*), resulting in atypical teratoid rhabdoid tumours (AT/RT) (Cho et al., 2014; Byers et al., 2017). AT/RT of the central nervous system are rare and highly malignant embryonal tumours that most often occur in children under the age of 3 years. Most are due to a somatic change in the tumour-suppressor gene *SMARCB*1 followed by a second hit, typically loss of heterozygosity, that can be detected by immunohistochemical staining.

3.6. Prevalence and clinical presentation of NF2-related tumours in carriers of a ring chromosome 22

The prevalence of *NF2*-related tumours in ring chromosome 22 individuals also remains largely unknown, although several case series and case reports have described the increased risk of *NF2*-related tumours in these individuals (Tsilchorozidou et al., 2004; Denayer et al., 2009). Ziats et al. (2020) evaluated the prevalence of *NF2*-associated tumours in a cohort of 44 individuals (average age 15 years, range newborn–45 years) with a ring chromosome 22, of whom 7 (16%) had an *NF2*-associated tumour or an NF2 diagnosis. However, one of these patients had an *NF2* deletion in addition to the ring chromosome, so 6/43 (14%) with a non-complex ring chromosome 22 had NF2 tumours (median age 31 years, range 15–39 years). It is unknown how many of these individuals fulfilled the NF2 criteria. Furthermore, there may be ascertainment bias in this cohort as the data is self-reported and most NF2 tumours were diagnosed clinically. Of the 11 individuals of 20 years or older, two were diagnosed with NF2 tumours before the age of 20.

In individuals with NF2 due to a germline *NF2* pathogenic variant, bilateral vestibular schwannomas affect 95% of all individuals, and penetrance is almost 100% by the age of 60 (Ardern-Holmes et al., 2017). If we assume that 10–20% of the deletion individuals have a ring chromosome (1 in 100,000–200,000 people) and 1% of all sporadic NF2 individuals with an *NF2*-related tumour have a ring chromosome (Evans et al., 2020), it is possible to calculate the proportion of ring chromosome 22 individuals meeting NF2 criteria to be 2–4%.[1] However, this comes with two caveats. First, the calculation is based on rough assumptions. Second, a greater proportion of ring chromosome 22 individuals may develop a single tumour or multiple tumours that are still insufficient to fulfil NF2 criteria (for instance a unilateral vestibular schwannoma or two meningiomas), as shown by the 14% reported by Ziats et al. (2020).

Table 2
Conclusions from the literature on ring chromosome 22 and tumour risk.

Current knowledge indicates that in 10–20% (maximum range 4–33%) of all individuals with a terminal 22q13 deletion, the deletion is caused by a ring chromosome 22
Individuals with a ring chromosome 22 have an increased risk for *NF2*-related tumours. However, the age at presentation and number of tumours may be more comparable to that seen in individuals with a mosaic *NF2* pathogenic variant
Currently, no surveillance scheme for early detection of *NF2*-related tumours is available for individuals with a ring chromosome 22
Individuals with a ring chromosome 22 have an increased, but still low risk for *SMARCB1*-related tumours, which occur especially below the age of 4 years

In total, 20 cases of ring chromosome 22 individuals with *NF2*-related tumours were identified in the current literature, but only 13 of them fulfilled the NF2 clinical criteria (Arinami et al., 1986; Denayer et al., 2009; Duncan et al., 1987; Kehrer-Sawatzki et al., 1997; Lyons--Warren et al., 2017; Nussbaum et al., 2021; Petrella et al., 1993; Tommerup et al., 1992; Tsilchorozidou et al., 2004; Ziats et al., 2020). The median age at tumour presentation was 20 years (range 15–52). All individuals presented after they developed symptoms, and systematic pre-symptomatic screening was rarely reported. The most common tumours were vestibular schwannomas, seen in 14 individuals (70%), followed by meningiomas (65%). Considering all tumours combined, two individuals had a single tumour (10%) and 18 had multiple tumours (90%). In most individuals, the tumours were removed surgically (9, 45%). Other treatments included the combination of surgery and monitoring (4, 20%), drugs (1, 5%), and only monitoring (1, 5%).

