European Journal of Science and Theology, June 2014, Vol.10, No.3, 49-59

DOWN SYNDROME BETWEEN GENETIC HAZARD AND DIVINE DECISION

Vasilica Toma[1], Liliana-Georgeta Foia[1], Doriana Forna[1], Cristian Marius Toma[2*], Daniel Cioloca[1], Gheorghe Bălan[3] and Adriana Bălan[1]

[1]'Gr. T. Popa' University of Medicine and Pharmacy, Faculty of Dental Medicine, Str. Universitatii, Iasi, Romania
[2]'Gr. T. Popa' University of Medicine and Pharmacy – Iasi, Department of Research Projects Management, Str. Universitatii, Iasi, Romania
[3]'Gr. T. Popa' University of Medicine and Pharmacy, Str. Universitatii, Iasi, Romania

(Received 17 November 2013, revised 21 February 2014)

Abstract

The Down syndrome (DS) represents the most frequent chromosomal disease determined by the presence of a supernumerary chromosome 21. The existence of the third chromosome 21 affects most of the tissues and organs, through the appearance of a suggestive craniofacial dysmorphia, various visceral malformations and psychomotor retard, the most common error being the maternal non-disjunction in the first meiotic division. Despite all the genetics progresses, the DS pathology has not been completely elucidated, the advanced maternal age (over 35) being at present the only determinant factor clearly responsible for the maternal meiotic non-disjunction. So far, the scientists do not know why sometimes the cells abnormally divide and produce additional genetic material (the third chromosome 21, in this case) which results in the DS appearance; who gives this verdict: the hazard, happening, or laws- whose laws? Did the life make its own laws and is subjected to them? Do the laws belong to those who found them or to the One who made them? Going beyond the science frontiers and listening to the Scripture text ("I the Lord your God am a jealous God visiting the iniquity of the fathers upon the children to the third and fourth generation at those who hate me but showing steadfast love to thousands of those who love me and keep my commandments"), we understand that the Author of Life and its laws is God, and not the hazard. He is the primary cause which configures the life in all its peculiarities, He decides our only configuration, without affecting the freedom of action of the man who chooses the sin or respects the laws of life and divinity.

Keywords: Down syndrome, chromosomal anomaly, etiopathogeny, God, laws of life

1. Introduction

The Down syndrome is a peculiar combination of the phenotype characteristics that include the mental retard and the characteristic face shape;

[*]Corresponding author, e-mail: tomamariuscristian@yahoo.com

caused by trisomy 21, it is one of the most common chromosomal anomaly in new-born children (1:650 births) [1] which affects most of the tissues and organs with the appearance of a suggestive craniofacial dysmorphia, various visceral malformations and psycho-motor retard in various degrees.

Found in the literature under the name of Langdon Down syndrome, Trisomy 21 (an adequate term, if one considers the ethiopathogenesis) or Mongolism (an inadequate term), this 'mental disease' was first noticed by Esquirol in 1838 [2]; later on (1846, 1866), Séguin consecrates a special chapter to the 'furfuraceous' cretinism in his book *Moral treatment, hygiene and education of idiots and other children retarded in their development* [3].

In 1866 Langdon Down [4] insists on the stereotypical physiognomy and behaviour of these sufferings. He defines the disease, differentiating it from the other forms of the mental debility, stating that "when these children sit together, one by one, it is hard to believe that the compared subjects are not the children of the same parents". He issues a theory according to which the mental retard of these children is caused by the repartition of the characters specific to the Mongolian race, hence the ascribed name of 'Mongolian idiot'.

Numerous other authors approached the DS pathogenesis (Jones 1890, Oliver 1891, Smith 1896, etc), but already in 1932, Werderburg suggested that the Mongolism is associated to a chromosomal aberration (especially specifying the non-disjunction), while Bleyer (1934) took into account the eventuality of an excess or lack of complete or partial chromosomes. In 1937, Turpin and Caratzali issued the hypothesis of a 'chromosomal anomaly', and Penrose (1939) assumed the possibility of the existence of a chromosomal aberration (in DS) in the form of the translocation of one of the chromosomes [5].

