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From the Genesis of Down syndrome: What we know and what we still need to know

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Abstract

Despite years of intensive studies on DS, the clinical importance and recent understanding between the syndrome and maternal age, paternal age, habitual and environmental risk factors are relatively identified. Studies indicated that the vast majority of errors leading to trisomy 21 are due to errors in the egg, as nearly 90% of cases involve an additional maternal chromosome. There are many cases that the maternal is not prone to these risk factors but still by chance give birth to a child with DS. However, this can be attributed to altered chromosomal recombination.

Today, technology has helped in the diagnosis of this anomaly with the invention of next-generation sequencing technologies which enabled testing of multiple disease genes simultaneously, ranging from targeted gene panels to Exome Sequencing (ES) and Genome Sequencing (GS). A growing number of studies demonstrate that GS can detect an unparalleled range of pathogenic abnormalities in a single laboratory workflow. GS has the potential to deliver unbiased, rapid and accurate molecular diagnoses to patients across diverse clinical indications and complex presentations, but the prognosis of DS remains enigma.

Most studies argued that pregnant women diagnosed of DS has the choice to either terminate or continue with the pregnancy, in which 90% usually terminate the pregnancy even before the general public notice. This shows there's still a lot to do on the prognosis. This review suggests ways with the invention of technology how this anomaly can be treated immediately after the diagnosis.

Keywords: Aneuploidy; Down Syndrome (DS); Exome Sequencing (ES); Genome Sequencing (GS)

History

Victor A. McKusick in his recently edited article on Down syndrome told some tales on DS where he referenced [1] who first reported the association between Down syndrome and heart malformation. Abbott [2] who drew attention to the association between Atrioventricular Septal Defect (AVSD) and Down Syndrome (DS). Also, Neri et al. [3] provided a detailed review of the history of the scientific developments leading to the molecular characterization of DS.

Speculation about the historic prevalence of DS has included references to apparent depictions of the syndrome in 15th [4] and 16th [5] century paintings. Martinez-Frias [6] reported what seems likely to be the earliest evidence of the syndrome in a terra-cotta head from approximately 500 AD belonging to the Tolteca culture of Mexico, in which 'it is easy to identify the short palpebral fissures, oblique eyes, midface hypoplasia, and open mouth with macroglossia, findings that clearly define the face of a person with DS.

Bernal and Briceno [7] examined pottery artifacts from the Tumaco-La Tolita culture, which existed on the border of present-day Colombia and Ecuador approximately 2,500 years ago, and described several figurines with characteristics suggestive of DS. Bernal and Briceno [7] believed these artifacts to be among the earliest artistic representations of disease.

Introduction

The whole journey started in 1866 when John Langdon Down initially identified DS approximately 153 years ago [8]. DS is the genetic manifestation of trisomy of chromosome 21 [9]. DS is a genetic disorder caused when abnormal cell division results in an extra full or partial copy of chromosome 21. This extra genetic material in turn causes the developmental changes and physical features of Down syndrome.

The body been made up of trillions of somatic cells with the capacity to divide into identical daughter cells facilitating organismal growth, repair, and response to the changing environment known as “mitosis.” and its counterpart in the gametes, a different form of cell division also occurs called “meiosis.” The outcome of meiosis is the creation of daughter cells, either sperm or egg cells, through reduction division which results in a haploid complement of chromosomes so that on

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joining with another sex cell at fertilization a new diploid chromosomal complement is restored in the fertilized egg [10].

Literature Review

Down syndrome results, when abnormal cell division involving chromosome 21 occurs. These cell division abnormalities result in an extra partial or full chromosome 21. Any one of three genetic variations can cause Down syndrome:

Trisomy 21: About 95 percent of the time, Down syndrome is caused by trisomy 21 — the person has three copies of chromosome 21, instead of the usual two copies, in all cells. This is caused by abnormal cell division during the development of the sperm cell or the egg cell.