3.7. Surveillance scheme for NF2-related tumours in ring chromosome 22 PMS individuals

In the literature, no systematic pre-symptomatic screening has been reported for ring chromosome 22. In NF2, surveillance begins at 10–12 years in asymptomatic carriers of *NF2* pathogenic germline variants and continues with a cranial (head & internal auditory meatus) performed every two years and a spinal MRI every 5 years, as long as no new symptoms occur (Evans et al., 2017; Halliday et al., 2023). Once tumours are identified, cranial MRIs should be performed annually and spinal MRIs every 3 years (Halliday et al., 2023).

Ziats et al. (2020) recommend conservative tumour screening in individuals with PMS due to a ring chromosome 22 including cranial MRI imaging starting at 10 years of age and formal clinical examinations with particular attention to skin, eye, hearing and neurologic systems beginning at the age of 2 years, based on their observations which, might be influenced by reporting bias.

[1] This is calculated using an NF2 birth incidence of approximately 1 in 30,000 (Evans et al., 2012, 2017). This would mean around 1 in 45,000 have *de novo* NF2 as about 2/3rds are *de novo* cases (Evans et al., 2020). As such, one can calculate the prevalence of tumours sufficient to fulfil NF2 criteria in individuals with a ring chromosome 22 to be 1 in 50 to 1 in 25 (2–4%) or $0.01 \times 1/45{,}000 = 1/4{,}500{,}000$ divided by either 1/100,000 or 1/200,000, which yields 2% or 4%, respectively.

3.8. Prevalence and clinical presentation of SMARCB1-related tumours in ring chromosome 22 individuals

SMARCB1 is located on 22q11.2 and thus, following the same mechanism of mitotic loss of the ring chromosome 22 and a second hit in the remaining *SMARCB1* gene, AT/RT may develop in patients with a ring chromosome 22 (Byers et al., 2017). Loss of SMARCB1 expression in tumour immunohistochemistry can be used as a diagnostic marker for AT/RT tumours.

In total, five individuals with a ring chromosome 22 and AT/RT tumours were identified in the current literature (Rubio, 1997; Sathyamoorthi et al., 2009; De Amorim Bernstein et al., 2013; Cho et al., 2014; Byers et al., 2017). The median age at tumour presentation was 22 months (range 11 months-4 years). All individuals presented after they developed symptoms such as emesis, lethargy, loss of skills, unilateral weakness/paresis and ataxia. Systematic pre-symptomatic screening was not reported. No individuals with multiple tumours were reported, and the locations of the tumours were the third and fourth ventricle and cerebellar vermis or cerebellopontine angle.

Table 2 summarises the conclusions from the literature on ring chromosome 22 and tumour risk, specifically on the prevalence of ring 22, *NF2*-related tumours, and *SMARCB1*-related tumours.

4. Considerations and recommendations

4.1. Referral to the clinical geneticist

There is always an indication for genetic counselling when a diagnosis of PMS is made (Table 3). Special points of consideration are the (limited) correlation of the genotype with the phenotype, the chance of recurrence depending on the underlying genetic variant, and where applicable the exclusion of a ring chromosome 22. The latter requires microscopic chromosome testing that can be combined with FISH for the 22q13.3 region, that can also be used for parental testing for increased recurrence risk (see below).

4.2. Recurrence risk and follow-up of parents

Parental analysis is not needed when the child is diagnosed with a mosaic deletion 22q13.3 or a mosaic pathogenic *SHANK3* variant as the mosaic status will most probably be a postzygotic event. If a non-mosaic pathogenic *SHANK3* variant is detected in the proband, targeted variant analysis should be performed in the parents to exclude a mosaic or, very rarely, non-mosaic carrier situation (Fig. 1, Table 3).

