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Genetics of Down Syndrome

Thomas Eggermann[1] and Gesa Schwanitz[2]
[1]Institute of Human Genetics, RWTH Aachen
[2]Institute of Human Genetics, University of Bonn
Germany

1. Introduction

1.1 Morphology

According to the International System for Human Cytogenetic Nomenclature (ISCN) human chromosomes (2n=46) are divided into two groups (Shaffer et al., 2009). These are the two sex chromosomes or gonosomes (X,Y) and the 44 non-sex chromosomes or autosomes, respectively. Chromosomes of the latter group are numbered as 1 to 22, according to their decreasing size. Autosomes in somatic cells are comprised of two homologous, genetically identical chromosomes.

The time of the first conference for nomenclature in 1959 is called the pre-banding area. Individual chromosomes could not yet be ascertained beyond reasonable doubt. Thus it happened that the second smallest chromosome, chromosome 21, which had been analysed three times in the patient's karyotype, was believed to cause Down Syndrome (DS). Later studies showed that DS is trisomic in the smallest chromosome. To avoid conflict between previous and subsequent publications, the position of the two smallest chromosomes (21 and 22) was switched, resulting in the definition of DS as trisomy 21.

The relative length of chromosome 21 is 1.9 ± 0.17 % of the total length of the human genome, and its size is approximately 60 Mb. Chromosome 21 belongs to the acrocentric chromosomes, i.e. the centromere is localised closer to the end of the short arm (p). The short arm 21p is heterochromatic but consists of different types of repetitive DNA (Figure 1)(Wyandt and Tonk, 2004).

The relative length of the short arm of chromosome 21 comprises 30 % of its total length (Figure 1). Variants in brilliant fluorescence after QFQ-staining are diagnosed in 2.0 % of band p11.2 and 10.0 % of band p13. Duplications in p12 show a frequency of 0.7-1.3 % and 0.1 % in the satellites of p13. Deletions in all three regions (p11.2, p12, p13) are rare (Kalz et al., 2004).

These frequencies are derived from population studies based on Europeans. Significant differences in comparison to other ethnic groups have been observed (Kalz et al., 2005). The polymorphic regions in the short arm of chromosome 21 allowed the first studies on the parental origin of trisomy 21 (Mikkelsen et al., 1980).

The long arm (q) of chromosome 21 is euchromatic, with the exception of the peri-centromeric region q11.1 and the distal telomere.

Chromosomes are usually presented and analysed in the metaphase of mitosis after *in vitro* cultivation, which is not identical to their appearance *in vivo*. Among the differentiated cells,
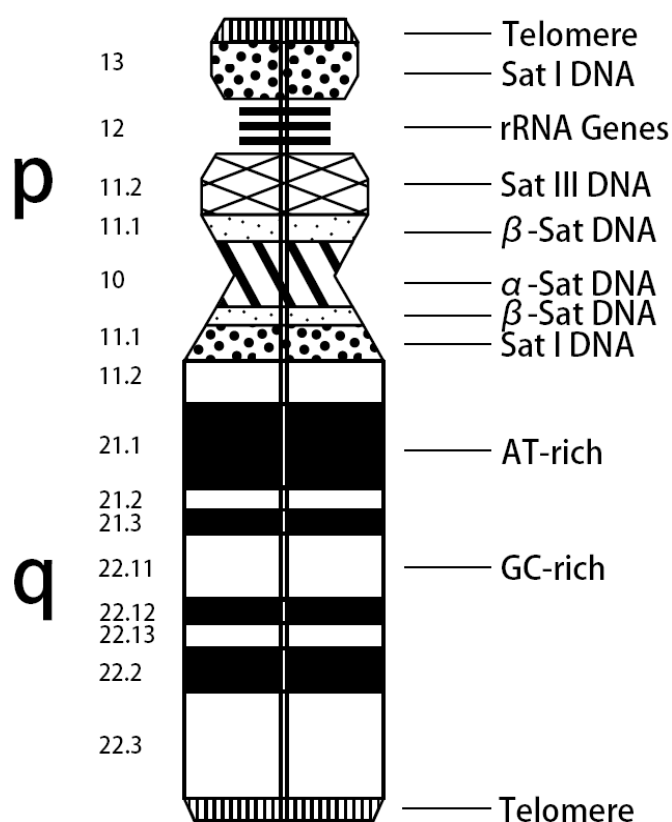
Fig. 1. Structure and morphology of chromosome 21. Ideogram according to the ISCN (Shaffer et al., 2009).

only some (i.e. T-lymphocytes in a blood sample) can be stimulated *in vitro* to enter the cell cycle again and thus represent a selected cell population. In addition, cells are treated with colcemid. This substance arrests the chromosomes in the c-metaphase of mitosis and, at the same time, increases the contraction of chromosomes, rendering the centromeres and the fissure between the two chromatids visible (Figure 2a).

1.2 Structure

The central part of the centromere of chromosome 21 consists of α-satellite DNA that is almost identical to the centromere of chromosome 13 (homology 99.7%)(Figure 1). On both sides α-satellite DNA is flanked by β-satellite DNA. These two non-coding regions can vary significantly in size through duplication or deletion. They are irrelevant for the carrier, unless their length is less than 20 % of the average length of the region and thus prevents the normal development of the kinetochores. This would result in the failure of exact separation of the chromatids in the anaphase of mitosis (Waye et al., 1989; Mitchell et al., 1992).

Distal of the β-satellite DNA, satellite DNA class III is situated on the short arm (p11.2). Significantly varying in size, this band shows a specific absorption of DNA-dyes. Therefore, it is defined as a polymorphic region. It is followed in the short arm by the band p12, which is also named the nucleolus organising region (NOR) and contains the ribosomal RNA-genes. It is characterised by its slightly lateral expansion (satellite stalks). It is polymorphic and can be deleted or amplified (Tagarro et al., 1994a). The most distal regions of the short arms are the satellites (p13 or s), consisting of Sat I DNA with the telomeres at the ends

(Tagarro et al., 1994b). Satellites are also polymorphic varying in size and staining characteristics. They also have the ability to duplicate.

