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Cytogenetic Analysis of Selected Genetically Determined Diseases in Eastern Slovakia

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A B S T R A C T

This work presents the results of cytogenetic analysis performed during the period 1990-2021. The work focuses on cytogenetic analysis of selected diseases that represent a serious medical and social problem in the Prešov region of eastern Slovakia. The analysis also included the determination of cytogenetic and molecular-genetic marker frequency related to selected clinical genetic diseases in a specified population of Roma ethnicity. Chromosome analysis confirmed a wide spectrum of chromosomal aberrations in patients with Down's syndrome and Turner syndrome, revealing a spectrum of aberrations from monosomy X, isochromosome Xq, and deletions Xp to marker chromosomes. Chromosomal aberrations cause 5.5% of fertility disorders in couples, with numerical and structural chromosomal aberrations found in 2.1 and 3.4% respectively, revealing a risk finding for offspring of carriers of balanced translocations. Microdeletions, combined microdeletions (AZFb,c) and complete deletion of the AZF region of the Y chromosome were found in men diagnosed with azoospermia. In addition, pathological karyotypes were detected in men and women (13 and 10%). Another set of analyses in patients with onco-haematological diseases revealed presence of Philadelphia chromosome (Ph1) in 94.4% of patients with chronic myeloid leukaemia, complex translocation of chromosomes 8, 9, 22; mosaic karyotype of Ph1. Chromosomal aberrations in patients with myelodysplastic syndrome also included also atypical and as yet unpublished cytogenetic markers. Myeloproliferative diseases were detected in 28.3% of patients with heterogenous chromosomal aberrations. Revelations from cytogenetic analysis enable improvement in the efficiency of health care, diagnostics, therapeutic significance and prognosis of affected people in the majority population and Roma minority in this region of Slovakia.

Key words: *cytogenetics, genetically determined diseases, karyotype, medical anthropology*

Introduction

Analysis of cytogenetic and molecular-genetic markers is currently the standard method of detecting genetically determined pathological conditions. Genetics, as a scientific discipline, made enormous progress during the 20th century, and medicine was included in its ever-growing influence. As part of this progress, the "geneticization" of medicine took place. Epidemiological studies confirm that diseases caused by changes at the level of sequence, organization and structure of the genome have a significant effect on the mortality and morbidity of human populations. Cytogenetics clarifies the correlation between microscopically detectable changes in genetic material at the level of chromosomes and phenotypic manifestations, but the mechanism of complex chromosomal changes has not yet been clarified.

Chromosomal aberrations represent an important cytogenetic marker of genetically determined pathological conditions. Chromosomal abnormalities occur in 0.6% of live births[1]. Chromosomal abnormalities are involved in the aetiopathogenesis of congenital developmental defects and 50% of spontaneous abortions, with repeated miscarriages an indicating factor for prenatal diagnosis and karyotype analysis of the parents to detect chromosomal rearrangements. Chromosomal abnormalities present in the parents' karyotypes increase the risk of conception of a foetus with chromosomal abnormalities with published statistics indicating a 2% prenatal incidence of cytogenetic aberrations[2].

Conventional cytogenetics of G-banded chromosomes is the most suitable method of analysis for metaphase chromosomes as it allows the detection of all types of chro-

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mosomal abnormalities[3,4]. Peripheral blood samples processed by standard culture methods[5] were used for the cytogenetic analysis of sets of individuals from the Prešov region (1991–2015) carried out as part of our studies. The samples were cultured short-term (72 hours) in RPMI-1640 medium with phytohemagglutinin stimulation. Colchicine was used to stop cell division. The cells were incubated for 20 minutes in a hypotonic solution of 0.075 M KCl at a temperature of 37 °C. They were fixed with a mixture of methanol and acetic acid (3:1). Selected metaphases were stained conventionally, with G-banding and C-banding methods. Identification and classification of chromosomes was performed according to the international system of cytogenetic nomenclature (ISCN 1995).

Analysis of the Occurrence of Down Syndrome in the Roma Ethnic Group

Chromosome aneuploidies represent the most frequent, clinically significant type of chromosomal aberrations. Trisomy of chromosome 21 is the most common chromosomal aberration in live births[6,7]. The symptomatology of Down syndrome is variable, including muscle hypotonia, congenital heart defects and a typical phenotype[8,9]. As the cytogenetic base of Down syndrome is aberrations on chromosome 21, chromosome analysis enables the detection of these cytogenetic forms of Down syndrome. Modern molecular genetic methods confirm correlations of allelic variants with phenotypic manifestations of chromosome 21 trisomy[10].

