

Influence of chromosome 6 deletion on the expressional characteristics in humans

Abstract

Deletion of chromosomal fragments bring about the devastating disease onset which is apparently almost incurable. Such deletions usually arise denovo as well as from the unstable chromosomal translocations, which in turn affect the terminal part of a chromosome or an interstitial region, making a large number of genes malfunctioning with the onset of various complications. Chromosome 6q deletion happens due to a missing copy of the genetic material existing within the long arm (q) of the chromosome, which causes the loss of multiple necessary genes ending up with an array of physical and mental abnormalities. current review discussed the background of such deleterious effects along with some examples, and depicted on the possible mechanisms; i.e., the genetic insights of chromosomal breakpoint based on the information gathered from the previous literature which could be useful in perspective of the surveillance of genetic disease as well as for the maintenance of the mass public health.

Keywords: chromosome 6q deletion, clinical complications, genetic insights of chromosomal breakpoint, public health

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Introduction

The genetic material (the deoxyribonucleic acid abbreviated as DNA which carries the genetic information) of eukaryotic cells is dispersed into multiple linear chromosomes, the number of which actually varies among the divergent organisms; for example, only 3 in the haploid fission yeast *Schizosaccharomyces pombe* whereas as much as 46 in the diploid humans.¹ Therefore, chromosomes are not indeed the naked DNA; and their structure, conformation and functions are orchestrated by a large collection of proteins to which they are bound as discussed in the earlier literature.¹ Briefly, there are DNA loops which are generated by complex of proteins that simultaneously binds to two different sites on a DNA molecule, and the human genome has been shown to be organized into tens of thousands of such chromosome loops which in turn influence several cellular functions including

1. Reducing the spatial distance of DNA elements relative to their genomic distance, Sequestering and insulating the stretches of DNA from the rest of the genome,
2. Bringing into juxtaposition at the base of the loop DNA-bound proteins,
3. Influencing the higher-order chromosome organizations like the interphase chromosome compaction, mitotic chromosome condensation, centromere organization, sister chromatid individualization and separation, etc.^{1,2}

It's well known that chromosomes usually come about in pairs: simply to be stated that one set is obtained from the mother, and the other set from the father.³ Each human cell normally carries 23 pairs of chromosomes which makes a total of 46 chromosomes.^{1,3} Additionally, it's also known that two types of chromosomes; i.e., autosomes and allosomes (the germline chromosomes from the 23rd pair) reside within the human genome which determines the gender of a human.³ Humans develop by going through cell division to create new cells and recover old and damaged cells.³

Chromosomal deletions are most likely to arise denovo as well as from the unbalanced chromosomal translocations, affecting the terminal part of a chromosome or an interstitial region, which in turn distresses a large number of genes along with the onset of disease syndromes. Chromosome 6q deletion usually refers to the chromosome abnormality due to a missing copy of the genetic material residing along the long arm (q) of the chromosome 6.⁴ Such deletions may involve multiple genes, and hence a possibility rises with the missing of the required genetic information even that's from one of the chromosomal pair.⁴ Eventually, if the missing part contains important genetic information, it can ultimately lead even to the neurophysiological imbalance.^{4,5} Indeed, the chromosome 6 (Ch6), consisting of 2344 to 2780 genes, is a metacentric chromosome of 171.11 Mbs in length, and it comprises approximately 6% of the total human genome.⁶ In Ch6, in between the 1002 and 1034, the genes encode for known, novel or putative proteins, and around 2.2% is occupied by exons (around 281 base pairs).⁶ The major significance of Ch6 underlies on its capacity to encode an array of small RNAs and proteins that are needed for various biological functions including the enhancement of immunity (like the formation of the major histocompatibility complex or MHC), inflammation, the neuronal activities and other critical activities required for the cellular homeostasis.⁶ Some Ch6 genes are known to influence somatic growth in response to different pathogenic microorganisms or drugs, and they are also protective against other diseases as can be exemplified by the non-HLA gene NFKBIL1 in the MHC region and the HLA-DRB1 which has been shown to be stringently shielding against the type 1 diabetes mellitus.⁶ However, the alteration or the malfunction of Ch6 has been shown to be functionally associated with more than 120 major human diseases, including cancer, heart disease, the immune disorders, and even leading to the mental illnesses.^{6,7}

Thus, the truncation of Ch6 may result in various psychophysiological impairments including the impedance of intellectual disabilities associated with various structural brain abnormalities.⁸ Indeed, such deletion has been reported to affect the molecular signalling pathway required mostly for the neurological

proliferation.⁸ Present review briefly compiled the impacts of Ch6 deletion which may aid new insights to the existing knowledge on the specific function of human chromosome.

