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Original Research Article

Application of array comparative genomic hybridization in clinical diagnostics of intellectual disability/developmental delay in children

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ABSTRACT

Background: This study was designed to analyze and evaluate the potential pathogenic genomic imbalance in children with unexplained intellectual disability (ID) and/or developmental delay (DD) and its association with phenotypes, and to investigate the value of array-based comparative genomic hybridization (array-CGH).
Methods: A total of 72 Children with ID/DD were evaluated by array-CGH for detection of genomic copy number variations (CNVs).
Results: The results of the array-CGH revealed that 10(14%) of the 72 patients had pathogenic CNVs, in that six cases had pathogenic CNV in a single chromosome, 2 cases had multiple microdeletions and 2 cases had combined microdeletion and microduplication, 2 cases had pathogenic CNVs in chromosome 1p36 and Xq28 region. One case had variation of unknown significance in chromosome region 15q11.2. Large bands of copy neutral loss of heterozygosity were detected in 2 cases comprising more than 10% of genome.
Conclusions: Array-CGH being a high-throughput and rapid tool, allows for the etiological diagnosis in some of the children with unexplained ID/DD.

Keywords: Comparative genomic hybridization, Array-CGH, Intellectual disability

INTRODUCTION

Developmental delay is a common clinical entity affecting many children around the world, leading to mental and/or physical disabilities. Shevell et al estimated, about 3% of general population have some type of moderate to severe intellectual disability.[1] There is no established aetiological diagnosis in 50% to 80% of all cases.[2] Yield of diagnostic evaluation for children with GDD/ID varies greatly (10-81%), which reflects many factors including different study populations and durations of the study, making systematic reviews more complicated to perform.[3] Consequently, there is no consensus regarding which studies should be performed on children with GDD/ID.[1-7;10-11]

In current genetic scenario chromosomal (chr) aberrations have been identified as most important cause of developmental delay.[2,10] Diagnosed patient are screened through karyotyping to detect any chromosomal abnormality but sensitivity of this test is low as it cannot submicroscopic chromosomal aberrations which are significant in altering gene expression.[5,10,11]

Clinical genetic testing, including high-resolution array comparative genomic hybridization (array CGH) or chromosomal microarray (CMA), has been suggested as a standard practice for children with diagnosis including unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASDs), and multiple congenital anomalies (MCA).[2,7,10]

In this study, we analyzed the clinically relevant chromosomal imbalances being the important etiology of ID/DD patients with the application of genome-wide array CGH.

METHODS

This retrospective study was carried out at Division of Genetics, Department of Pediatrics, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, over a period of 5 years (2011-2016) to identify the frequency and pattern of chromosomal aberrations among 158 patients with ID, DD, autism, or MCA referred to the Genetic Clinic of Pediatrics at Lok Nayak Hospital.

Before cytogenetic analysis a detailed interview was conducted to obtain the medical history of all the cases. Patients presented with multiple congenital anomalies, intellectual disabilities, mongoloid features, mental retardation and/or developmental delay.

Developmental, intelligence, and social quotients (DQ, IQ, SQ) were measured formally. DQ was assessed in children aged 3-30 months using developmental assessment scale for Indian infants, IQ in those aged 30 months to 12 years using Binet Kulshreshtha test, and SQ in all patients using Vineland social maturity scale. The severity of ID as mild (IQ 50-69), moderate (IQ 35-49), severe (IQ 20-34) and profound (IQ under 20) was classified using the ICD-10 classification.

Out of the 158 patients, 72 were selected based on a detailed clinical history and examination as per a structured proforma. Informed consent and ethical approval were obtained.

Sample collection and DNA extraction

3 ml blood sample was collected from the patients. DNA was extracted from peripheral blood leukocytes using a salting-out method according to standard protocols. Genomic DNA concentration was measured by Nanodrop spectrophotometer (Eppendorf).

Array-CGH analysis

Chromosomal microarray analysis (CMA) was performed using human CytoSNP-12 chip which has 300,000 probes across the whole genome that are designed to target SNP markers for region prone to chromosomal aberrations. DNA digestion, labeling, and hybridization were performed following the manufacturer instructions.