Down syndrome is a genetic disease affecting individuals of any population. The Roma ethnic group in eastern Slovakia is genetically distinct from the majority population and forms a significant part of the region's population. Despite the numerous anthropological studies of Roma populations focused on the issue of anthropometry and the study of genetic polymorphisms, relatively little attention is paid to the incidence of chromosomal aneuploidy in this ethnic group. Data on the occurrence of Down syndrome in Slovakia focused on the Roma ethnic group were not collected or published for a long time. Knowledge of blood group distribution, serum and isozyme variants, HLA system and DNA polymorphisms[11] indicate kinship of the Roma ethnic group with the Indian population. Published data state the incidence of Down syndrome in India at 1:853 live births[12,13].

In a study carried out in the Prešov Region between 1991 and 2003, chromosome analysis was carried out in a set of individuals with a clinical diagnosis of Down syndrome with the specification of Roma ethnicity[14]. From the total number of 4748 chromosome analyses, 61 cases of Down syndrome were detected (1.28%): 54 cases of Down syndrome in individuals of the majority population (1.13%), and 7 cases of Down syndrome in individuals of Roma ethnicity (0.15%). Free trisomy of chromosome 21 was detected in 95.1% of cases, mosaic form of trisomy of chromosome 21 in 3.3% of cases, and translocation form of trisomy of chromosome 21 in 1.6% of cases. The sex ratio in cytogenetically confirmed cases of Down syndrome was 1:2 in favour of males. The predominance of male individuals with Down syndrome is consistent with the hypothesis that trisomy cells containing XY heterochromosomes show more intensive proliferation compared to cells with the XX gonosome complement[15,16].

Detection of the Spectrum of Gonosomal Aberrations in Patients with Turner Syndrome

Most chromosome aneuploidies are lethal in the prenatal period, and only detected postnatally in the mosaic form. Turner syndrome is a disease with a frequent finding of mosaic forms of gonosome aneuploidy. Turner syndrome is characterized by gonadal dysgenesis, short stature, congenital lymphedema, congenital developmental defects of the cardiovascular and uropoietic tract, and frequent skin and bone changes[17].

Turner syndrome is associated with structural and numerical abnormalities of the X chromosome, or the presence of the Y chromosome in whole or in part. The predominant cytogenetic finding is the predominant cell line 45,X[18]. Detection of risky Y-specific sequences forms part of the standard diagnostic procedures in patients with Turner syndrome[19]. Analyses of genotype-phenotype correlations in patients with Turner syndrome revealed correlations between specific physical characteristics and loss of the corresponding part of the X chromosome[20,21]. Deletions involving the short arm of the X chromosome are associated with short stature, deletions involving the long arm of the X chromosome are associated with ovarian dysgenesis. Prueitt et al.[22] confirmed that the loss of the interstitial or terminal part of the long arm of the X chromosome (Xq^-) correlates with ovarian dysfunction. Distal deletions in the long arms of the X chromosome (Xq^-) are unlikely to affect body height while loss of chromosomal material of the short arm of the X chromosome (Xp^-) results in the typical phenotype of Turner syndrome. Loss of the distal part of the short arms of the X chromosome is usually associated with short stature and typical skeletal abnormalities. This is a result of haploinsufficiency of the genes responsible for short stature, the homeobox genes (*SHOX* gene). In addition, aneuploidy itself can cause growth disorders[23] and conventional chromosome analysis detects the presence of Y chromosome material in 4–20% of Turner syndrome patients[24,25].

From the total number of 2072 chromosome analyses in the set of female patients with suspected chromosomal aberration in the Prešov region (1991–2003), Turner syndrome was cytogenetically confirmed in 24 cases (1.16%)[26]. Mosaicism was confirmed in 70.8% of pathological karyotypes and non-mosaic complement was detected in 29.2% of pathological findings of karyotypes. The most common type of mosaicism was the 45,X/46,XX karyotype detected in 25% of cases in our study. Karyotype 45,X was also

confirmed in 25% of abnormal cytogenetic findings. In 12.5% of cases, an isochromosome for the long arms of the X chromosome was detected during karyotyping, one cytogenetic case with a non-mosaic complement, two cases of a mosaic form with cell line 45,X. Deletion of the short arms of the X chromosome was detected in 4.2% of abnormal chromosome cases in mosaic form with the 45,X cell line. Other forms of mosaics were confirmed in 33.3% of cytogenetic cases, the classical karyotype 45,X being detected in combination with one or more additional cell lines with karyotype 47,XXX; 47,XXY; 46,XY or normal cell line 46,XX. In 12.5% of cases, chromosome analysis revealed the presence of a chromosome marker in a karyotype. Molecular genetic diagnosis was recommended for patients with a pathological karyotype of 45,X/46,X,+mar. Y chromosome material was confirmed by PCR analysis in 16.7% of patients with Turner syndrome.

The symptomatology of Turner syndrome is variable and differs even with cytogenetically identical findings. Accurate mapping of part of the chromosomes at the level of individual genes will make it possible to clarify correlations between clinical manifestations and lack of genetic information[21,27,28]. Identification of patients with Y chromosome material and the presence of Y specific sequences is important due to the increased risk of gonadoblastoma. In these patients, prophylactic gonadectomy is recommended[17,29-31].

