

BVDH e. V. • Coordination Office QA
c/o Die Tastatur Feldstr. 30 52249 Eschweiler/Germany

Ring Trial Structural Analysis 2018 Final Report, 24 October 2019

Dear participants of the Structural Analysis 2018 Ring Trial,
With the assessment having now been completed, we would like to thank you very much for your participation in this interlaboratory comparison. In addition, we would like to thank you for your patience, as scheduling difficulties delayed the evaluations. *You will find the individual evaluation of your laboratory in the password-protected member area under "Interlaboratory comparisons - completed" in the row 'RV Structural Analysis 2018', via the button 'Assessment'.* The reviewer's commentary on your findings is intended to serve as clarification.

Special thanks go to the twelve co-assessors: Prof. Dr. rer. nat. Iris Bartels (Göttingen), Dr. rer. nat. Frank Dechend (Hildesheim), Dr. rer. nat. Katrin Fröbius (Marburg), Dr. Angelika Köhler (Gießen), Dr. Anja Louis (Mannheim), Dr. Gisela Raabe-Meyer (Hanover), Dr. sc. hum. Andreas Rätsch (Stuttgart), Dr. rer. nat. Martin Schliephacke (Gießen), Dr. rer. nat. Azadeh Taghipour (Hanover), Dr. rer. biol. hum. Hanne Tittebach (Nuremberg) and Prof. Dr. rer. nat. Markus Stumm (Berlin). They all examined the 166 findings with remarkable care and dedication.

Case 1 was prepared and made available for the ring trial thanks to Dr. Ilona Dietze-Armana, Neu-Ulm. Case 2 was kindly provided by Dr. rer. nat. Maurus, Institute of Human Genetics Innsbruck, Austria. Many thanks for the interesting and instructive cases!

For the specific tasks, please refer to the documents made available via the RV-database www.bvdh-ringversuche.de. Due to the provided images for Case 2, only one karyotype formula should have been collected.

The number of participants has remained largely constant at 83, of which 8 are located in Switzerland, 2 in Austria, and 1 in Romania.

**Berufsverband Deutscher
Humangenetiker (BVDH) e.V.**

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Prof. Dr. rer. nat. Jürgen Kunz (chairman)
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Dr. rer. nat. Eveline Fiedler
Prof. Dr. med. Claudia Haferlach
Sarah Matos Meder, M. Sc.
Prof. Dr. med. Harald Rieder
Dr. med. Dieter Schäfer

24. October 2019

Coordination Office Quality Assurance

c/o Die Tastatur – Susanne Brandt &
Rainer Göbbels GbR
Feldstr. 30
52249 Eschweiler
Germany

Tel. +49 2403 83 80 54
Fax. +49 2403 83 80 56

brandt@bvdh.de
www.bvdh-ringversuche.de

RT-Supervisors Structural Analysis

Priv.-Doz. Dr. rer. nat. Barbara Fritz
Zentrum für Humangenetik
UKGM Standort Marburg
Baldingerstr.
35033 Marburg, Germany

Tel.: +49 6421 5 86 29 86

barbara.fritz@uk-gm.de

Dr. rer. physiol. Ilona Dietze-Armana (deputy)
genetikum® Neu-Ulm
Wegenerstr. 15
89231 Neu-Ulm, Germany

Tel.: +49 731 98 49 00

dietze-armana@genetikum.de

Administration Office

Liniestraße 127
10115 Berlin, Germany

Tel. +49 30 55 95 44 11
Fax +49 30 55 95 44 14

info@bvdh.de
www.bvdh.de

Case 1

As in the previous round robin tests, the evaluation was carried out in three categories, namely analysis, interpretation, and formalities. The focus of the evaluation (at $\geq 50\%$) was on the evaluation of the karyotype formula, as that is the correct basis for interpretation of findings. The interpretation of the findings should reflect the "usefulness of the findings with respect to the clinical problem". A maximum of 29 points were available.

