

ESSENTIAL READINGS - Chromosomal abnormalities and early development in Down syndrome

Learning Objectives

The genetic mechanisms that lead to the developmental anomalies encountered in Down Syndrome and subsequent cancer and premature aging in postnatal life

Content

The human chromosome complement was established as recently as 1956 as 23 pairs, i.e. 46 chromosomes. This is called the diploid number of chromosomes. Down syndrome was the first disorder in which a chromosome abnormality was discovered by Lejeune and colleagues in 1958. They established that the majority (95%) of Down syndrome subjects had an additional 21 chromosome. More sophisticated cytogenetic techniques reveal that a variety of different chromosomal mechanisms result in Down syndrome although these all share the common abnormality of triplication of chromosome 21 genes.

Cytogenetic Mechanisms Responsible for Down Syndrome

Trisomy 21	95 %
Translocation	2.5%
Mosaicism	2.5%
Other	<1%

What are the Mechanisms which Produce Trisomy 21

During meiosis (the formation of germ cells), the chromosome complement is halved to 23. This is called the haploid number. There are 2 steps, Meiosis I in which the diploid number is halved to 23, and Meiosis II in which the chromosomes are replicated similar to a mitotic step. Non-disjunction, i.e. the non-segregation of paired sister chromosomes to 2 daughter cells, results in a germ cell with 24 chromosomes and a corresponding germ cell with 22 chromosomes.

Molecular Cytogenetic and DNA polymorphism studies demonstrate that the error occurs in maternal meiosis I in 75% and meiosis II in 25% of patients. When the error occurs in paternal meiosis the ratios are reversed meiosis I (25%) and II (75%). Epidemiologic studies show that an increased incidence of trisomy 21 Down syndrome is strongly connected with the maternal age >37 years. Errors occur in meiosis in women at all ages. At 40 years, the incidence of Down syndrome is approximately 1:100 compared with an incidence of 1:1000 in women 29 years.

Translocation

Physical fusion of two chromosomes (or part of chromosomes) is known as translocation. This anomaly may be stably inherited. Fusion between chromosomes which have their centromere at one end (acrocentrics) i.e. chromosomes 13, 14, 15, 21 and 22 are known as Robertsonian translocations. A Robertsonian translocation which does not affect the absolute number (dosage)

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DJ Losen



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Table of Contents Readings In Early Development For Occupa

1. Understanding the eBook Readings In Early Development For Occupa
 - The Rise of Digital Reading Readings In Early Development For Occupa
 - Advantages of eBooks Over Traditional Books
2. Identifying Readings In Early Development For Occupa
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Readings In Early Development For Occupa
 - User-Friendly Interface

4. Exploring eBook Recommendations from Readings In Early Development For Occupa
 - Personalized Recommendations
 - Readings In Early Development For Occupa User Reviews and Ratings
 - Readings In Early Development For Occupa and Bestseller Lists
5. Accessing Readings In Early Development For Occupa Free and Paid eBooks
 - Readings In Early Development For Occupa Public Domain eBooks
 - Readings In Early Development For Occupa eBook Subscription Services
 - Readings In Early Development For Occupa Budget-Friendly Options
6. Navigating Readings In Early Development For Occupa eBook Formats
 - ePub, PDF, MOBI, and More
 - Readings In Early Development For Occupa Compatibility with Devices
 - Readings In Early Development For Occupa Enhanced eBook Features
7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Readings In Early Development For Occupa
 - Highlighting and Note-Taking Readings In Early Development For Occupa
 - Interactive Elements Readings In Early Development For Occupa
8. Staying Engaged with Readings In Early Development For Occupa
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Readings In Early Development For Occupa
9. Balancing eBooks and Physical Books Readings In Early Development For Occupa
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Readings In Early Development For Occupa
10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
11. Cultivating a Reading Routine Readings In Early Development For Occupa
 - Setting Reading Goals Readings In Early Development For Occupa
 - Carving Out Dedicated Reading Time

12. Sourcing Reliable Information of Readings In Early Development For Occupa
 - Fact-Checking eBook Content of Readings In Early Development For Occupa
 - Distinguishing Credible Sources
13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
14. Embracing eBook Trends
 - Integration of Multimedia Elements
 - Interactive and Gamified eBooks

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