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# Phenotypic Modifications of Patients with Full Chromosome Aneuploidies and Concurrent Suspected or Confirmed Second Diagnoses

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## Abstract

The coexistence of two or more distinct genetic conditions is known to be a rare phenomenon. Full chromosome aneuploidies can be associated with a broad variety of cytogenetic abnormalities or single gene disorders resulting in phenotypic modifications that confuse the diagnostic process. We present six patients with primary aneuploidies and a suspected or confirmed secondary genetic diagnosis or unusual birth defect. Among the cases included, we report the first patients with concurrent Down syndrome in combination with Prader-Willi, Craniofacial Microsomia, and Stickler syndromes. We also describe only the second reported case of a neonate with Down syndrome and Marfan syndrome. In all cases, the unusual clinical presentations lead to further molecular cytogenetic studies as well as single or multi-gene molecular evaluations. We make emphasis on the importance of entertaining the possibility of coexistent diagnoses when the phenotype is not what is expected for aneuploidies rather than attributing the unusual findings to rare or unreported associations of the primary aneuploidy.

### Keywords

turner syndrome; down syndrome; aneuploidy; array CGH

## INTRODUCTION

Aneuploidy is defined as an abnormal number of chromosomes within a cell. It is the leading known cause of congenital birth defects and miscarriages [Nagaoka et al., 2012].

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Recent evidence suggests that aneuploidy is not due to a single causal factor but rather a multi-step process caused by errors at several distinct stages that begins in utero and continues throughout the reproductive lifespan of the woman and is exacerbated by age [Nagaoka et al., 2012].

The coexistence of two or more distinct genetic conditions in a single individual is known to be a rare phenomenon. For example, double aneuploidy has been documented only in a small proportion (< 3%) of spontaneous abortion cases in whom cytogenetic studies were conducted [Diego-Alvarez et al., 2006; Korucuoglu et al., 2008]. Cases of double trisomies can be observed in liveborns (albeit less frequently) with variable resulting phenotypes, suggesting that the lethality of the abnormality depends on which chromosomes are involved [Spencer, 2013].

The literature is also full of examples of concurrent cytogenetic abnormalities, single gene disorders or the combination of both. Some remarkable cases include full chromosome aneuploidies with a second underlying condition that modifies their phenotype and confuses the clinical diagnostic process [Velagaleti et al., 2000; Alkuraya et al., 2005; Delicado et al., 2005]. For instance, the combination of Klinefelter syndrome with Prader-Willi syndrome (PWS) resulted in individuals who have a predominant PWS phenotype but can be at the upper end of normal for height [Butler et al., 1997; Nowaczyk et al., 2004; Schneider et al., 2004]. The coexistence of Jacobsen and Klinefelter syndromes in a patient resulted in predominance of the clinical features of Jacobsen syndrome, but gynecomastia and a eunuchoid body habitus were also present [Matheisel et al., 2000]. A patient with classic features of Cornelia de Lange syndrome, who also had peripheral lymphedema and a webbed neck, was found to have mosaic Turner syndrome [Wierzba et al., 2012].

For patients with a coexistent aneuploidy and a second genetic disorder, the above examples illustrate that the clinical presentations are variable depending on the chromosome involved in the aneuploidy. However, in general, the resulting phenotype appears to be that of a combination effect of the underlying defects. We present six cases of chromosome aneuploidies in whom further genetic testing was conducted to evaluate for a possible second disorder given the presence of rare birth defects and/or a phenotype that did not match that of the chromosomal aneuploidy alone. We emphasize the importance of entertaining the possibility of coexistent diagnoses when the phenotype is not what is expected for aneuploidies, rather than attributing the unusual findings to rare or unreported associations of the primary aneuploidy.

## MATERIALS AND METHODS

Patients were evaluated at the Genetics clinic at the Arkansas Children’s Hospital or Children’s Hospital of Philadelphia from 2000–2013. Approval for the review and reporting of these cases was given by the Institutional Review Board of the University of Arkansas for Medical Sciences.