Mosaic Down syndrome: In this rare form of Down syndrome, a person has only some cells with an extra copy of chromosome 21. This mosaic of normal and abnormal cells is caused by abnormal cell division after fertilization.

Translocation Down syndrome: Down syndrome can also occur when a portion of chromosome 21 becomes attached (translocated) onto another chromosome, before or at conception. These children have the usual two copies of chromosome 21, but they also have additional genetic material from chromosome 21 attached to another chromosome.

The overwhelming majority of trisomy 21, or Down syndrome, is caused by the failure of chromosomes to separate properly during meiosis, also known as chromosome nondisjunction, which occurs when chromosomes fail to segregate during meiosis; when this happens, gametes with an abnormal number of chromosomes are produced. Errors in chromosome segregation lead to aneuploidy, a state where the number of chromosomes in a cell or organism deviates from multiples of the haploid genome. Aneuploidy arising through chromosome mis-segregation during meiosis is a major cause of infertility and inherited birth defect. During cell division, there are two parts to the cell cycle: interphase and mitosis/meiosis. Interphase can be further subdivided into growth 1 (G1), synthesis (S), and growth 2 (G2). During the G phases, the cell grows by producing various proteins, and during the S phase, the DNA is replicated so that each chromosome contains 2 identical sister chromatids (c). Mitosis contains 4 phases: prophase, metaphase, anaphase, and telophase. In prophase, the nuclear envelope breaks down, and chromatin condenses into chromosomes. In metaphase, the chromosomes line up along the metaphase plate, and microtubules attach to the kinetochores of each chromosome. In anaphase, the chromatids separate and are pulled by the microtubules to opposite ends of the cell. Finally, in telophase, the nuclear envelopes reappear, the chromosomes unwind into chromatin, and the cell undergoes cytokinesis, which splits the cell into 2 identical daughter cells.

Nondisjunction can also happen during mitosis. In humans, chromosome changes due to nondisjunction during mitosis in body cells will not be passed on to children (because these cells don't make sperm and eggs). But mitotic non-disjunction can cause other problems: cancer cells often have abnormal chromosome numbers

When an aneuploid sperm or egg combines with a normal sperm or egg in fertilization, it makes a zygote that is also aneuploid. For instance, if a sperm cell with one extra chromosome (n+1) combines with a normal egg cell (n), the resulting zygote, or one-celled embryo, will have a chromosome number of 2n+1.

Meiosis goes through all 5 phases of mitosis twice, with modified mechanisms that ultimately create haploid cells instead of diploid. Homologous chromosomes are separated instead of sister chromatids, creating haploid cells. It is during this process where we see crossing over and independent assortment leading to the increased genetic diversity of the progeny. Meiosis II progresses the same way as mitosis, but with the haploid number of chromosomes, ultimately creating 4 daughter cells all genetically distinct from the original cell (**Figures 1-3**).

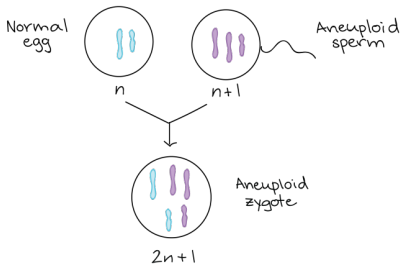

Figure 1: Nondisjunction occur when pairs of homologous chromosomes or sister chromatids fail to separate during meiosis I or II.

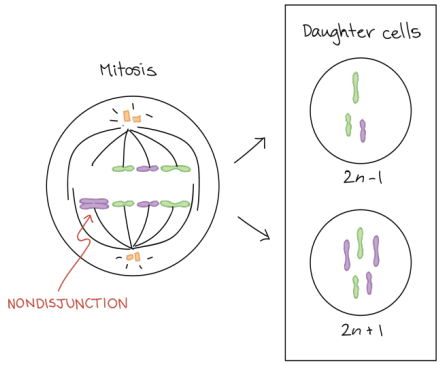

Figure 2: Meiosis I: The diagram below shows how nondisjunction can take place during meiosis I if homologous don't separate, and how this can lead to production of aneuploid gametes (eggs or sperm).

