

22q11.2 deletion (DiGeorge) syndrome: a mother's open letter

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Dear E.G., this is an open letter on 22q11.2 deletion syndrome (DiGeorge syndrome). You are the mother of a beautiful 3 year old child. And you are one of the most active members of Aidel22, the Italian Association of 22q deletion syndrome patients and families. We would like to hear your story and learn from you.

But before that, we asked some scholars in the field to help us understand what 22q11.2 deletion syndrome is.

What is 22q11.2 deletion (DiGeorge) for a molecular biologist?

Answer (Prof A. Baldini)

This is a genetic condition associated with a variable clinical picture (phenotype) caused by the loss (deletion) of a DNA segment from one of the 2 copies of chromosome 22. In most cases, the deletion occurs *de novo* (i.e. is present in the patient but not in the parents). In 10-15% of the cases, the deletion is inherited.¹

The deletion is caused by a mechanism known as aberrant homologous recombination between small DNA segments naturally located at the extremities of the region prone to deletion. It is unknown whether or not there are conditions of any kind that can trigger this aberrant recombination event. Investigators hypothesize that this a chance event.²

The deleted DNA carries several genes. The loss of one copy of these genes has clinical consequences (the DiGeorge syndrome or 22q11.2 deletion syndrome). Intense research of the last 10 years has shown that most of the phenotypic manifestations are caused by the loss of one of the genes included in the deletion, named *TBX1*.² Research aimed at the discovery of *TBX1* functions is at the forefront of current efforts to understand how the disease develops and if there are ways to ameliorate or prevent certain clinical symptoms. The *TBX1* gene encodes a transcription factor, i.e. a protein that regulates the expression of other genes. Some of its functions, for example regulation of cell proliferation and differentiation of heart cell progenitors, have already been discovered using mouse models of the disease.

What is 22q11.2 Deletion (DiGeorge) for a paediatrician and expert in clinical genetics?

Answer (Dr. M.C. Digilio)

The syndrome is a genetic condition with a broad, complex and extremely variable spectrum of clinical manifestations. Symptoms can be mildly or severely expressed, and a different phenotypical expression is described also in affected patients from the same family.³

A congenital heart defect is present in 75% of the cases. Additional cardinal features include palatal anomalies (which can be expressed as a complete or partial cleft palate, a submucous cleft palate or velopharyngeal insufficiency), immunological problems (usually due to deficiency of T-cell formation), frequent respiratory infections, and neonatal hypocalcemia. Feeding difficulties can be linked to palatal anatomic and functional anomalies, nasal regurgitation and predisposition to gastroesophageal reflux. True mental retardation is detectable in a small percentage of affected subjects, but delays in motor, linguistic and cognitive domains of variable degree have been reported, as is a typical behavioural phenotype with a withdrawn personality and tendency to anxiety. Nevertheless, none of the clinical features is present in 100% of the cases.

The syndrome is relatively common, since it has been estimated that it occurs in about 1 in 4000 live births.

Early diagnosis is important for the treatment of symptoms and for prevention of clinical problems known to be associated with the syndrome, particularly those developing with time. Once the diagnosis has been established, a careful multispecialistic follow-up should be organized, based on the specific protocol identified for the syndrome, and an individualized clinical and educational program should be offered.⁴ The aim is to ensure the children receive the best care to be able to attain their maximal potential.

What is 22q11.2 deletion syndrome (DiGeorge) for a pediatric cardiologist?

Answer (Prof B. Marino)

The impact of a cardiac problem is very important in children with 22q11.2 deletion, since congenital heart defects affect 75-80% of the patients. The cardiac malformations most frequently diagnosed in patients with 22q deletion are conotruncal defects, including tetralogy of Fallot in 25% of the patients, pulmonary atresia with ventricular septal defect in 25%, subaortic ventricular septal defect in 15%, truncus arteriosus in 9%, and interrupted aortic arch in 8%.⁵ Also asymptomatic aortic arch

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malformations, alone or in association with additional intracardiac anomalies, can be detected.