The chromosomal theory, rejected until that moment, was confirmed in 1959 by the discovery made by Lejeune Gautier and Turpin, of a chromosome in excess, therefore 47 instead of 46 chromosomes at these subjects. This fact was also confirmed by Ford et al. in 1959, on a case of trisomy 21 and recognized by all the cytogenetics laboratories and by the subjects of all the races [6].

In 1960, Poland presents the first case of translocation [7], and in 1961 Clarke reports cases of mosaic trisomy [8].

2. Clinical framework, physiopathology, etiopathogeny, epidemiology

The existence of the third chromosome 21 in DS affects most of the tissues and organs, through the appearance of numerous disease pheno-types. These include complications that can set the life in danger, significantly affectation of the life course (mental retard) and characteristic physical dysmorphia. Moreover, the Down syndrome was associated with multiple lethal complications that reduce the pre-natal viability and increase the post-natal morbidity and mortality. The affected children present retardation in their growth and maturation, mental retard, delays in bone development and teeth eruption.

In the case when there is only a copy of a region of chromosome 21 (21q22.3), the physical phenotype is specific: mental retard, characteristic face (brachycephaly, flat occiput, large fontanelle which closes late, 90%- absence of frontal and spheroidal sinus, hypoplastic cheek bone, hypoplasic median stage of the face, small nose with anteverted nostrils, relative mandible prognathism, upward and outward palpebral slots, epicanthus, iris with Brushfield spots, fine crystalline opacities, strabismus, cataract, small ears with small or absent flap, 10-20% atlanto-axial instability, thick, fissured, dry lips, open mouth, protruding tongue that seems larger due to microstomia, often with fissured aspect/geographic map), anomalies at hands level, congenital defects of heart (especially atrio-ventricular septus defects) and of gastro-intestinal tract (duodenum stenosis, anal miss-function and Hirschsprung disease). 90% of all the DS patients have a significant hair loss and can manifest the neuro-pathological marks of Alzheimer disease at a much younger age than the Alzheimer patients without trisomy 21 [9].

The molecular analyses of the sequence 21q22.1-21q22.3, also called DSCR (Down Syndrome Critical Region) rendered evident that the genes localizes at that level are involved in the appearance of the congenital cardiac defects encountered in DS. At the same time, a gene - DSCR 1, localized on the regions 21q22.1-q22.2 is over-expressed in the brain and at cardiac level, being involved in the pathogenesis of this genetic disease, especially in the mental retard and cardiac defects; the physiological disturbances also affects the thyroid homeostasis and intestinal absorption.

Due to the immune- adverse response, the DS-associated infections are frequent, as are the auto-immune diseases, such as Hashimoto thyroiditis. Moreover, due to the metabolic homeostasis alteration, the DS-affected children are predisposed to hyperuricemia and hyperglycemia, increased resistance to insulin, while the malfunctions of the hematogenouse marrow favor the appearance of leukemia-type modifications (especially transitory myelo-proliferative disorder and acute megakariocytic leukemia). At most of the children who developed leukemia, a mutation was noticed in the gene that codifies the hematopoietic transcription factor GATA 1. The appearance of leukemia at the children with DS is conditioned by three factors: trisomy 21, mutation at the level of gene GATA 1 and a yet undefined genetic alteration [H. Chen, B. Buehler, J. Bowman, D. Flannery and M.L. Windle, *Down Syndrome*, 2007, available at http://emedicine.medscape.com/article/943216-overview].

The recent studies back-up the hypothesis according to which the Trisomy 21 results from the super-expression of the genes localized on the chromosome 21, one of these genes being the one for superoxide dismutase (SOD), whose activity increases in DS; the SOD enzyme converts the superoxide anions (free radicals) in hydrogen peroxide and water. The radical species produced in excess at the cell level determine both functional and structural alterations; that is why an enzyme with the role of free radicals neutralization (such as SOD in this case) has an overwhelming importance [C.K. Janniger, A.L. Dourmishev, A.C. Yan, M.J. Wells, R.A. Schwartz and D.M. Elston, *Dermatologic Manifestations of*

Down Syndrome, 2008, available at http://emedicine.medscape.com/article/1113071-overview].