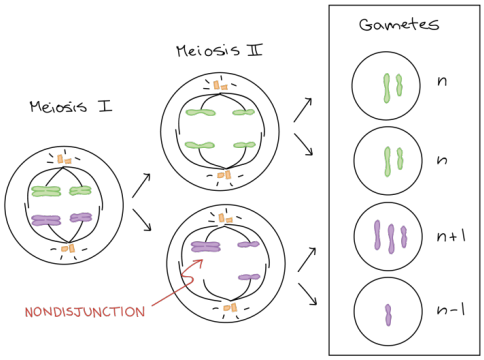

Figure 3: Meiosis II: Nondisjunction can also happen in meiosis II, with sister chromatids (instead of homologous chromosomes) failing to separate. Again, some gametes contain extra or missing chromosomes.

Errors that affect chromosome segregation could occur at several stages during the development of the oocyte: in the fetal ovary, either during the mitotic proliferation of oogonia or the early stages of meiosis; in the “dictyate” oocyte, during the 10–50 year period of meiotic arrest; or during the final stages of oocyte growth and maturation, when meiosis resumes and the meiotic divisions take place. Recent evidence from studies of human oocytes and trisomic conceptions and from studies in model organisms implicates errors at each of these stages.

As nondisjunction is the leading cause of pregnancy loss, mental retardation and birth defects, it is imperative that we understand the biology underlying this phenomenon. Characteristics of chromosome 21 nondisjunction are typical of many of the other human autosomes. That is, the overwhelming majority are due to errors during oogenesis: at least 90% of cases of chromosome-21 nondisjunction are due to maternal meiotic errors [11]. Two risk factors for maternal nondisjunction of chromosome 21 are increased maternal age and altered recombination.

Why and how maternal age does affects the risk of Down syndrome in their baby?

The process of oogenesis is lengthy and involves meiotic arrest, which makes it more vulnerable to miss-segregation of chromosomes than spermatogenesis. The age of the mother at the time of the conception of a fetus with DS is, by far, the most significant risk factor for meiotic NDJ of Ch21. Recent studies have shown that with increasing age, there is rapid degradation of cellular proteins named "cohesin and securin" involved in spindle formation, sister chromatid cohesion or anaphase separation of sister chromatids in oocytes, which imposes the risk of Non disjunction both at Meiosis I and Meiosis II

Aside from maternal age, another factor that has been identified unambiguously to be associated with increased susceptibility of maternal NDJ, namely altered recombination patterns. Warren [12] provided the very first evidence to suggest that a proportion of maternal non disjunction errors were associated with reduced recombination along chromosome 21. Further examination has shown that, in addition to the absence of an exchange along the non disjoined Chromosome 21, the placement of an exchange is an important susceptibility factor for nondisjunction.

Chiasmata are physical connections between homologous chromosomes at the site of recombination and they function to stabilize the paired homologues or tetrad at MI along with sister chromatids and centromere cohesion. It aids in proper chromosome orientation on the meiotic spindle and ensure their proper segregation to opposite poles. Absence of chiasma formation left the homologous pair free to drift randomly to the poles and if they move together to the same pole, aneuploidy results. As far as chromosome 21 non disjunction is concerned, chiasmate meiosis is the major cause of reduction in recombination frequency [13], although fall in double exchange frequency was reported too [14].

Recombination, initiated in the fetal ovary, stabilizes the tetrad and ensures proper segregation of chromatids to opposite poles. But the process is random and may be absent even in euploid samples [15] These achiasmate meioses are at risk for Non disjunction, and this risk increases with age due to rapid deterioration of ovarian proteins that make up the surveillance and `back-up' system for resolving and separating these non-exchange chromosomes [16]. It has been shown that nondisjoined chromosomes often show altered patterns of recombination [17] and for trisomy 21, a chiasmate meioses contribute about 45% of maternal MI cases [18]. Therefore, the ovarian microenvironment of older women appears to become more error prone due to accumulation of environmental and age related insults.

