



De Novo San Luis Valley Syndrome-like der(8) Chromosome With a Concomitant dup(8p22) in a Mexican Girl

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Dear Editor,

The rec(8)dup(8q)inv(8)(p23.1q22.1) chromosome associated with San Luis Valley Syndrome (SLVS OMIM 179613) is usually diagnosed in Hispanic patients from the USA Southwest where a founder carrier Spaniard lived around 1800 [1, 2]. This rec(8) has an 8q duplication of 47.90 Mb and an 8p deletion of 11.65 Mb [3, 4]. Excluding two *de novo* rec(8)dup q chromosomes characterized only by G-bands and included in a recent compilation [5], cytogenomic analyses identified nine comparable *de novo* der(8)dup q/del p chromosomes with or without a simultaneous 8p gain. We describe a Mexican mestizo girl with a *de novo* SLVS-like der(8) but with a concomitant 8p22p23.1 duplication.

The patient was the first child of a 27-yr-old mother and a non-consanguineous 37-yr-old father. She was born via vaginal delivery with a normal Apgar score at the 38th week of an uncomplicated pregnancy. Although hypotonia was recorded in early infancy, her developmental milestones were normal until 14 months of age; thereafter, she started language therapy owing to speech delay secondary to mild bilateral hypoacusia. At 4 yr and 10 months,

her weight was 12 kg (Z score of -2.35), length 96 cm (Z score of -3.51), and occipital-frontal circumference 50.5 cm (at the 90th centile). She exhibited mild intellectual disability, some craniofacial dysmorphisms, and deep plantar creases but not cardiac abnormalities. The chromosomes of the patient and her parents were analyzed on G-banded lymphocyte metaphases; in the patient only, FISH assays with 8p (dJ580L5 clone) and 8q (489D14 clone) subtelomeric probes (Cytocell, Cambridge, UK) were performed. Then, under informed parental consent, the trio had their genomic DNA analyzed against the respective Agilent sex-matched controls, using the SurePrint G3 Hmn CGH+ SNP 4×180K microarray according to the manufacturer's protocol v7.3 (Agilent Technologies, Santa Clara, CA, USA). The resulting images were analyzed using the Agilent CytoGenomics software v.2.9.1.3 (assembly GRCh37/hg19).

The patient had (n = 30 metaphases) an 8p+ with a G-banding pattern suggestive of a rec(8)dup(8q)inv(8)(p23q22) (Fig. 1A). FISH revealed that the 8p+ had two 8q subtelomere signals but lacked 8p subtelomeric repeats (Fig. 1B). Parental karyotypes were normal. Microarray analysis confirmed a terminal

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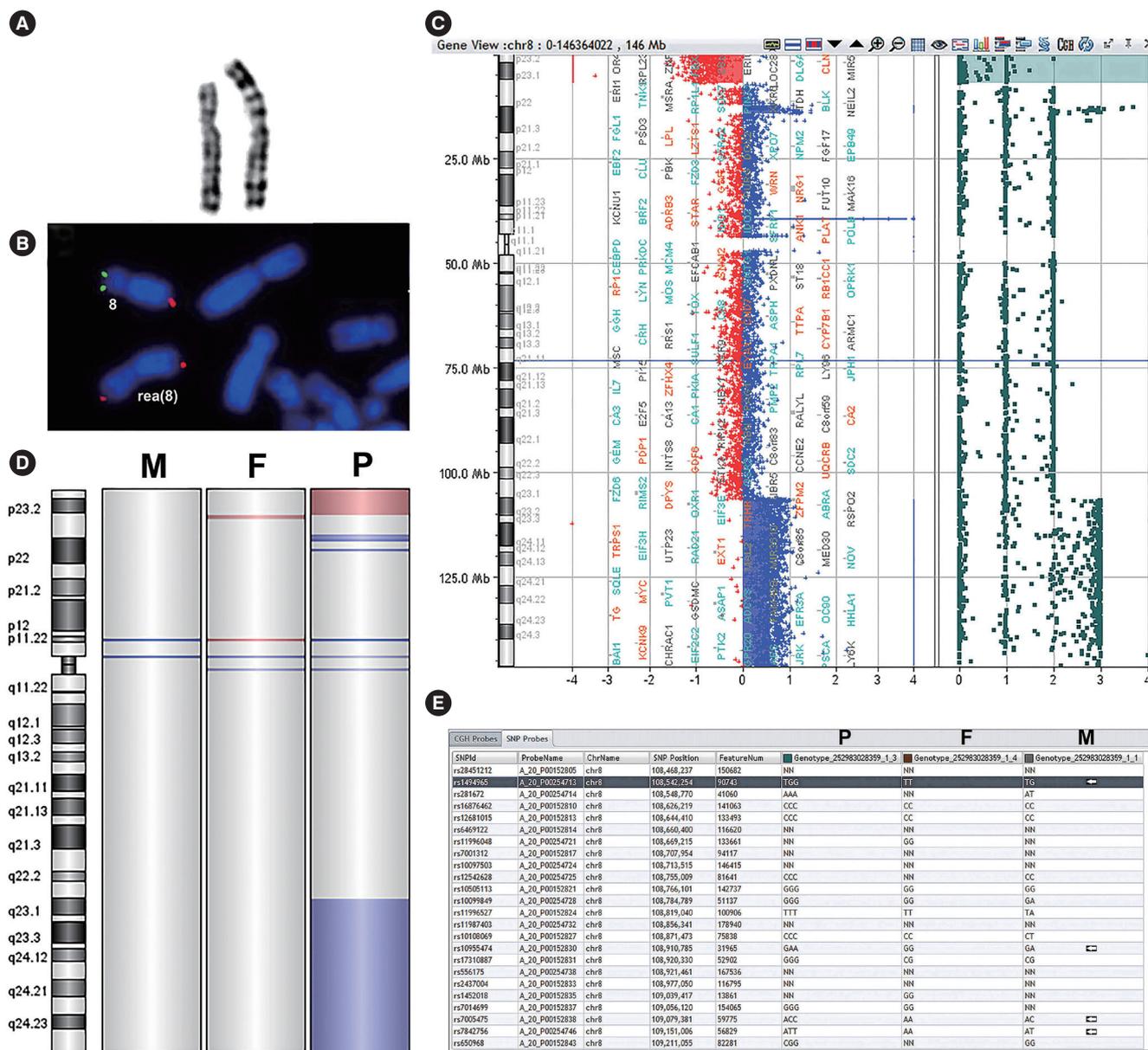