Determination of the Frequency of Chromosomal Abnormalities in Couples with Fertility Disorders and Analysis of Microdeletions on the Y Chromosome

Fertility disorders currently affect 10–15% of couples[32,33]. Chromosome anomalies belong to genetic factors significantly involved in the aetiology of fertility disorders with gonosomal abnormalities being the most common genetic cause of reproductive disorders[34,35]. The goal of chromosome analysis of couples with fertility disorders is the detection of constitutional chromosomal aberrations that indicate the emergence of unbalanced gametes[36-38]. Part of cytogenetic analysis of couples with fertility disorders is the analysis of heterochromatin variants. Chromosome variants are an expression of the morphological variability of chromosomes caused by changes in the amount of heterochromatin. Our studies included cytogenetic analysis of C-banded metaphase chromosomes with a focus on the detection of heterochromatin polymorphisms.

In a set of 287 couples (n=574) with fertility disorders, chromosome analyses were carried out in the Prešov region between the years 1998–2003[39]. In these couples, pathological karyotypes were detected in 7% of men and 4.2% of women. Structural chromosomal aberrations accounted for 53.1% of pathological karyotypes while numerical abnormalities of chromosomes accounted for 46.9% of pathological karyotypes. Mosaic karyotypes were detected in 1.4% of cytogenetically abnormal karyotypes. Chromosome polymorphism was confirmed in 15.1% of couples with fertility disorders. Reciprocal chromosome translocations were found in 437 of Prešov region couples with reproductive disorders between the years 1998–2010[40]. Cytogenetic analysis detected 48 aberrant karyotypes (5.5%). Numerical chromosomal abnormalities were confirmed in 2.1% of cases and structural chromosomal aberrations in 3.4% of couples with fertility disorders. Reciprocal chromosome translocations were detected in 1.4% of couples with fertility disorders (0.9% of women, 0.5% of men). Chromosome analysis also confirmed the presence of a mosaic form of reciprocal chromosome translocation.

Constitutional chromosomal aberrations were detected in 4–5% of couples with fertility disorders[41]. In the analyzed set of couples with fertility disorders in the Prešov region, the percentage of cases with chromosome aberrations was 5.5%. The detected frequency of chromosomal aberrations in our study was 10 times greater than that in the general population. Čapková et al.[42] also detected a 10-fold higher frequency of chromosome anomalies by cytogenetic analysis of couples with fertility disorders. Düzcan et al.[43] confirmed the presence of chromosomal abnormalities in 13% of couples with reproductive disorders. Data on the frequency of chromosomal aberrations in individual studies are influenced by many factors (size of the analyzed set, different selection of individuals, different cytogenetic analysis techniques). Detection of pathological karyotypes supports the recommendations of genetic analysis of couples with fertility disorders. Detection of balanced forms of chromosomal aberrations in the karyotype is an indication for pre-implantation and prenatal diagnostics[44].

Chromosomal aberrations were detected in 2.6% of infertile men by karyotype analysis using G-banding and C-banding methods in a set of 1426 individuals from the Prešov region between the years 1998–2014 (948 infertile men, 478 individuals of the control group)[45]. The most frequently detected chromosomal aberration was karyotype 47,XXY, cytogenetically confirmed in 1.8% of cytogenetic findings of pathological karyotypes. Among other chromosomal aberrations in the set of infertile men, chromosome inversions were detected: 46,XY,inv(2)(p23;q21), 46,XY-,inv(8)(p23;q13), 46,XY,inv(14)(q11;q23), balanced chromosome translocations: 45,XY,t(14;21)(q10;q10), 45,XY, t(13;15)(q10;q10), 46,XY,t(15;16)(p15;q13) and a mosaic form of translocation 46,XY/46,XY,t(6;15)(q16;q12). Autosomal abnormalities included 16% of chromosome translocations and 12% of autosome inversions. A significantly higher frequency of chromosomal abnormalities (11.5%) was detected in the group of infertile men with azoospermia compared to the group of men with oligospermia (1.0%) ($p < 0.01$). Heterochromatin variants were also detected in 13% of men with fertility disorders in the Prešov region. The most frequently detected polymorphisms were heterochromatin variants of the Y chromosome (Yqh^{+}/Yqh^{-}) (2.6%). The detected frequency of heterochromatin variants was significantly higher in the group of infertile men (13%) than in the control group (4.8%) ($p<0.0001$; 95% CI 1.703–4.50). The results of the mentioned study, as well

as the results of our previous studies, confirmed the importance of chromosome anomalies in the pathogenesis of fertility disorders[46].