If the individual carries a deletion detected by microarray analysis, conventional karyotype screening for ring chromosome 22 must be performed (Fig. 1, Table 3). If there is no ring chromosome in the index patient, the next diagnostic step is to determine the recurrence probability of the deletion 22q13. This is preferably done using FISH with a probe for 22q13.3 overlapping *SHANK3* in both parents and the proband (to confirm that the deletion can be detected by the FISH-probe used). FISH can detect a mosaic or non-mosaic deletion or a translocation or other balanced rearrangement in the parents. At least 30 metaphases should be analysed to exclude a mosaic deletion. If the deletion is too small to be detected by FISH, microarray analysis should be performed in the parents to exclude a (mosaic) deletion. However, a balanced chromosomal rearrangement cannot be excluded by microarray. If the proband has been diagnosed with a ring chromosome 22, a mosaic state in the parents should be ruled out by FISH analysis or conventional karyotyping of at least 30 metaphases. Mosaic studies in parents, preferably done in tissues other than blood (e.g. buccal cells or bladder epithelial cells in urine), are advised if a second child with a deletion 22q13.3 or pathogenic *SHANK3* variant is born into the family without a genetic explanation.

When carrier status of a chromosomal anomaly has been determined in one of the parents, the chance of recurrence is increased (Fig. 1), but this cannot be given as an exact number because it depends on the properties of the chromosomal anomaly (break points of the translocation or percentage of mosaicism in the germ cells). If a parent carries the pathogenic *SHANK3* variant or the deletion, the recurrence risk is 50% for each sibling of an affected child%. However, the chance of this being present in one of the parents is very low.

With every parent of a child with PMS, reproductive options should be discussed if they wish to have more children, even if the variant in their child seems to be *de novo*. If parents who do not themselves have a pathogenic variant/deletion or a balanced chromosome rearrangement have an affected child, the recurrence risk for each sibling is slightly increased due to the possibility of parental germline mosaicism (Edwards, 1989) (for risk figures see Fig. 1). Moreover, it should be kept in mind that a constitutional mosaic deletion 22q13 in parents can be missed, even by FISH.

Even if parents do not wish to have more children, further investigation in both parents can be important to determine the mechanism of occurrence and the chance of a child with PMS for other family members. If a balanced chromosomal rearrangement is found in one of the parents, cascade screening should be offered (Zwanenburg et al., 2018).

Table 3
Consensus recommendations agreed upon by the European PMS Consortium.

All individuals with PMS and their parents (or direct relatives[a]) should be referred for genetic counselling. In genetic counselling, the clinical geneticist or other experienced clinician should explain the relationship between the genotype and phenotype (e.g. effect of deletion size or *SHANK3* variant) and determine if there is an increased recurrence risk for another child with PMS for parents and other relatives.
After a diagnosis of PMS has been made, further genetic studies should be performed for proper genetic counselling (see Fig. 1).
Follow-up of individuals with PMS should include a check whether genetic work-up has been complete and up-to-date.
In subsequent pregnancies, the parents of the child with PMS should be offered prenatal diagnostic testing.
In an individual with a ring chromosome 22, personalised monitoring for potential NF2-tumours should be discussed with the patient or their representatives[b].
In an individual with a ring chromosome 22, cerebral imaging (MRI) is recommended at the age of 14–16 years, if not already available. In case of obvious hearing loss, discuss with the patient or their representatives repeating of the MRI[c]

[a] In case of adult individuals with PMS and questions from siblings, also discuss referral for genetic counselling.

[b] There is currently no screening guideline, but this may include annual hearing screening as well as eye and neurological examinations every 1–2 years starting between the ages of 15 and 20 years.

[c] If the MRI is made under general anaesthesia, combine it with spinal MRI. Discuss repeating the MRI every 5 years (in the absence of symptoms).

4.3. Prenatal testing

Once a 22q13.3 deletion or a pathogenic variant in *SHANK3* has been identified in a family member, prenatal testing (and in some countries preimplantation genetic diagnosis (PGD)) can be offered for subsequent pregnancies with increased recurrence risk (Table 3). In some countries, prenatal testing is offered to any parent who had a child with a genetic neurodevelopmental disorder for psychosocial reasons due to the burden of having had a child with such a disorder.

