Genetic Counseling in Phelan-McDermid syndrome

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on behalf of the
European PMS guideline consortium
https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline

Conflicts of interest

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- Nothing else to declare

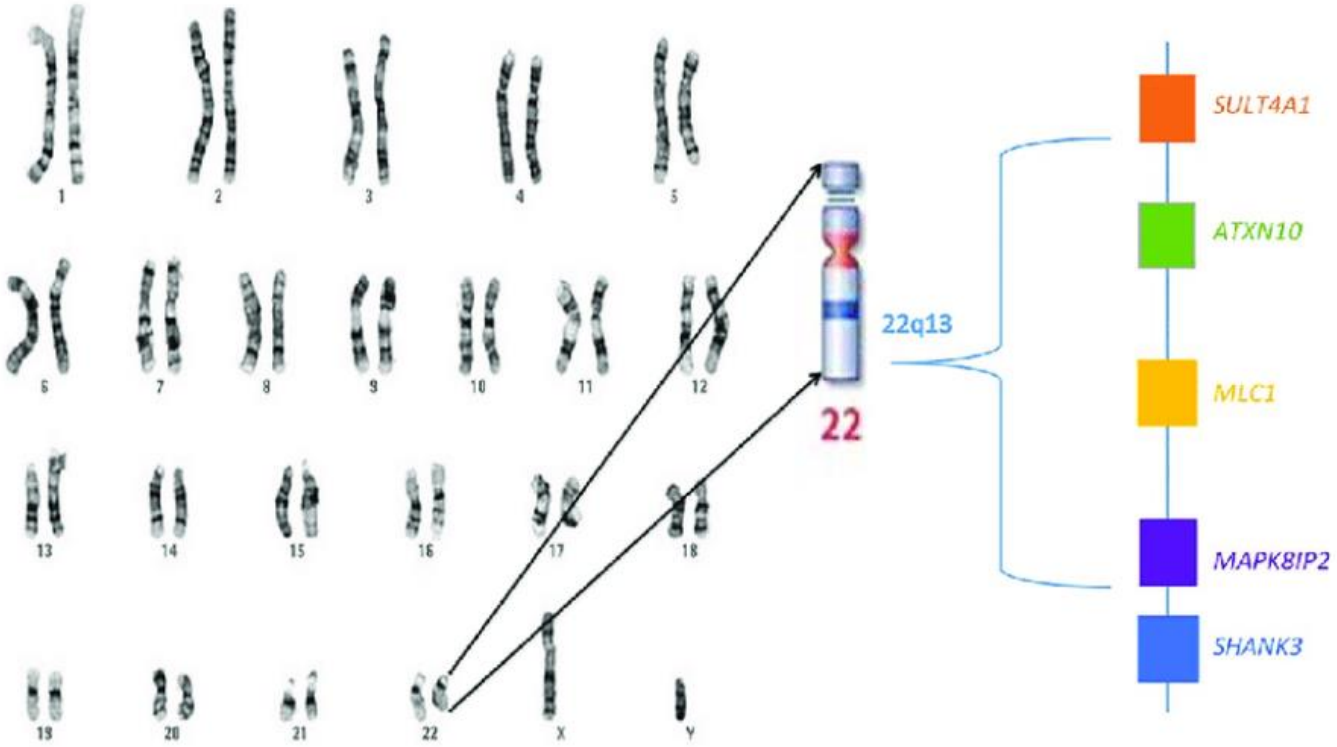
Genetics of Phelan-McDermid syndrome

- *SHANK3*-related:
  - Deletion 22q13.3, including *SHANK3*
  - Pathogenic variant in *SHANK3*

- *SHANK3*-unrelated:
  - Deletion 22q13, not including *SHANK3*

- Deletion 22q13.3:
  - Simple terminal deletion
  - Translocation
  - Ring chromosome 22