Published cohort studies of men with fertility disorders report Klinefelter syndrome as the most common karyotypic abnormality detected in 7–13% of men with azoospermia, with the chromosomal abnormality being associated with severe spermiogenesis impairment[47]. Balanced translocations associated with chromosome pairing and segregation in meiosis I provide the potential for the formation of unbalanced gametes[48]. Gonosome mosaicism in men with fertility disorders is considered a possible cause of assisted reproduction failure[49]. Special attention is currently being paid to genetically determined male infertility, with molecular genetic methods allowing the causes of male infertility to be clarified. Deletions in the AZF region of the euchromatin part of the Y chromosome cause spermiogenesis disorders[50-52]. The aims of molecular genetic analyses are the AZFa, AZFb and AZFc loci with the localization of key genes involved in the etiopathogenesis of spermiogenesis disorders. A significant proportion of men with azoospermia and oligospermia have the genetic aetiology of fertility disorders[53]. Deletions in the euchromatin part of the long Y arm of the AZF region cause disorders relating to spermatogenesis. It is believed that these deletions directly damage the genes responsible for the proper course of spermatogenesis. Complete and partial deletions are not the only type of rearrangements within the AZF region. Inversions and duplications, which, together with deletions, are the result of intrachromosomal non-allelic homologous recombination of repetitive blocks located in this region, have also been reported.

In the study by Behulová et al.[54], molecular analysis was performed on a set of Slovak men with various forms of male infertility with the aim of detecting microdeletions in AZF subregions of the Y chromosome (1998–2008). The analyzed group of 822 men (average age: 31.7 years) was divided into two groups: patients with azoospermia (n=349) and patients with oligospermia (n=473). A PCR method using three different sets of sY sequences was used to identify Y-specific sequences. Microdeletions were detected in 6.88% of men with azoospermia and 2.95% of men with oligospermia. Most deletions were detected in the AZFc subregion of the Y chromosome, and the most frequently deleted sequence was the sequence sY283, which corresponds to the location of the *DAZ* gene (Deleted in Azoospermia). The product of the *DAZ* gene is an RNA-binding protein that is important to the function of spermatogonia. Microdeletions in the AZF region of the Y chromosome were confirmed in all subregions of AZF (a, b, c), with the complete deletion of the entire AZF region of the Y chromosome also confirmed. It is questionable whether it is possible to assemble certain haplogroups within different populations of men with spermatogenesis disorders. Given the fact that individual genes in the mentioned region encode proteins with different functions at different stages of spermatogenesis, it is assumed that specific types of deletions are also correlated with different clinical manifestations. Despite the established criteria for the selection of sequences to prove deletions in the AZF region, different frequencies of microdeletions and ambiguous phenotype-genotype correlations are still published in the literature.

Cytogenetic analysis between 2005–2009 in a group of Slovak men with azoospermia (n=239, average age 31.74 years) confirmed a normal karyotype in 94.56% of subjects, and a pathological karyotype in 5.44%[55]. In the analyzed set, 12 findings of gonosome aneuploidy were detected: 47,XXY (Klinefelter syndrome) and one finding of balanced translocation of autosomes: 46,XY,t(15;16)(qter;p13). Azoospermia was confirmed in all patients with Klinefelter syndrome. In the group of men with azoospermia (n=349) and oligospermia (n=473), 38 deletions in AZF subregions of the Y chromosome were confirmed. Microdeletions in the Y chromosome were confirmed in all AZF subregions (a, b, c), in addition to a complete deletion of the entire AZF region of the Y chromosome. In a group of men with azoospermia and a cytogenetically confirmed normal karyotype (n=226), the presence of microdeletions in AZF subregions of the Y chromosome were revealed in 3.35% of subjects, with microdeletions of the AZFc subregion of the Y chromosome the most frequently detected. Karyotype 47,XXY (Klinefelter syndrome) was confirmed in 5% of men with azoospermia in our study; in these men Y chromosome microdeletions were not detected. The results of the study confirmed that the frequency of microdeletions in AZF subregions of the Y chromosome in Slovak men with azoospermia is low, but significant from a prognostic perspective.

Deletions in the AZF region of the Y chromosome cause spermiogenesis disorders. Y chromosome microdeletions were detected in 7.5%–38.5% of men with spermiogenesis disorders[56-58]. In general, microdeletions in the Y chromosome are detected at a higher frequency in men with azoospermia compared to those with oligospermia; the detected frequencies varying in the range of 2–10%[59-62]. In our study, the confirmed frequency of microdeletions in the AFZ region of the Y chromosome falls within the range of population studies. The success of assisted reproduction methods is significantly lower in men with AZFc deletions in the Y chromosome subregion. Opinions on the impact of deletions in the AZF region of the Y chromosome on offspring are controversial; however, many authors point to the risk of chromosomal abnormalities as a result of instability of the Y chromosome with deletions in the AZF region[63,64].