The technique used for prenatal testing depends on the national guidelines. Chorionic villus sampling is an early method to acquire placental cells for genetic testing of the foetus. It is carried out from about the 12th week of gestation (in comparison: amnion cells are available by amniocentesis from about the 16th week of gestation). The genetic analysis method used on foetal cells, in particular chromosomal microarray testing to detect deletions and single-gene testing to detect *SHANK3* variants, depends on the index patient findings.

One possible way to avoid a familial pathogenic finding in the foetus is to perform PGD, which can be offered to affected families in some countries. The respective provisions for this reproductive technology,

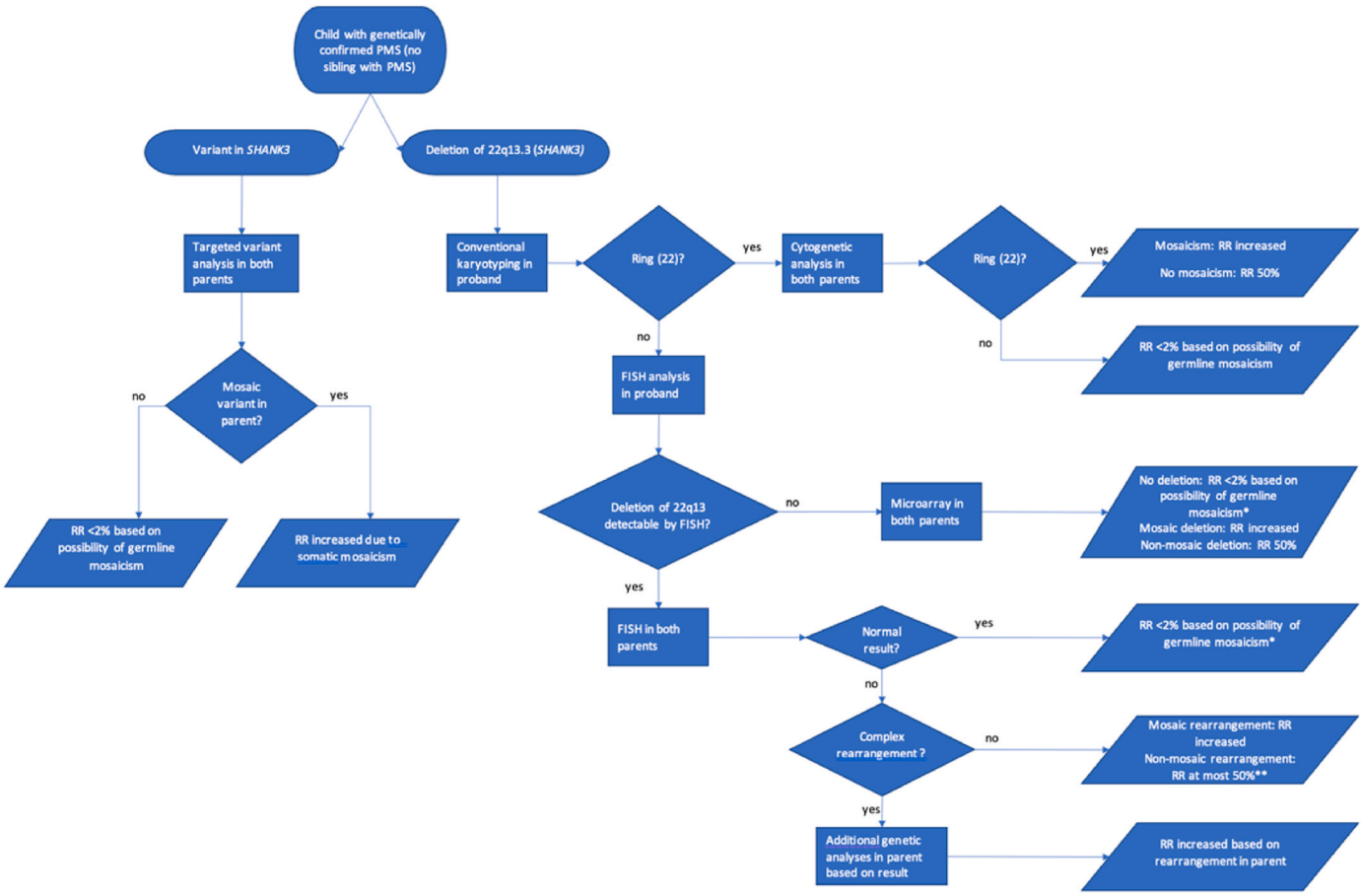

Fig. 1. Decision tree: Additional investigations and recurrence risk after a Phelan-McDermid syndrome diagnosis has been made.
*The most common cause of PMS is a *de novo* deletion 22q13.3. ** The most common non-mosaic rearrangement in a parent is a balanced reciprocal translocation involving a breakpoint in 22q13. PMS = Phelan-McDermid syndrome; RR = recurrence risk.

which is used along with an in vitro fertilisation (IVF) procedure is, country-specific.

In addition to prenatal testing and PGD, other reproductive options such as sperm donation, egg donation and adoption should be considered.

5. Screening for tumours in individuals with a ring chromosome 22

Given that a ring chromosome 22 represents a 'mosaic' form of NF2 and is less severe than typical NF2 due to heterozygous pathogenic germline variants, asymptomatic monitoring in ring chromosome 22 individuals could begin later and be less frequent, also depending on discussions with the individual and caretakers about what interventions would be considered if tumours become symptomatic or require treatment. Halliday et al. (2023) recommend performing a baseline MRI of the spine, head, and internal auditory meatus for individuals with mosaic NF2 with follow-up at 5, 10, and 20 years after the initial assessment. If lesions are found, follow-up continues in the same way as individuals with NF2 (annual cranial MRI and spinal MRI every 3 years) (Halliday et al., 2023). We suggest that if individuals present with features suggestive of NF2, they should have a full evaluation for other clinical evidence of NF2. This should include hearing assessment by audiology, brain and spinal MRI, ophthalmic examination and expert cutaneous examination at baseline.