Analysis and CNV classification

All chromosomal abnormalities identified, including deletions and duplications of at least adjacent probes or of a minimum region of 300 kb, were compared with genomic variants described in databases of benign and pathogenic changes to define their possible pathogenicity (DGV http://projects.tcag.ca/variation/, UCSC Genome Browser http://www.genome.ucsc.edu/, ISCA https://www.iscaconsortium.org/, and DECIPHER http://decipher.sanger.ac.uk/).

Furthermore, gene content was also evaluated using databases such as the NCBI Gene Database, GeneCards, and OMIM.

RESULTS

Among the total of 158 children, 89 (56.3%) were male and 69 (43.6%) were female and median age at presentation was 20 months (3 months-12 years). Clinical description of our cohort and clinical summary of patients with pathogenic CNVs is tabulated (Tables 1 and 2).

Table 1 shows 36.1% of cases had profound ID, and among 10 cases having cryptic chromosomal imbalances; 80% were dysmorphic, 60% were having malformations, 30% were having abnormal magnetic resonance imaging (MRI) and only 1% were born to consanguineous parents.

Table 1: Clinical description of our cohort.

Total (n)=158, CMA analysis (n)=72	No. n (%)
Severity of ID Phenotype	
Mild ID	8 (11.1)
Moderate ID	16 (22.2)
Severe ID	22 (30.5)
Profound ID	26 (36.1)
Cryptic chromosomal imbalances n=10, loss of heterozygosity=2	
Deletions in single chromosome	6
Duplications in single chromosome	2
Both duplication and deletions	2
Large bands of copy neutral loss of heterozygosity	2
Clinical description of patient with pathogenic CNVs (n)=10	
Facial dysmorphism	8 (80)
Malformation (skeletal anomalies, cardiac and limb defects)	6 (60)
Seizures	1 (10)
Visual deficit	3 (30)
Hearing deficit	5 (50)
Abnormal MRI	3 (30)
Consanguinity	1 (10)
Family history	2 (20)

Table 2 shows patients with ID/DD not only had single deletion or duplication at a single region but they can also have multiple or combined deletions/duplications at different regions as in case 7, 42, 49, 69 and can also have regions of loss of heterozygosity as in case 3 and 62.

Table 2: Brief clinical summary of patients with pathogenic CNVs and large bands of copy neutral loss of heterozygosity.

S. no.	Case no.	Age (month/year)	Gender	Phenotype	Investigation	Array CGH
1	Case 4	6	Female	Moderate intellectual disability, facial dysmorphism and seizures, hypertelorism, prominent nasal bridge, arched eyebrows, hallux valgus, blepharophimosis, low set ears, asymmetric face, bilateral esotropia, proportionate short stature	MRI brain: Partial agenesis of corpus callosum, 2d Echo: atrial septal defect	An 832 kb deletion in chromosome 15q25.3 – 26.1 region (Figure 3(c))
2	Case 7	1½	Female	Facial dysmorphism, development delay, lethargy and oculo-visual abnormalities, brachycephaly, microcephaly, sparse hair, arched eyebrows, anteverted ears, bulbous nasal tip, proportionate short stature, joint contractures, bilateral fifth finger clinodactyly, hypotonia	MRI brain: Diffuse thinning of corpus callosum, X-ray: spine hemi-vertebrae at D6, D8 and D11 level along with mild scoliosis, fundus examination: bilateral optic atrophy, BERA: moderate to severe hearing loss	3 microdeletions, 295 kb deletion in chromosome 2p24.3 region, 391 kb deletion in chromosome 3q13.2 region and 521 kb deletion in chr 17p11.2 region (Figure 3 (a))
3	Case 15	5	Female	Severe intellectual disability, craniofacial dysmorphism, flat occiput, plagiocephaly, low set-small ears, broad and bulbous nasal tip, flat ear lobule, anteverted nares, lines of blaschko, pectus excavatum, syndactyly of 2nd and 3rd fingers of left hand, deep vertical crease on soles of bilateral foot, presence of sandal gap, bilateral shortening of 3rd 4th and 5th toe	X-ray: Spine hypoplasia of 12th rib and mild scoliosis to left side	A 160 kb deletion in chromosome Xp11.4 region (Figure 1)
4	Case 29	10.5	Male	Moderate intellectual disability, hearing impairment, facial dysmorphism, preauricular tags, smooth wide philtrum, lumbar lordosis, short fingers and toes, genu valgum, wrist widening, bilateral calcaneo-valgus	X-ray: Bilateral wrist metaphysial irregularity in distal metaphysis of bilateral radius, ulna and mild epiphyseal plate widening, X-ray spine: osteopenia and coarsening of trabeculae with spina bifida, BERA: mild to moderate hearing loss	A 1.3 mb deletion in chr 19p13.3 region (Figure 2)
5	Case 36	1	Male	Development delay, sensineural hearing loss, facial dysmorphism, widely spaced eyes, flat mid face, deep set eyes, bilateral epicanthic folds, straight eyebrows, brachycephaly, delayed closure of anterior	MRI brain: Delayed myelination, brachycephaly, BERA: mild to moderate hearing loss, 2d Echo: mild left ventricular dysfunction	5.9 mb deletion in chromosome 1p36 region (Figure 3 (b))