What is PMS?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X
Y
22q13
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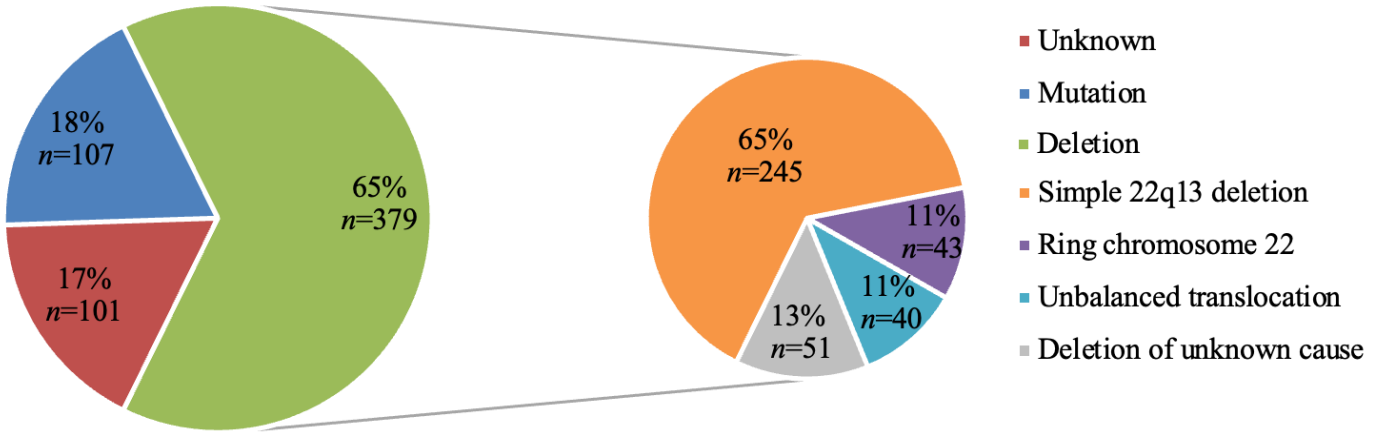
SULT4A1
ATXN10
MLC1
MAPK8IP2
SHANK3

Survey: genetics

Cause of PMS (*n*=587)



SHANK3 variants in Parental survey: 22%
Literature: 8%

The effect of the genotype on the clinical signs

Genotype-phenotype correlations

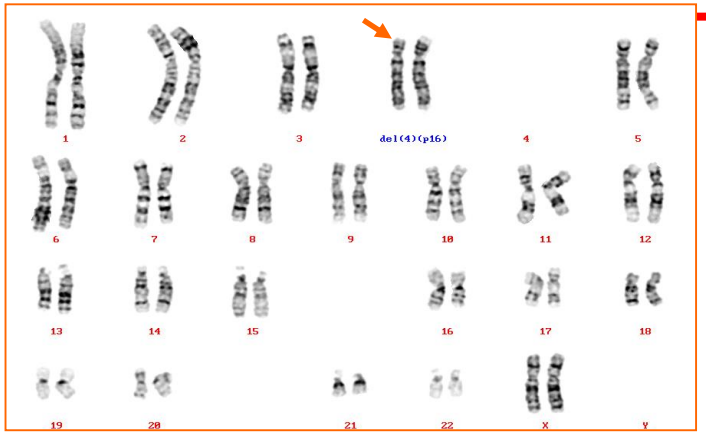
It is important to know the genotype because:

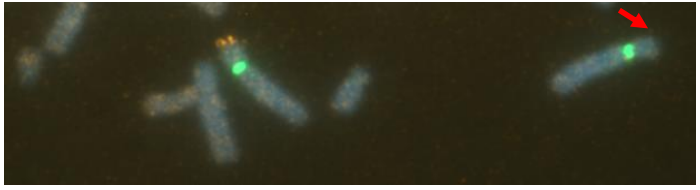
1. Deletions and variants have partly different phenotypes
2. Translocation: increased risk for reoccurence
3. Ring chromosomes: increased risk for certain types of tumours

