The Journal of Medical Laboratory Science & Technology South Africa. 2023;5:31-38
https://doi.org/10.36303/JMLSTSA.92

JMLSTSA
ISSN 2664 2549 EISSN 2708 3063

REVIEW

A review of 22q11.2 microdeletion syndrome: clinical and diagnostic perspective

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Chromosome 22 is the second smallest human chromosome, covering more than 51 million base pairs and comprising between 1.5% and 2% of the total DNA in cells. Microdeletion of chromosome 22q11.2 underlies the most commonly diagnosed human deletion syndrome and is associated with over 180 clinical features. The condition is highly underdiagnosed in developing countries and diverse population groups. A variety of laboratory techniques have been used over the years to detect the 22q11.2 microdeletion, resulting in the discovery that more than one gene on chromosome 22 is involved. Many patients with the syndrome now survive into adulthood. The clinical and genetic manifestation of this syndrome is present in all medical disciplines with care for both adults and children being relatively intricate. Genetic counselling involves increasing a family's knowledge about the condition, laboratory testing, and related procedures. This review describes the clinical features and findings, some of the molecular genetics, genetic counselling, and laboratory techniques that have evolved over the years in the diagnosis of the 22q11.2 deletion syndrome.

Keywords: microdeletion syndrome, congenital disease, 22q11.2 deletion syndrome

Introduction

The occurrence of microdeletion around the 22q11.2 region is common in diseases such as velocardiofacial syndrome (VCFS), DiGeorge syndrome (DGS), and conotruncal anomaly face syndrome. These diseases share similar chromosomal abnormalities with different phenotypes and are very common in humans with an incidence of 1:4 000–1:6 000 live births and remain undiagnosed in diverse populations.[1,2]

There is a constant need to advance medical technology and science for clinical and diagnostic applications. This is particularly important in human genetics as more insight into the human genome is warranted. Over many years, there has been an evolution in the techniques used to diagnose genetic conditions.[3] Each technique has enabled a new and improved method of viewing the human genome.[4] Routine chromosome analysis has been used to diagnose inherited and acquired genetic conditions for over 50 years.[5] This includes the discovery of various chromosome abnormalities such as chromosome loss/gain, duplications, amplifications, deletions, insertions, and ring chromosomes. Apart from this, high-resolution banding allowed for the detection of microdeletions.

Cytogenetics has prompted the discovery of genes responsible for a variety of conditions. Fluorescence in situ hybridisation (FISH) is a laboratory technique used to locate and visualise a particular gene or deoxyribonucleic acid (DNA) sequence within an individual's genome. Quantitative fluorescent polymerase chain reaction (QF-PCR) is used in the field of congenital or inherited genetics to overcome the prerequisite of cultured cells from prenatal and postnatal samples, which allows for rapid diagnosis of the common chromosomal aneuploidies. Multiplex ligation-dependent probe amplification (MLPA) is a sensitive technique that allows the quantification of nucleic acid sequences, quickly and efficiently. Next-generation sequencing (NGS) is a sequencing technology that offers ultra-high throughput, scalability, and speed. The technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA. Microarray or array comparative genomic hybridisation (aCGH) can detect chromosome abnormalities at a higher resolution than conventional cytogenetics or FISH. In most instances, laboratories use either conventional cytogenetics (by karyotype analysis) or aCGH as a first-tier test for suspected chromosomal conditions, since this offers a broader view of the human genome.[6] Where aCGH is the first-tier test, either cytogenetics or FISH may be used as a follow-up test if there is a suspicion of variants that may be due to a translocation, inversion, or possible marker chromosome.[6,7] This may be done to attempt the identification of non-recurrent abnormalities or suspected mosaicism by a different method.[7]

This review is based on describing the clinical features and findings common in 22q11.2 deletion. It will also evaluate some of the molecular genetics, as well as various laboratory techniques that have evolved over the years. Further, genetic counselling will be discussed regarding knowledge about genetic diseases and laboratory testing.