In PMS, cerebral MRI is often performed as part of the diagnostic trajectory, given the clinical presentation with, amongst others, a significant motor acquisition delay. After the aetiological diagnosis of PMS, its interest must be weighed against the methods used (sedation, anaesthesia) given the limited clinical relevance/benefit in the absence of epilepsy or focal neurological signs. Nonetheless, in ring chromosome 22 individuals, baseline imaging is recommended at age 14–16 years. Since the reported age at youngest presentation of NF2-related tumours was 15 years (median 20 years), we recommend that an individualised surveillance scheme starting between the ages of 15 and 20 years and taking into account the psychosocial and medical situation of the individual be discussed with parents. The added value of early detection of tumours may be limited, but awareness may prevent, for instance, permanent hearing loss. When performing an MRI, the burden of anaesthetics and the need for preparing the individual for the procedure should be discussed with parents and assistance with the preparation for the procedure should be offered.

The risk of AT/RT tumours seems to be considerably lower than that for *NF2*-related tumours in individuals with a ring chromosome 22. Nonetheless, clinicians should be aware that a cerebral MRI is indicated if there are neurological signs including lethargy, unilateral weakness and ataxia, especially in children younger than 5 years of age. Loss of skills is often reported in PMS and can be temporary. However, it should warrant further neurological evaluation to decide whether an MRI is indicated to exclude a tumour.

The recommendations given in Table 3 are based on the, rather limited, current knowledge. The working group wants to stress that further prospective studies are greatly needed and that a surveillance scheme should always be individualised and should be periodically evaluated based on new insights. For more information on tumour screening in individuals with intellectual disability see www.Oncodefi.

org.

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Data availability

No data was used for the research described in the article.

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