The alteration of the genes located in the so-called 'critical' zone 21q22.1-22.3 (also named DSCR - Down Syndrome Critical Region) is responsible for the generation of most of the clinical signs characteristic for the Down syndrome. The genes are:

- APP - the gene for the precursor protein of beta amyloid;
- S1000B - the gene for calcium-binding protein (correlated with Alzheimer-type neuropathy at patients with Down syndrome);
- SOD1- the gene for superoxide dismutase 1;
- ETS-2 - Oncogene ets-2 (involved in the high risk of leukemia at subjects with Down syndrome);
- CBS - gene for cystathionine-beta-synthesis (involved in folates metabolism);
- CRYA1 – gene responsible for eye lens alpha protein (correlated with increases frequency of cataracts).

Among the genes candidates for the mental retard in the Down syndrome, the best described are:

- DYRK1A, which codifies a protein-kinase (involved in neuroblast proliferation control);
- SIM 2, necessary for cell division synchronization during the brain development;
- GART, which codifies a phospho-rybosyl glyacinamide-formyl-transferase (involved in the pre birth brain development);
- PCP4, the type 4 protein of the Purkinje cells (role in cerebellum development)
- DSCAM, Down Syndrome Cell Adhesion Molecule (considered to be involved in the axonal growth, as well as a candidate gene for cardiac congenital defects);
- GEIK1, glutamate receptor (involved in the operation of cortex pyramidal cells) [10].

The chromosome analysis in DS can render evident:

- *free and homogeneous trisomy 21*, in about 92-95% of Down syndrome cases; they are produced through meiotic non-disjunction, most frequently of maternal origin (85-90%) and especially in meiosis I (75%);
- *free and mosaic-wise trisomy 21* (type 47/46) in about 2-3% of cases; it results through the post-zygotic mitotic non-disjunction or, quite rarely, by loosing a chromosome 21 in the cells deriving from a trisomic zygote ("rescuing" of an homogeneous trisomy);
- *trisomy 21* through unbalanced Robertsonian translocation between chromosome 21 and another aerocentric chromosome (noticed in 4-5% from cases), the most frequent being the 14q; 21q translocation, which in most of cases is inherited from one of the parents (mostly from the mother,

yet with no connection with mother's age); the translocation 21q; 22q or 21q:21q are much rare and most of them appear de novo;

- *partial trisomy 21*, noticed in less than 1% of cases; it results through the meiotic segregation of derivative chromosomes, formed as the result of balanced translocations (that involve a segment of the chromosome 21), existing at one of the parents [10].

The most common error is represented by maternal non-disjunction in the first meiotic division [11]. It appears three times more frequent at the meiosis I than at meiosis II. The paternal origin and the errors of the meiosis II are also to be considered. The mother's advanced age remains the best documented factor for the meiotic non-disjunction in these cases [12].

In conclusion, free Trisomy 21 results from the meiotic non-disjunction at one of the parents. This is correlated with the mother's and eventually father's old age. The translocation can appear *de novo* or can be transmitted by one of the parents, involving the chromosome 14 (translocation 14/21), chromosome 21 (translocation 21/21) or chromosome 22 (translocation 22/21.

Anyway, with all the accomplished progresses, the DS pathogenesis still has many enigmas.

Having the incidence of 1/650 births and currently affecting over 300000 individuals only in the United States of America [1], the trisomy 21 remains the most frequent chromosomal anomaly. The frequency of the products of conceptions with trisomy 21 is much higher (1:200), yet much of them do not have viability being removed through spontaneous abortion. The disease is more frequent in male children, the ratio being 3 boys to 2 girls [10].

The Britain statistic reports show that, each day one or two DS affected children are born in the United Kingdom, which means that 1:1000 suffers from this affection [13].