Chromosome analysis of heterochromatin variants of chromosomes in a group of 948 women with fertility disorders and a control group of women (n=478) in the Prešov region (1998–2013) using G-banding and C-banding techniques revealed pathological cytogenetic findings in 1.37% of women in the analyzed set[65]. Detection of numerical chromosomal aberrations in the set of women with fertility disorders was 0.53% while structural chromosomal aberrations were detected in 0.84%. Detected chromosomal aberrations also included mosaic forms of gonosomal

aberrations: 45,X/46,XX; 46,XX/47,XXX. Cytogenetic analysis in a set of infertile women revealed balanced translocations, autosome inversions and detection of derived chromosomes:

45,XX,t(13;14)(q10;q10), 46,XX,t(17;19)(q12;p13)

46,XX,t(1;15)q34;q15), 46,XX,der(13;14)(q10;q10)

46,XX,inv(4)(p13;q31), 46,XX,inv(9)(p13;q13)

46,XX,inv(3)(p11;q13), 46,XX,der(12).

The mosaic form of autosome translocation 46,XX /46,XX,t(7;14) (q22;q11) was also detected.

Heterochromatin variants of chromosomes 1, 9, 16 and the Y chromosome were detected in 10.02% of women with fertility disorders, while the most frequently chromosomal polymorphisms detected in the group were heterochromatin variants of chromosome 9 (9qh+/9qh-/inv(9)). The study confirmed statistically significant differences in the frequency of heterochromatin variants of chromosomes 1, 9 and 15 (p=0.048, 95% CI 1.047–19.714; p=0.0377, 95% CI 1.111–9.288; p=0.016; 95% CI 1.316–24.046). The results of statistical analyses of the frequencies of heterochromatin variants in the group of women with fertility disorders compared to the frequencies of heterochromatin variants in the control group of women (10.02% vs. 3.15%) confirmed statistically significant differences (p<0.0001; 95% CI 1.971–5.996). The results of the study confirmed a significantly higher frequency of chromosomal anomalies in women with fertility disorders in the Prešov region, which justifies their indication for cytogenetic examination. The results of the study also confirmed the association of heterochromatin variants with fertility disorders.

The aetiology of fertility disorders is a complex problem influenced by many factors, including chromosomal abnormalities. While the exact mechanism by which chromosomal aberrations cause fertility disorders has not yet been clarified, the findings of pathological karyotypes confirm the validity of genetic screening of couples with fertility disorders[46,66-70]. Molecular methods of CNV (copy number variation) detection[71] and NGS analysis technologies[72,73] are currently used to clarify the aetiology of fertility disorders. Genomics and proteomics provide new possibilities in elucidating the aetiopathogenesis of fertility disorders[74].

Determination of the Frequency of Chromosome Markers of Selected

Onco- haematological Diseases

Chromosome analysis is currently an integral part of diagnostics, prognosis determination, treatment strategy and assessment of the results of treatment of onco-haematological diseases. Genetic analyses are part of standard treatment protocols[75,76]. An important field of oncocytogenetics is the detection of chromosomal abnormalities and chromosome breakpoints in relation to the localization of oncogenes. Non-random chromosomal changes have been described in onco-haematological diseases. Cytogenetic and molecular-genetic analyses confirmed the importance of non-random chromosome rearrangements in the aetiology of onco-haematological diseases. Chromosome analyses confirm the presence of specific chromosomal aberrations associated with the development and progression of malignant disease. Associations of specific types of chromosomal aberrations with the prognosis of the course of the disease have been confirmed in onco-haematological diseases. Quantification of pathological clones correlates with survival prognosis of patients with onco-haematological disease and detection of chromosomal aberrations confirm the importance of chromosomal anomalies in the etiopathogenesis of haemoblastoses.

Conventional onco-cytogenetic analysis in our study was performed by analyzing the cells of bone marrow samples by standard culture methods in RPMI medium[5]. Three parallel cultures were established from each bone marrow sample (1 hour, 24 hours, and 48 hours). After incubation with a hypotonic solution of 0.075 M KCl, the cells were fixed with a mixture of methanol and acetic acid in a ratio of 3:1. Metaphase chromosomes were then stained conventionally, with G-banding and C-banding methods. Identification and classification of chromosomes was performed according to the international system of cytogenetic nomenclature.

Determination of the frequency of the Philadelphia chromosome in patients with chronic myeloid leukaemia

Chronic myeloid leukaemia (CML) is a malignant clonal disease of hematopoietic stem cells, characterized by the presence of a specific cytogenetic abnormality, the Philadelphia chromosome (Ph^1), which is caused by a reciprocal translocation of t(9;22)(q34;q11)[77]. Molecular genetic studies confirmed the fusion of part of the Abelson oncogene (c-abl) of the 9q34 region with the bcr gene (break point cluster region) of the chromosome region 22q11.2[78,79]. Ph^1 is a characteristic chromosome marker associated with CML, with the formation of the bcr/abl hybrid gene having a key role in its pathogenesis[80].