Continued.

S. no.	Case no.	Age (month/year)	Gender	Phenotype	Investigation	Array CGH
				fontanelle, low set ears, broad and bulbous nasal tip		
6	Case 42	10 months	Male	Abnormal genitalia, global development delay, oculo-visual abnormalities, very thin upper, lip long smooth philtrum, visual impairment, widely spaced nipples, hearing impairment, micropenis, cryptorchidism	BERA: Moderate to severe hearing loss, ultrasound: bilateral hydronephrosis	A large interstitial deletion of 11.9 mb in chr 9p24.3 region and large duplication of 15.4 mb in chr 7p22.3 region
7	Case 49	1	Female	Global development delay, facial dysmorphism, failure to thrive, frontal bossing, depressed nasal bridge, bilateral flat ears, wide mouth, coarse facies and tapering fingers	2d Echo: Atrial septal defect with mild pulmonary artery hypertension	A 11mb deletion in chr region 18q22.1 and 1 mb deletion in chr region 16p11.2
8	Case 52	3 ½	Male	Global development delay, constipation, abdominal distension, Straight eyebrows and deep-set eyes, intestinal biopsy Hirschsprung's disease	Intestinal biopsy: Hirschsprung's disease	6 mb duplication in chromosome region Xq28
9	Case 54	8 months	Male	Global development delay and family history of recurrent abortions	Clinical investigations were normal	215 kb duplication in chromosome region 15q11.2
10	Case 69	4	Female	Moderate intellectual disability, cranio-facial dysmorphism, ocular abnormalities. Microcephaly, frontal bossing, hypertelorism, posterior rotated low set ears, clinodactyly	BERA: Moderate hearing loss	A large duplication of 39.8 mb in chr 8q23.1 region and 385 kb duplication in chr 20
11	Case 3	4	Female	Moderate intellectual disability, facial dysmorphism, sensineural hearing loss, Depressed nasal bridge, long philtrum, flat nose, hypertelorism, proportionate short stature	BERA: Profound hearing loss	Large regions of loss of heterozygosity on chr 2, 3, 4,5,7,10,11,12,15,19,20,21 representing about 14.7 % of genome
12	Case 62	1.5	Male	Severe intellectual disability, craniofacial dysmorphism, Alopecia, depigmented hair, left eye ptosis, left bifid thumb, right 2-3 syndactyly of the toes, hypotonia	USG KUB: Increased bilateral kidney echogenicity	Multiple regions with loss of heterozygosity on chr 2, 3, 7, 15, 16, 17 representing 11 % of genome

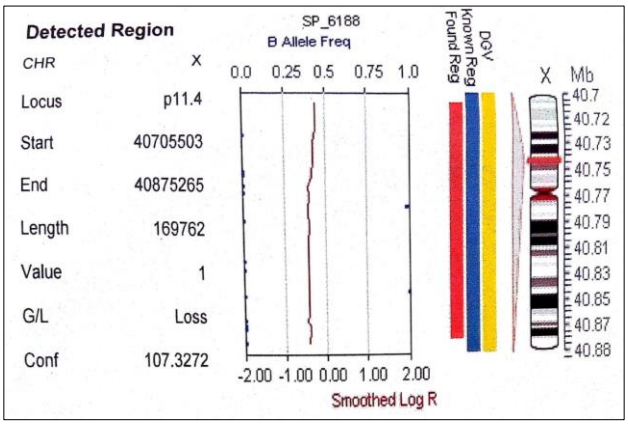

Figure 1: An overview of pathogenic CNV found in case 15, array CGH revealing a 160kb deletion in X chromosome Xp11.4 region.