Despite that the progress made in the prenatal diagnosis allows early detection of the disease, the DS incidence in Romania does not seem to diminish significantly, partly due to the increase of the mother's age [14]. In Romania there is no clear statistics, but the data made available by the Ministry of Labour, Family and Social Protection through the General Direction Protection of the Disabled Persons appreciate that there are about 50000 persons with DS. This figure does not reflect the reality, because it only includes the persons who made the official steps to be registered and to obtain a certificate of disabled person, the 'deep' casuistry of Romania being not found in the official statistics.

The fact that the risk of giving birth to a child with Trisomy 21 increases with mother's age was recognized long ago [15], and the reports show that the risk to give birth to a DS child at 30 year is of 1 to 1000, while it increases to 9:1000, at the age of 40 years [16]. That is why the mother's age of 35 was chosen as an indication of echographic and biochemical screening, as well as for the prenatal diagnosis (the risk of a foetus with DS being higher than the risk of abortion associated with the procedures of diagnosis, as well as the biopsy of chorial villosities or amniocentesis). A delicate problem is the risk in those families where there is a blood relation with DS or unknown caryotype. Taking

into account the trisomy frequency in terms of mother's age, as well as the possibility of a translocation, the highest calculated risk is of 1:640 (therefore close to the prevalence among the population), and is real especially for the child of the sister, of the DS subject.

3. Down syndrome and the laws of life

The exact causes of the DS appearance are not known yet, which makes it different from the other genetic affections, such as cystic fibrosis or falciform anaemia, which can be hereditary. The DS is hereditary only in a proportion of 1%, and these persons present Robertsonian translocation that implies the chromosome 21.

Therefore the essential problem in DS remains the elucidation of the aetiology of this frequent trisomy. The mother's age is the only evident determinant factor of the non-disjunction [12], yet *only about 25% of the patients with DS are born from women over 35*. Nevertheless, the fact that 80-90% of the cases result from maternal non-disjunction (3/4 in meiosis D) suggests the intervention of a risk factor that acts at this level [17]. The scientists claim that what is sure is that nobody is to blame, since up to now no environment factor that might contribute to the development of the affection was identified: "the appearance of DS is not caused by external factors, so that nothing of what a pregnant woman does during her pregnancy determines the disease". The scientists do not know why sometimes the cells abnormally divide and produce the additional genetic material, which results after, in the DS occurrence.

With all these unknowns, we are asking ourselves: "Is it that God has no word to say in biology? Just nothing? No sense? No direction? He made the laws and left the world? Why is then that He raised the matrimony at the rank of sacrament among the seven ones, and placed under the care, therefore under the responsibility and right of the Church to thoroughly pursue the sacrament fruits, these buds of life- the children? It is not because He considered them as His own sons with right mind and body, and not on the contrary, the wrongdoing sons? Jesus arrival in Canaa Galileea does not have a deeper meaning? The fact that at that wedding He produced the first proof of His Divinity would not mean something more? Is it not true that from now on God must be considered at being present at the Life wedding? " [18]

Taking into account the heredity laws, we can state that life has its own mathematics, therefore its own explanation and thus one can intervene in its variables; moreover, considering the chromosome theory in Biology, to what extent man can intercede in life organization, remains to be elucidated. If there is a possible explanation, it should be looked for in the cell structure, as any living being consists of cells and comes from a unique cell within which one must arrange all the hereditary factors that determine the individual's character; the possibilities to group the tens of thousands genes are almost infinite, much beyond the human imagination.

And, if the Medicine - and generally the Science - could not establish yet who determines the DS, we wonder "What circumstance generates the gene recession such that to result in recessive genes? Where do these accidents of life come from?*"* Who keeps the book for the little infinity? Who performs the calculus of probabilities and has not finished the probabilities? What are the laws to which the maternal germinal cell is subjected to when, in the fecundation process, it removes through the two germinal cells, half of its nucleus, which means the reduction of the chromosomal formula from 2N to N or from 48 to 23-24 chromosome pairs? Does the same thing happen at the same time with the paternal cell which 'breaks it neck' and suffers from the same chromosomal reduction?