Genomic organisation of chromosome 22

Chromosome 22 is the last autosomal pair of the 23 pairs of chromosomes in human cells. Usually, each cell has two copies of chromosome 22, comprising about 51 million DNA base pairs. Both chromosomes represent between 1.5% and 2% of the total DNA complement.[8] Chromosome 22 was the first human chromosome to be fully sequenced; this was done by researchers working on the Human Genome Project in 1999.[9] The sequence obtained contained approximately 500–600 genes and 134 pseudogenes.[9] Protein coding genes were found on the q-arm of chromosome 22, but none on the p-arm.[9] The p-arm is a short satellite arm containing repetitive DNA sequences that appear to play a role in controlling gene activity and sustaining chromosome structure.[10] Satellite DNA is the basis of the centromere and forms heterochromatin; densely packed DNA that is vital for controlling gene activity and sustaining chromosome structure.[11]

22q11.2 deletion syndrome

Chromosome 22q11.2 deletion syndrome (22q11.2DS) is one of the most common recurrent human genomic syndromes with a prevalence of ~1:4 000–1:6 000 live births.[12,13] It is also known as DGS (OMIM#188400) or VCFS (OMIM#192430).[14] Males and females are equally affected, irrespective of their ethnicity and there is no "founder" effect.[15,16] This microdeletion stems primarily from de novo non-homologous meiotic recombination events in more than 90% of affected persons, is inherited in about 10% of individuals, and occurs frequently in all populations, as shown in Table I.[2,17] Around 60% of individuals with 22q11.2DS inherit a smaller deletion, around 1.5 Mb, from an affected parent and children of these affected individuals have a 50% risk of inheriting the deletion.[16,17] The deletion has no relationship to parental age and can occur from either parent's chromosome.[12] Individuals affected have an approximate life expectancy of 42 years.[16]

Table I: Relationship of age and sex in diverse populations[2]

Population	Sex ratio – male:female	Age range (y)
Global	50:106	Infant–43
African	26:55	1–44
Asian	12:27	Infant–43
Latin American	12:24	1–39

Clinical presentation

There is some overlap in the clinical presentation of DGS and VCFS where microdeletions on chromosome 22q11.2 have been seen in each of these disorders.[18] The aetiology is multifactorial and affected patients suffer from congenital heart defects/disease, cleft palate, dysmorphic facies, skeletal anomalies, thrombocytopenia, learning disabilities, and immune deficiency.[13,18–23] It is worth noting that the clinical features of 22q11.2DS change with age, but diagnosis can be made at all ages, although the pre/postnatal period is preferred (Table II).[2,16,23] Clinical manifestations of 22q11.2 and 22q11.2-like deletion syndromes are shown in Table II.[16,23]

Various medical interventions across disciplines will be required throughout their lifetimes due to the multiple health issues that may be experienced by 22q11.2DS patients.[19] Symptoms which can present from early childhood into adulthood may include seizures, endocrine issues, immune deficits, cardiovascular problems, early-onset Parkinson disease, and premature mortality.[19] Some patients may demise due to cardiac complications or infections due to poor immune function.[15]

Immunodeficiency is experienced by individuals with 22q11.2DS due to thymic hypoplasia and impaired T-cell production.[17] There is an increased risk of atopy and autoimmune disease related to T-cell lymphopenia.[17] Another autoimmune disorder associated with 22q11.2DS, idiopathic thrombocytopenia purpura (ITP), is seen 200 times more frequently than in the general population.[24]

Neuropsychiatric diseases encompass the most common group of later-onset conditions in 22q11.2DS; schizophrenia being the most prevalent. Evidence suggests that 22q11.2DS is a well-known risk factor and a clinically relevant cause of schizophrenia.[12,25,26] One out of four to five affected 22q11.2DS adults develop psychosis, representing an approximately twentyfold risk increase over the general population. Individuals with 22q11.2DS account for 1–2% of schizophrenia cases.[12,25,26] The International 22q11.2DS Brain and Behaviour Consortium (IBBC) aims to discover additional genetic factors and genetic modifiers that contribute to the occurrence of schizophrenia in patients with 22q11.2DS.[12,25] It is possible that other rare copy number variants (CNVs) outside of the 22q11.2 deletion region might be involved in the manifestation of schizophrenia in 22q11.2DS patients.[12,20,25]

Table II: Clinical manifestations of 22q11.2 and 22q11.2-like deletion syndromes (adapted)[16]

Chromosomal regions affected				
	22q11.2	**10p14–13**	**4q34.1-q35.2**	**3p10.3**
Frequency	1:4 000	> 100	Rare	Rare
Length of DNA	3 Mb or 1.5 Mb	5 Mb	17.4 Mb	300 kb
Clinical phenotype percentage occurrence				
Congenital heart disease (CHD)	75%	82%	15%	Yes
Dysmorphic craniofacial features	50%	50%	95–99%	Yes
Developmental delay	50%	80–90%	65%	Yes
Learning problems	70%	80–90%	65%	Yes