1. Task:

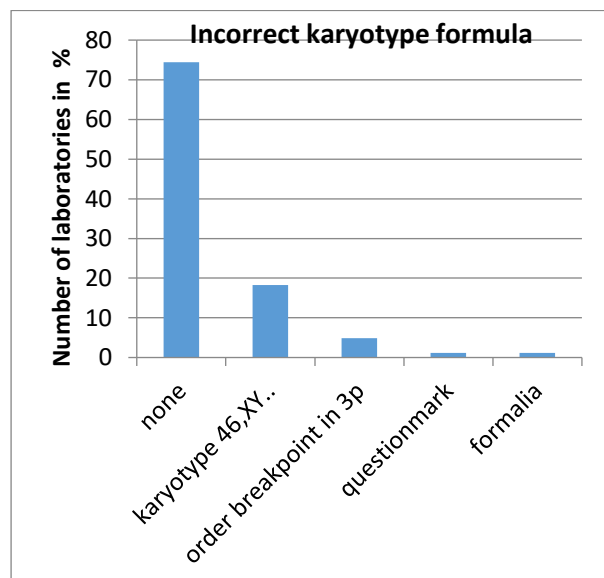
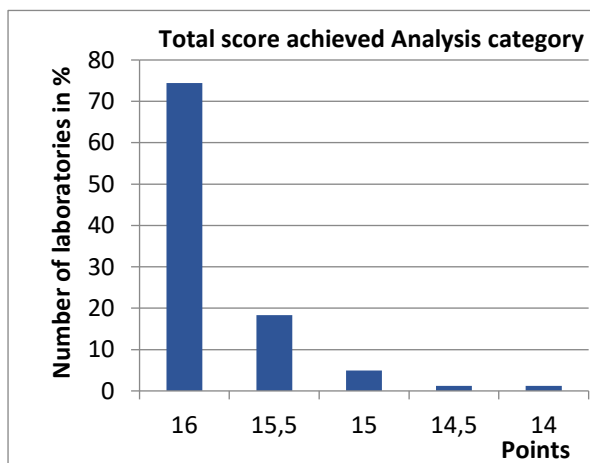
The cytogenetic examination of a 45-year-old man was brought about by infertility due to azoospermia. As part of the fertility treatment, a TESE was planned. A chromosome analysis, in addition to a mutation analysis of the CFTR and TEX11 genes, was requested in order to verify the presence of infertility. An external laboratory had already ruled out the deletion of the azoospermia factor. The family history was inconspicuous.

The chromosome analysis revealed a reciprocal translocation between the Y chromosome and chromosome 3, which was verified by FISH with subtelomere probes. The karyotype formula was **46,X,t(Y;3)(q11.22~23;p24.2)**.

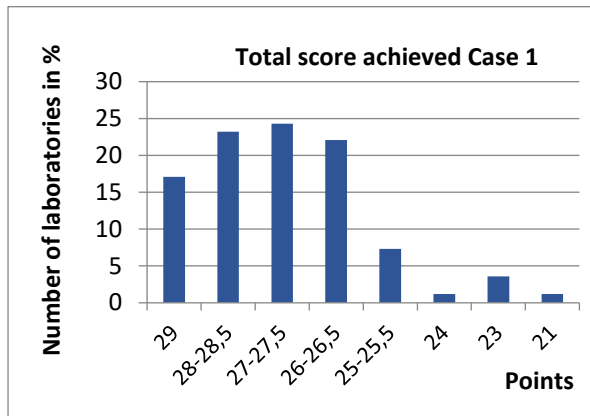
Yq autosome translocations are rare chromosome aberrations and only at ca. 30% do the translocations involve a non-acrocentric chromosome, as is the case here.

2. Analysis Category:

Overall, this case was very positive. The structural aberration was recognized and correctly described by 82 participants (98%). Only one participant did not recognize the structure aberration and described an inversion of the Y chromosome.



The median score was 27 points, with more than 85% of the participants scoring at or above 26 points, and 17% scoring the maximum number of points.



Within the category “Analysis”, the results were fairly homogeneous, with an average score of 15.8. Negligible deductions resulted mainly from minor errors in the karyotype formula.