What calculus is made at that moment, what is the verdict that decides the extrusion on the material of exactly these pairs and not of others? Is it the hazard? This is the answer? The laws? Whose laws? Mendel's laws? Do the laws belong to who finds them, or to Him who made them? Who pursues their application? Mendel? Morgan? *The science or their Author*? Did the life issued by itself its own laws and obeys to them?

So, if Science knows the laws, why does not create itself the living cell? Can't it? No! Because both the life and the laws go beyond the science borders and they can not be absolutely comprised and known except by He Who created the life! The author of life and its laws is God, their wise supporter, and not hazard. The reality, whichever it is, can't be explained enough without referring to its author, the God, not man's science. That is why there are so many contradictions, because the reality is alive, and the man is seen mainly through his material side, subjected to senses, analyses and microscopes. The man in his integrity is more and more unknown. That is why those who confine themselves to unilateral knowledge will, no doubt, reach the 'shadow corner of arrogance'. He who really knows much, such that, pushing aside the questions, had reached the limits of the scientific knowledge, will be driven by his consistency and theoretical probity, to the sphere of faith, as 'much science' will close the man to God, while less science moves him away from both, men and God.

The divergences between Science and religion do not entail giving up the scientific attitude; the Science can keep developing its specific values within the big framework of world mystery. "Yet, what must be fought against is the scientific arrogance, narrow and blind pragmatism, vices never practiced by the real scientists." [19]

Therefore the problem of heredity goes beyond the limits of Biology and probability, the knowledge of heredity factors going beyond the limits of positive science: *should Science be able to catch the moment when a recessive gene appears within the parents, or when a dominant gene becomes recessive, this would be a real triumph!...* Yet, only God is under the absolute conditions of knowledge, He who all knows, without affecting the man's freedom of manifestation. Therefore, since He knows absolutely everything, He gave the man the laws of his life and the freedom to comply with them or not, namely the dangerous honesty of his will. Should the man comply with God's laws, he lives

freely according to his nature; yet, should the man go against the nature laws, he vitiates his freedom, put his life in danger, determining the infirmity of his temper and falling into sin; therefore the sin means disobeying the laws of life by abusing of his freedom.

Through the original sin, Adam left the way on which God set him at his creation and therefore the man went off the purpose destined through his nature. Ceasing to tend to God with all his heart and to open to the uttermost of his power his uncreated charisma, he darkened the mirror of his soul, which ceased to reflect his Procreator. And since Adam no longer communicated from the spring of total completion, his virtues weakened and he lost the resemblance with God which he had started to accomplish from the very moment of his creation. The never fading God's image still exists in the fallen man, but it is not highlighted through the man connection with God and, unable to reach completion by getting the similarity, which is his real vocation, he disfigured himself and got darker. While man advance to completion made this image brighter, lit by the Holy Ghost, the sin darkened it suddenly. Man has forgotten his real nature, no longer knows his real destiny and real life and knows nothing about his primary health [20-24].

Only the advent of Christ completely restored the mankind in its original nature, and the man regained the capacity to reach the completion he was created for. Once becoming man without ceasing to be God, Christ gave back the human nature, through its unity in His Own person, with His divine nature, the entire original perfection brought to completion. At that moment, through God love impersonated by His Son, the final destiny of mankind was accomplished and revealed to all, namely the completion of human nature, intimately and totally united with God [25].

Science can't answer the question: how have the recessive genes appeared in ascendants, through what accident or according to what laws? Through what independent circumstance, prior to heredity process, these degenerative infinitesimal grains appear inside the chromosomes, from where they were, with disastrous consequences for an eventual progeny? Therefore the answer is: the recessive genes appear in ascendants independently, not according to the laws of probability, but according to the laws hanging over the outrages. All the men's facts are 'written' somewhere [18] in an unseen book, "*Thy eyes did see my imperfect being, and in thy book all shall be written: days shall be formed, and no one in them."* (Psalm 138.16), but they are also imprinted in his seed, and with this he drives his descendants under the burden of his deeds: "*The fathers have eaten sour grapes and the children's teeth are set on edge"* (Ezekiel 18.2). Are some moments of pleasure during your youth, consciously or unconsciously, worth paying with long years of our children's suffering under the burden of parents' sin?

