



May 2, 2021

To the Editor, Washington Post:

As the leading family support organization in the United States, board members of the International 22q11.2 Foundation, Inc. (22q.org), founded in 2003, read with great interest the story published on May 1, 2021 in the Washington Post, under the headline, “Doctors said the boy was suffering from teenage psychosis. What he really had was a rare genetic condition.” However, our enthusiasm quickly fell to disbelief as we noted countless inaccuracies throughout the piece, which we strongly believe could harm the individuals we serve, including due to the following:

1. The chromosome 22q11.2 deletion is actually quite common. It is the most common identifiable cause of syndromic palatal anomalies and schizophrenia. It is the 2nd most common cause of congenital heart disease and developmental delay after Down syndrome. In fact, recent studies to establish incidence have identified this chromosomal difference in 1 in 992 pregnancies (Grati, 2015) and 1 in 2148 livebirths (Blagojevic, 2021 in press). This just meets the criteria for a “rare” disorder (under 1 in 2000). One can only imagine the family’s reaction to having this condition referred to as rare, out of this context, as many have struggled with a protracted diagnostic odyssey prior to receiving a unifying diagnosis of 22q11.2 deletion to explain seemingly disparate features. As a result, families have mandated the promotion of early detection and general population awareness.
2. The International 22q11.2 Foundation, Inc. has worked tirelessly with organizations around the world on the “Same Name Campaign” which seeks to move all of the previously described clinical conditions, including possible descriptions in 1671 and 1829 by Stenson and Harrington respectively, under the unifying name of the chromosome **22q11.2 deletion syndrome**. Again, the context is important, together with the importance of using the current name that emphasizes that this is a known **genetic** condition. Historically, the combination of clinical findings now known to most frequently result from a chromosome 22q11.2 deletion included the neonatal co-occurrence of thymic aplasia and hypoparathyroidism, as described by Lobdell in 1959 and most notably by DiGeorge in 1965. Congenital heart disease (CHD) was later added to complete the well-recognized “triad” of DiGeorge syndrome (DGS). Additional, now hallmark features of the chromosome 22q11.2 deletion syndrome (22q11.2DS), including hypernasal speech and dysmorphic facial features, were described in 26 children of Czech origin by Sedlackova in 1955. Thirteen years later, Strong reported an association of right sided aortic arch, learning differences, and a characteristic facial appearance in four members of one family. In 1976, Kinouchi reported dysmorphic facial features in Japanese patients with conotruncal cardiac anomalies and termed the condition conotruncal anomaly face syndrome (CTAF). Two years later, Shprintzen described a familial condition of cleft palate/velopharyngeal incompetence (VPI) leading to hypernasal speech, CHD, learning

differences, and characteristic facial features, naming it velocardiofacial syndrome (VCFS). In 1980, Shimizu reported similarities between patients with CTAF and those with DGS. Shprintzen then reviewed the patients reported to have CTAF in 1981 and suggested they had VCFS. Nine years later, Stevens reported a patient with DGS whose father had cleft palate, immunodeficiency, and facial features consistent with VCFS. Contemporaneously, recognition of congenital heart disease by Takao, as a key feature of DGS, contributed to the theory that a mechanism leading to perturbation of neural crest cell migration, particularly affecting the third and fourth pharyngeal arches, may underlie the embryogenesis of DGS – a principle that continues to this day. Concurrently, throughout the 1980's, in cytogenetic laboratories on both sides of the Atlantic, unbalanced chromosomal translocations involving chromosome 22 in patients with features of DGS were being identified and reported by de la Chapelle in 1981, Kelley in 1982, Greenberg in 1984, Schwanitz and Zerres in 1987, and Dallapiccola in 1989. Thereafter, cytogenetically visible chromosome 22q11.2 deletions were identified in a subset of patients with DGS syndrome but the puzzle remained: what about the outstanding patients with DGS where no chromosome 22q11.2 deletion was visible using standard chromosomal studies? This led to the development of fluorescence *in situ* hybridization (FISH) probes specific to chromosome 22q11.2 by Scambler in 1991 in the UK and Driscoll in 1992 in the US. Utilizing these FISH probes, in 1992 Driscoll reported submicroscopic 22q11.2 deletions in the majority of patients with DGS and VCFS, definitively establishing the 22q11.2 deletion as the most frequent cause of DGS. Moreover, the chromosome 22q11.2 deletions observed in patients with DGS were found to be identical to the deletions seen in patients with VCFS, conclusively elucidating the reason for overlapping features in these two separately described clinical conditions, providing indisputable evidence for a common etiology, and demonstrating that the majority of cases of DGS and VCFS were the same condition. By 1993 reports of overlapping clinical features in patients with DGS and VCFS, such as hypocalcemia and immunodeficiency and comparable findings in older patients with DGS and VCFS, reinforced the mounting evidence that the two diagnoses were indistinguishable. But DGS and VCFS were not alone in this overlap. Soon, patients with CTAF were reported to have 22q11.2 deletions by Burn in 1993 and Matsouka in 1994. Likewise, Giannotti identified 22q11.2 deletions in Italian patients with Cayler cardiofacial syndrome in 1993, broadening the ever-evolving phenotypic spectrum to include asymmetric crying facies. Finally, in 1995, McDonald-McGinn described the association of chromosome 22q11.2 deletions in a subset of patients with features of autosomal dominant Opitz GBBB syndrome, adding wide spaced eyes, cleft lip and palate, significant airway and genitourinary tract anomalies to the catalog of causally related conditions. Consequently, Fryburg, LaCassie and Arriaza reported their own patients with Opitz GBBB syndrome and 22q11.2DS in 1996, supporting the emerging understanding that features associated with 22q11.2DS beyond the classically described DGS and VCFS features, contributed to significant morbidity, and occasionally mortality, in this population. Thus, it became increasingly evident that these seemingly unrelated conditions with overlapping features initially presumed to be independent of one another were most frequently the result of a chromosome 22q11.2 deletion. This included the majority of patients with DGS, VCFS, CTAF, Cayler cardiofacial syndrome, and a subset of patients with Opitz GBBB syndrome. Wholly described by clinicians concentrating on specific areas of expertise, including DGS by an