Fig. 1. The patient's der(8) *de novo* chromosome. (A) One G-banded chromosome 8 pair with the der(8) on the right. (B) FISH revealed that the rearranged chromosome had two 8q red subtelomere signals but lacked 8p green subtelomeric repeats. (C) Loss and gain profile analysis indicated by log2 ratio (red/blue plotting) and single nucleotide polymorphism (SNP) panel (green plotting/shading) showing the alleles distribution and zygosity profile after visualization with the Agilent CytoGenomics software v.2.9.1.3; green shading represents the loss of heterozygosity in the deleted segment. (D) Differential aberration analysis from the trio denoting a *de novo* origin of all three imbalances; (E) Informative alleles (arrowed) showing the maternal origin of the recombinant-like chromosome. Note: the origin of the concomitant 8p gain was also maternal (data not shown). Abbreviations: P, patient; M, mother; F, father.

deletion of ~6.7 Mb spanning until 8p23.1, and a duplication of ~39.9 Mb involving 8q23.1qter. There was also a duplication of ~2.1 Mb in 8p23.1p22.3, separated from the deletion by a 5.1-Mb single-copy region (Fig. 1C). Thus, the patient's karyotype was 46,XX,der(8)(qter→q22::p23→qter)dn.ish der(8)(8psubtel-

8qsubtel+++).arr 8p23.3p23.1(191,530-6,911,531)×1,8p23.1p22(12,039,930-14,161,136)×3,8q23.1q24.3(106,371,945-146,274,835)×3. Differential aberration and single nucleotide polymorphism (SNP) profiles revealed that all imbalances were *de novo* and occurred in the maternal homolog (Fig. 1D and E).

