22q11.2 Microdeletion

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Chromosomal 22q11.2 deletion syndrome (22q11.2DS) (ORPHA:567) caused by microdeletion in chromosome 22 is the most common chromosomal microdeletion disorder in humans. Despite the same change on the genome level like in case of monozygotic twins, phenotypes are expressed differently in 22q11.2 deletion individuals. The rest of the genome, as well as epigenome and environmental factors, are not without influence on the variability in phenotypes**.** The penetrance seems to be more genotype-specific than deleted locus-specific. The transcript levels of deleted genes are not usually reduced by 50% as assumed due to haploinsufficiency. 22q11.2DS is often undiagnosed condition, as each patient may have a different set out of 180 possible clinical manifestations. Diverse dysmorphic traits are present in patients from different ethnicities, which makes diagnosis even more difficult. 22q11.2 deletion syndrome serve as an example of genetic syndrome that is not easy to manage at all stages: diagnosis, consulting and dealing with.

Keywords: 22q11.2 microdeletion ; 22q11.2 deletion syndrome ; consequence ; penetrance

1. Introduction

Chromosomal 22q11.2 deletion syndrome is the most common chromosomal microdeletion disorder occurring in approximately 1 in every 1000 fetuses [1][2], affecting 1 in every 4000 individuals [3][4][5][6]. De novo deletion, that is, neither parent has the deletion, is currently identified in 90–95% patients. Microdeletions are approximately 0.7–3 million base pairs in size and result in varied clinical symptoms [7][8][9]. The 22q11.2 region is one of the most structurally complex areas in the human genome mainly due to several large blocks of LCRs (low copy repeats) or segmental duplications [10]. These LCRs are above 96% identical, which is why the locus is susceptible to meiotic errors [11][12][13]. Like in other microdeletion and microduplication syndromes, the 22q11.2 region can be deleted or duplicated [14]. Clinical manifestations of 22q11.2 duplication syndrome (Dup(22)(q11)) can be different even in members of the same family. These include: hypotonia, slow growth, delay in development, intellectual disability, heart defects, and velopharyngeal insufficiency [15][16]. The incidence of Dup(22)(q11) is estimated as being half of that of 22q11.2DS [15]. Theoretically, meiotic errors that lead to duplication and deletion should happen at equal frequencies; however, in early selection during gametogenesis, one is chosen more often than the other. In the case of Dup(22)(q11), many individuals have little or no symptoms, and the duplication may not be identified. This coincides with a general observation that microduplications seem to cause milder or no clinical manifestations compared with reciprocal microdeletion [14]. The penetrance of 22q11.2 microdeletion is high, meaning that almost all individuals with the deletion will have some of symptoms. Clinical presentations of 22q11.2DS can be associated the dysfunction of many organs such as, among others: the heart, palate, brain, immune systems, and endocrine, genitourinary, gastrointestinal systems [17][18][19][20][21][22]. Clinical symptoms are so varied that, in the absence of typical craniofacial traits and other common birth defects, such as those of the heart or palate, a diagnosis may be difficult to make. Some adults are only diagnosed after the birth of a sick child [23]. The genetic mechanism of phenotypic variations of the quantity and intensity of these presentations cannot be explained by deletion size or by 22q11.2 hemizygosity. Apart from multi-gene, a combination of other factors, such as modifications of protein coding and regulatory genes outside the 22q11.2 region as well as the sensitivity of individual genes within the 22q11.2 region to gene dosage and alleles in the counterpart chromosome, may influence the 22q11.2DS phenotype [18]. Even members of the same family with identical genetic alterations are characterised by high phenotypic diversity, variable expression and incomplete penetrance of some of the traits [23][24]. The possible association between the clinical phenotype and the size and location of 22q11.2 deletion may be masked by other genetic and/or epigenetic modifying factors [25]. The correlation between genotype and phenotype is difficult to determine, due to great inter- and intrafamilial clinical diversity, even between mono-oval twins [23][26].

2. Mouse Model of the 22q11.2 Deletion Syndrome

Several mouse models have been developed based on the conserved linkage between human chromosome 22 and mouse chromosome 16 [27][28][29][30]. The most recent imitates 3.0 Mb deletion (Del(3.0 Mb)/) and was generated using the CRISPR/Cas9 system. The deletion was introduced between Pi4ka and Hira genes on mouse chromosome 16. CGH (comparative genomic hybridization) was used to confirm the reduction in genomic copy numbers in this region. Adult male mutants were evaluated with the use of: behavioural tests (prepulse inhibition, fear-conditioning memory, measurements of locomotor activity, visual discrimination learning), circadian behavioural rhythm, and visual-evoked potential. Mice with the deletion (Del(3.0 Mb)/+) were hypoactive—they travelled shorter distances and were less active in their subjective night. This may reflect the tendency of 22q11.2DS patients to tire more quickly. When it comes to social interaction tests, mice with the deletion had encountered difficulties with social recognition of a novel mouse, while the social memory of Del(3.0 Mb)/+ mice was intact. Additionally, Del(3.0 Mb)/+ mice showed a reduction in auditory prepulse inhibition and attenuated cue-dependent fear memory. Del(3.0 Mb)/+ mice displayed a quicker adaptation to experimental jet lag as compared with wild-type mice. This model is the first model with 3.0 Mb deletion and could be very useful for understanding psychiatric disorders in 22q11.2DS [31].