From the general population of patients with conotruncal heart defects, at least 60-80% of patients with interrupted aortic arch have 22q deletion, 40% of those with pulmonary atresia and ventricular septal defect, 35% of those with truncus arteriosus, and 15% of those with tetralogy of Fallot. Specific additional cardiovascular defects may be present in children with conotruncal malformations and 22q deletion. Most congenital heart defects in 22q11.2 deletion cases are diagnosed in the first days of life, and patients must undergo heart surgery.⁶ Heart malformations can be successfully operated, and 22q deletion does not represent a risk factor for mortality after repair. Specific clinical protocols are used in order to prevent surgical and postoperative morbidity due to extracardiac problems typical of the syndrome, including immunological problems leading to a predisposition to infections, so as upper airways and gastrointestinal malformations causing respiratory and feeding difficulties.

And now, E., tell us about your experience as a mother and as a member of Aidel22

As a mother

When we bring a child into the world we arrogantly think that bad things won't happen to us. We think our child will be just perfect – perfect, at least, according to the standards we have in today's world. My son taught me that perfection is only a point of view, a detail among the variety of possibilities that life

gives us. My son was diagnosed with a congenital heart defect (tetralogy of Fallot) and a scrotal inguinal hernia right after birth. My sister-in-law, who is a paediatrician, suspected a genetically-based conotruncal heart disease and advised us to request the fluorescent *in situ* hybridization test to verify if we were facing 22q deletion syndrome. That diagnosis came when my son was one-month-old and, regardless of my being a medical doctor, I felt lost. I felt my son would be lost, too, and that both his future and mine were doomed.

I am a doctor and I did the only thing I knew to do then: I looked for scientific information and read all the papers I could find to understand what was happening. The course of action when an individual or his/her child is diagnosed with a genetically-determined condition is very complicated. It is of the utmost importance that the diagnosis be communicated by someone who is able to explain what to expect while stirring the least possible anxiety and damping the fear of the unknown and of the unsolvable which come with it. We are not all able – nor ready – to carry such a burden, nonetheless it is necessary to start the process that will lead all of us rare parents to choose the best route and guarantee our rare kids the highest possible quality of life. The meeting with the geneticist was fundamental for me, because then I realized things could have been much worse and also because I was shown the way I could take to face all the problems that could and would come. Show a mother the road she needs to take and she will follow it to the end of the world.

As a member of Aldel22

Aldel22 is not just an association: it is a family. Our President, Giulietta Cafiero, put together a home for us where at once you feel

welcome and supported so that you can start working on what is critical. As soon as you get in, you understand the way to go is long but you realize you won't be going alone anymore. We are a family, a family of parents who share their experience and their life and learn how to *make peace* with the deletion. We are people who saw the strength that drives our children and who strive personally and socially to get the best for them, for the research, for adequate care and for the support of families.

I will never forget the day my son's paediatrician told me to look for the association, to look for more parents in my situation and talk to them. Thanks to his advice I made my first call and since then I haven't felt lost and rare anymore.

I realized that, as a doctor, I had the chance to look for and understand lots of information and to identify and improve care paths that already exist but are not adequately fostered. I decided that the fact that I am a parent and a doctor gives me a double point of view, which is an additional opportunity. When I became a member of the Aldel22 family my point of view widened even more, as I realized I would also pick up and consider – share – everyone's needs and suggestions: I am simply able to see farther.

I met many other parents and together we share the happiness for our kids' progress and the confidence in their future and we support each other in that house of the heart that Giulietta built and that we all live in.

Through Aldel22 I also discovered the world of rare disease associations. In Italy there are more than 600 rare pathologies represented by patient associations. All of them proactively work at a regional, national and European level to improve care paths and social welfare for rare patients, to spread information and to instruct patients and practitioners who deal

with rare diseases at any level. What I am learning and what every rare disease patient's parent should be taught is that there is always an alternative to the anger and the feeling of being lost experienced during the first few months after the diagnosis. The choice of that alternative is a chance that should be granted to each of us.

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