MOLECULAR AND EXPERIMENTAL BIOLOGY IN MEDICINE

LETTER TO THE EDITOR

# EXPERT KNOWLEDGE ON HUMAN GENETIC COUNSELLING AND CHROMOSOMICS ARE NECESSARY FOR SOUND GENETIC LABORATORY DIAGNOSTICS

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Nowadays human genetic laboratory diagnostics is driven by three forces: money[1, 2], quality[3-5] and quick adaptation of high throughput approaches.[1-6] In other words, clinical laboratory geneticists (CLG)[3] have to deliver quick, reliable and for low costs, a most comprehensive result for individual patients. In principal this is a positive development, as more and more genetic test results are extremely meaningful for diagnoses and therapy of constitutional and acquired diseases (e.g. [7-9]). At the same time there is a trend to adapt quickly high throughput approaches (like next generation sequencing), and, instead of adding their power to the existing methods, to replace immediately traditional by new techniques.[10-13]. However, it is a well-known truism, that no technique can comprehensively answer all questions. For example, array-comparative genomic hybridization (aCGH) provides a higher resolution than banding cytogenetics, but only the latter can distinguish a gain of copy numbers detected by aCGH, to be either an unbalanced translocation, insertion, direct or indirect duplication or array-comparative genomic hybridization (aCGH) a small supernumerary marker chromosome. Each kind of rearrangement may have different ways of formation and probability of inheritance within a family.

Being in the field of human genetic research and diagnostics since about 2 decades, during the last 10 years the author of this editorial was involved in numerous national and international education programs for young colleagues (e.g. [14]). It could be observed, that some important aspects during education of future-CLGs definitely need more and special attention. Some of them are more general; others maybe associated to the developments in our field mentioned in paragraph 1 and are discussed below.

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**1. Genetic laboratory diagnostics is for the patient!**

When a sample arrives in the laboratory, first it needs to be checked what the referring colleague wants the laboratory to do, and for what reason a specific test was chosen. Accordingly a CLG needs to be able to understand basics of medical terminology and be able to understand symbols of a pedigree. As genetic diagnostics is for the patientõs sake and well-being, it is the responsibility of a CLG to check in detail each order for (1) its plausibility, and (2) if all legal and ethical standards to start the test are fulfilled. This means, a CLG should contact the referring MD in case a requested test seems inadequate or may lead to incomplete results. Also a CLG needs to know, if a requested diagnostic has its peculiarities or just can be performed as a routine case ï e.g. if a test for Chorea Huntington is ordered for an individual or a family, this is only indicated after intense genetic counselling took place, due to the massive consequences such a diagnose has for the affected and all relatives.

**2. CLGs must work hand in hand with genetic counsellors**

Genetic counselling is a very special kind of patient-MD-consultation. Only based on genetic counselling responsible decisions on necessary genetic laboratory diagnostics can be found. Thus, it is a good idea for each CLG to find possibilities to sit in to a genetic counselling as an observer at least once in their professional life. It is necessary to get a kind of ñfeeling for this situationò, in which no one else besides the consulters are allowed to make a decision on their own case. This is something completely different than going to an MD because of a broken leg, where patients advisably expect the MD to make all

decisions how to proceed in this case (Table 1, Question 1).

### 3. Identifying a genetic aberration is not enough

In daily routine, quick adaptation of high throughput approaches is requested from CLGs, even though new test systems are far from being really comparable to each other.[15] Apart from low concordances of data in different read-depth based programs[15], application of high throughput methods comprises two additional problems: (i) they provide information on the genetic content of many thousands (if not millions) of cells, and (ii) they seem to be comprehensive, but the connection to the structure of the human genome, organized in chromosomes is easily lost.

A CLG needs to know advantages, disadvantages, possibilities and short-cuts of all approaches available in his/ her laboratory. A result pointing towards a chromosomal imbalance (e.g. in aCGH) must also be understood on chromosomal level (Table 1, Questions 2 to 3). Besides, a negative aCGH result together with an abnormal GTG-banding result may indicate for further testing (Table 1, Question 4). Sometimes, even simple questions like in case of Turner syndrome may cause problems (Table 1, Question 5); however, here it is important to react correctly due to the clinical consequences, i.e. removal of streak gonads of the Turner syndrome patient.

As outlined by Prof. Uwe Claussen in 2005 ñchromosomicsò should be considered as a central part of our interpretation done for genetic and genomic data[16]. A CLG must, after having a genetic test result in hands, a clear idea what it really means on chromosomal level (Table 1; Questions 2 to 5). This is perquisite to get an idea what this genetic finding may mean for the patient and, possibly, for its whole family and future generations.

**Table 1. What is the correct answer for the following question?**

| | |
|---|---|
| Q1: | In sonography of a 22-year-old woman at 20th week of gestation, a fetal brain malformation with enhanced ventricles was found. The genetic counsellor discusses with the parents the diagnosis and the unpredictability of the outcome. The woman expresses her reluctance/ dislike to terminate the pregnancy. Her husband is very quiet for long time and says after he is directly asked by counsellor he will most likely abide with his wife's decision. The most appropriate next step is here to:<br>a) support the woman's decision<br>b) engage the husband in the decision-making process<br>c) refer the couple for family therapy<br>d) suggest the couple continue this discussion at home<br>e) the MD must take a final decision |
| Q2: | In aCGH you see a loss in 22q13.32-qter; what will you see in GTG-banding? |
| Q3: | In a patient with mental retardation you get as aCGH result: duplication in 11q of ~18 MB and in 22q near the centromere of ~3 MB in size; what will you see in GTG-banding? |
| Q4: | In a patient with mental retardation you get as aCGH result: no imbalance. In GTG-banding you see a karyotype 46,X,t(X;15)(p11.2;q11.2). What do you need to consider here to test additionally? |
| Q5: | In a patient with Turner syndrome one finds a karyotype 46,X,+mar. Which probes to apply now first in fluorescence in situ hybridization (FISH) to find out the chromosomal origin of the marker chromosome? |

Legend: Qï question

Correct answers:
1. b
2. either a del(22)(q13.32) or a r(22)(p12q13.3)
3. 47,XN,+der(22)t(11;22) = Emanuel-syndrome
4. X-chromosome inactivation and test for uniparental disomy for chromosome 15.
5. centromeric probe for X and Y-chromosome; if marker is derived from Y-chromosome the girl has a 20% enhanced risk for gonadoblastoma

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