High-resolution metaphase chromosome preparations were obtained by the standard methods with ethidium bromide. Metaphases were fixed and dropped on to cleaned slides,

stained by GTG banding, and analyzed. When performed, *EDA1*, *COL2A1*, *TSC1*/*TSC2*, and *FBN1* sequencing used genomic DNA. All coding exons were amplified by standard polymerase chain reaction (PCR), sequenced in both forward and reverse directions, and analyzed by a standard fluorescent sequencing protocol. *EDA1* deletion/duplication analysis was done using a targeted array CGH with exon level resolution while *TSC1*/*TSC2* deletion/duplication analysis was performed using Multiplex Ligation-mediated Probe Amplification (MLPA) of genomic DNA. Different chromosomal microarray platforms were used. Patients 1 and 2 underwent analysis using a 180 K Oligo array (Agilent Technologies, Santa Clara, CA). Patients 3 had a CytoscanHD whole genome SNP array (Affymetrix, Santa Clara, CA). Patients 4, 5 and 6 had Illumina (San Diego, CA) SNP arrays (CombiSNP, HumanQuad610 BeadChip or Omni1 Quad BeadChip). Prader Willi methylation analysis was performed in patient 3 by detection of methylation status at the *SNRPN* locus by use of methylation specific PCR.

Exome sequencing was performed on patient 2 using the pro-band's sample and parental specimens as controls. Once genomic DNA was extracted from peripheral blood, exons were captured with Agilent SureSelect kit Target enrichment system (Agilent Technologies, Santa Clara, CA) and sequenced with 2 × 100 bp paired end reads on an Illumina HiSeq 2,000 according to the manufacturer's recommendations (Illumina, San Diego, CA). Initial data processing, base calling, alignments and variant calls were generated by various bioinformatics tools. More than 90% of the bases sequenced are expected to have quality scores of Q20 or higher for 90% coverage at 10× or higher. To search for previously described gene mutations and polymorphisms, the Human Gene Mutation Database (http://www.hgmd.org), the Single Nucleotide Polymorphism database (dbSNP, http://www.ncbi.nlm.nih.gov/projects/SNP/), and 1,000 Genomes Project (http://www.1000genomes.org) were used.

## CLINICAL REPORTS

The patients' clinical features, development, dysmorphic facial features, and genetic testing work-up are summarized in Table I. Descriptions of the cases follow.

### Patient 1

The female proband was born preterm at 35 weeks gestation with a birth weight of 2.410 kg (25th centile adjusted). By one year of age, she was diagnosed with global developmental delays and hypotonia. A microarray revealed two separate large copy number losses of the X chromosome. Furthermore, a <1 copy loss at Xp21.1q21.31 suggested possible mosaicism. These results were followed by high resolution chromosome analysis that confirmed the mosaic karyo type with 58% of the cells containing one normal and one ring X chromosome and having only one X chromosome in 42% of the cells: 46,X,r(X)(p21.1q21.3)[14]/45,X[10].

Over time, given her more significant developmental delay and the development of multiple well-circumscribed and mostly round hypopigmented macules by her second birthday, testing for tuberous sclerosis was ordered (*TSC1*/*TSC2* sequencing and del/dup analysis) with negative results. At two and a half years of age, she was noted to have sparsity of scalp

hair, eyelashes and eyebrows (Fig. 1). No teeth abnormalities were documented, and the patient reportedly had some sweating. A sweat visualization test showed a mosaic distribution of her sweat glands across the back (Fig. 1). *EDA1* gene analysis revealed only the expected mosaic deletion of the entire gene. Other studies include thyroid function, brain MRI scan, echocardiogram, kidney and pelvic ultrasounds, and electroencephalogram, all within normal limits.

## Patient 2

The male patient was born at 38 weeks gestation with a birth weight of 2.52 kg (3rd centile). The family history was unremarkable. At 23 days of age, he was evaluated for congenital anomalies in his extremities and a history of hypospadias with chordee. In addition to dysmorphic facial features, he was noted to have cutaneous bilateral toe syndactyly (2–4 on the right, 2–5 on the left), hammertoes, strikingly angulated halluces, and broad thumbs with ulnar deviation (Fig. 2). An initial skeletal survey at this age showed multiple abnormalities: elevated orbital roofs, diastasis of the cranial sutures, platybasia with J-shaped sella, triradiate shape of the pelvis with flaring of bilateral iliac wings, metadiaphyseal widening of the long bones in bilateral upper and lower extremities, hypoplastic thumbs and great toes, hallux valgus, and dysmorphic phalanges. A renal ultrasound revealed left grade 1 hydronephrosis while an echocardiogram showed a small secundum atrial septal defect. Over the following months the patient had significant dysphagia and feeding problems. An evaluation by otolaryngology documented glossoptosis, possible choanal stenosis, and bilateral mild-moderate conductive hearing loss, and an ophthalmologic assessment revealed bilateral cataracts. The patient was documented to have persistent hypotonia and a brain MRI scan at two years of age showed mega cisterna magna. A cervical spine CT showed wide foramen magnum, incomplete ossification of the anterior and posterior arches of C1, and dysmorphic left C3–C4 facet. Maxillofacial CT at two years of age revealed severe deviation of the nasal septum to the left with severe stenosis of the left nasal cavity, mandibular hypoplasia with loss of the mandibular angle, and dysmorphic maxillary and mandibular teeth. The patient was not found to have craniosynostosis by any of the cranial image modalities at any point.