In describing the structure of the short arm of chromosome 21, only the main components of the different bands are mentioned. Especially p11.1, p11.2, and p13 contain further subgroups of repetitive DNA.

a)   b)
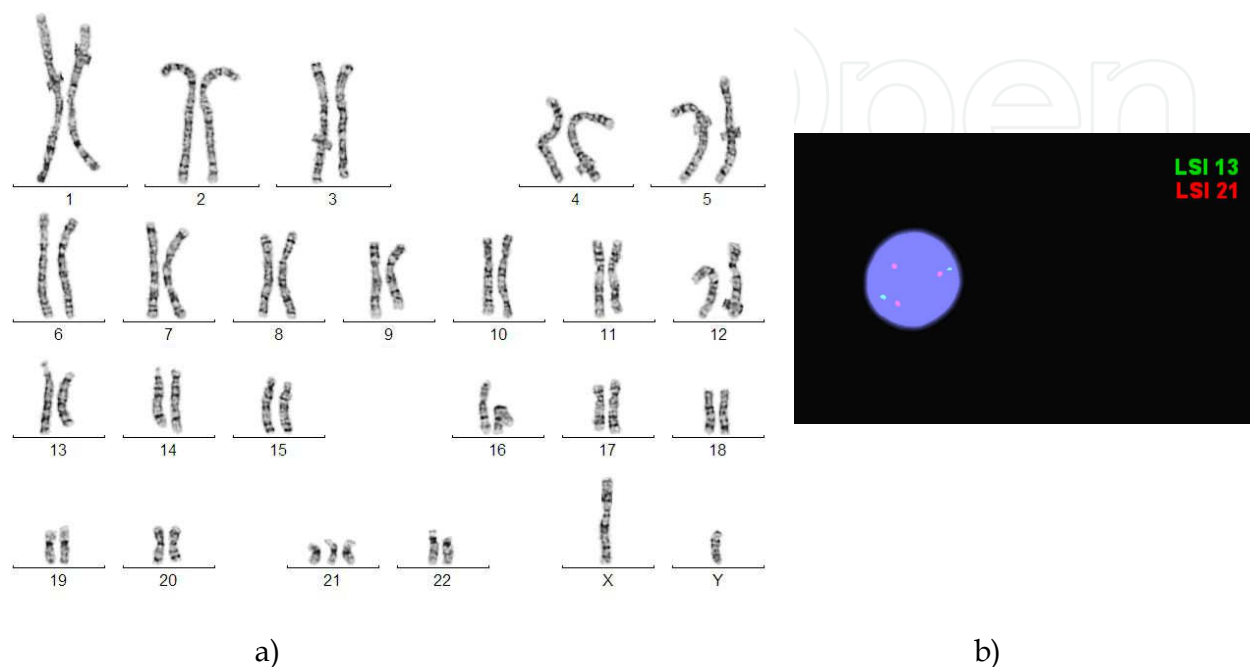
Fig. 2. Routine diagnostic workup for identification of trisomy 21. **a)** Standard karyotype (47,XY,+21) by GTG banding (by kind courtesy of U. Mau-Holzmann, Tübingen). **b)** Interphase FISH showing three signals of chromosome 21 and two of chromosome 13 (LSI21:21q22.13q22.2; AneuVysion multicolor DNA probe Kit, Vysis).

According to the literature, the proximal heterochromatic region of the long arm (q11.1) of chromosome 21 consists of β-satellite DNA boarding the central α-satellite DNA and followed distal by Sat I DNA (Waye et al., 1989; Mitchell et al., 1992; Tagarro et al., 1994a, 1994b). The main part of the long arm is euchromatic. AT- and GC-rich bands have characteristic sequences and can be differentiated by their typical staining features (figure 1). These bands of single copy DNA are interspersed by non-coding repetitive DNA (SINEs and LINEs).

1.3 Aneuploidy and gene content

A complete or partially aneuploid chromosome is associated with a pathologic phenotype in the carrier, the expression of which depends on the type and amount of the aberrant genetic material.

In contrast to chromosome 22, chromosome 21 consists of a high number of AT sequences which contain a smaller amount of vitality-determining genes than the GC-rich ones.

GC-rich or housekeeping genes are expressed in most cell types. They lead to proteins that carry out various metabolic and structural functions. In contrast, the AT-rich genes are tissue-specific and are only active in certain cell types while being inactivated in others by methylation. This gene inactivation is accompanied by a more condensed structure of the

chromatin and, consequently, the DNA of these genes is not accessible to the transcription factors. These AT-rich DNA regions show a higher staining intensity and can thus be localised by chromosome analysis.

Because of its high content of AT-rich regions, trisomy 21 is compatible with life, and in the majority of cases, leads only to retardation in the development of the carrier and not, as in trisomy 22, to lethality.

The gene map of chromosome 21 was initially constructed by combining the analyses of small structural aberrations with the results of different gene product analyses (dosage effect). Chromosome 21 was sequenced in 2000 (Hattori et al., 2000), and 225 loci (genes) were identified, which was less than expected. This might explain the relatively mild phenotype of the carriers.