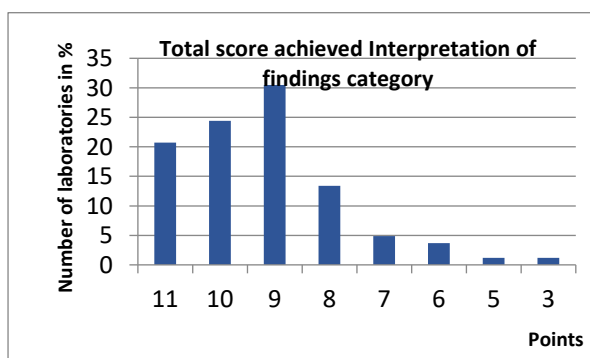
3. Interpretation of Findings Category:

Here, we would like to underline once again that it is essential to evaluate the result critically with regard to the clinical indication (*cf. module Cytogenetic Laboratory Diagnostics: 8. Findings, "The finding itself and the conclusions should be clearly highlighted and the diagnostic question should be answered"; E.C.A. Cytogenetic Guidelines and Quality Assurance: 8. Reporting*). Thus, the interpretation of the translocation with regard to infertility was generally expected. In addition to information on possible mechanisms leading to infertility due to this translocation, also expected were statements on possible imbalances in the case of successful TESE as well as a statement on the familiarity of structural aberration.

Here, we would like to underline once again that it is essential to evaluate the result critically with regard to the clinical indication (*cf. module Cytogenetic Laboratory Diagnostics: 8. Findings, "The finding itself and*

As in recent years, the category “Interpretation of Findings” showed a much wider range of results. A maximum of 11 points were available, which 21% of the participants reached. The average score was 9.2 points.

The interpretations of the findings were often formulated in a more general sense, resulting in point deductions: Only approx. 60% of the participants stated a spermatogenesis disorder caused by the translocation of autosomal chromosomal material into the so-called sex vesicles, leading to the cessation of spermatogenesis with subsequent degeneration of the sperms, and thus leading to azoospermia-related infertility (*cf. Pinho et al. 2005, PMID:1566501*).



The possible imbalances were often described in very general terms and the particularities of a Y-autosome translocation were not discussed: e.g. that only girls can show a normal karyotype and only boys can be carriers of a balanced translocation, but then presumably they also have fertility disorder. There is a high probability that fetuses with an unbalanced set of chromosomes are viable, and corresponding malformation syndromes are described in the literature. Although the translocation most likely occurred de novo,

a chromosome analysis of the father should still be performed, since few cases of paternal transmission have been described (e.g. Teyssier et al., 1993, PMID:8488881; Sklower Brooks et al., 1998, PMID:9674899). In familial Y autosomal translocation, variations in fertility may occur in different male family members.

Further investigations were reported to almost all laboratories. FISH analyses with wcp3/wcpY and/or subtelomere probes for these chromosomes were most frequently mentioned. In addition, 23 laboratories recommended conventional CBG/DAPI or QFQ staining for further clarification and 28 laboratories wanted to perform array diagnostics to exclude smaller genomic imbalances.

The **administrative data** (that is, paperwork) did not cause any problems.

Case 2

Chromosome analysis of a 32-year-old man with azoospermia revealed a male karyotype with an isodicentric Y chromosome. The absence of almost the entire arm of the Y chromosome can explain the present azoospermia. The results of the chromosome preparation in the form of GTG/QFQ banded karyograms and mitoses were available in the database for this case. In addition, 2 images of FISH additional examinations were provided. Regarding this case, the correct karyotype formula should have been detected within the given karyotype formulas and, taking into account all results presented, a karyotype formula should have been given according to ISCN 2016. A maximum of 7 points were possible.

All participants were able to complete the task, with 6.5 being the median number of points awarded. The partial point deductions were limited to inconsistencies regarding the karyotype creation as per the ISCN nomenclature (e.g. incorrect break points, incorrect sequence of the FISH probes).

A detailed analysis of the two cases will be presented at the upcoming QS-Workshop in Cologne on the 22nd of November, 2019, after which the presentation will be made available to RV participants via www.bvdh-ringversuche.de.

Regarding the interlaboratory test and individual evaluation results, participants may contact the coordinating office via email (brandt@bvdh.de) with any complaints. All complaints must be filed in text form by 22 Nov 2019.

Finally, we would like to thank you once again for your kind participation. We are always open to suggestions and criticism, and we look forward to relevant and interesting cases from your laboratory! As a preliminary inquiry, please send us a sample picture of the case. And, as it concerns the 2020 ring trials, we would be very grateful to any participants who would like to take on the additional role of evaluator.

With kind regards,



PD Dr. Barbara Fritz
Ring Trial Supervisor



Dr. Ilona Dietze-Armana
Deputy RT Supervisor



Prof. Dr. Jürgen Kunz
Chairman of Expanded
Comittee for QA