3. 22q11.2DS Phenotype

22q11.2 deletion syndrome affects many organs with different severity and penetrance (Table 1). Palatal anomalies are very common in 22q11.2DS patients. These are mainly: velopharyngeal insufficiency (27–92%), submucous cleft palate (5–16%), cleft palate (9–11%), and bifid uvula (5%) [5]. In terms of immune profile, immunodeficiency is very common. Sixty-seven percent of patients experience impaired T cell production, six percent—an IgA deficit, 23 percent—humoral defects (relevant in reaction to vaccines). The immune system usually normalises itself by the first year of life; however, more infections may occur in adulthood [23][32][33]. Cardiac anomalies in 22q11.2 individuals include: Tetralogy of Fallot (20–45%), an interrupted aortic arch (5–20%), ventriculoseptal defects (10–50%), truncus arteriosus (5–10%) [5][17][34] During the screening of patients with congenital heart disease, 22q11.2DS is detected in half of the cases of interrupted aortic arch, among one third of the patients with truncus arteriosus, and in one-sixth of patients with Tetralogy of Fallot. These studies demonstrate that there is a reasonable amount of cases of 22q11.2 deletion among patients with these conditions [35][36]. Endocrine problems include mainly: hypocalcemia (50%) and growth hormone deficiency (4%). Hypocalcemia is often resolved at a neonatal stage. Calcium deficiency may recur in times of disease and stress. Calcium levels should be monitored yearly. Major findings in renal abnormalities include having a single kidney (12%), multicystic dysplatic kidney 4%, or hydronephrosis 5% [37]. Feeding and swallowing anomalies include: gastroesophageal reflux, esophageal dysmotility, constipation, prolonged tube feedings, and G-tube placement [38][39]. Tortuous retinal vessels (58%) and posterior embryotoxon (69%) are common ophthalmologic abnormalities. Neurological problems include: cerebral atrophy (1%) and cerebral hypoplasia (0.4%). Skeletal abnormalities are not very common. They include cervical spine anomalies (40–50%), vertebral anomalies (19%) and anomalies of lower limbs (15%) [5]. Additionally, there are characteristic dysmorphic features, which are mild and are not visible for non-professionals or can only be noticed when individuals with 22q11.2DS are gathered together. They are the following: elongated face, low-set small dysplastic ears, microstomia, small teeth, congenital tooth or enamel agenesis, almond-shaped eyes, hypertelorism, a prominent long bulbous nose, retro- and micrognathia, a short neck and characteristic arachnodactyly [40]. According to human phenotype ontology database Abnormal facial shape (HP:0001999), Epicanthus (HP:0000286), Bulbous nose (HP:0000414), Wide nasal bridge (HP:0000431), Prominent nasal bridge (HP:0000426), Telecanthus (HP:0000506), Upslanted palpebral fissure (HP:0000582), and Low-set ears (HP:0000369) are very frequent [41]. Psychiatric problems occur mainly in adolescence. About 25% of 22q11.2 individuals have schizophrenia [42][43][44][45]. One per 100 patients with schizophrenia has 22q11.2 deletion [5]. The beneficial effects of omega-3 supplementation on attentional control and in transition to psychosis could support its early use in the 22q11DS population [46]. Pituitary dysmaturation is also present and could be associated with pleiotropic psychopathology and atypical neurodevelopment [47]. Sleep problems and motor coordination problems are also common in young 22q11.2DS patients [48]. Development delays need to be checked at every step of infancy and childhood, as early intervention can help provide support for children with the deletion [49][50]. The most common problems are motor delays and speech difficulty, which can be connected with very frequent conductive hearing impairment (HP:0000405) and muscular hypotonia (HP:0001252) [41][51][52][53][54]. Delays in reaching motor milestones and the emergence of language are common in children with 22q11.2DS. Motor delays may be associated with congenital heart disease and are less severe, while delays in language development are more noticeable and are not associated with any major medical issues [55]. A recent pilot study of motor phenotypes shows that the developmental history of 22q11.2DS children differs from that of their siblings (control). They fail to thrive (42%), are more likely to experience feeding difficulties (84%), and parents have reported on their clumsiness (79%). Only 32% are able to talk by the age of 2, in contrast to 92% of their siblings. Sixty-eight percent stated special educational needs and were using a health care

plan. Children with 22q11.2 deletion syndrome are able to button their clothes at 6.2 years (median) and to do up their laces at 9.75. Upon examination, 95% show evidence of movement disorders and dystonia [51]. The mean IQ of such individuals is about 70, and 22q11.2DS children have problems with mathematics and other skills that require abstract reasoning [56][57][58][59]. Children with 22q11.2 deletion are also withdrawn and struggle in social situations, which makes their school lives harder [60][61][62][63][64]. Parents of children with 22q1.2 deletion syndrome are more stressed compared to parents of typically developing children, so this could also be another burden on the young 22q11.2DS patient [65]. Such children nevertheless usually go through the normal educational system, with the help of their parents and teachers [66]. It is not easy for 22q11.2 to gain employment after graduation; however, about 33% of 22q11.2DS adults were employed in an open market and about 25% in an assisted-employment environment [67]. Professions occupied by 22q11.2 adults include: cooks, farmers, security guards, maintenance staff, office employees, nurses, homemakers, early childhood educators, family therapists [23]. The life expectancy for adults with 22q11.2DS is lower than expected among other members of their families. According to data on 309 adults with 22q11.2DS, the range of deaths is 18.1–68.6 years, with a median age of 46.4 [68].

