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SHORT COMMUNICATION ARTICLE

RECENT DEVELOPMENTS IN GENETICS, DIAGNOSIS AND TREATMENT: DOWN SYNDROME

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ABSTRACT

Down syndrome (DS) which is produced by trisomy of chromosome {Hsa21} & moreover it is linked with a number of deleterious phenotypes, which includes learning disability, heart defects ,early –onset Alzheimer's disease & even childhood leukemia. Individuals with DS are usually affected via these phenotype to a variable point; understanding the origin of this variant is a key challenge ,at this juncture we are analyzing research progress in DS ,mutually in patient & in relevant animal models .In particular ,we highlight exciting progresses in therapy to recover cognitive function in people with DS & the important developments in understanding the gene content of Hsa21 .Additionally we discuss future research directions in light of new technologies ,in precise ,the use of chromosome engineering to produce new trisomic mouse models & large scale studies of genotype – phenotype associations in patient are expected to suggestively contribute to the future understanding of DS.

KEY WORDS: Down Syndrome, HSa 21 , DYRK1A

INTRODUCTION:

Down syndrome (DS) is caused by trisomy of human chromosome 21 (Hsa21) (Table 1).Nearly .045% of human conceptions are trisomic for Hsa21.The frequency of trisomy is influenced by maternal age & varies amongst populations (between 1 in 250 and 1 in 800 live births are trisomic for Has 21) .Trisomic fetuses are at an high risk of miscarriage & people with DS have an increased risk of developing several medical disorders. Recent progresses in medical treatment & social inclusion have suggestively increased the life probability of people with DS. In economically developed countries, the typical life span of people who are trisomic for Has 21 is now more than 55 years. With the help of this analysis we will discuss innovative findings in the understanding of DS & will focus on future important possibilities of research.

BASIS OF THE ADDITIONAL HSA21:

The parental source of the extra HSA21 in trisomy 21 was determined by means of highly useful polymorphic markers in DNA from parents & DS offspring. DNA markers adjoining the centromere specify the phase of meiosis thru which the separation error arose. Homozygosity for all polymorphic markers during 21q (the long arm of HSA21) is suggestive of a mitotic, post-zygotic error. Additional information (table-1) lists the several backgrounds of human trisomy 21. The added copy of Hsa21 ,in people with DS is anticipated to result in increased expression of many of genes encoded on this chromosome .The inequality in manifestation of Hsa21 & non –Hsa21 genes is assumed to result in the numerous phenotype which characterize DS. But, only a number of Hsa21 genes are expected to be dosage –sensitive, hence the phenotype they confer is transformed by gene-copy number.

There have been a number of new advances in genomics related to DS. For example, a quantity of fusion transcripts which are encoded by two or more genes previously known to be distinct have been described, such as the transcriptions encoded by exons from the Hsa21, DONSON, & ATP50 genes. In particular as algorithms to classify non-coding RNAs(e.g. microRNAs)improve ,the number of recognized on Hsa21 .Micro RNAs control the expression of other genes, & their role in DS is not fully understood .Spatial & temporal mapping of the Hsa21 gene expression is also important in understanding of DS. Trisomy of Hsa21 is related with a small number of conserved features happening in all individuals ,including mild –to moderate learning disability ,craniofacial abnormalities & hypotonia in early infancy .Although these phenotypes are always present in people with DS ,the point to which an individual is affected differs. Additionally, trisomy of Hsa21 is also linked with different phenotypes which only affect some people with DS, like Atrioventricular septal defects (AVSD) in the heart ,Acute megakaryoblastic leukemia (AMKL) & a decrease in a frequency of some solid tumours.

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(Table-1) Characteristics of Human Chromosome 21		
	Property	**Description**
Physical size	21p	5 -15 mb
	21q	33.5mb
	sex average	61.7 - 67.3 cM
Genetic Size	male meiosis	47.3 - 54.3 cM
	female meiosis	76.4 - 80.1 cM
	SINE	10.84%
Repeat content	LINE	15.15%
	DNA Transposons	2.40%
Non-Coding RNA	miRNA	5
	rRNA gene	Estimated -40-50 in 21p