Patients with schizophrenia have a significantly higher polygenic risk score (PRS) of the common variations in 22q11.2DS than those individuals with no psychotic disorders.[25] It is recommended that any 22q11.2DS patient with schizophrenia should be treated with antipsychotic medication and managed according to clinical practice guidelines.[12] A study using mouse models demonstrated that the *COMT* and *TMRT2A* genes form an intrinsic genetic component regulating psychosis risk through differential neural activity in 22q11.2DS.[27] Individuals with 22q11.2DS often present with thrombocytopenia where there is increased macrothrombocytopenia.[28] There may also be a high risk of developing autoimmune cytopenias, and an increased prevalence of malignancy where the prevalence is higher in twins.[28]

Molecular genetics

The 22q11.2 locus has one of the highest proportions of duplicated sequences carrying eight low copy repeats (LCRs).[8] LCRs allow for non-allelic homologous recombination (NAHR) that result in both deletions and duplications.[29] The cluster of LCRs on the long arm of chromosome 22 influences various combinations of recurrent CNVs. There are four distinct blocks of LCRs on chromosome 22, namely LCR A-D (Figure 1), where A is the most proximal and these LCRs are larger and more complex than any other in the human genome associated with chromosomal deletion syndromes.[15] There is haploinsufficiency of 46 protein-coding genes, 7 microRNAs (miRNA), 10 non-coding RNAs and 27 pseudogenes in those with the 3 Mb deletion (LCR22A–LCR22D).[16,20] Variability in the breakpoints between LCR22A–LCR22H which result in either microdeletions or microduplications is due to LCR-mediated non-allelic homologous misalignments which predispose copy number changes and lead to unequal recombination (NARH) during meiosis.[8,16,20,30] These copy number variations are atypical, i.e. do not overlap the commonly deleted region on 22q11.2DS due to the variability of the LCRs. This illustrates the complexity of aberrations in the 22q11.2 region.[30,31] Genetic and epigenetic changes can influence the clinical phenotypes of 22q11.2DS and impact *TBX1* and other genes' functioning.[16] Genetic and epigenetic modifiers of 22q11.2 deletion syndrome with disease

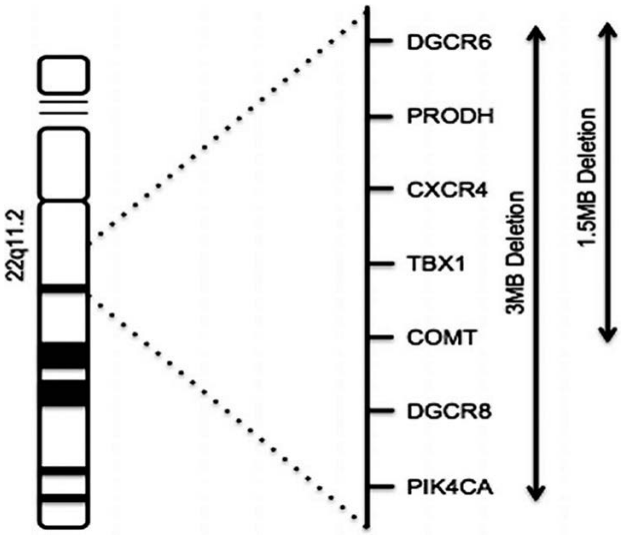

Figure 1: The typically mutated 22q11.2 gene region known as the DiGeorge region genetic loci, identified within each region are: DiGeorge critical region 6 (DGCR6); proline dehydrogenase (PRODH); CXC chemokine receptor type 4 (CXCR4); T-box transcription factor 1 (TBX1); catechol-O-methyltransferase (COMT); DiGeorge critical region 8 (DGCR8); phosphatidylinositol 4-kinase alpha (PIK4CA)[32]

connections are shown in Table III.[16] Studies of 22q11.2DS provide opportunities to dichotomise genetic and environmental risk factors or modifiers within the 22q11.2 region and elsewhere in the genome.[20]