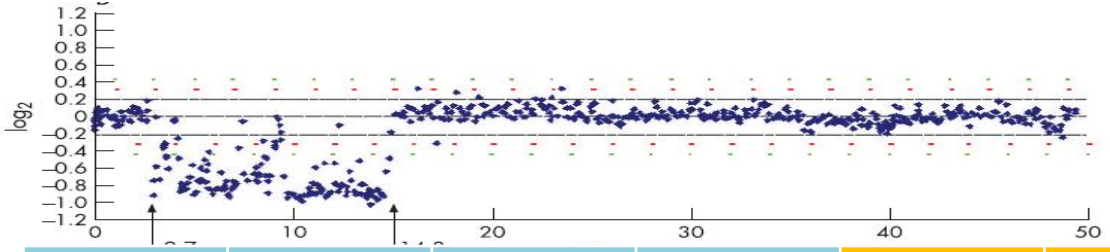
1. Deletions verus variants

Sign / Symptom	22q13.3 deletions (%)	*SHANK3* variants (%)	Sign / Symptom	22q13.3 deletions (%)	*SHANK3* variants (%)
Development			**External phenotype**		
Developmental delay	493/504 (98%)	48/50 (96%)	Dolichocephaly	84/319 (26%)	2/28 (7%)
Speech impairment	507/572 (88%)	31/44 (70%)	Long eyelashes	149/312 (48%)	19/39 (49%)
Neurology			Down-slanting fissures	16/74 (22%)	3/10 (30%)
Seizures (one or more)	148/542 (27%)	14/53 (26%)	Periorbital fullness	69/239 (29%)	7/39 (18%)
Hypotonia	333/451 (74%)	42/51 (82%)	Ptosis	62/286 (22%)	2/28 (7%)
Structural brain anomalies	118/223 (53%)	12/42 (29%)	Epicanthal folds	122/378 (32%)	8/39 (21%)
Senses			Ear anomalies	232/492 (47%)	16/41 (39%)
Vision disturbances	70/316 (22%)	9/34 (26%)	Wide nasal bridge	156/349 (45%)	15/42 (36%)
Strabismus	59/243 (24%)	4/28 (14%)	Broad nose	169/349 (48%)	15/40 (38%)
Hearing loss	32/372 (8%)	3/29 (10%)	Short philtrum	22/138 (16%)	0/21 (0%)
Increased pain tolerance	204/314 (65%)	38/48 (79%)	Thin upper vermillion	15/56 (27%)	3/11 (27%)
Behaviour			Thick lower vermillion	4/44 (9%)	5/21 (24%)
ASD	162/282 (57%)	26/33 (79%)	Malocclusion	109/297 (37%)	10/29 (34%)
Hyperactivity	33/112 (29%)	21/29 (72%)	Retrognathia	29/115 (25%)	0/31 (0%)
Aggression	50/267 (19%)	18/49 (37%)	Pointed chin	154/309 (50%)	18/29 (62%)
Self-injury	10/80 (13%)	8/27 (30%)	Large fleshy hands	180/392 (46%)	11/28 (39%)
Sleep disorder	62/237 (26%)	24/46 (52%)	Clinodactyly 5th finger	79/405 (20%)	10/28 (35%)
Internal organs			2-3 Syndactyly of toes	65/232 (28%)	5/11 (45%)
Gastro-oesophageal reflux	31/122 (25%)	5/29 (17%)	Sandal gap	30/56 (54%)	6/9 (7%)
Cardiac anomalies	49/387 (13%)	3/46 (7%)	Small / malformed nails	138/438 (32%)	13/29 (45%)
Freq. airway infections	75/280 (27%)	15/47 (32%)	Lymphedema	29/270 (11%)	0/34 (0%)
Urogenital problems	9/62 (15%)	0/24 (0%)	Eczema	48/225 (21%)	14/46 (30%)
Renal abnormalities	20/137 (15%)	0/17 (0%)	Hypohidrosis	31/84 (37%)	2/24 (8%)
Growth			Hyper-extensible joints	4/18 (22%)	6/10 (60%)
Short stature (≤ P3)	37/392 (9%)	4/41 (10%)			
Tall stature (≥ P98)	84/392 (21%)	3/41 (7%)			
Macrocephaly (≥ P98)	55/329 (17%)	6/39 (15%)			
Microcephaly (≤ P3)	53/329 (16%)	5/52 (10%)			