In the following years, a high number of small regions in 21q has been analysed in order to localise the DS critical region (Figure 3)(Wong, 2011), but recent investigations revealed in contrast to the first assumptions that a direct genotype-phenotype correlation does not exist, since a large number of gene products from chromosome 21 also influences gene products and their function on heterologous chromosomes (Gardner and Sutherland, 2004; Weinhaeusel et al., 2011).
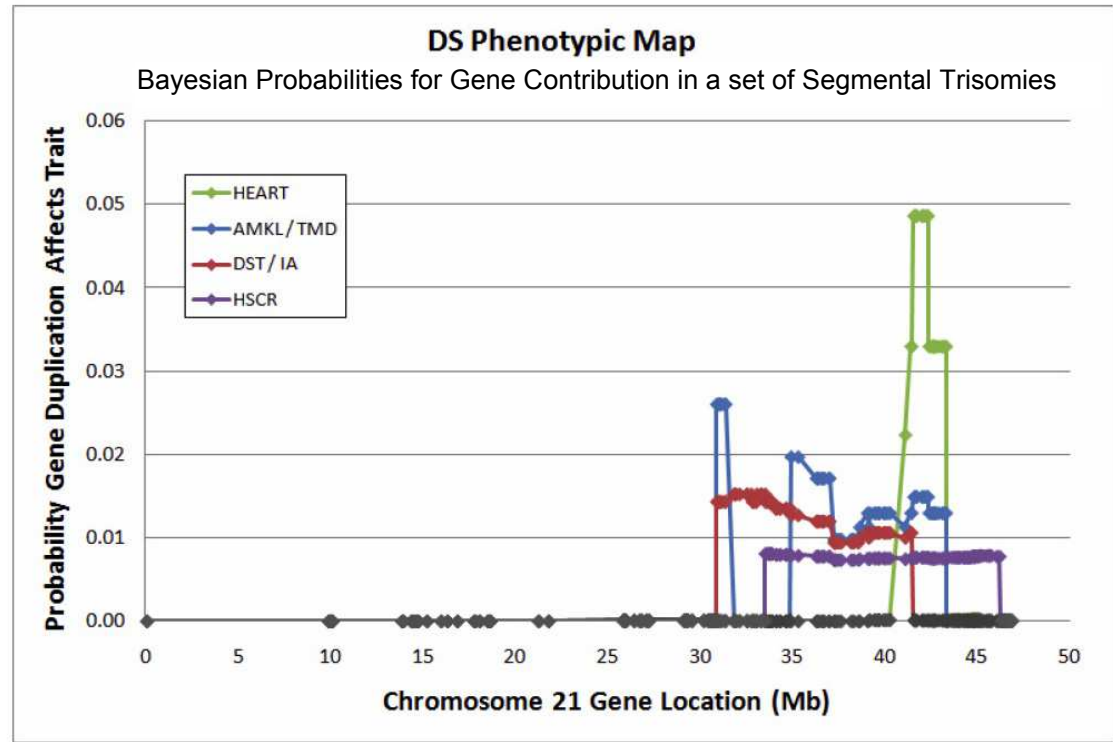
(AMKL acute megakaryocytic leukemia; TMD transient myeloproliferative disorder; DST duodenal stenosis; IA inperforate anus; HSCR Hirschsprung disease)

Fig. 3. Genotype-phenotype correlation in trisomy 21 based on partial trisomy 21 cases (from Korbel et al., 2009). (with kind permission of J.R. Korenberg)

2. Historic development of the cytogenetics of DS

DS was the first malformation complex that could be delineated as a chromosome abnormality in 1959. This was enabled by the new technology to prepare chromosomes in

the metaphase of mitosis. In the early years, mitoses were analysed after direct preparations of bone marrow cells and long term cell cultures of tissue biopsies. Starting in 1960, the lymphocyte culture of peripheral blood was established. Thereby screening of handicapped persons on a large scale became possible. At the beginning of the 1980s, prenatal diagnoses were started for high-risk groups.

Any extension of the spectrum of investigations, any more precise definition of the localisation of the aberration and characterisation of the patients´ symptoms were combined with an improvement of the investigation methods.

The direct preparation of meristematic somatic cells was followed by long-term and short-term cell cultures of differentiated somatic cells removed postpartum, by the culture of amniotic fluid specimen and biopsy of chorionic villi, as well as the analysis of germ cells and their precursor stages in certain special cases, of polar bodies and early postzygotic stages like morula and gastrula in preimplantation diagnostics.

Initially, the presentation of chromosomes was only possible through homogeneous staining, which was succeeded by application of radioactive markers and subsequently of the differentiated characterisation of the chromosomal banding patterns (GTG, GAG, QFQ, RBG, RBA, CBG, and others).

Today, a necessary requirement in diagnostic investigations is a high differentiation of the euchromatin (usually 550 bands per genome). By that way, structural aberrations of chromosome 21 can be safely detected microscopically, starting with a minimal length of 5 Mb. In the 1980s, fluorescence-in-situ hybridisation (FISH) as a new technique was introduced (Figure 2b). By FISH the characterisation of either the entire euchromatin or the centromeric areas or selected euchromatic bands with specific DNA-probes became possible. Simultaneously, this allowed the analysis of cells in interphase and the rapid investigation of larger amounts of cells without cell culture. This so-called rapid aneuploidy testing is especially important for prenatal diagnostics.

Further improvement of the investigation spectrum provided the development of the comparative genomic hybridisation (CGH) with the advancement to the microarray, which has been depicting an improvement and specification of diagnostics on the molecular-genetic level through development of specific tiling arrays.

The newest development is next-generation sequencing. This method is still known to be in trial tests, and its establishment in diagnostics is to be expected.

The various methods of investigation are often combined to improve diagnostics.

3. Types and frequencies of chromosome 21 aberrations

In addition to the predominance of standard trisomy 21 as the cause of DS, further types of aberrations exist. They differ in relation to the type of abnormality, and they lead to different prognoses as to the chances of development of the carrier and recurrence risks for the relatives of a carrier.

Therefore, the indication for a chromosome analysis is always given in the presence of the distinct phenotype of DS.

3.1 Standard trisomy 21

In this type of aberration, the carrier has 47 chromosomes, including three chromosomes 21. It accounts for nearly 90% of DS cases. Standard trisomy 21 typically occurs sporadically, therefore the recurrence risk is low.

The majority of free trisomy 21 cases (85-90%) originates from errors in maternal meiosis. In particular, maternal meiosis I is the most frequently affected stage of nondisjunction (>75%), whereas maternal meiosis II errors account for >20%. In 5% of free trisomy 21, paternal meiotic errors can be observed, here meiosis II nondisjunction is more frequent than meiosis I errors. In addition, postzygotic mitotic errors have also been reported (5%). The predominant influence of disturbed maternal meiosis is reflected by the decreased number of of chiasmata in meiosis I increasing with maternal age. Indeed, the reason for this association is unknown, however numerous hypotheses have been proposed (for review: Hultén et al., 2010).

3.2 Robertsonian translocations

Trisomy 21 due to an unbalanced translocation of chromosome 21 with a hetero- or homologous acrocentric, satellite-bearing chromosome (13, 14, 15, 21, 22) is called a Robertsonian translocation. However, the frequency of translocation partners varies and is a result of homologies in the heterochromatin of the short arm, thus leading to failures in the pairing of meisosis I. The resulting fusion products can be monocentric or dicentric with an inactive centromere.

In monocentric translocation chromosomes, the centromere can derive from each of the two partners or can be a hybrid structure originating from both of them.

Robertsonian translocations involve about 5% of the cases of trisomy 21. Approximately 75% are formed de-novo in the carrier , and 25% are familial (for review: Gardner and Sutherland, 2004). Among these, translocation 21/21 is an unusual rearrangement, but in the majority of cases, it is not a fusion of homologous but the formation of an isochromosome.