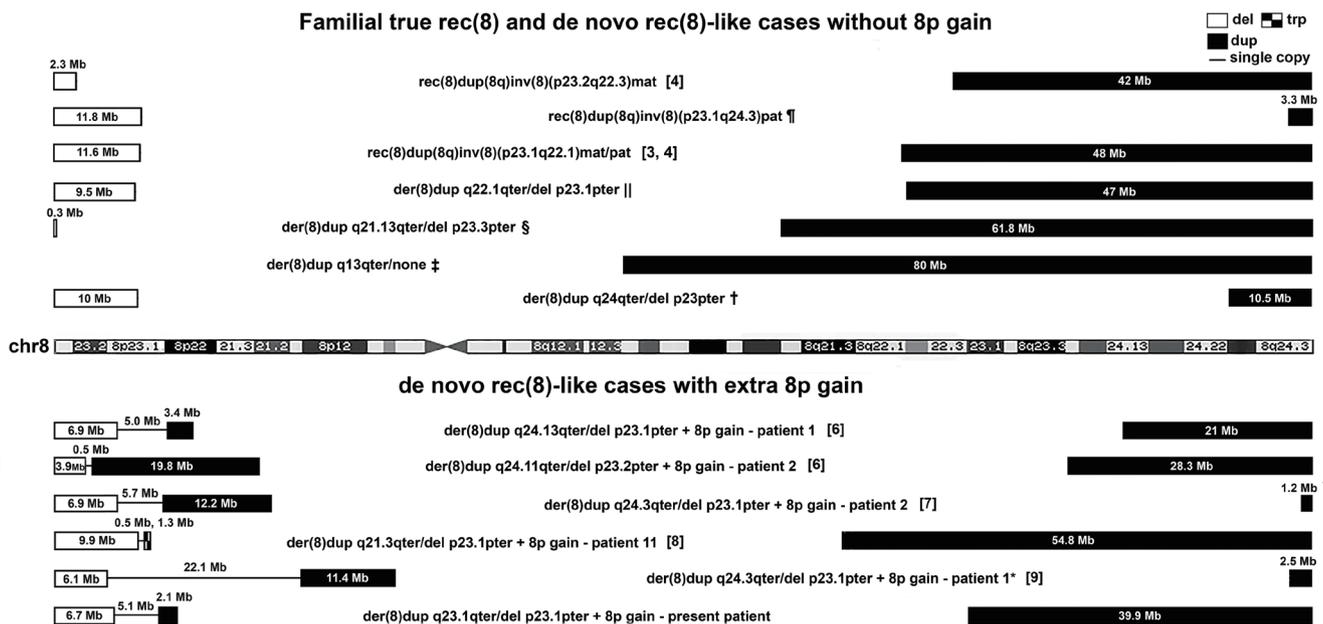


Fig. 2. Scheme denoting Familial true rec(8) and *de novo* rec(8)-like cases without 8p gain characterized by microarray analysis (above the ideogram) as compared with the *de novo* rec(8)-like cases with a concomitant 8p gain (below the ideogram) similarly assessed. The size in megabases (Mb) is placed outside some imbalances only because of space restraints.

*This patient had an extra mosaic r(8)(p11.21q11); †Case presented by Sani *et al*, at the IX Congreso Nazionale, Societa Italiana di Genetica Umana 2006; ‡Case presented by Cohen *et al*, at the Meeting of The American Society of Human Genetics 2007; §Case presented by Hannachi *et al*, at the 4th Congress of the European Academy of Paediatric Societies 2012, abstract in Arch Dis Child 2012;97(Suppl 2): A213; ¶Case presented by Tos *et al*, at the Meeting of The European Society of Human Genetics 2015; ††Case presented by Gruchy *et al*, at the 5-eme Assisses de Genetique Humaine et Medicale 2010, abstract in Med/Sci 2010;(hors serie)26:223-4.

The lack of heart defects in the present patient, whose clinical picture otherwise resembles SLVS [2], is consistent with the fact that her deletion did not extend into the underlying minimum critical interval assigned to a ~3-Mb region (8.85 to 11.79 Mb) in 8p23.1, which contains the GATA-binding protein 4 and other cardiogenic genes [4]. Actually, the size of her 8q duplication and 8p deletion differed from the corresponding imbalances of the SLVS rec(8) chromosome and indeed, from all other comparable recombinants characterized by microarray analyses (Fig. 2). The six instances of a *de novo* der(8)dup q/del p and a concomitant 8p duplication or even triplication (Fig. 2) may be conceived either as recombinants from a hypothetical pericentric inversion with an extra 8p gain or as “inverted duplication deletion” 8p chromosomes capped with a duplicated 8q telomeric segment. Although the present der(8) is similar to inv dup del 8p chromosomes [6] in terms of the size of both the deletion (6.7 vs 8 Mb) and the single-copy region interposed between the deletion and the duplicated region (5.1 vs 4-5 Mb), the latter imbalance was noticeably smaller (2.1 vs ≥ 12 Mb) in our observation.

The observed variation, mainly in the size of the interposed regions and 8p deletions, indicates that a nonallelic homologous

recombination between olfactory receptor (OR) repeats [6] cannot account for these six analogous cases (Fig. 2). Actually, a previous patient’s rearrangement [9] resulted from a mechanism seemingly unrelated to OR clusters. In another subject, the reportedly inverted 8p duplication was not proven [7], and in still another [8], there was an 8p triplication instead of duplication. Otherwise, the lack of an 8p gain in the other four *de novo* der(8)dup q instances assessed by microarray analysis suggests that these chromosomes are true *de novo* recombinant-like chromosomes.

Finally, the common Hispanic ancestry of most SLVS patients [1, 2], two *de novo* recombinant-like der(8)dup q chromosomes [5; present case], and one *de novo* complex 8p rearrangement [10] suggest an underlying Hispanic-specific genome architecture rather than a mere coincidence.

A comparable *de novo* add(9)(q34.3) chromosome entailing gain of ~11.6 Mb at 9p24.3p23, gain of ~793 kb at 9q34.3 and a terminal loss of 1.23 Mb at 9q34.3 has recently been described (Martín-de Saro *et al*, Cytogenet Genome Res 2015;147:124-9). Hence, these complex rearrangements may constitute a distinct subgroup of *de novo* recombinant-like chromosomes.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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