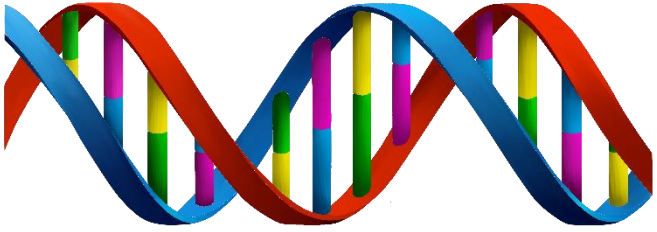
2 & 3. Different genetic methods needed



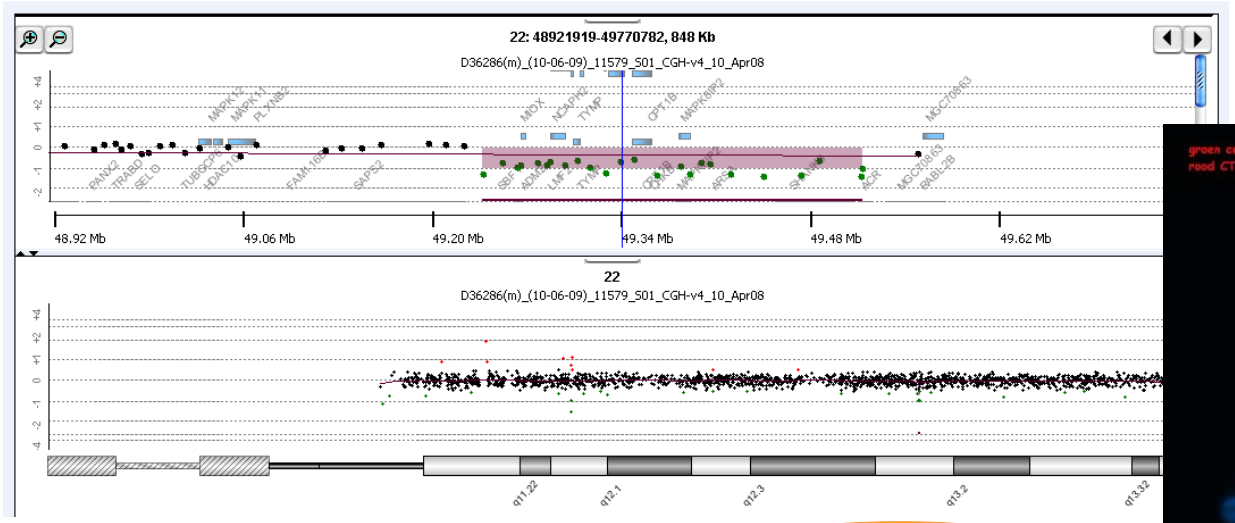




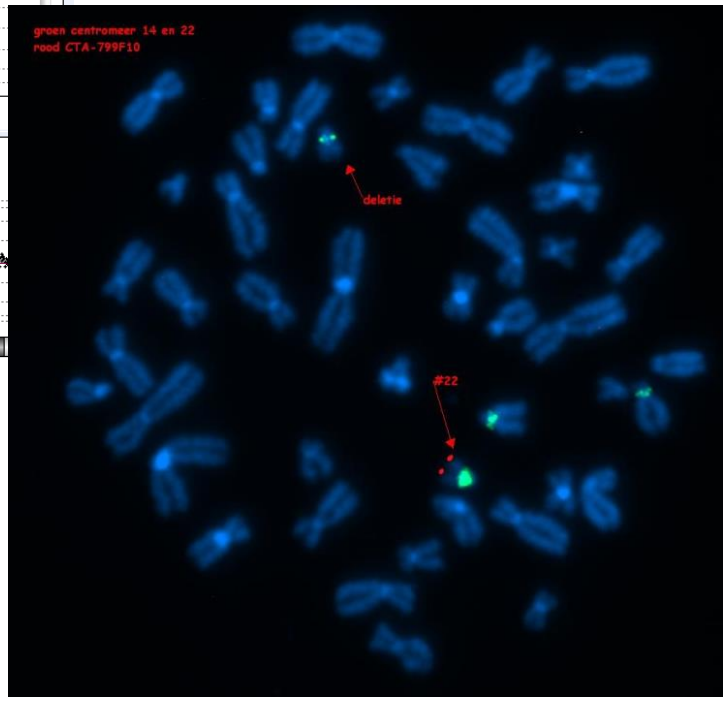
- Karyotyping
- FISH
- Microarray
- Whole Exome Sequencing