T-box transcription factor

Common proximal breakpoints in LCR22A encompass either the A–D or A–B blocks.[15] The congenital malformations associated with 22q11.2DS are linked to genes mapping to the LCR22A–B region, among which is the T-box transcription factor (*TBX1*) gene that encodes a T-box type of transcription factor.[15,16,20] The haploinsufficiency of *TBX1* does not always lead to the same congenital malformations due to heterozygous mutations, making it apparent that genetic and epigenetic factors can change the clinical phenotypes of 22q11.2DS.[16,20] Different tissues and organs have varied sensitivity to *TBX1* dosage.[20] Apart from *TBX1*, another gene, *CRKL* (CRK-like proto-oncogene), maps to LCR22C–D region encoding a cytoplasmic adaptor

Table III: Genetic and epigenetic modifiers of 22q11.2DS with disease connections (adapted)[16]

Gene name	Chromosome location	Function	Human syndromes	Mechanism
Genes on chromosome 22q11.2				
TBX1	22q11.2	T-box transcription factor regulates expression of 2 000 genes	22q11.2 del	Interacts with histone 3 methyltransferase, BAF60a, and SMAD1
DGCR8	22q11.2	miRNA binding protein	22q11.2 del	Epigenetically regulates gene expression through miRNAs
DGCR6	22q11.2	Regulates neural crest migration	Congenital heart disease (with PRODH deletion)	Negatively regulates *TBX1* expression
Morphogens				
Retinoic acid	-	Morphogen involved in embryonic patterning	22q11.2 del-like	Complexes retinoic acid receptor to regulate gene expression
Gestational Diabetes	-	Teratogen during pregnancy	22q11.2 del-like	Affects multiple development processes in the embryo, with the pharyngeal apparatus particularly sensitive

protein implicated in growth factor signalling and is expressed ubiquitously in all cells.[20]

DiGeorge syndrome critical region 8

The DiGeorge syndrome critical region 8 (*DGCR8*) is an important gene that is responsible for brain and heart development or function and whose haploinsufficiency in 22q11.2DS can impact the severity of clinical presentation/features.[16,20,26] The gene has the potential to dysregulate downstream target genes which contributes to the neuronal phenotype.[16,26] DGCR8 is a binding protein of the microprocessor complex involved in miRNA biogenesis.[16,20,26] Patients with 22q11.2DS have a dysregulation of DGCR8 protein that causes hypervariable miRNA expression and can differ per patient.[16,26] The loss of miRNAs leads to premature synaptic disruptions, which are characteristic of schizophrenia associated with 22q11.2DS patients.[12,16,25,26] *DROSHA* is the catalytic subunit of the microprocessor complex that initiates miRNA maturation in the nucleus by recognising and cleaving hairpin precursors embedded in primary transcripts. In addition, *DGCR8* works in a complex where it binds to primary miRNA and *DROSHA* and regulates the expression of many transcripts.[16,26] The expression of these transcripts results in a 50% reduction in *DGCR8* expression, leading to the expression of hundreds of miRNAs and potentially affecting neuronal physiology.[16,26]

DiGeorge syndrome critical region 6 and proline dehydrogenase 1

Genes within the proximal variable breakpoint include DiGeorge syndrome critical region 6 (*DGCR6*), proline dehydrogenase 1 (*PRODH*), and three transcripts with unknown functions.[14,16,20] Deletions or duplications of *DGCR6* with *PRODH* are linked to chronic heart disease.[16] Fluctuations in *DGCR6* downregulates *TBX1*, while missense mutations within *PRODH* are associated with schizophrenia.[14,16]

MicroRNA expression

The microRNA (miRNA) are small non-coding RNAs that regulate gene expression at the level where messenger RNA translates to protein.[16,20,26,33] One study involving the putative miRNAs showed in 22q11.2 deletion region has an increased miRNA density, and the target genes are enriched in gene sets of brain function and its development, and other developmental processes and pathways.[33] By profiling the miRNA with confirmed deletions on chromosome 22q11.2, miRNA expression behaviours show strong connections to immunological and cardiac abnormalities.[34] There are at least 18 miRNAs that have statistically significant differential expression, with miR-185 being expressed at 0.4 × normal levels.[33-35]