God, man's Creator, collaborates with the parents, sparing their freedom yet preventing them that, if they defy His laws, they defy the life of their own children: *"I, the Lord your God am a zealous God sentencing the faults of the fathers upon the children to the third and fourth generation at those who hate*

me but showing steadfast love to thousands of those who love me and keep my commandments" (Deuteronomy 5.9).

Therefore, considering the chromosome theory, the recessive genes appear in the descendants according to the laws of heredity and probability; yet, according to Scripture, it is clear that all the recessiveness appears in parents as a consequence of their sin.

The laws of life are Procreator laws; if you defy them, you can't avoid God blame. The Creator has something to say in biology as the arrival of Jesus at the wedding (John 2.1-11) has a special meaning for every man coming in the world.

Before we start to exist as persons on the Earth, we exist as God's thought and intention. Who knows if He has to bring to earthly life, during the river time, so many human beings that their number fulfils all configuration possibilities that the genetic human structure can offer [25]? The fact that we somehow precede our earthly existence was told by God to Jeremiah (Jeremiah 1.5)*: "Before I formed you in the womb I knew you, and before you were born. I consecrated and appointed you prophet to the nations"* and *"For you created my inmost being; you knit me together in my mother's womb"* (Psalm 138.13).

The man, who has no God and no interest in anything but his debauch, can be sure that his progeny will gather in itself all the lack of balance with the great divine environment in which we are moving, living and existing (Deeds 17.28).
It is not possible to get out of this swirl, according to which "You are punishing yourself with your hatred and you alone beat yourself with your Atheism", unless by living the unseen presence of Christ in ourselves, living the Christian learning in all the aspects of life - which makes possible for God to take off the recessive weeds through the heredity mechanism and, at the moment of man endeavour, to determine the return of the multitude of recessive genes to dominant genes (Mathew 19.26): "*With men this is impossible but with God all things are possible*".

The power of our faith, given by the God blessed power, has an unexpected influence on our eventual infirmities. The miracle of recovery can happen everywhere, anywhere, if there is enough faith and God will, to modify the recessive configuration to a dominant one; the prayer of a mother, for her beloved bud, expressed from the depth of her heart, can change the destiny from bad to good. "And then address your behaviours, mother, toward the God, Who accomplish through you the miracle of joining a man cub with a Heaven cub, as a reward for your endeavour." [18]

4. Conclusions

Down syndrome (DS) represents the most frequent chromosomal disorder, determined by the presence of supernumerary chromosome 21. The existence of the third chromosome 21 affects most of the tissues and organs by the appearance of a suggestive craniofacial dysmorphia, various visceral

malformations and psychomotor retard, the most common error being the maternal non-disjunction during the first meiotic division.

Despite all the progresses accomplished in genetics, the DS pathology has not been completely elucidated, the advanced maternal age (over 35 yo) being at present the only determinant factor clearly responsible for the maternal meiotic non-disjunction.

Science can't decide who gives the verdict in the fecundation process, reducing the chromosomal formula from 48 to 23 or 24 pairs of chromosomes: the hazard, the chance, or the laws- whose laws? Did the life give its own laws and is subjected to them?

Jesus Christ accompanies and even governs the creation of every human being arriving in the world, based on His universality as God. He is the primary cause that shapes the life in all its peculiarities, so that every person is unique!

It is He who decides in the small infinity, which qualities and defects should be dismissed from the two germinal cells that include half of the chromosome number, not the hazard. *It is He who chooses (respecting our freedom to obey to His laws of life, or to brake them by sinning), our unique configuration*. He creates our destiny such that a specific positioning in the small infinity has huge consequences on our future acts and structure.