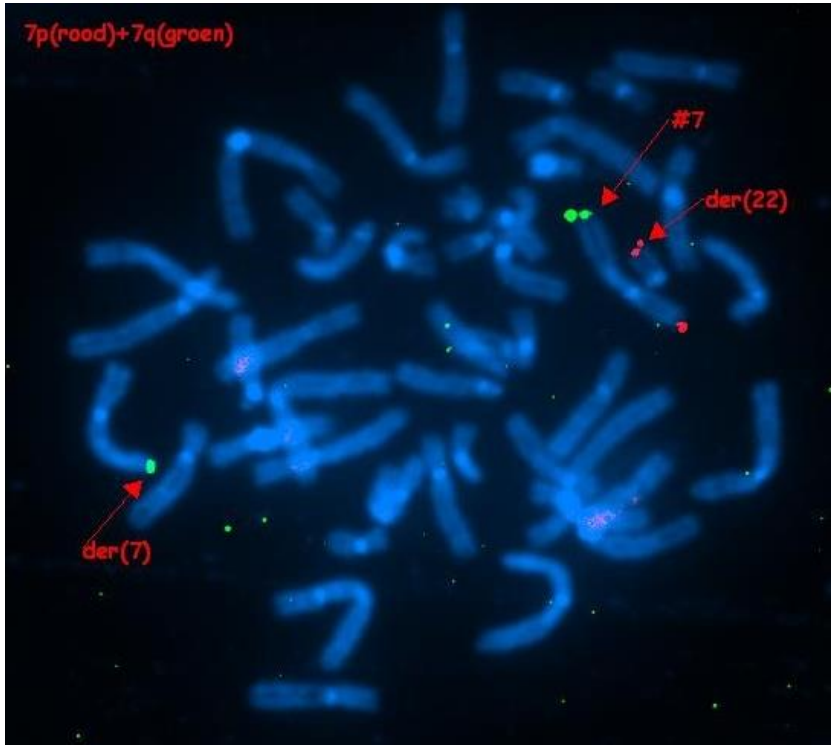


2. Recurrence risk?



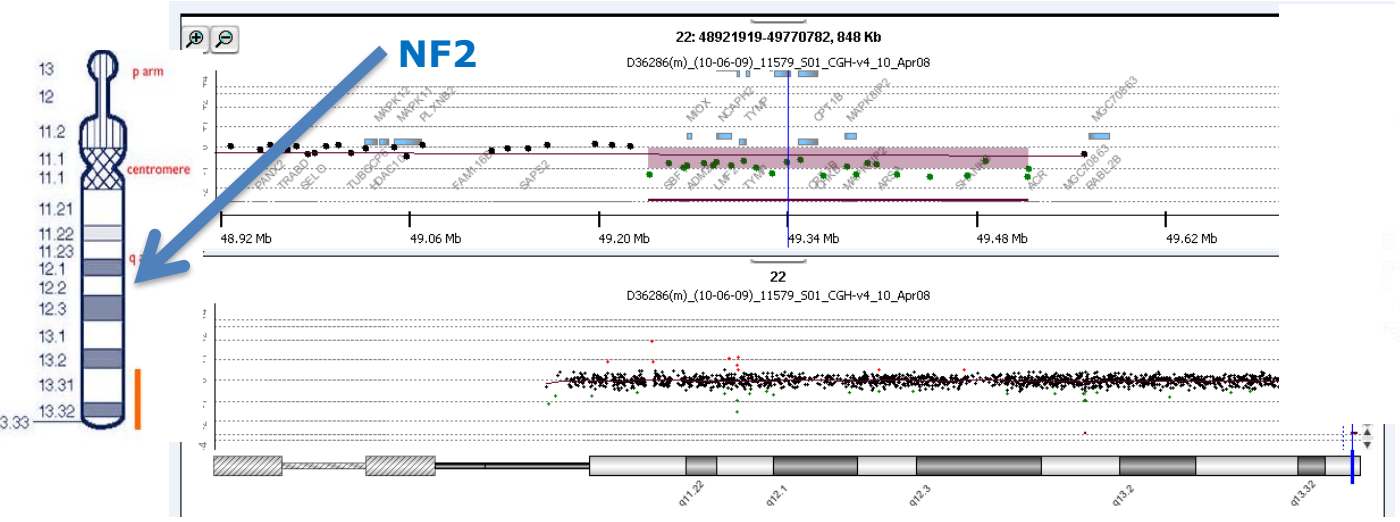
22