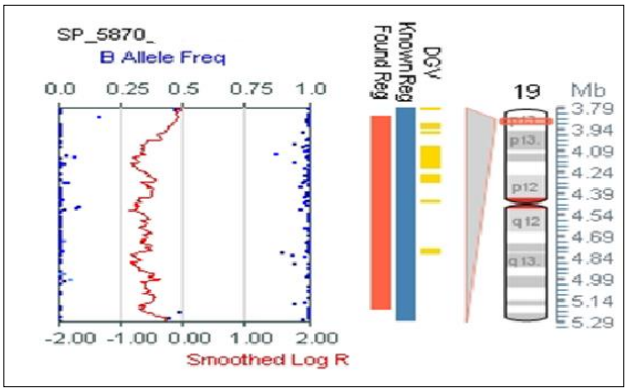

Figure 2: An overview of pathogenic CNV found in case 29, array CGH revealed a 1.3mb deletion in chr 19p13.3 region.

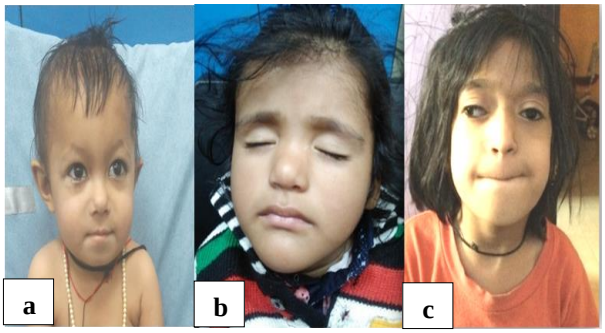

Figure 3: (a) Case 36, note distinct dysmorphic features widely spaced eyes, flat mid face, deep set eyes, broad nose, depressed nasal bridge, straight eyebrows, bilateral epicanthal folds, bulbous nasal tip; (b) case 7 with cranio-facial features of brachycephaly, microcephaly, sparse hair, arched eyebrows, anteverted ears, bulbous nasal tip; and (c) case 4 with cranio-facial features of hypertelorism, prominent nasal bridge, arched eyebrows, blepharophimosis, asymmetric face, bilateral esotropia.

DISCUSSION

Array CGH scans the genome with a high resolution, for small chromosomal aberrations (gains/losses) or copy number variants (CNV), which are not detected on conventional karyotyping. We used DNA oligonucleotides to analyse selected patients with normal karyotype in whom a chromosomal abnormality was suspected due to the combination of clinical features.

In this study, we identified CNVs in 10 of 72 patients (13.8%). Although the selection criteria for array-CGH investigations are highly variable, similar reports in the Indian population showed approximately the same detection rate of pathological CNVs. Sharma et al accounted for 15% of CNVs among 106 Indian ID/GDD patients.[12] Boggula et al detected 18% of pathogenic CNVs in 86 patients from North India who had ID.[13]

In this study 10 patients (13.8%) with DD/ID, ASD, and MCA were found to have at least one pathogenic CNV. The detection rate achieved in this study was similar to previous studies 13-28% not depending on the choice of oligonucleotide-based or SNP-based platforms 15-19%.[14-20] However, the smaller size CNVs identified were mostly benign.

Pathogenic CNVs with few reported cases

In case 4 deletion in chr region 15q25-26 was detected resulting in hemizygous deletion in ACAN gene. Monoallelic loss of function of ACAN is associated with spondyloepiphyseal dysplasia Kimberley type with features of proportionate short stature with degenerating osteoarthropathy.[31] In case 15 deletion in chr region Xp11.4 was detected leading to monoallelic loss in USP9X gene. A study by Reijender et al suggested that de novo loss of function mutation in USP9X causes a female specific recognizable syndrome with development delay and congenital malformations.[21] Homan et al reported that mutation in USP9X is associated with X linked intellectual disability.[22] In case 29, deletion was detected in chr region 19p13.3. Risheg et al reported 3 patients with overlapping deletion of 19p13.3 and suggested the role of genes ZFR2, ATCAY, NMRK2, DAPK3, EEF2, PIAS4, ZBTB7A and MAP2K2 in causation of abnormal phenotype and intellectual disability due to involvement of above genes in all three cases.[23]