Major diseases associated with Ch6

The common disorders related to the malfunction of Ch6 have been noticed through the onset of Alzheimer's disease, schizophrenia, rheumatoid arthritis, celiac disease, orofacial clefting, short neck, clinodactyly, corneal opacity, facial dysgenesis, Juvenile diabetes, lymphoblastic leukemia, multiple sclerosis, seizure, hypotonia, microcephaly and hypoplasia of the corpus callosum, and deafness etc.^{6,9-12} The altered expression of the protein coding genes of Ch6 may result in the heightened expression of the vascular endothelial growth factor (VEGF) which is known as the POEMS syndrome (characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell proliferative disease, developmental delay, intellectual disability and skin change); and also, VEGF is known to be linked with metastatic cancers.^{6,10} The overexpression of BMP6 has been noticed to allied with the prostatic cancer.⁶ The expression of KIFC1 in the extended class II sub region of MHC has been shown to be related to the brain metastasis.⁶ This is to be mentioned that the loss of heterozygosity in MHC genes has been closely related to the acute lymphoblastic leukemia (ALL) as mentioned before.^{6,11} The other prominent diseases due to the Ch6 deletion includes Ankylosing spondylitis, autism, Behcet's disease, bipolar disorder, complement deficiency, Crohn's disease, Ehlers-Danlos syndrome, epilepsy, Fanconi anemia, Hashimoto's thyroiditis, macular degeneration, maple syrup urine disease, narcolepsy, lymphoid neoplasms, nephritis, neuroblastoma, Parkinson disease, polycystic kidney disease, psoriasis, retinitis pigmentosa, spinocerebellar ataxia, sudden infant death syndrome, systemic lupus erythematosus, joint laxity, hydrocephalus, dimpling on elbows and knees, and hyperactivity/ADHD, etc.^{6,12}

Genetic makeup of chromosome 6 deletion

Analysis of the chromosomal breakpoints using 14 cases by Lee and colleagues (in 2011) detected 44 cases of subtelomeric 6q deletion without any overlapping.¹² However, 27 out of those 44 cases were the pure terminal deletion. Further analysis using 14 cases by the same group unravelled a potential common breakpoint interval which is 8 to 9 Mb from the chromosome 6q terminus where the FRA6E fragile site (the most frequently expressed fragile sites of the human genome, harbouring several genes of which one is *parK2*, bearing the information for the Parkinson's disease) exists; and thereby suggesting that the breakage at the FRA6E fragile site may principally account for the chromosome 6q subtelomeric deletion.¹² Interestingly, the smallest deletion (~0.4 Mb with 3 known genes) and the largest deletion (<11 Mb with more than 34 known genes) showed no apparent phenotypic variances regarding the intellectual disability, developmental delay, dysmorphic features, brain anomalies and others.¹²⁻¹⁴

A separate study regarding such breakpoint analysis showed that the *qki* gene (encoding the RNA-binding protein that regulates pre-mRNA splicing, exports mRNAs from the nucleus, translates protein, and imparts the stability to the mRNA) which is within 6q26 is disrupted, possibly suggesting that the haploinsufficiency of this gene may play a role in the 6q deletion syndrome.¹⁵

Conclusion

Along with a number of complications, the subtelomeric changes of chromosomes in a considerable ratio brings about the with intellectual

debility with the developmental delay as a result of chromosomal abnormality. Together with the previously published papers and from the current review, it is quite clear that messes connected with the Ch6 deletion are truly distressing as well as chronic. However, recent advancements in the genomic-, proteomic-, and metabolomics research as well as the public health surveillance aided a lot to understand the evidence-based impact of such chromosome deletion. Such a multi-disciplinary approach would even help to develop specific biomarkers and to detect novel targets for the therapeutic developments as and when necessary.

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Authors' contributions

Taskina Murshed (TM) initially drafted the manuscript. Rashed Noor (RN) revised and finally approved the manuscript.

Conflicts of interest/Competing interests

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