Table 1: Characteristics of Human Chromosome 21

Genetic variation in both Hsa21 & non Hsa21 gene may account for much of this polymorphism .Genome wide association studies to identify these variation found a promising approach to gain novel visions into the pathology of DS. A Crucial goal of DS research is to recognize which of the genes on Hsa21 ,when present in three copies ,lead to each of the dissimilar DS-associated Phenotypes & to illuminate how the expression clues to molecular ,cellular & physiological changes causing DS pathology. Two diverse methods are being used to address these concerns. First, genomic association studies helping in identification of genes which play a significant role in pathology .Secondly ,a number of animal model of Hsa21 trisomy have been produced .Recent developments in chromosome engineering has directed in the creation of mice trisomic for different sets of mouse genes syntenic to Hsa21 ,& a mouse strain ,Tc(Hsa21)1TybEmcf (Tc1),carrying most of Hsa21 , easily segregating chromosome .These strains are being used mutually to plot dosage –sensitive genes on Hsa21 & to recognize pathological mechanism.

RECENT DEVELOPMENTS IN KNOWING PHENOTYPES LINKED WITH DS

Trisomy of Hsa21 has a remarkable effect on the development of many tissues ,most abnormally the heart & the brain .Trisomy of the Hsa21 genes 1A (DYRK1A) & regulator of calcineurin 1 (RCAN1) ,may influence on the progress of multiple tissues .DYRK1A is a priming kinase which assists in further phosphorylation of several proteins by other kinases .It is up regulated in a number of tissues from the people of DS.RCAN 1 is a regulator of the protein phosphatase calcineurin .According to recent study ,increased DYRK1A gene dosage was shown to decline the expression level of RE1-silencing transcription factor(REST).As REST is essential for both to preserve pluripotency & to facilitate neuronal differentiation ,a perturbation in REST expression may modify development of many cell types. Certainly over-expression of DYRK1A in some animal models is related with a number of phenotypes, including heart defect & abnormal learning & memory.

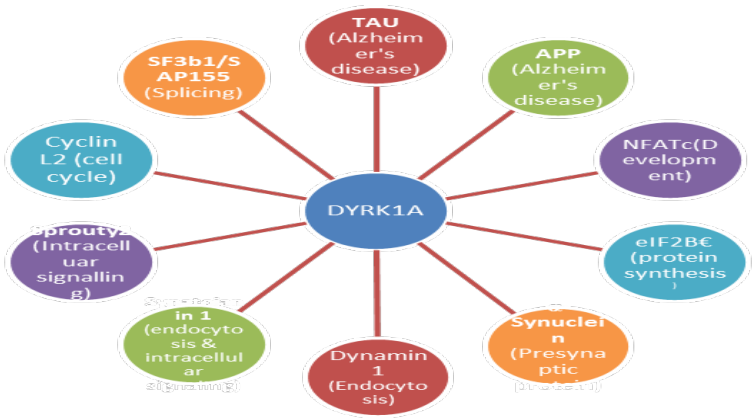

Figure 2: Phosphorylation targets of DYRK1A .The Hsa21 –encoded kinase DYRK1A has been shown to phosphorylate a multitude of targets ,being associated with a number of biological processes & DS-associated phenotypes containing endocytosis & AD.

Trisomy of Hsa21 is linked with a decrease in brain volume, the size of hippocampus & cerebellum is mainly affected .Trisomic granule cell precursors from the cerebellum have a reduced mitogenic response to morphogen sonic hedgehog. This was shown to underlie the reduced number of cerebellar granular cells observed in the Ts65Dn mouse models of DS. Hypo cellularity in the hippocampus also has a developing origin; abnormalities in cell cycle length, apoptosis & neocortical neurogenesis have been shown to subsidize to this phenotype.Ts65Dn pups exhibit a delay in attaining several; developmental milestones such as forelimb grip & the righting reflex, mimicking the developmental delay observed in babies with DS.

HEARTS DEFECTS:

Trisomy of Hsa21 is associated with a number of congenital heart defects, the most common being a AVSD that occurs in 20 % of the people with DS. Mutations in nonHsa21 CRELD1 gene may contribute to the development of AVSD in DS. CRELD1 has also been linked to AVSD by mapping the deletion breakpoints, on chromosome 3, in people with 3p-syndrome.

A number of Hsa21 trisomy mouse model exhibit hearts defects similar to those observed in DS, suggesting that trisomy of one or more of the approximately 100 genes common to these models influences development of the heart.