In general rule, carriers of the balanced Robertsonian translocation display only 45 chromosomes, the unbalanced ones show 46, as in the majority of carriers, and two short-arm regions are lost. The loss of two NOR-regions does not lead to clinical symptoms in the carriers of balanced translocations.

Among the different heterologous translocations of the acrocentric chromosomes with chromosome 21, the combination with chromosome 14 (rob(14q21q)) is the most frequent one with about 60%. This is followed by the translocation rob(21q21q) or by the formation of isochromosome i(21q21q), respectively, in 35% of the cases. The other translocations are rare and do not exceed 5%. (for review: Gardner and Sutherland, 2004)

Current studies of meiosis are leading to new insights on frequency of formation and postzygotic selection of Robertsonian translocations in familial cases. These studies are largely based on analyses of translocation rob(14q21q) as the most common subgroup. According to these, women with a balanced translocation have an aberrant karyotype in about 20 % of their polar bodies as well as in the oocytes and men in 10-15% of their sperms. These frequencies decrease postzygotically in the course of the development of the embryo, therefore the risk of a child with heterologous translocation trisomy 21 amounts to only 8% if the mother is the carrier and to 4 % with the father (for review: Gardner and Sutherland, 2004).

It is noticeable that in families with translocations, children with a normal phenotype carry a balanced translocation more often than the normal karyotype if the origin is maternal (60:40), while the ratio is equal with paternal origin (50:50).

3.3 Reciprocal translocations

Reciprocal translocations are caused by the exchange of euchromatic regions of chromosome 21 with the euchromatin of different autosomes or gonosomes. In addition to trisomic

regions in various length and location of chromosome 21, unbalanced forms at the same time show partial monosomy for the exchanged regions of the second translocation chromosome. As a result, the phenotype in the carriers of unbalanced translocations is not consistent.

Caused by the rare occurrence of these translocations, there are no reliable data for their incidence, a frequency of less than 1:1000 standard trisomies can be assumed. According to the literature, the most common partners for a reciprocal translocation seem to be the chromosomes 18 and 22 (Schinzel, 2001).

3.4 Duplications

This type of aberration is always formed de-novo in carriers with a noticeable pathologic phenotype. If the duplicated segment is only of small size or originated from a postzygotic mosaic, the impairment of the carrier may be mild, and he might have an almost unrestricted life opening the possibility of inheriting the duplication to his offsprings.

A duplication in the cells of the carrier can be caused by an unequal pairing of homologous chromosomes in the pachytene of meiosis I and an aberrant crossing-over as the consequence.

A paracentric inversion in the long arm of a parental chromosome 21 may present an increased risk for the formation of a duplication. According to published cases, the size of the duplicated region can vary significantly, and so far, no preferential sites for the exchange have been documented. With the few existing case reports, no data concerning the frequency of duplications can be given.

3.5 Submicroscopic aberrations

Investigations with FISH probes and applications of molecular-genetic methods for small euchromatic regions enabled the detection of structural aberrations in chromosome 21 in a size of less than 5 Mb. The amount of disorders that can be attributed to small duplications and deletions of chromosome 21 therefore has risen significantly within the last years. The phenotype of the carriers is predominantly not characteristic for the DS.

3.6 Gene mutations

Meanwhile, extensive genotype-phenotype correlations on the basis of structural aberrations of chromosome 21 have been reported, which help to narrow down the DS critical regions (Figures 3, 4)(for review: Korbel et al., 2009). A small number of genes has been proposed to cause the specific DS features, and among them are: DSCR1, DYRK1A or APP (for further details see other chapters of this book).

3.7 Mosaicism

The frequency of trisomy 21 mosaics after chromosomal analysis is about 3-5 %. This number is most likely too small since tissue-specific mosaics cannot always be detected.

Mosaics always originate from mitotic aberrations during the early postzygotic development of the conceptus. Their formation may be caused by an aberrant zygote loosing one of the three chromosomes 21 of a standard trisomy in a portion of the cells. Alternatively, the zygote can have a normal karyotype, but in a postzygotic mitosis, nondisjunction of chromosomes 21 takes place.

Structural aberrations of chromosome 21 as mosaics are always caused by postzygotic rearrangements. Carriers of mosaics with the aberrant cells occuring only in the gonads have an increased risk compared to the general population of the same age for the birth of a child with the aberration in all cells.

The risk of mosaic carriers for a retardation or affected offspring can not be specified because of the different types of aberrant karyotypes and their unequal distribution in the organism.

If the percentage of trisomic cells in all somatic tissues is small (0.5 – 5 %), the phenotype of the carrier can be normal.

Carriers with mosaics have a better prognosis than carriers of non-mosaic trisomies, but there is always a risk of uneven distribution of pathologic cells in the various tissues. Therefore, only the analyses of cells type stemming from different germ layers can lead to a reliable prognosis concerning the development of the patient.

3.8 Tetrasomy 21

A specific type of hyperploidy 21 is the tetrasomy where the chromosome 21 is present for four times. In the literature, only single cases have been published (Gardner and Sutherland, 2004). This abnormality can either consist of four free chromosomes 21 or of two normal chromosomes and in addition an isochromosome 21. The aberration is usually lethal in the conceptus in early pregnancy, but a mosaic constitution has been diagnosed in patients postnatally.

4. Techniques for DS testing

Many different cytogenetic as well as molecular-genetic techniques have been developed in the past to detect standard trisomy 21 and structural aberrations of chromosome 21. Whereas the "simple" detection of genomic imbalances can be performed with numerous molecular techniques (short tandem repeat typing, MLPA, molecular karyotyping), information on structural rearrangements is usually up till now achieved by classical microscopic methods, e.g. chromosome analysis and FISH. In future the development of high resolution next generation sequencing techniques will allow a nearly complete overview on all numerical and unbalanced structural rearrangements in one molecular assay.

4.1 Chromosome analyses

Chromosome investigation is the conventional cytogenetic method based on cells undergoing mitosis to obtain metaphase spreads. The chromosomes can be pre-treated and stained according to different protocols to induce specific banding patterns. By karyotyping, the specifically banded chromosomes can be arranged into seven groups (A to G) based on descending order of size and of the position of the centromere. According to the type of induced banding pattern, two subtypes can be defined: a) those resulting in bands distributed along the length of the whole chromosome, such as G-, Q- and R-bands, and b) those that stain specific chromosome structures (e.g. C-bands, nucleolus organizing regions, telomeric bands)(Shaffer et al., 2009).