Table 1. Selected clinical manifestation in patients with chromosome 22q11.2 deletion syndrome [5][23][41].

Clinical Manifestation	Frequency in 22q11.2 DS	Human Phenotype Ontology Database *
Palatal anomalies	**69–100%**	**Cleft palate (HP:0000175), Abnormality of the pharynx (HP:0000600), Platybasia (HP:0002691)**
Learning disabilities	**>95%**	
Speech delay	**79–84%**	
Cardiac anomalies	**49–83%**	**Abnormality of cardiovascular system morphology (HP:0030680), Abnormal aortic arch morphology (HP:0012303), Truncus arteriosus (HP:0001660), Ventricular septal defect (HP:0001629), Abnormal pulmonary valve morphology (HP:0001641), Tetralogy of Fallot (HP:0001636), Atrial septal defect HP:0001631**
Immunodeficiency	**77%**	**Immunodeficiency (HP:0002721), Abnormality of the tonsils (HP:0100765), Hypocalcemia (HP:0002901), Impaired T cell function (HP:0005435)**
Developmental delay in infancy	**75%**	
Ophthalmologic abnormalities	**7–70%**	**Posterior embryotoxon (HP:0000627), Corneal neovascularization (HP:0011496), Ptosis (HP:0000508)**
Endocrine	**60%**	**Hypoplasia of the thymus (HP:0000778), Hypoparathyroidism (HP:0000829)**
Behaviour/psychiatric problems	**9–50%**	
Developmental delay in childhood	**45%**	**Short stature (HP:0004322)**
Renal anomalies	**36–37%**	**Renal hypoplasia (HP:0000089)**
Feeding and Swallowing Problems	**35%**	**Anorectal anomaly (HP:0012732), Constipation (HP:0002019)**
Skeletal abnormalities	**17–19%**	**Arachnodactyly (HP:0001166), Abnormal skull morphology (HP:0000929), Short neck (HP:0000470)**
Neurologic	**8%**	
Dental: Delayed eruption, Enamel hypoplasia	**2.5%**	**Abnormality of the dentition (HP:0000164), Carious teeth (HP:0000670)**

4. 22q11.2DS in Different Populations

22q11.2 deletion syndrome is an underdiagnosed condition. Many patients are diagnosed secondary to CHD (75%). Physical examinations differ between population groups, making the 22q11.2DS diagnosis difficult, especially for individuals of African descent, as they have different craniofacial dysmorphisms compared to the standard recognised anomalies found in Caucasians [69]. Only learning problems and ear anomalies are present to the same extent across ethnicities. To help with diagnosis in countries where laboratory tests are limited or unavailable, researchers have created

a website where all the facial, hand and foot dysmorphy are presented on photographs for different counties [70]. They have also proposed digital facial technology as an alternative tool to molecular testing among mixed populations. This could be really a helpful tool for 22q11.2 deletion syndrome diagnosis.

Data for the 22q11.2 population can be obtained from the Decipher database, which uses Ensembl Resources [71]. According to the Decipher database (214 matching patients for 22q11.2 deletion, 109 46XX, 105 46XY), the origin of the deletion is de novo in 24%, of unknown origin in 48%, maternally inherited in 19%, paternally inherited in 4%, and a result of imbalance arising from balanced parental rearrangement in 5%. The five most common phenotypes are: intellectual disability (81 patients), micrognathia (67), hypocalcemia (64), ventricular septal defect (64), abnormality of the pinna (58). In female patients, the deletion is de novo in 23%, of unknown origin in 50%, maternally inherited in 20%, paternally inherited in 3% and a result of imbalance arising from balanced parental rearrangement in 5%. The five most common phenotypes are: intellectual disability (39), arachnodactyly (35), micrognathia (32), ventricular septal defect (32), abnormality of the pinna (31). In male patients, the deletion is de novo in 26%, of unknown origin in 46%, maternally inherited in 20%, paternally inherited in 3%, and a result of imbalance arising from balanced parental rearrangement in 5%. The five most common phenotypes are: intellectual disability (42), hypocalcemia (37), micrognathia (35), ventricular septal defect (32), delayed speech and language development (28). The prevalence of specific phenotypes appears to be similar in both genders, except for delayed speech and language development, which is three times higher in boys than in girls. However, this is most likely due to the higher occurrence of communication, language, and speech disorders in boys than in girls in the general population and may not be related to the 22q11.2 microdeletion [72].

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