Cases with multiple microdeletions of known clinical significance

In case 7 multiple microdeletions of clinical significance were detected. Deletion in chromosome region 2p24.3 region resulted in hemizygous deletion of NBAS gene with phenotypic features of microcephaly, micrognathia, hypertelorism, low set ears, bilateral epicanthic folds reported in other cases with deletion in similar chromosomal region while the karyotype of parents was normal. NBAS or neuroblastoma amplified sequence

encodes a protein that is thought to function as a component of endoplasmic reticulum tethering complex that interacts with P31 and STX18.[32] Pathogenic variation in this gene is known to cause SHOP syndrome (short stature, optic nerve atrophy and Pelger huet anomaly) and infantile liver failure syndrome.[32,33] Deletion in chromosome region 3q13.2 resulted in hemizygous deletion of PHLDB2, TAGLN3, C3ORF52, GCSAM, SLC9C1 genes. Molin et al studied 15 patients with deletion in chromosome region 3q11-3q23 with features of plagiocephaly, brachycephaly, proportionate short stature, corpus callosum agenesis and localized the breakpoints to chromosome 3q12-3q21.3.[8] 521 kb deletion was detected in chr region 17p11.2 but no gene was involved. Deletion in this region is associated with Smith-Magenis syndrome with clinical features of brachycephaly, midface hypoplasia hypotonia, brachycephaly, hearing impairment being described in the cases reported previously.[9] This syndrome can also be caused by mutation in RAI1 gene which was not identified in our case. Case 49 revealed a 11 mb deletion in 18p22.1 region, 2 mb deletion in region 9p13.1 and 1 mb deletion in 16p11.2 region. Copy number changes observed in region 18p22.1 is overlapping with the critical region 18q22.3q23 of 18q deletion syndrome with highly variable phenotype, generally characterized by mental retardation, short stature, hypotonia, hearing impairment, carp like mouth, short palpebral fissures external ear anomalies, tapering fingers, scoliosis. Genotype phenotype correlation have been evaluated for short stature, white matter disorders, delayed myelination and growth hormone deficiency reported to be due to deletion at 18q22.3q23 and congenital aural atresia due to deletion at 18q22.3.[34] CNCs at 9p13 region is known to cause mild to moderate ID, social and interactive personality and behavioural problems along with features of short stature, prominent antihelices, hypoplastic nails and precocious puberty.[27] Fernandez et al reported 3 cases with 16p11.2 deletion with features of low nuchal hairline, short neck, flat face, low set ears, narrow palpebral fissures, short nose, smooth philtrum, tapering fingers, short toes and autism spectrum disorder.[40] In these cases, pathogenic CNVs detected through array cgh may provide an explanation for a severe phenotype but localization of disease causing variation is difficult and will require further extensive analysis.

Pathogenic CNVs in known region

In case 36 deletion was noted in chr 1p36 region which is known regions with well described microdeletions syndromes.[24] Rosenfeld et al reported 5 patients with 200 to 823 kb overlapping interstitial deletions of chromosome 1p36.33 with features of deep-set eyes, straight eyebrows, bulbous nose, midface hypolasia, bilateral epicanthic folds, retrognathia, narrow palpaberal fissures, overfolded helices, prominent nose, synophrys, bilateral medial prominence of foot, hypotonia.[24]

In case 49 duplication was detected in chr region Xq28 with gain of MECP2, HAUS7, BGN, ATP2B3, FAM58A, SLC6A8 and 15 other genes. Role of MECP2, SLC6A8, FLNA gene duplication in causation of a distinctive disorder with features of intellectual disability, intestinal pseudo-obstruction and bladder dysfunction is already reported with one case reporting its association with hirschprung disease.[28,29]