The advantage of classical cytogenetics is that both unbalanced as well as balanced chromosomal aberrations are detectable. However, the technique is limited by the microscopic solution. Therefore, imbalances <5 Mb are not analysable by routine cytogenetics. Another disadvantage is that the majority of cell types has to be cultured in vitro either as a short-term

or long-term culture. The long culture times bear the risk of *in-vitro* chromosomal changes. The direct preparation of mitoses is only possible when analysing meristematic cells (bone marrow biopsies, trophoblast cells, germ cells and their precursors). This mehtod has the advantage that the chromosomal analysis reflects the situation in-vivo.

Chromosome analyses are mainly done after lymphocyte culture from peripheral blood samples. The cells are easily obtained and stimulated to mitosis, and the time of cultivation is only 48-72h.

The chromosomes are arranged in a formal karyotype, according to their size, centromere position, and banding pattern (Figure 2a) following the International System for Human Cytogenetic Nomenclature (ISCN; Shaffer et al. 2009).

4.2 Fluorescence-in-situ-hybridization (FISH)

FISH is a widely used method to analyse different target DNA sequences by supplying specific DNA - probes. It combines cytogenetic and molecular genetic techniques. The principle of FISH is the interaction of a labelled single-stranded DNA with a denatured metaphase or interphase.

Since a much higher resolution than chromosome analysis, FISH is used to identify and characterise small structural chromosome aberrations in clinical cytogenetics, including microdeletions and microduplications. A precise and detailed breakpoint analysis is possible. However, a FISH investigation is only applicable if the aberration in question is suspected.

At first this technique was restricted to metaphase analysis, meanwhile, it has gained importance in interphase diagnostics as well. In particular the latter procedure is extremely helpful to detect low-level mosaicism. Furthermore, it has enabled rapid prenatal testing for the frequent aneuploidies in the fetus, including trisomy 21 (for review: Caine et al., 2005).

4.3 Microsatellite typing

Short tandem repeat markers (STRs, microsatellites) are highly informative molecular markers which are easy to handle. STRs have been described as an abundant class of DNA - polymorphisms in the human genome, consisting of highly repetitive short DNA - sequences. They can be typed by using PCR and single-copy primers flanking the repeats, followed by denaturing on a high resolution gel or by capillary electrophoresis. In 1991, Petersen and co-workers were the first to describe the application of these markers in order to determine the parental origin of the extra chromosome in families with a trisomy 21 patient. Meanwhile, numerous studies on the origin of unbalanced chromosomal aberrations have been published.

It is the advantage of microsatellite analysis that it needs only minimal amounts of genomic DNA. Furthermore, it is a fast and simple method which is widely established. It is therefore not amazing that this technique is one of the most frequently used methods for rapid prenatal aneuploidy testing (Mann et al., 2004). It circumvents time-consuming cell cultivation and needs approximately 6-8 h from taking the sample to final report. In addition, the comparison of the allelic distribution of a fetus and his parents allows the exclusion of a maternal contamination in fetal DNA - samples.

However, the technique does not allow the detection of balanced rearrangements. Furthermore, a reduced informativity of microsatellite markers might hamper the interpretation. In particular in case of parental consanguinity, the informativity might be reduced.

4.4 Multiplex Ligation-dependent Probe Amplification (MLPA)

Multiplex Ligation-dependent Probe Amplification (MLPA) is a simple, high throughput method that allows detection of DNA copy number changes of up to 40 sequences in a single reaction. It is based on the semi-quantitative polymerase chain reaction principle and can be applied for detecting copy number changes and has been developed by MRC Holland (http://www.mlpa.com/). MLPA has rapidly gained acceptance in genetic diagnostic laboratories due to its simplicity compared to other methods, its relatively low costs, the capacity for high throughput, and its robustness. Typical for the MLPA is that not target sequences are amplified but MLPA probes that hybridise to the target sequence. In contrast to a standard multiplex PCR, a single pair of PCR primers is used for MLPA amplification. The resulting amplification products of an MLPA assay range between 130 and 480 nucleotides in length and can be analysed by capillary electrophoresis. By comparing the peak pattern obtained to that of reference samples it can be delineated which sequences have aberrant copy numbers. The MLPA reaction can be divided into five major steps: 1) DNA denaturation and hybridisation of MLPA probes; 2) ligation reaction; 3) PCR reaction; 4) separation of amplification products by electrophoresis; and 5) data analysis. For trisomy 21 and further frequent aneuploidies (trisomies 13 and 18), an aneuploidy MLPA kit is commercially available.

The advantage of MLPA is indeed the low amount of genomic DNA needed for genotyping and the fact that that parental samples are not necessary for comparison. However, the procedure is time-consuming and needs at least two days.

4.5 Array analysis

Molecular karyotyping is meanwhile a well established method to identify genomic imbalances. In particular the resolution is much better than that of conventional cytogenetics. While chromosome analysis detects imbalances (deletions and duplications) >5 Mb, array typing has a resolution of <100 kb (figure 4). Microarray analysis allows the identification of any type of segmental imbalance by virtue of its design, but it does not allow the identification of balanced rearrangements or small mosaics.
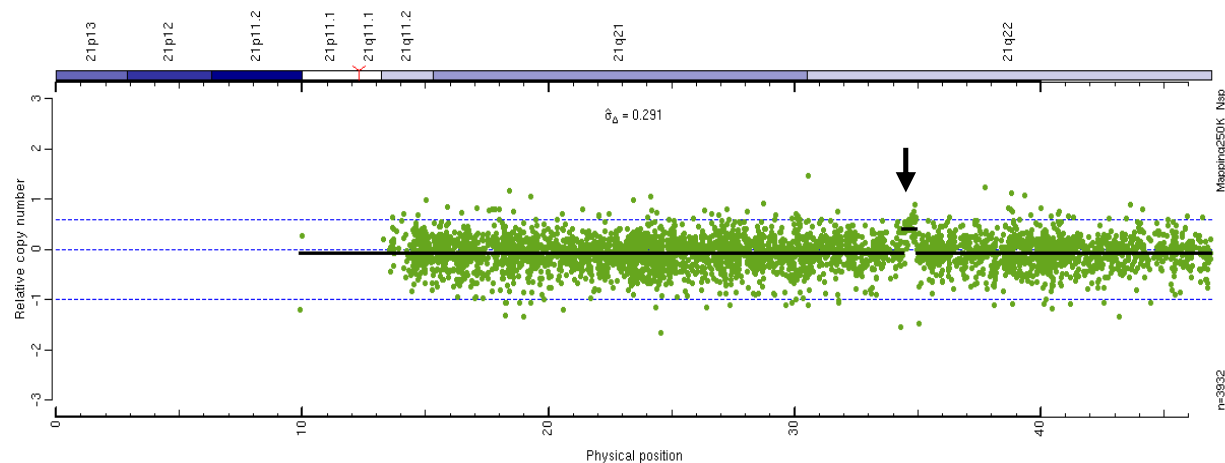