Acknowledgement

All authors have equal contributions to this article.

References

[1] R.M. Winston, C.M. Conn, J. Cozi, J.C. Harper and J.D. Delhanty, J. Med. Genet., **36** (1999) 45-50.
[2] É. Esquirol, J.B. Baillière (and sons) (eds.), *Des maladies mentales considérées sous les rapports médical, hygiénique et médico-légal*, Vol. 1, J.B.Bailliere, Paris, 1838, 236.
[3] É. Séguin, *Traitement Moral, Hygiène et éducation des idiots et des autres enfants arriérés*, Baillière, Paris, 1846.
[4] J.L.H. Down, Clinical Lecture Reports. London Hospital, **3** (1866) 259–262.
[5] K.C. Carter, Bulletin of the History of Medicine, **76** (2002) 528-63.
[6] J. Lejeune, M. Gautier and R. Turpin, *Les chromosomes humains en culture de tissus*, C.R. Acad. Sciences, Paris, 1959, 26.
[7] P.E. Polani , C.O. Carter, J.L. Hamerton, A. Gunalp and S.D.V. Weller, The Lancet, **7152** (1960) 678-680.
[8] C.M. Clarke, J.H. Edwards and V. Smallpeice, The Lancet, **185** (1961) 1028-1030.
[9] A. Goate, M. Owen, J. Hardy and M. Rossor, The Lancet, **8665** (1989) 743.
[10] M. Covic, D. Stefanescu and I. Sandovici , *Genetică medicală*, Polirom, Iasi, 2004, 332-333.
[11] S.E. Antonarakis, M.C. Petersen, M.G. McInnis P.A. Adelsberger, A.A. Schinzel, F. Binkert, C. Pangalos, O. Raoul, S.A. Slaugenhaupt and M. Hafez, Am. J. Hum. Genet., **50** (1992) 544-550.

[12] G. Sujoy, E. Feingold and K.D. Subrata, Am. J. Med. Genet. A, **149A(7)** (2009) 1415-1420.
[13] I.C. Bray and D.E. Wright, Prenat. Diagn., **18** (1998) 1045-1054.
[14] V. Toma, The Medical-Surgical Journal, **3(suppl. 1)** (2007) 321.
[15] L.S. Penrose, J. Genet., **88** (2009) 9-14.
[16] E.B. Hook, Am. J. Hum. Genet., **35** (1983) 110-116.
[17] P.W. Yoon, S.B. Freeman, S.L. Sherman, L.F. Taft, Y. Gu, D. Pettay, W.D. Flanders, M.J. Khoury and T.J. Hassold, Am. J. Hum. Genet., **58** (1996) 628-633.
[18] A. Boca, *Cararea Imparatiei*, Episcopia Ortodoxa Romana a Aradului, Arad, 2004, 232.
[19] T. Vianu, *Filosofia culturii*, Publicom, Bucureşti, 1945, 92.
[20] T. Bodogae and N. Neaga, *Origen, Omilii la Cartea Facerii*, vol. XIII, Institutul Biblic şi de Misiune al Bisericii Ortodoxe Romane, Bucureşti, 1981, 4.
[21] J.C. Larchet, *Terapeutica bolilor spirituale*, Sofia, Bucureşti, 2006, 20.
[22] Sfantul Grigorie Palama, *150 de capete despre cunoştinţa naturală, despre cunoaşterea lui Dumnezeu, despre viata monohală şi despre făptuire*, in Filocalia, vol. VII, IBMBOR, Bucureşti, 1995, 39.
[23] Sfantul Grigorie de Nazianz, *Cuvîntări. XXVI*, Herald, Bucharest, 2008, 10.
[24] Sfantul Macarie Egipteanul, *Omilii duhovniceşti, XXVI*, Institutul Biblic şi de Misiune al Bisericii Ortodoxe Romane, Bucureşti, 1992, 4.
[25] A. Boca, *Tinerii, familia si copiii nascuti in lanturi*, Credinta Strămoşească, Iaşi, 2003, 118.