Between the years 1995–2004, cytogenetic analyses were carried out on bone marrow samples of patients with a suspected diagnosis of CML (n=72) in order to determine the frequency of the Ph^1 chromosome in the Prešov region[81]. The presence of the Ph^1 chromosome was cytogenetically confirmed in 94.4% of patients with CML. Cytogenetic analysis also detected a complex translocation of chromosomes 8, 9 and 22 (pathological karyotype 46,XY,t(8;9;22)(q13;q34;q11)). The Ph^1 mosaic karyotype was confirmed in 5.9% of patients of the analyzed group. Ph^1 was detected in 39% of men and 61% of women with a clinical diagnosis of CML in our study[66]. Chromosome analysis also confirmed the presence of additional numerical and structural chromosomal aberrations in the karyotype of patients in the Prešov region with a clinical diagnosis of CML.

Standard chromosome analysis of bone marrow samples detects Ph^1 in 95% of patients at their initial diagnosis of CML[82]. In 5% of CML cases, detection of Ph^1 is not possible on the cytogenetic level (submicroscopic bcr/abl fusion) or includes complex rearrangement variants that must be analyzed by FISH/RT-PCR methods with higher sensitivity for the detection of cryptic chromosomal aberrations[83]. In most cases of CML, the t(9;22)(q34;q11) translocation and its variants are the only chromosomal abnormality during the chronic phase of the disease[84]. Additional chromosomal abnormalities of clonal evolution indicate progression of the disease to the blast phase in 70–80% of CML cases[85,86]. In the majority of patients with CML, additional cytogenetic abnormalities (extra Ph^1, trisomy of chromosome 8, isochromosome 17q, trisomy of chromosome 19) appear during the blastic transformation of the disease. A specific cytogenetic profile at the time of blast transformation allows differential diagnosis of lymphoid (chromosome 7 abnormalities) and myeloid (chromosome 8 trisomy, isochromosome 17q, chromosome 19 trisomy) subtypes of leukaemia[82]. Additional cytogenetic changes appear several months before the clinical and haematological manifestation of the malignant stage of the disease, which allows for their use as a prognostic marker. NGS analysis methods are currently used in the molecular genetic diagnosis of CML[87-89]. However, conventional cytogenetic analysis is still the standard method of diagnosing and monitoring therapeutic response and detection of minimal residual disease in patients with chronic myeloid leukaemia.

Determination of the frequency of chromosomal aberrations in patients with myelodysplastic syndrome

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematopoietic stem cell diseases characterized by ineffective hemopoiesis of one or more cell lines and peripheral cytopenia with a high risk of progression to acute myeloid leukaemia[90]. The cause of these diseases is a somatic mutation of the progenitor cells of the bone marrow, which induces the proliferation of an abnormal cell population. The disease mainly affects older patients (median 60–75 years) and develops into acute leukaemia in 30% of patients. It is a neoplastic disease of the bone marrow characterized by non-random chromosomal abnormalities. The most common chromosomal aberrations include monosomy of chromosomes 5, 7, loss of chromosome Y, deletion in long arms of chromosomes 5, 7, 11, 20, and trisomy of chromosome 8[91,92]. Although chromosomal abnormalities are not specific, the frequency of these chromosomal aberrations varies comparably between individual MDS subtypes. Additional chromosomal abnormalities are a cytogenetic marker of clonal evolution of haemato-oncological disease[93-95].

Cytogenetic analysis of patients with a clinical diagnosis of MDS (n=39) in the Prešov Region between 1995–2004 revealed structural and numerical chromosomal abnormalities in 25.6%[96]. Cytogenetic findings detected in patients with MDS included: trisomy of chromosome 8, deletion in the short arms of chromosomes 4, 12, deletions in the long arms of chromosomes 5, 6, 20, the presence of derived chromosomes, marker chromosomes, and findings of complex chromosome translocations:

47,XY,+8

47,XY,-C,+2mar

45,XX,del(5q),del(6q)t(18;22),der(l3)

44,XY,4,-5,-6,-7,-11,-12,-17,t(5;7),t(6;11),der(4),+der(7),+mar1,+mar2

46,XY/47,XY,+8

42-46,XY,t(7;21)(pl3;q22),$4q^{-}$,$12p^{-}$,$16q^{+}$

46,XY,$4p^{-}$

47,XY,+C/46,XY

46,XY/46,XY,del(D)/46,XY,del(2)

45,XX,-4,del(5)(q22),del(20)(q11)[66].

In addition to frequently detected findings, karyotype analysis also confirmed atypical, yet unpublished cytogenetic detection of pathological karyotypes:

47,XY,-C,+2mar

45,XX,del(5q),del(6q),t(18;22),der(13)

46,XY,-4,-5,-6,-7,- 11,-12,-17,t(5;7),t(6;11)+der(4),+der(7),+der(17),+mar1,+mar2

46,XY,t(7;21)(p13;q22),$4q^{-}$,$12p^{-}$,$16q^{+}$

46,XY/46,XY,del(D)/46,XY,del(2)[66,97].