Fig. 4. Example of Micro-array based characterisation of a partial trisomy 21 in a patient affected by Silver-Russell syndrome (Eggermann et al., 2010). The patient did not exhibit any symptoms of DS, thus the trisomic region could be excluded to be involved in the specific phenotypic expression of DS.

As a large number of strategies and platforms are commercially available and cannot be covered here, we strongly emphasize checking the updated literature. Dependent on the array type, molecular karyotyping allows the detection of imbalances with a size of a few kb. And thus the detection rate for chromosomal aberrations in patients with mental retardation could be increased impressively (for review: Shaffer and Bejjani, 2010). However, the interpretation of microarray data is currently hampered by the large genomic instability mainly in non-coding regions, resulting in the analysis of a growing number of copy number variations (CNVs).

Nevertheless, first guidelines for molecular karyotyping have recently been published (Vermeesch et al., 2010).

4.6 Next generation sequencing

Due to the development of genome-wide sequencing (next generation sequencing) the cheap and accurate characterisation of whole genomes in a short time has become possible. Indeed, the methods and applications are extremely manifold and can be merely covered in this short paragraph (for review: Metzker, 2010). Of course, it is too early to apply this complex technology for characterisation of whole chromosome aberrations like trisomy 21. However, target assays will be developed, and it has to be considered that next generation sequencing will allow to rapidly identify and reliably characterise genomic disturbances – balanced as well as unbalanced – and breakpoints in cases of structural rearrangements.

5. Probability for the birth of a child with DS

As the clinical symptoms of a child with the phenotype of DS cannot be considered as a reliable classification, the diagnosis must always be accompanied by a chromosome analysis.

The occurrence of trisomy 21 in young mothers lead to screening investigations to ascertain whether exogeneous factors might play a role in the aetiology of trisomy 21 besides the well-known genetic risk factors.

5.1 Subjects for discussion on exogeneous risk factors

Different substances known as mutagens, co-mutagens, and teratogens have been investigated in detail.

The atomic bomb blasts in Japan at the end of the World War Two and the explosion of the atomic reactor in Chernobyl in 1986 are well-known examples of exposures and have been thoroughly explored. However, they did not lead to an increased birth of children with DS (Dean et al., 2000).

Furthermore, neither contact with different organic substances or heavy metals nor an increased consumption of caffeine, alcohol, or nicotine could be shown to increase the number of births of children with trisomy 21 or other chromosome aberrations.

5.2 Endogeneous risk factors

This group encloses carriers of balanced and unbalanced chromosome 21 aberrations and includes the risk of advanced maternal age at pregnancy as well.

5.2.1 Carriers of standard trisomy 21

Adequate therapy has increased the life expectancy of carriers of trisomy 21 significantly within the last decades. Furthermore, a largely normal life by a specific support of motor and

mental abilities has become possible for many DS individuals. This leads to pregnancies in DS women and makes adequate genetic counselling necessary. The theoretical risk for a woman with trisomy 21 to have a child with trisomy 21 is 50%, but it is reduced by the high amount of abortions in early pregnancy. An empirical risk of 30-40% can therefore be delineated.

However, genetic counselling has also   to take into account the risks of a pregnancy in a DS woman suffering from malformations such as heart defects or kidney anomalies. Males with a trisomy 21 are usually sterile.

5.2.2 Recurrence risk in carriers of mosaic trisomy 21

In mosaic cases, the risk of a female or male in rare cases carrier to have a child with full trisomy 21 cannot be estimated precisely, because only the amount of trisomic cells in the somatic tissues can be analysed but not the one in the gonads. The ratio of trisomic cells may even be 100% in the ovaries and testes, leading to the same risk factor as in carriers with a full trisomy.

A special situation is given if the carrier has a normal karyotype in all somatic cells investigated, and the trisomic cells are restricted to the gonads (parental germline mosaicism). In these cases the empiric recurrence risk is delineated as 1-2%, but in two cases of two or more pregnancies with trisomy 21 it is estimated to be much higher (empirical value of more than 10%) (Warburton et al., 2001).

Mosaics are usually found in free trisomy 21 but mosaicism of translocation trisomy 21 has also been observed.

5.2.3 Carriers of a balanced heterologous Robertsonian translocation

Significant differences concerning risk factors have been observed   for female and male carriers of heterologous translocations. In female carriers, the empiric risk of having a child with an unbalanced translocation is about 10%, and in males it is only 1-2% (Ferguson-Smith, 1983; Daniel et al., 1989). In both sexes, the translocations rob(14q21q) and rob(15q21q) harbour the additional risk of uniparental disomy 14 or 15 as a consequence of trisomic rescue (Kotzot and Utermann, 2005) which is associated with specific clinical syndromes.

5.2.4 Robertsonian translocation rob(21q21q) and isochromosome 21

Balanced carriers of these two types of rearrangements have a risk of 100% that the offspring will inherit a translocation trisomy 21, regardless of the sex.

5.2.5 Parents with a balanced reciprocal translocation

In the rare group of parents carrying a balanced chromosome rearrangement affecting whole or partial 21q, the risk of having a child with a complete or partial trisomy 21 is relatively high, with about 20% in females and 10% in males. If the translocation chromosomes and their normal homologous show pairing difficulties in meiosis I, the additional risk of a 3:1 segregation has to be taken into account, leading to a recurrence risk of up to 30%. Offspring with an unbalanced translocation show monosomy of the heterologous chromosomal segment, in addition to the complete or partial trisomy 21. As a result, the phenotype will be complex and heterogeneous, depending on the origin of the second translocation chromosome.