Copy number variants

Genetic variants such as deletions, duplications, and insertions of DNA sequences are usually described as CNVs and are responsible for a substantial percentage of genetic variation among individuals.[36] Currently, the size of CNVs ranges from 50 bp to several Mb, which may result in genomic structural changes associated with disease and phenotypes, and can be seen in both human and animal models.[27,36-38] They modify the expression of genes located within and close to the rearranged region. There are six known mouse models used for studying human 22q11.2DS that possess the majority of functional genes and are congenic.[27] In 22q11.2DS, CNVs make idyllic candidates to study polygenic interactions such as schizophrenia where it is an important single genetic risk factor.[27] There is a large group of CNVs strongly associated with brain development, neuropsychiatric disorders, and conditions involving abnormal morphology of organ systems.[39] A study using cell lines found multiple effects of the large deletion CNVs on chromosome 22q11.2 where widespread changes caused by the 22q11.2DS spread across the whole chromosome and nucleus, rather than being confined to the deletion region only.[39] Case studies show that some individuals may have different or unusual characteristics, which makes the diagnosis of 22q11.2DS a little more complicated.[30,31] This includes atypical deletions that do not overlap the commonly deleted regions and phenotype that may be found in different genetically determined conditions.[30,31]

Secondary mutations

Only 1% of 22q11.2DS patients have secondary mutations at other unrelated loci, among which are microdeletions on 10p13, 4q34, and 3p12.3 respectively.[16] Patients with the deletions of the terminal end of chromosome 4q34 and interstitial deletion of chromosome 3p12.3 report clinical presentation and phenotypes of 22q11.2DS.[16] Other prominent diagnoses resulting from secondary mutations include cystic fibrosis, 17p12 deletion syndrome, G6PD deficiency, CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital and ear anomalies), and von Willebrand disease.[16]

Indications for testing

Prenatal testing is typically requested based on ultrasound findings as well as family history.[19,21] Prior to prenatal testing, parents should either be referred to a clinical geneticist or a genetic counsellor, or both, to assist with the diagnosis and follow-up of the condition.[19,25] The most common reason for postnatal referral is the presence of a congenital heart defect, facial dysmorphism, and developmental delay.[13] A multidisciplinary approach is often required to provide adequate care for children, adolescents, and adults with 22q11.2DS.

Genetic testing and diagnosis for 22q11.2DS

In the field of human genetics, there has been an evolution in the techniques used to diagnose genetic conditions. This is particularly important as more insight into the human genome is warranted. Each technique has enabled a new and improved method of viewing the human genome. Routine chromosome analysis or cytogenetics has been used to diagnose conditions caused by chromosomal aberrations for over 50 years.[15-17] Cytogenetics prompted the discovery of genes responsible for a variety of conditions such as chromosome loss/gain, duplications, amplifications, deletions, insertions, and ring chromosomes. Apart from this, high-resolution banding allowed for the detection of microdeletions. Microdeletions are deletions of sizes at, or below, the current level of resolution

of the light microscope and standard current banding levels of approximately 400–500 bands per haploid karyotype.[17] Some of the well-known microdeletion syndromes are Wolf-Hirschhorn, Cri-du-chat, Williams, Langer-Giedion, Prader-Willi/Angelman, Miller-Dieker, Smith-Magenis, and 22q11.2DS.

Chromosomal microarray (CMA) is widely suggested as the first line of testing for CNVs in many developed and developing countries.[7] However, costing exercises show that locus-specific testing, i.e. MLPA and FISH, are more cost-effective in the developing world.[40,41] The cheapest being MLPA, offering significantly more coverage of chromosome 22 than FISH.[40,41]

Conventional cytogenetics

Cytogenetic analysis involves microscopic examination and screening of the whole genome at the cellular level to detect large chromosome rearrangements.[42] To visualise chromosomes, slides are prepared from peripheral blood cell cultures, then treated with a trypsin solution and stained with a Giemsa stain, this is referred to as G-banding. Traditionally, cytogenetic diagnosis of microdeletion syndromes was achieved by treating cell cultures with ethidium bromide. Resulting in chromosome elongation and methotrexate or thymidine for synchronisation of cell cycles to reach a high-resolution banding of up to 850 chromosome bands per haploid karyotype.[42,43] This high-resolution banding allows macroscopic visualisation of regions where microdeletions occur and was used to describe many of the well-known microdeletion syndromes, including 22q11.2DS.[15] However, the process to achieve this level of banding is labour intensive and is no longer routine practice due to the advancement of molecular techniques that allow for better diagnosis of microdeletions.[14,15,20]