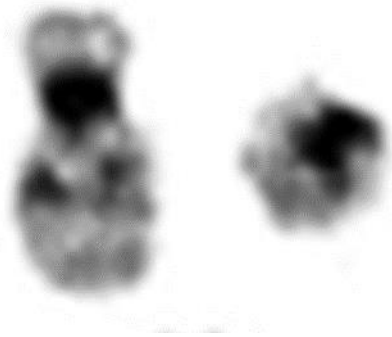




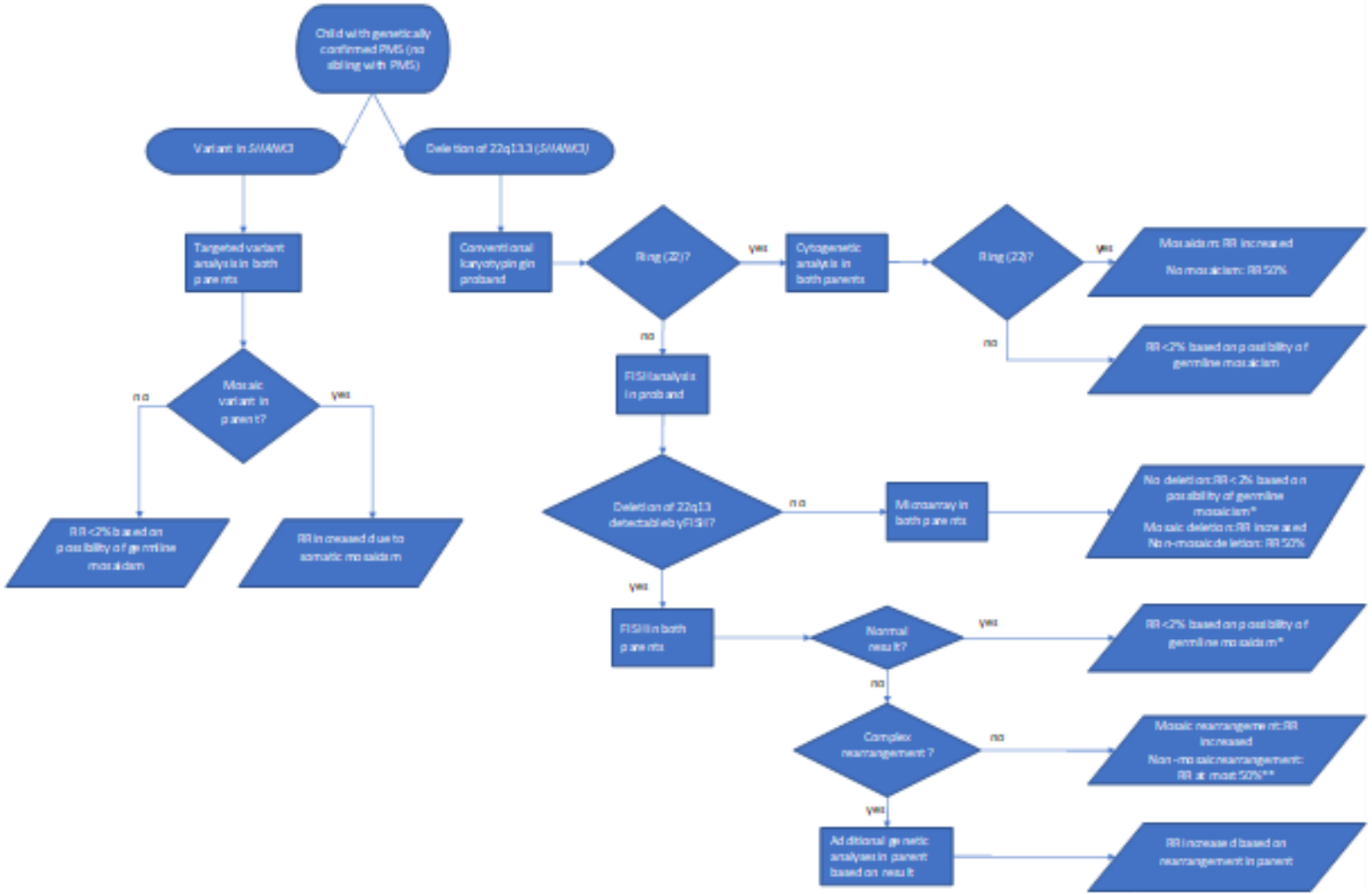
Father: translocation (7;22)

