

Committee for Quality Assurance

Members elected:
Prof. Dr. rer. nat. Jürgen Kunz (chairman)
Dipl.-Biol. Susanne Anders
PD Dr. rer. nat. Barbara Fritz
PD Dr. rer. nat./med. habil. Thomas Liehr
Dr. rer. nat. Anja Weise

RT managers:
Dr. rer. nat. Sebastian Eck
Dr. rer. nat. Eveline Fiedler
Prof. Dr. med. Claudia Haferlach
Sarah Matos Meder, M. Sc.
Prof. Dr. med. Harald Rieder

Final Report to RT Array diagnostics 2018, revised version

Dear Colleagues,

We have now completed the sixth “array diagnostics” round robin test. We would first like to thank the experts, Dr. Fauth and Dr. Krabichler, Innsbruck, Dr. Dahlum, Ulm, Dr. Darchinger, München, Dr. Gläser, Freiburg, Dr. Hinderhofer as well as Dr. Jakob-Obeid, both Heidelberg, and Dr. Röpke, Münster, who supported us with their precise and detailed evaluation.

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Here are the results of the two cases in detail:

Case F1:

Round robin test, Felix; date of birth: 6 June 1987

Altogether max. 13.5 points achievable.

RT Managers Array Diagnostics

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Karyotype (ISCN 2016): **arr[GRCh37] Xp11.22(51484276_54318296)x2**

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Result:

*One hemizygous interstitial microduplication was found in the chromosomal region Xp11.22 with a minimum size of 2.84 Mb. The additional material covers a small segment of the critical region of the **Xp11.23-p11.22 duplication syndrome** (OMIM 300801) and the entire region of the **Xp11.22 duplication syndrome** (OMIM 300705).*

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Evaluation:

Description of the clinical phenotype on the basis of the literature and with reference to the phenotype of the patient.

*e.g.: ... In studies of multiple affected families, it was shown that various overlapping duplications within this region with a size of 0.3-0.8 Mb in male family members cause a “**Xp11.22-linked intellectual disability syndrome**“ with mental retardation, and frequently also with behavioural problems, arrested linguistic development and hyperactivity (Froyen 2008, Santos-Reboucas 2015, Moey 2016). The phenotype of the patients examined was largely non-syndromal,*

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*with mild to moderate mental retardation. It is assumed that various genes in this region, particularly the gene **HUWE1**, are read in a dose-sensitive manner, and that overexpression in men results in cognitive developmental disorders.”*

Furthermore:

- Obesity (Grams 2016; Santos-Reboucas 2015; Froyen 2012)
- Muscular hypotonia (Moey 2016; Grams 2016; Baquero-Montoya 2014; Tran Mau-Them 2014)
- Microsomia (Moey 2016; Grams 2016; Baquero-Montoya 2014; Santos-Reboucas 2015)
- Or also DECIPHER patients...

In summary...

We recommend molecular cytogenetic examination of the brother with similar phenotypical presentation, and of the mother of the patient, in order to...

Case F2 (dry run):

Altogether max. 6 points achievable.

Oligonucleotide array

- 1) Karyotype (ISCN 2016): arr[GRCh37] Xq21.1q21.31(82945783_90731126)x0
- 2) Hemizygous deletion in Xq21.1 to Xq21.31, also in PAR3 (log₂R= - 1.49), therefore no “real” deletion in Yp11.2 (Y1), Y2: no PAR3 region = artefact (or benign polymorphism)
- 3) Pathological change; “X-linked mental retardation (MRX97)”, deletion of the gene ZNF711; cause of clinical phenotype
- 4) Molecular cytogenetic examination of the mother, possibly of other family members, potential repeat risk if further children desired

We also counted mosaic findings as valid! This task should lead to consideration of the analysis software to be used for X/Y chromosomes.

Affymetrix Array

- 1) arr[GRCh37] 15q11.2q13.1(22770421_28545355)x4
- 2) Partial tetrasomy 15q11.2q13.1 in the critical region of PWS/AS, 5.75Mb; presence of a marker chromosome (isochromosome 15 or isodicentric chromosome 15)
- 3) Pathological change; marker chromosome 15 (?) cause of clinical phenotype (muscular hypotonia, developmental retardation)
- 4) FISH analysis (marker chromosome, balanced rearrangement, minimal mosaic) of parents, microsatellite analysis of UPD15 (mat, pat)

Illumina Bead Array

- 1) arr[GRCh37] 5p13.2q11.2(35333673_58886873)x3[0.5]
- 2) Log₂R in the pericentromeric region of chromosome 5 is slightly elevated, B allele frequency is split, mosaic (~50%) with marker or ring chromosome
- 3) Partial duplication of chromosome 5 as a mosaic (23.5 Mb) with the NIPBL gene, marker or ring chromosome; phenotype depends on the size, gene in sequence segment, extent of the mosaic in various tissues; developmental disorders, macrocephaly, dysmorphia and recurrent respiratory infections are described (Camerota 2017, Iorov 2015, Melo 2011), cause of phenotype
- 4) FISH analysis, investigation of parents (mosaic?).

GENERAL:

2f) Statements on practical resolution should be explained!

e.g. "...the resolution in the region of microdeletion and microduplication syndromes is less than 10 kb ... In the interest of statistical reliability, initially 5 changed, consecutive 60-mer oligonucleotides and/or imbalances over 50 kb are assessed and analysed..."

3e) Correct recommendation from human genetics advisory service

Genetic Diagnostics Act (GenDG) Art. 10 Para. 1: "... In the case of a diagnostic genetic examination... if the affected person is found to have a genetic characteristic with significance for a disease or health disorder, ... Sentence 1 shall apply, with the condition that the responsible physician shall offer to provide the advisory service ..."

Mrs Judith Scherr, the legal adviser of the BVDH, has provided her opinion on this and written the following:

"...The comment on GenDG by Kern (Art. 10, marginal note 5 etc.) makes specific reference to these notes.

Based on the aforementioned documents, it is my opinion that the following conclusions can be drawn regarding diagnostic genetic advisory services under Art. 10 Para. 1 Sentence 2 GenDG, i.e. with significance for disease / health disorder:

The physician is required to offer advisory services to the patient. Phrasing using the word "may" is not sufficient (e.g. you may arrange an appointment). It is not necessary, however, to use the word "must". The phrase "Please make an appointment (...)" represents a practicable solution in my opinion..."

We will insert a summary of the statistical analysis on the platform. You will find the results of your laboratory under the button "Auswertung" ("Analysis"). If you have any questions, Ms Brandt at the coordination office will be happy to help you.

The next array diagnostics round robin test will take place in January 2019. We would be delighted if you would also like to make yourself available as an expert.

We are always grateful for suggestions and constructive criticism.

Best regards,

Yours sincerely



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