Fluorescent in situ hybridisation

FISH is a molecular cytogenetic technique used to detect where a specific gene or DNA sequence is located within an individual's genome. In a process known as hybridisation, a small double-stranded DNA sequence, called a probe, is attached to a fluorescent molecule, which binds to a complementary nucleotide sequence on a patient's DNA. Due to the nucleotide sequence specificity of FISH, the nucleotide sequence acting as the probe's binding site in the gene or region of interest on a chromosome must be well-defined, since probes are designed to precisely target the region of interest.[18,45] FISH has the ability to detect the typical heterozygous deletion found in 22q11.2DS patients and has been in use since 1992.[15] The probe used to diagnose 22q11.2DS covers the specific region involved and may not detect any other abnormalities involving chromosome 22.[15,18,20,22] The probe allows for detection of aberrations found at the hybridisation site on the locus D22S75 or *TUPLE1* (*HIRA*), close to the centromere, which is the most common 3 Mb deletion, while a second probe serves as a control closer to the telomere on the q-arm of chromosome 22.[15,22] For congenital conditions, FISH is usually done on synchronised cell populations, which ensures a variety of nuclei in different stages of the cell cycle.[18,45] Since not all the 22q11.2 deletions have the typical A–D endpoints, variants occurring within the LCR22A–LCR22H region will only be detected via FISH if they encompass the *TUPLE1* region.[15] However, the size or the extent of the deletion, or being able to distinguish between the classic/typical and atypical deletion, may not be indicated.[30,41] Follow-up testing using FISH may work for family members of an affected individual, but first, the extent of the deletion needs to be established to potentially customise a FISH probe targeting precisely the same region to confirm whether other family members carry the same CNVs. Since the use of high-resolution banding for conventional cytogenetics has been phased out as a routine practice, the 22q11.2 deletion cannot be seen on karyotypes with 550 banding resolution. Therefore, by using FISH as a diagnostic test, the detection rate is much more significant.

Multiplex ligation-dependent probe amplification

Multiplex ligation-dependent probe amplification (MLPA) was first developed and described by a team of scientists at MRC Holland.[45] MLPA is a semi-quantitative method that can assess the copy number of up to 40 DNA target sequences in a single multiplex PCR-based reaction, thereby detecting deletions and duplications in the DNA sample.[45] Copy numbers are established by comparing the peak heights of reference probes and target probes in the patient samples with those in reference samples with a known normal copy number. MLPA allows for a more inclusive determination of gene quantities with increased accessibility, and at a reasonably lower cost compared to CMA.[22,46,47] Additionally, MLPA can be used to detect microdeletions that may not be identified by FISH and is more accurate for describing the nomenclature.[21,22,46] In this technique, genomic DNA is hybridised in a solution to set probes that consist of a target-specific sequence flanked by a universal primer sequence and a second adjacent target-specific sequence (RPO) at the end, also with a flanking universal primer sequence for facilitating selective PCR amplification of the targeted sequencer.[45] For 22q11.2DS, genomic DNA is denatured and hybridised to the MLPA probe set (P023 Kit: DiGeorge Syndrome; MRC-Holland), the kit contains PCR primers for 39 loci of which 11 are on the long arm of chromosome 22.[46] They are advantageously placed in and around the region flanked by LCR22A–LCR22D while the remaining six additional loci are located on chromosomes 4, 7, 8, 10, 17, and 18, for the detection of haploinsufficiency caused by the presence of LCRs in LCR22A–LCR22D.[22,46] Chromosomal microarray may be done as a reflex test to detect if only one probe has an abnormal copy number, as it could be an artefact or any atypical deletions which could be missed.

Chromosomal microarray

CMA analysis is recommended for patients with multiple congenital abnormalities, developmental delay, as well as autism spectrum disorders, all of which may be associated with 22q11.2DS.[13] The CMA uses high-resolution oligonucleotide-based microarrays to visualise breakpoints of approximately 10 kb or higher.[3,7,14,48-50] There are two mainstream microarray designs that are used for determining chromosomal abnormalities, i.e. comparative genomic hybridisation and single

nucleotide polymorphism (SNP).[7,51] The aCGH uses fragments of patient and control DNA samples, each labelled with a different fluorescent colour. The DNA is mixed in equal quantities and put onto an array slide containing multiple probes, where they hybridise to complementary sequences within the probe DNA on the array. SNP arrays are used to identify differences between patients at a single base pair site using DNA probes derived from various genomic regions known as SNPs. This type of array measures the probe intensity of the patient DNA compared to various normal control DNA samples that were each individually run, normalised, and combined to create a reference set.[51] The array data obtained can subsequently be analysed and interpreted using various software. In individuals with suspected 22q11.2DS, CMA increases the capacity to detect sub-microscopic aberrations, including atypical deletions.[13,16,20,21]