The results of cytogenetic analysis confirmed the presence of pathological cytogenetic findings in bone marrow samples of 25.6% of patients with MDS. Detection of complex karyotypes included unbalanced chromosomal rearrangements, as a result of loss of genetic material. Karyotype evolution is the result of the creation of an abnormal clone or the progression of one original abnormal clone into several more.

Chromosomal abnormalities are detected in 50% of patients with primary MDS and in 80% of patients with secondary MDS (after chemotherapy or radiotherapy)[98]. In our analyzed set of patients in the Prešov region with MDS, a normal karyotype was detected in 74.4% of cases. Patients diagnosed with MDS without chromosomal aberrations have a better prognosis compared to patients with chromosomal abnormalities. The beneficial effect of an increased proportion of normal metaphases was also observed in other onco-haematological diseases[99]. Karyotype evolution is associated with progress to acute leukaemia in 60% of MDS patients[90]. Complexity of abnormal karyotypes is a frequent finding in karyotypic analysis of therapy-induced MDS[100]. Clonal chromosomal abnormalities are present at the time of diagnosis in 40–70% of patients with primary MDS and in 95% of patients with therapy-induced MDS[90]. The most frequently detected chromosomal aberrations in patients with MDS are abnormalities of chromosomes 5, 7, and 8. Detection of additional chromosomal abnormalities are a common finding in karyotyping samples from patients with myelodysplastic syndromes[101,102]. Newly detected cytogenetic abnormalities are a marker of an unfavourable prognosis of the

disease and are continuously implemented in the prognostic scoring system[98]. Identification of aberrant chromosomes in the bone marrow cells of patients with MDS places the patient in a category with a less favourable prognosis and with a higher risk of transformation into acute leukaemia. Cytogenetic findings represent an important independent prognostic marker. The results of classical cytogenetics are now supplemented and refined by the use of molecular genetics methods[103,104]. The detection of new, so far unidentified, chromosomal aberrations in patients with MDS is important in terms of determining survival prognosis, the risk of transformation into acute leukaemia, and understanding the molecular nature of the disease[105]. Molecular-genetic identification of cytogenetic markers contributes to understanding of aetiopathogenesis of hemoblastosis.

Determination of the frequency of chromosomal abnormalities in patients with myeloproliferative diseases

Myeloproliferative diseases (MPOs) are clonal diseases of hematopoietic stem cells[106]. According to the WHO classification, the basic groups of myeloproliferative diseases are: chronic myeloid leukaemia, chronic neutrophilic leukaemia, chronic eosinophilic leukaemia, polycythaemia vera, essential thrombocythemia, and chronic idiopathic myelofibrosis[93,107]. The spectrum of chromosomal aberrations in patients with MPOs is heterogeneous, including numerical and structural aberrations as well as unbalanced chromosome translocations.

Cytogenetic analysis of bone marrow samples was performed between 1995–2004 in 265 patients from the Prešov region with a suspected diagnosis of MPO[108]. Chromosomal abnormalities were detected in 28.3% of patients with MPO. The most frequently detected chromosomal aberrations were the translocation t(9;22), trisomy of chromosomes 8 and 9, and deletion on chromosome 20 ($20q^{-}$). The spectrum of detected chromosomal aberrations in the analyzed set of patients with MPO was heterogeneous, with different types of chromosomal aberrations found.

Chromosomal abnormalities have been detected in 3–40% of MPO patients, depending on the MPO subtype[109]. Cytogenetic findings are classified as favourable (normal karyotype/$13q^{-}$/$20q^{-}$) or unfavourable (presence of other chromosomal abnormalities)[110,111]. Chromosome analysis enables differential diagnosis of variant types of MPO with prognostic significance. Patients with a chromosomally abnormal clone at the time of diagnosis generally have an unfavourable survival prognosis compared to patients with a cytogenetically confirmed normal karyotype. Karyotype analysis in patients with myeloproliferative disease has an important role in diagnosis, it provides information on the course and prognosis of onco-haematological diseases. The results obtained by methods of classical oncocytogenetics are currently supplemented by methods of molecular genetics. The implementation of new generations of sequencing methods in diagnostics provides opportunities for gene panel analyses and clarification of gene causality in onco-haematological diseases[112]. The combination of cytogenetic and molecular-genetic methods enables the detection of specific chromosomal changes and the clarification of their significance in the etiopathogenesis of onco-haematological diseases.

Conclusions

The results of our analyses at the cytogenetic level within anthropogenetic studies provided the following results in summary:

Through the detection of trisomy of chromosome 21 in individuals of the Roma ethnicity in the Prešov region, we confirmed the occurrence of Down's syndrome in the Roma ethnicity.