5.2.6 Parents with normal karyotype having a child with DS

This is the main group of consultants. The maternal age at pregnancy is significantly elevated in the majority of cases, and therefore, an increased risk for elder women can be

delineated (risk of 1:1667 at 20 years and 1:32 at 45 years (Morris et al., 2002). There is a second slight increase of risk in very young mothers (1:1000 at 15 years). The probability for a child with DS is not correlated with paternal age.

However, in a small cohort of families an age independent high risk for pregnancies with different trisomies has been observed (Munné et al., 2004; Baart et al., 2006).

Molecular investigations made it probable that in these cases the increased aneuploidy rate is caused by an autosomal recessive mutation. To identify this group of carriers a thorough pedigree analysis is necessary, cytogenetic karyotyping is indicated for the consultants and their offspring – children and miscarriages. Failures from pregnancy induction by IVF (in-vitro fertilisation) have to be included in the risk estimation. These couples are usually recommended to a special IVF program for   a further pregnancy, and preimplantation-testing procedures might be considered (Stumm et al., 2006).

5.2.7 Siblings and 3rd degree relatives of a patient with DS

Healthy relatives of a patient with a free trisomy 21 have no increased risk for the birth of a child with trisomy 21 when compared to the average population of the same age.

Relatives of a proband with DS caused by an unbalanced structural rearrangement have an increased risk if they are balanced carriers of the translocation (see above). The risk factor depends on the type of rearrangement and on the sex of the carrier.

5.2.8 Prenatal findings of symptoms characteristic for DS detectable by ultrasound

At the end of the first trimester of pregnancy (10th to 12th week,) ultrasound investigations are routinely recommended. At that age, the majority of fetuses with trisomy 21 show a number of characteristic features. These include nuchal translucency, absence of nasal bone, heart defect and growth retardation. In the second trimester, the main symptoms detectable by ultrasonography are a flat occiput, a flat profile of the face, small nose, dysmorphic and deep seated ears, receding chin and short neck, malformations of the internal organs, and growth retardation.

These observations by ultrasound are an indication for prenatal chromosome analysis either by chorionic villi sampling (CVS) or by amniocentesis (AC).

5.2.9 Comparison of invasive and non-invasive prenatal investigations

Non-invasive methods

The main technique in prenatal diagnostics is ultrasound. In Germany, it is usually applied three times during pregnancy. Ultrasound can meanwhile be regarded as a prerequisite for CVS, AC, or fetal blood sampling (FBS) since morphologic abnormalities are caused by a pathologic karyotype in 20-50% of the cases (personal observation).

A second group of non-invasive parameters   are specific biochemical factors (AFP, β-HCG, estriol) analysed from maternal blood. They are combined with the risk delineated from the given maternal age. If the result differs from expectation and corresponds to an increased risk for DS, invasive methods to determine the karyotype are applied.

A third possibility for non-invasive investigations in pregnancy is the analysis of fetal cells and fetal DNA in the maternal blood. By special procedures, fetal DNA can be isolated and enriched from maternal blood, however, this method is still under development and is currently not applied in routine prenatal testing.

Invasive prenatal investigations

Three different methods are usually applied: CVS in the first trimester, AC in the second, and AC, FBS, and placenta biopsy in the third.

All three methods generally include an investigation risk of about 1%. Therefore, these methods should only be applied if the genetic risk is higher than the risk of investigation.

Sometimes different methods have to be combined to receive a diagnosis. However, this increases the time of investigation and prolongs the psychological stress of the parents (Geskas et al., 2011).

Usually, a reliable, final diagnosis can only be achieved by invasive investigations but the non-invasive methods enable the investigator to get information of an increased or decreased extent of the pre-existing risk in the individual pregnancy.

6. Comparison of type and contretype of DS

As a full monosomy 21 is lethal in life-born children and also exceedingly rare in spontaneous abortions, the phenotype of carriers of this aberration is delineated from mosaic cases and partial deletions. The clinical findings revealed a number of symptoms, especially facial dysmorphic features that can be defined as opposite type or "contretype" to patients with trisomy 21 (Table 1).

Trisomy 21	Partial monosomy 21
Muscular hypotonia	Muscular hypertonia
Overextension of joints	Spasticity
Hyperflexible fingers	Camptodactyly
Flat occiput	Protuberant occiput
Upslanting palpebral fissures	Downslanting palpebral fissures
Small round ears	Large ears
Aplastic nasal bridge	Protuberant nasal bridge

Table 1. Phenotypes of trisomy and (partial or mosaic) monosomy 21. (Schinzel, 2001)

7. DS and uniparental disomy

As trisomic rescue is the most frequent way of uniparental disomy formation, this type of cytogenetic aberration has to be discussed in context with trisomy 21. Uniparental disomy (UPD) is the inheritance of both homologous of a chromosome pair from only one parent. The concept of UPD was first postulated to cause specific phenotypes in the eighties (Engel, 1980). This hypothesis was then confirmed by UPD of different chromosomes in association with typical syndromes. The best examples of this type of aberration are maternal UPD15 (upd(15)mat) in Prader-Willi and paternal UPD15 (upd(15)pat) in Angelman syndrome.

Different mechanisms may lead to UPD (Spence et al., 1988): each of them includes at least two errors either during meiosis or in postzygotic mitoses. During meiosis, a nondisjunction of two homologous chromosomes occurs, which leads to a trisomy in the zygote. In most cases, this zygote will not be viable, unless a correction or a "trisomic rescue" happens. Statistically, in one third of cases, the chromosome of the parent who did not contribute to the trisomy is lost, thus resulting in UPD.

A cytogenetic hint for a trisomy rescue is the confined placental mosaicism (CPM), which describes the presence of a partial chromosomal aberration (usually a trisomy mosaic) in the placenta but not in the fetus. This constitution can be diagnosed in approximately 1-2% of chorionic villous samples (Kalousek et al., 1989). CPM can have relevant clinical consequences since it may lead to placental insufficiency and then induces intrauterine growth retardation.