endocrinologist, VCFS by a speech pathologist, and CTAF by a cardiologist, all prior to the availability of microdeletion studies. In 1997, McDonald-McGinn likened the difficulty of distinguishing these conditions from one another without a definitive laboratory test to a group of myopic veterinarians trying to identify an elephant by each examining a separate part. All were entirely accurate in providing individual descriptions, but none was able to see the big picture. So too was the case of the chromosome 22q11.2 deletion syndrome prior to the introduction of FISH studies by Scambler and Driscoll in the early 1990's. Today, the term DGS is generally reserved for those instances when the etiology of clinical features is not caused by a 22q11.2 deletion. Otherwise, **the broad phenotypic spectrum, with or without features of classic DGS, or any other associated clinical condition, including VCFS, is referred to by the very specific etiologic cytogenetic nomenclature - the chromosome 22q11.2 deletion syndrome - providing a key unifying diagnosis for families, caregivers, payors, and support organizations alike.** Given this complex history, one can only imagine the perpetuation of confusion and lack of awareness which will ensue should families remain unaware of the link between these clinically described conditions. Your publication, concentrating on the term velocardiofacial syndrome, has only served to propagate this misinformation and divide a community that seeks to remain integrated under a single unifying causative umbrella.

3. 22q11.2 deletion syndrome is quintessentially a multisystem disorder. A simple google search would have most certainly led the writer, representing such an esteemed and storied publication as the Washington Post, to the pediatric and adult healthcare guidelines (Bassett 2011; Fung 2014) and Nature Reviews Disease Primer (McDonald-McGinn 2015) - all produced via expert international collaborative efforts and outlining all associated features (with appropriate references), including related psychiatric illness, such as schizophrenia, and stressing that all problems (physical, cognitive and behavioral) are treatable. To state that psychiatric conditions identified in individuals with 22q11.2 deletion syndrome are not the same as in the general population (and therefore treatment strategies are unavailable), not dissimilar to suggesting that the presence of cleft palate or congenital heart disease is different in these same persons as compared with individuals from the general population without a chromosome 22q11.2 deletion simply because an underlying genetic cause has been identified, is at best misleading and at worst dangerous. Should our families decide to forgo proven effective management, based on the information contained in your prose, including for birth defects, medical issues, cognitive deficits and behavioral features, who will be responsible - Dr. Graf, Robert Shprintzen, the Washington Post? We sincerely hope you will consider the potential far-reaching ramifications of this article, including suggesting treatment for psychiatric illness in individuals with chromosome 22q11.2 deletion syndrome using a medication that has been officially trialed in a single individual.

All said, the reporting standard of this article was woefully inadequate. We therefore respectfully request a retraction, erratum or at least an editorial note to address these egregious errors. We also hope that you will kindly respond to this email as we expect to be inundated with questions from around the globe and would like to reassure everyone that the Washington Post is aware and has been responsive to our concerns.

Sincerely,

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