Facial analysis technology

Digital facial analysis technology can be used to assist in the diagnosis of 22q11.2DS by using algorithms that characterise the similarities and differences in clinical presentations of 22q11.2DS in diverse populations, especially when there is limited access to laboratory testing.[2] The catalogue was put together using ethnically diverse individuals who were diagnosed with 22q11.2DS. Four population groups were chosen, i.e. Caucasian, African, Asian, and Latin American. Sensitivity of detection is equal to or greater than 96.6% for each population group, and specificity is equal to or greater than 96.3%.[2]

Genetic counselling

Genetic counselling involves identifying families at possible risk of a genetic condition by ascertaining and evaluating family history and inheritance patterns along with calculating recurrence risk. The counsellors provide information to increase a family's knowledge about genetic diseases, testing and related procedures. Written, informed consent should always be obtained for both or either sampling of amniocentesis and chorionic villi samples. The pre-test counselling should include a risk assessment based on family history or frequency of the deletion, and couples should be told of the benefits and limitations of the testing.[17,19,21] Information should be included about the 22q11.2DS and an explanation of the unpredictability and prognosis of the condition.[15,19,21] Although 22q11.2DS is only inherited in approximately 10% of cases, it is worth mentioning that if found in a parent, male or female, there is a 50% probability of having an affected child at each pregnancy.[15,17,19] Individuals affected with 22q11.2DS who have children have a 50% risk of their children also having the 22q11.2DS.[16,17] In the case of de novo deletions, parents should be given accurate information regarding the variability of clinical phenotype, psychomotor development, and psychiatric risks.[19] Since there are various organ systems involved in the manifestation of 22q11.2DS, different medical disciplines are recommended for the treatment and management of these patients. Follow-up genetic counselling is warranted when a deletion is detected and is an essential aspect for the ongoing management of all affected patients and family members, from adolescence to adulthood.[17,25,26] Due to the increased risk for psychotic illness, informed discussions regarding early signs, diagnosis, and prevention of schizophrenia as a lifelong condition is a crucial discussion from adolescence.[12,17,25,26] If possible, local or online support groups should be recommended to patients and families and can be helpful for couples considering pregnancy options.[12,17,19]

Conclusion

Chromosome 22 is the last of the autosomal pairs of chromosomes found in humans. Since the discovery of 22q11.2DS, there are still many facets of the disorder that are yet to be determined, especially on the molecular level. Improved clinical screening methods could be developed based on further understanding of the mechanism of chromosome 22q11.2 deletions and the genes responsible for specific phenotypes. Males and females are equally affected, and the condition is underdiagnosed in diverse populations and developing countries, although life expectancy has increased. DNA and RNA sequencing methods are providing insight into genetic and epigenetic modifiers that have an impact on the disease penetrance and severity. Understanding the genetic and epigenetic factors for each patient affected with 22q11.2DS will also be able to assist in future care. High-resolution methods of diagnosing 22q11.2DS have made it possible to define breakpoints and identify the genes involved. Molecular diagnosis also allows for the delineation of other syndromes or diseases that may present like 22q11.2DS. Schizophrenia has been found to be associated with CNVs and common polygenic risk factors. It is also important to determine the relationship between genotypic variation, behavioural and physical features of 22q11.2DS. More information regarding adult outcomes in 22q11.2DS is needed to assist in proper genetic counselling and improve care and patient management. The condition also serves as a model to understand how genetics and environmental factors can impact the phenotype. Variations in clinical and genetic presentation mean that each patient may require unique management with approaches that are a well-coordinated multidisciplinary effort. Further studies are always warranted to establish the genetic involvement, neurobiological pathways, and any potential therapeutics that may assist in the treatment and management of the condition.

Acknowledgements

We are grateful to the Division of Human Genetics, National Health Laboratory Service and the University of Johannesburg.

Conflict of interest

The authors declare no conflict of interest.

Funding source

No funding was required.

Ethical approval

No ethical approval required.

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