Karyotype analysis in a group of patients in the Prešov region with Turner syndrome confirmed a wide spectrum of chromosomal aberrations of gonosomes (monosomies X, isochromosome Xq, deletions Xp, marker chromosome) useful in clarifying phenotype-genotype correlations and clinical management of patients with Turner syndrome.

The frequency of chromosomal aberrations in couples in the Prešov region with fertility disorders was 5.5%. Numerical chromosomal aberrations were detected in 2.1% of couples with fertility disorders, while structural chromosomal aberrations were present in 3.4%. This captures the balanced forms of reciprocal chromosome translocations that represent a risk finding for offspring of carriers.

Molecular analysis in a set of men with fertility disorders diagnosed with azoospermia confirmed microdeletions in subregions AZFa, AZFb, AZFc of the Y chromosome, a combined form of microdeletions AZFb,c as well as a complete deletion of the entire AZF region of the Y chromosome.

The frequency of chromosome polymorphism was detected in 13% of men and 10.02% of women in couples in the Prešov region with fertility disorders. The detected frequency of findings of pathological karyotypes confirms the validity of genetic screening of couples with fertility disorders.

When determining the frequency of occurrence of chromosome markers of selected onco-haematological diseases:

The Philadelphia chromosome (Ph^1) was confirmed in 94.4% of patients in the Prešov region with a clinical diagnosis of chronic myeloid leukaemia. Cytogenetic analysis of bone marrow samples from patients with CML also revealed a complex translocation of chromosomes 8, 9, 22; mosaic karyotype of Ph^1 and the presence of additional chromosomal aberrations in the clonal evolution of the disease.

Chromosomal aberrations were detected in 25.6% of patients with a clinical diagnosis of myelodysplastic syndrome. In addition to frequent chromosomal changes, karyotype analysis also confirmed atypical, hitherto unpublished, prognostically significant cytogenetic markers.

Chromosomal abnormalities were detected in 28.3% of patients in the Prešov region with myeloproliferative disease. The cytogenetic profile of patients with MPO was heterogeneous with the finding of various types of chromosomal aberrations useful as prognostic markers of the pathogenesis of myeloproliferative diseases.

Cytogenetic and molecular-genetic methods are widely used in the diagnosis and treatment of cancerous and non-cancerous diseases. These methods lead to efficient and rational diagnosis and are the basis of recommendations (guidelines) to optimize the diagnosis and treatment of genetic pathologies. The results of the analysis contributed to the mapping of the occurrence of chromosomal aberrations, as part of population-genetic analyses and monitoring of the population's health status. For the above reasons, and in the context of the genetic health of populations, they are of societal importance.

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CITOGENETIČKA ANALIZA ODABRANIH GENETSKI UVJETOVANIH BOLESTI U ISTOČNOJ SLOVAČKOJ

SAŽETAK

U ovom radu prikazani su rezultati citogenetske analize provedene u razdoblju 1990.-2021. Rad se fokusira na citogenetsku analizu odabranih bolesti koje predstavljaju ozbiljan medicinski i društveni problem u regiji Prešov u istočnoj Slovačkoj. Analiza je također uključivala određivanje učestalosti citogenetskih i molekularno-genetskih biljega vezanih uz odabrane kliničke genetske bolesti u određenoj populaciji romske nacionalnosti. Kromosomska analiza potvrdila je široki spektar kromosomskih aberacija u pacijenata s Downovim i Turnerovim sindromom, otkrivajući spektar aberacija od monosomije X, izokromosoma Xq i delecija Xp do marker kromosoma. Kromosomske aberacije uzrokuju 5,5% poremećaja plodnosti u parova, s numeričkim i strukturnim kromosomskim aberacijama u 2,1 odnosno 3,4%, što ukazuje na rizik za potomstvo nositelja uravnoteženih translokacija. U muškaraca s dijagnosticiranom azoospermijom pronađene su mikrodelecije, kombinirane mikrodelecije (AZFb,c) i potpuna delecija AZF regije Y kromosoma. Osim toga, patološki kariotipovi su otkriveni u muškaraca i žena (13 i 10%). Drugi set analiza u bolesnika s onkohematološkim bolestima otkrio je prisutnost Philadelphia kromosoma (Ph1) u 94,4% bolesnika s kroničnom mijeloičnom leukemijom, kompleksnom translokacijom kromosoma 8, 9, 22; mozaični kariotip Ph1. Kromosomske aberacije u bolesnika s mijelodisplastičnim sindromom uključivale su i atipične i još neobjavljene citogenetske markere. Mijeloproliferativne bolesti otkrivene su u 28,3% bolesnika s heterogenim kromosomskim aberacijama. Rezulltati citogenetske analize omogućuju poboljšanje učinkovitosti zdravstvene zaštite, dijagnostike, terapijskog značaja i prognoze oboljelih osoba u većinskoj populaciji i romskoj manjini u ovoj regiji Slovačke.