Paternal risk factor for chromosome-21 nondisjunction: The paternal error constitutes nearly 5 to 10% of total occurrence of live born DS cases, depending upon the populations studied. The first significant report was provided by Savage [19] who found reduction in recombination in MI nondisjoined cases, but not in MII errors. Moreover, the authors inferred that altered chiasma positioning may not associate with non disjunction in spermatogenesis, as the authors recorded coherent pattern of chiasma distribution among DS cases and control. In their extension study with more paternally derived samples, Oliver [20] determined that majority of Ch21 NDJ errors in spermatogenesis occurs at MII (32%MI;68%MII), and the authors did not found significant reduction in recombination either in MI or in MII errors. Moreover, their sample did not exhibit any advanced age effect for either of meiotic outcome groups. The authors argued that the time scale of spermatogenesis is much shorter starting at puberty runs continuously without meiotic halt and this explains why advancing paternal age does not complicate and associate Chromosome 21 Non disjunction in spermatogenesis. This study is significant in the realization that etiology of Chromosome 21 Non disjunction differs in two sexes. In general the frequency of recombination for normally segregating chromosome is less in male than in female. But further reduction in recombination frequency may not cause Non disjunction in male.

Habitual risk factor for chromosome-21 nondisjunction: Beside maternal age and altered pattern of recombination, set of prospective environmental or habitual risk factors have been identified in several epidemiological studies. These factors show various degrees of associations with DS birth. The list includes maternal cigarette smoking, use of oral contraceptive, peri-conceptional alcohol consumption by mother, exposure to radiation and low socio-economic status. Number of studies reported a negative association between maternal smoking around the time of conception and the risk for DS birth [21].

A study by Ghosh [22] analyzed the effect of chewing tobacco and contraceptive pill use on the Chromosome 21 NDJ in interaction with known risk variables like maternal age, meiotic stage of Non disjunction and pattern of recombination i.e., amount of exchange and positioning of chiasma on the recombining homologues. The study used various logistic

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regression models designed to examine every possible interaction among all above mentioned risk factors. Smokeless chewing tobacco was associated with significant risk for MII NDJ and a chiasmate (non exchange) MI error among the younger mothers. For both of these groups, the highest frequency of tobacco user was recorded in young age group (≤ 28 yrs) with successive gradual decrease in middle (29-34 years) and old (≥ 35 years) age group. According to risk prediction model (mentioned above) of DS birth, the chewing tobacco may impart some maternal age-independent risk of DS birth. In explaining the possible adverse influence of chewing tobacco on subcellular components of oocyte, the authors speculated that, regardless of oocyte age and the amount and location of recombination, tobacco probably affects some molecular system common both to meiosis I and meiosis II stages, for example the spindle apparatus. Conversely, the prevalence of oral contraceptive pill exhibited a trend of increasing frequency of occurrence with advancing maternal age, suggesting maternal age dependent risk of contraceptive pill in both the meiotic I and meiotic II error groups. Moreover, both risk factors, when present together, exhibited a strong age-dependent effect.

Epidemiology of environmental pollutants associated with Down syndrome birth: The epidemiological evidences in favour of the association between DS birth and environmental pollution are also surprisingly high, although controversial. Several pollution events are known to be followed by higher incidence of DS birth in an affected geographical locality. Early reports in the 1950s from USA suggested that fluoridation of water supplies might result in an increase in the frequency of DS birth [23]. Subsequent comparison of overall DS birth rates in fluoridated and non-fluoridated areas in Massachusetts found no evidence for a difference [24]. In this study prevalence rates of DS at birth were compared for Massachusetts residents ingesting fluoridated and non-fluoridated water. The observations included nearly all children born alive with DS in Massachusetts during the 17-year period 1950–1966. A rate of 1.5 cases per 1000 births was found both for fluoride-related births and appropriate comparison groups. Analysis of data from 51 American cities also found no difference in maternal age-specific DS rates between fluoridated and non-fluoridated areas [25].