3. ring chromosome 22





- Terminal loss 22q13 → 10-20% caused by a ring chromosome 22
- Additional effect on phenotype: short stature
- Mitotic loss of ring + mitotic mutation of remaining NF2
  → increased risk for tumours (~ 5%)


Child with genetically confirmed PMS (no sibling with PMS)
Variant in SMAWC3
Deletion of 22q13.3 (SMAWC3)
Targeted variant analysis in both parents
Conventional karyotyping proband
Ring (22)?
yes
Cytogenetic analysis in both parents
Ring (22)?
yes
Mosaicism: RR increased
No mosaicism: RR 50%
no
RR <2% based on possibility of germline mosaicism
no
FISH analysis in proband
Mosaic variant in parent?
no
yes
RR <2% based on possibility of germline mosaicism
RR increased due to somatic mosaicism
Deletion of 22q13 detectable by FISH?
no
Microarray in both parents
No deletion: RR < 2% based on possibility of germline mosaicism*
Mosaic deletion: RR increased
Non-mosaic deletion: RR 50%
yes
FISH in both parents
Normal result?
yes
RR <2% based on possibility of germline mosaicism*
no
Complex rearrangement?
no
Mosaic rearrangement: RR increased
Non-mosaic rearrangement: RR at most 50%**
yes
Additional genetic analyses in parent based on result
RR increased based on rearrangement in parent

7. Recommendations:
Genetic counseling

- All individuals with PMS and their parents should be referred for genetic counselling. [genotype – phenotype; recurrence risk]
- After a diagnosis of PMS has been made, further genetic studies should be performed for proper genetic counselling.
- 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.

7. Recommendations:
Ring chromosome 22

- In an individual with a ring chromosome 22, personalised monitoring for potential NF2-tumours should be discussed with the patient or their representatives.

- In an individual with a ring chromosome 22, cerebral imaging (MRI) is recommended at the age of 14 to 16 years, if not already available. In case of obvious hearing loss discuss with the patient or their representatives repeating of the MRI.

8. Clinical synopsis: ring 22

PMS due to a ring chromosome 22

For detailed background information see: Koza et al., EJMG 2023.

Few genotype-phenotype relationships have been reported. However, certain clinical characteristics distinguish Phelan-McDermid syndrome due to a ring chromosome 22 from a simple deletion 22q13.3. A ring chromosome 22 confers increased risk of NF2-related schwannomatosis (formerly neurofibromatosis type 2) and atypical teratoid rhabdoid tumours associated with the tumour suppressor genes NF2 and SMARCB1, respectively, both located on chromosome 22. The prevalence of PMS due to ring chromosome 22 is estimated at 10-20%, while the risk of developing a tumour although not fully known is estimated at 2-4%. However, those who do develop them, often have multiple tumours.

European consensus recommendations concerning ring chromosome 22

- In an individual with a ring chromosome 22, personalized monitoring for potential NF2-tumors should be discussed with the patient or their representatives[1].
- In an individual with a ring chromosome 22, cerebral imaging (MRI) is recommended at the age of 14 to 16 years, if not already available. In case of obvious hearing loss discuss with the patient or their representatives repeating of the MRI[2].

The EU-PMS Consortium

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The guideline's website

https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline

Link to all PMS guidelines materials

Questions?