LEARNING AND MEMORY:

All people with DS have mild to moderate learning disabilities .over –expression of a number of Hsa21 genes ,including DYRK1A ,Synaptojanin 1 and single-minded homologue 2 (SIM2) ,results in learning and memory defects in mouse models suggesting that trisomy of these genes may contribute to learning disability in people with DS.in addition ,trisomy of neuronal channel proteins such as G-protein –coupled inward-rectifying potassium channel subunit 2 (GIRK2) ,may also influence learning in people with DSA .

Recent work on the Tc1 trans chromosomic mouse model of DS has examined in detail the learning pathways affected by trisomy of Hsa21 ,the learning deficits are correlated with specific abnormalities in long term potentiation (LTP) in the dentate gyrus of the hippocampus .LTP is an electrophysiological process proposed to be the cellular basis of the learning and memory .these data provide insight into which learning mechanism may be affected by Hsa21 trisomy and can be used to further understand their genetic causes.

LEUKEMIA AND CANCER:

DS increases the risk of developing AMK1 and acute lymphoblastic leukemia (ALL),approximately 10 %of the DS new born present with a transient myeloproliferative disorder(TMD),characterized by a clonal population of megakaryoblasts in the blood .this transient disease usually spontaneously resolves :however 10-20% of the DS patients with TMD develop AMKL before 4 years of age .the development of TMD requires both trisomy 21 and mutations in the transcriptions factor GATA1 .it is likely that further mutations are required for TMD to develop into AMKL .

The GATA1 mutations found in TMD and AMKL always have the same effect, causing translation to initiate at the second ATG of the coding region, leading to the production of a shorter protein, termed GATA1s .trisomy od Hsa21 on its own, even in the absence of GATA1s lead to an expression of the megakaryocyte-erythroid progenitor population in fetal livers from human DS abortions. However both loss and gain of function mutations have been found, so this may not be viable treatment, stem cell factors/KIT signaling has recently been demonstrated to stimulate TMD blast cell proliferation and inhibitors of this pathway may be a treatment for severe TMD.

Although the incidence of leukemia and cancer of the testis are increased in DS, the risk of developing most solid tumours re reduced .protection against the development of tumors required three copies of the Hsa21 'proto-oncogene' Ets2, which may act as tumours suppressor gene.

ALZHEIMER'S DISEASE:

People with DS have a greatly increased risk of early –onset Alzheimer's disease (AD). By the age of 60, between 50 and 70% of the people with DS develop dementia. The known AD risk factor amyloid precursor dementia(APP) is encoded on Hsa21 .trisomy of APP is likely to make a significant contribution to the increased frequency of dementia n people with DS ,indeed ,triplication of a short segment of Hsa21 that include APP in people without DS has been recently shown to be associated with early-onset AD .

Hsa21 gene other than APP may also contribute to the early onset of AD in people with DS ,indeed the Ts1Cje mouse model ,which is not trisomic for APP ,exhibits tau hyper phosphorylation ,an early sign of AD ,recent evidence suggest that trisomy of DYRK1A can phosphorylate Tau in people with DS.DYRK1A may also influence the alternative splicing of the Tau and phosrylation of APP. further studies are required to

determine the identity of the trisomic genes that contribute to these phenotypes.

RECENT ADVANCES IN THERAPY AND FUTURE PROSPECTS:

as recent progress demonstrate, mouse models can be used in parallel with the data collected from people with DS to test genetic associations, to explore biological mechanism and to trial therapies .in addition to the long standing Ts65Dn and TslCje model, the newly developed mouse strains such as Tcl,Dp1Yu and Ts1Rhr have generated a range of models with distinct sets of trisomic genes .

Ds was once thought to be an intractable condition because of the genetic complexity underlying it.

To develop new therapeutic targets, it is necessary to determine the identity of gene that contributes to DS phenotypes. This requires a precise and standardized definition of the phenotype. Ideally these measurements should be formulated into a standardized protocol that can be applied at multiple centers, to permit sufficiently large numbers of samples for meaningful analysis to be controlled. This can be facilitated by a carefully designed and curated bio bank of detailed phenotypic data alongside DNA and tissue samples from participating individuals. These collection can then be used for both candidate gene and genome side analyses, by different investigators permitting the identification of both dosage sensitive trisomic Hsa21 and non Hsa21 genes that contribute to DS phenotypes .pooling large data set has led to recent important finding in the study of schizophrenia, diabetes and obesity, the careful collection of additional patient data will add much to our recent understanding of DS.

COMPETING INTERESTS:

The authors declare that they have no competing interests.

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