Similarly, water contamination with pesticide trichlorfon has been reported to cause an outbreak of DS birth incidence. It was reported in the village of Hungary in 1990s [26] to increase in teratogenic births, including that of DS. In Woburn, Massachusetts, toxic chemicals (industrial solvents, mainly trichloroethylene) from a waste disposal site were detected in municipal drinking water wells [23] and people of this area reported increased incidence of several congenital anomalies. Lagakos [27] followed up this finding by compiling an exposure score for residential zones in Woburn, using information on what fraction of the water supply in each zone had come from the contaminated wells annually since the start of the wells. The authors found a positive correlation between contaminated water use and higher birthrate of DS in this locality.

Attempt to resolve the etiology of DS birth is a continuous process and we hope this will bring new insight in understanding the hidden truth in near future. But the problem lies in its multi factorial nature which inevitably suggests necessity of multi-faceted research efforts from the several directions. For example, it is needed to analyze the polymorphisms of certain genes that regulate meiotic recombination or genes that control maternal molecular aging or those who are involved in faithful chromosome segregation system in meiosis. But their role and allelic variations have not been explored in the context of Ch21 NDJ and subsequent DS birth. Apart from genetic components, several environmental influences are known to associate with DS birth as risk factors. But proper molecular study on how their adverse effect interacts and imperils faithful chromosome separation apparatus is tantalizingly low. At this level it is almost certain that environmental hazards or aneugen in various forms are associated with accidental increase in DS birth rate at different parts of world. But scientific evidence in favor of their interaction with genetic component is lacking and needs in depth study [22].

The authors of this review article suggest researchers to look into the application technology in other to fasten and reveal the obscure etiology of the anomaly in relation to its multi factorial nature that made it multi-faceted [28]. Researchers should incorporate the use of nanotechnology with the invention of biosensors and 3D-bioprinting in other to bring new insight to the hidden truth of this anomaly.

Nanotechnology involves the study, manipulation, creation and use of materials, devices and systems typically with dimensions smaller than 100 nm. Nanotechnology is playing an increasingly important role in the development of biosensors. The International Union of Pure and Applied Chemistry (IUPAC) defines biosensor as “A device that uses specific biochemical reactions mediated by isolated enzymes, immune systems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals”.

Basically, a biosensor is an analytical device, used for the detection of a chemical substance(s) that combines a biological component with a physicochemical detector. They are able to capture biological data and, through the help of biometric algorithms, translate this data into understandable, actionable information.

The application of nanotechnology to biosensor design and fabrication promises to revolutionize therapy at the molecular and cellular level. The convergence of nanotechnology, biology, and photonics opens the possibility of detecting and manipulating atoms and molecules using a new class of fiberoptic biosensing and imaging nanodevices [29].

For example, with the invention of DNA biosensor (also called genosensor), DNA microarrays(commonly called gene chips) etc. which can be implanted in pregnant women diagnosed of DS child to monitor in real time the mitotic and meiotic activities occurring during the fetal life. This will go a long way in helping us to fully understand the activities happening at this time of fetal development. Having understand the process taking place at this stage of life, there should be integration of bioprinting technology which will help to mimic the actual micro- and macro-environment seen.

Farai Mashambanhaka defined bioprinting as an additive manufacturing process where biomaterials such as cells and growth factors are combined to create tissue-like structures that imitate natural tissues [30]. The greatest importance of bioprinting lies in the resulting tissue-like structures that mimic the actual micro- and macro-environment of human tissues and organs.

Conclusion

Application of this infant technology into this research will greatly help in carrying out testings and clinical trials such as devising of drugs, which will also help in identifying side effects of drugs, development of 3D printed affected organs, regeneration of affected tissues that will boost the therapeutic effort in curbing and saving the lives of innocent children who by chance formed abnormally.

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