Clinical features in context with UPD can be caused by:

a. hidden chromosomal mosaicism originating by the UPD formation via trisomy rescue;

b. by the imbalanced expression of imprinted genes in the respective chromosomal region resulting in a specific imprinting disorder;

c. homozygosity for recessive mutations. Interestingly, this phenomenon led to the detection of the first case of UPD. Spence et al. (1988) reported a patient suffering from cystic fibrosis who was homozygous for the mutation F508del in the CFTR gene. Only his mother was a heterozygous carrier for F508del transmitting the mutant gene copy twice to her child. Therefore, UPD always involves the usually unpredictable risk for homozygosity of mutant genes in addition to imprinted gene effects.

Due to the frequency of trisomy 21, UPD of this chromosome should be a well-known aberration. Indeed, maternal as well as paternal UPD21 (upd(21)mat, upd(21)pat) have been reported for several times (for review: Kotzot and Utermann, 2005), including healthy carriers. Based on the latter finding, it can be decided that the clinical course of upd(21)mat or upd(21)pat carriers is rather caused by a hidden chromosomal mosaicism which can be delineated from the UPD formation mechanism or by homozygosity of a recessive allele than by the UPD itself. Imprinted genes involved in the aetiology of imprinting disorders are not localised on chromosome 21. A different epigenetic effect was shown by recent investigations.

It could be demonstrated that trisomy 21 affects the methylation pattern of different heterologous chromosomes by decreasing their extent of methylation (Weinhaeusel et al., 2011) and thus leas to clinical abnormalitiesof the carrier.

8. The simultaneous occurrence of trisomy 21 and other chromosomal aberrations

This group of combined aberrations comprises numerical and structural abnormalities which present as pathologic karyotype in all cells of an organism or as different types of mosaicism. Investigations usually rely on conventional chromosome analyses of spontaneous abortions as in this group the frequency among conceptus with pathological karyotype is about 25% compared to life-born children with 0.2% (own investigations and findings from the literature).

8.1 Double aneuploidies

Trisomy 21 can be combined with aneuploidies of different heterologous chromosomes (Micale et al., 2010). The maternal age of a pregnancy with a conceptus showing a double aneuploidy is on average higher than that with a single trisomy. The life expectance of the carrier is lower in prenatal and postnatal period than in single trisomies. Double trisomies of autosomes show a higher lethality than combinations of autosomes and gonosomes.

8.1.1 Combinations with gonosome aberrations

Gonosomal aneuploidies in patients with an additional trisomy 21 were diagnosed in the four possible combinations with monosomy X, XXY, XYY and XXX. The most frequent gonosome aberration in this context is XXY. Monosomy X often presents as mosaic.

The phenotype of the patients usually corresponds to that of trisomy 21. The reason might be the inactivation of more than one X chromsome and the low number of genes on the Y chromosome. The combinations of these double aneuploidies are more frequent than the total amount of the two single trisomies, or the trisomy combined with that of monosomy X.

8.1.2 Combinations with heterologous autosome aberrations

In life-born children, only three combinations of trisomy 21 with additional heterologous chromosomes have been observed: +8, +13, +18, and trisomy 8 is always occurring as mosaic. The double trisomy 21 and 18 seems to be the most frequent combination with an average of 1:1000 among trisomy 21 carriers. The frequency of this combination is much higher in spontaneous abortions with about 2.5 in 100 trisomies. This is explained by the high and early lethality of conceptus with a double autosomal trisomy.

Clinical investigations reveal a heterogenous picture: The carrier can show the phenotype of one of the 2 trisomies or a combination of both. The majority of double trisomies presents as a mosaic with one or two trisomic cell lines.

8.2 Trisomy 21 in combination with structural aberrations

The most frequent aberration is a trisomy 21 in combination with a balanced Robertsonian translocation rob(13q14q). It has been hypothesized that a familial translocation rob(13q14q) induces frequently errors of pairing of heterologous chromosomes in the prophase of meiosis I leading to an aneuploid gamete (interchromosomal effect). Recent investigations could not prove this hypothesis. It is nowadays assumed that the reduced fertility of the translocation carriers is the reason for pregnancies at increased maternal age, which leads to an elevated risk for pregnancies with trisomy 21.

Further single cases of trisomy 21 combined with structural aberrations comprise unbalanced and balanced reciprocal translocations, deletions, and sub-microscopic aberrations.

9. Differential diagnoses

Carriers of trisomy 21 are characterised by a number of clinical symptoms caused by disturbances during early embryonic development. This abnormal course of differentiation can also occur in other syndromes based on an aberrant embryogenesis.

These syndromes can be caused by other chromosome abnormalities, by monogenic mutations, and by exogeneous factors or teratogenic agents.

Chromosome syndromes with a phenotype that, especially in early childhood, resembles that of children with trisomy 21 are the two poly-X syndromes, penta-X syndrome in the female, and XXXXY in the male.

A monogenic disease with a phenotype similar to that of trisomy 21 is hypothyroidism.

The best-known differential diagnosis to trisomy 21 though, is fetal alcohol syndrome.

The similarity between them is so high and the facial dysmorphic features are so characteristic for both that even in the general population the typical phenotype is well-

known but often misinterpreted. Therefore, it may happen that a child with DS is wrongly mistaken as one with fetal alcohol syndrome and which can lead to discrimination of the family.

The possibility that the phenotype of DS may be caused by other diseases than trisomy 21 makes it necessary for all patients with the clinical diagnosis of DS to be investigated cytogenetically because otherwise prognosis, therapy, and estimation of recurrence risk might not be correct.

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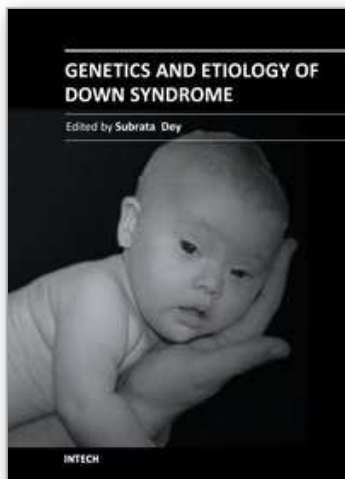
Genetics and Etiology of Down Syndrome

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This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book has been divided into four sections, beginning with the Genetics and Etiology and ending with Prenatal Diagnosis and Screening. Inside, you will find state-of-the-art information on: 1. Genetics and Etiology 2. Down syndrome Model 3. Neurologic, Urologic, Dental & Allergic disorders 4. Prenatal Diagnosis and Screening Whilst aimed primarily at research workers on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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