Cases with combined deletion and duplication

Case 42 had a deletion in chr region 9p22-24 encompassing 42 genes and duplication in region 7p22 involving 105 genes. Parental karyotype was normal. Features of cryptorchidism and micropenis correlates with pathogenic variation in DMRT1 gene, which is essential for male reproductive development as suggested by Ying et al.[35] Swinkels et al characterized 13 patients with chromosome 9p deletion with features of trigonocephaly, flat midface, low set ears, short/flat nose with anteverted nostrils, thin upper lip, long philtrum, high palate, cryptorchidism, hypospadiasis and hypotonia and localized the critical region to a 8 mb band in 9p22 region.[25] Duplication detected in this case is of unknown significance with LFNG, IQCE, FTSJ2, EIF3B genes within the region suggested to be associated with asperger syndrome (autism spectrum disorder).[26]

In case 69 large duplication was detected in chr region 8q23 and deletion of unknown significance in chr 20p12.1.Overlapping regions of cytoband 8q23 are reported in patients with phenotypes including pre and post natal growth retardation, microcephaly, a peculiar face with frontal bossing, hypertelorism, strabismus, upslanting palpebral fissures, depressed nasal bridge, high palate, posteriorly rotated low set ears, short and broad neck, overriding toes and mostly severe mental retardation.[36] Heterozygous deletion in MACROD2 gene in chr region 20p12.1 in a case with kabuki syndrome.[37]

CNVs of unknown significance

In case 52 duplication of unknown significance was detected with involvement of a single gene NIPA1. Van der Zwaag et al suggested that microduplication of chr 15q11.2 region involving two genes NIPA1 and CYF1P1 is associated with risk of developing autism spectrum disorder.[30]

In case 3 and 62 large bands of copy neutral loss of heterozygosity were detected representing 14.7% and 11% of genome respectively. Both patients were born through non-cosanginous marriage with no history of inbreeding in pedigree of three generations. Such large bands of loss of heterozygosity have been reported to occur in case of uniparental disomy in which pair of allelic genes (heterodisomy) or two copies of a single allele (isodisomy) are inherited from a single parent.[38] In case of isodisomy, it leads to unmasking of several rare disorders with abnormal phenotypes due to inheritance of two copies of a recessive gene mutation from a carrier parent.[38] Loss of heterozygosity has been detected in development of

certain type of cancers but its role in causation of rare disorders with intellectual disability is still unknown and will require further analysis for disease causing variation which might be located within the area of loss of heterozygosity.[38]

In our study 80% of cases having pathogenic CNVs had facial dysmorphism and 60% had malformations signifying the importance of thorough phenotypic assessment in patient with ID/DD as such severe phenotypes are associated with increased probability of detecting a pathogenic CNVs in array analysis. We also identified more cryptic chromosomal imbalances in the form of copy number losses than gains signifying the association of microdeletion syndrome with more severe phenotypes. These finding have been supported by the studies of Horev et al demonstrating severe effect of deletion on phenotype, including viability, brain structure, and behavior, in mice.[39]

Riggs et al recommend a definitive diagnosis for patients with ID and/or MCA to ensure early and high-quality medical management including genetic counseling.[14,15] Our study highlights the role of genetic factors, especially chromosomal abnormalities, in the etiology of DD/IDD and MCA. Despite a diagnostic challenge for the treating physician due to multiple microdeletions of clinical significance and large bands of loss of heterozygosity, it underscores the importance of implementing genetics services like array-CGH in developing countries as a cost-effective first-line analysis for DD/ID and MCA.

Limitation of study was small sample size and increasingly better understanding of array cgh in order to detect all influences undergoing specific genetic condition and detail clinical characterization of large cohort was required.

CONCLUSION

In conclusion, array comparative hybridization is more effective than conventional karyotyping in detecting clinically significant chromosomal imbalances in patients with intellectual disability. It also contributes to the discovery of new genetic syndromes. Implementing appropriate size filters can reduce false-positive results. Multiple microdeletions of clinical significance and large bands of loss of heterozygosity present a diagnostic challenge for the treating physician. Larger cohort studies are needed to gain a better understanding of array CGH and its impact on specific genetic conditions.

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Appendix

Comparison of clinical information of CNV's related to ID/DD with previous reported cases (Table 3) and their references. Available at: https://mega.nz/file/fZE0mA5b#XeuVZxl61eaM48EUneO2nWi14mzRKZ6Q72DVp0JP4yU

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