The patient had a long history of developmental delays. By 17 months of age, the patient was pulling to stand, sitting independently and saying one or two words. By two years of age, he started walking with assistance and waving bye but had no further progress in his speech. By three years of age, he was walking independently, trying to run and putting words together with a limited vocabulary. At the time of his last appointment at age three, his weight was 9.24 kg (1st centile), height was 83cm (1st centile) and head circumference was 47.5 cm (7th centile). A repeat skeletal survey at three and half years revealed other findings suggestive of a skeletal dysplasia such as multiple intrasutural wormian bones, a widely patent anterior fontanelle, cone-shaped epiphyses of the proximal aspect of the second through fifth metacarpals, triphalangeal left thumb and bilateral halluces, accessory middle phalanx of the right third toe, and widening of lower extremity bones metaphyses.

An initial microarray at one month of age revealed a whole chromosome 21 gain consistent with trisomy 21. Other studies performed included *CREBBP* sequencing and del/dup

analysis and 7-dehydrocholesterol level, both normal. Recognizing that his features were unreported in the setting of trisomy 21, whole exome sequencing on him and his parents was ordered and did not reveal pathogenic abnormalities.

### Patient 3

A four year-old Hispanic female presented to genetics clinic with a known diagnosis of Down syndrome. Prenatal history included normal ultrasounds, but decreased fetal movement was noted. She was born at 39 weeks gestation with a birth weight of 2.26 kg (1st centile). Features of Down syndrome were noted and a chromosome analysis revealed 47,XX, + 21. During the following few months she was found to have several cardiac septal defects, severe hypotonia, strabismus, and difficulties sucking which required a gastrostomy tube placement. Her development had been severely delayed, and at the age of four years, she was able to sit unsupported but was unable to walk or talk. On examination, her weight was 13.29 kg (5th centile), length was 91 cm (<3rd centile, −2.83SD), and head circumference was 43.5 cm (<3rd centile, −4SD). She was noted to have typical Down syndrome facies, residual strabismus, and remarkable hypotonia (Fig. 2). Serum TSH, free T4, IGFBP3 and IGF1 levels were all normal. Family history was noncontributory.

A SNP microarray was indicated for developmental delays and growth failure beyond what is typically seen in kids with Down syndrome. The microarray revealed not only the known trisomy 21, but also a 6 Mb deletion at 15q11.2q13.1 within the Prader-Willi/Angelman syndrome region. Methylation analysis followed which revealed only the maternal allele of the *SNRPN* gene and confirmed the diagnosis of Prader-Willi syndrome (PWS).

### Patient 4

The male patient was born at 37 weeks gestation to his then 37-year-old mother by cesarean section because of bradycardia. Family history was unremarkable. His birth weight was 3.23 kg (40th centile). Postnatally he was diagnosed with an atrioventricular septal defect that eventually needed surgical repair. Furthermore, early dysmorphic features led to a karyotype that revealed 47, XY, + 21. He also had early pulmonary hypertension and respiratory difficulties requiring tracheostomy and ventilator support. Other medical problems included hypothyroidism, cryptorchidism, tethered cord, seizures, C1 ring stenosis with no symptoms of instability, right foot equinovarus deformity, and chronic lung disease. During childhood he displayed developmental delay and was diagnosed with autism.

Of interest, the patient also had a history of a left-sided preauricular skin tag that was removed, cleft palate that needed surgical repair, a right-sided epibulbar dermoid, partial fusion of C6–C7, and heterotopic gray matter as diagnosed by brain MRI scan at six years of age. To evaluate for other potential underlying abnormalities, the patient underwent microarray analysis that only found the known trisomy 21. At the time of his most recent evaluation at age 12, his weight was 43.2 kg (46th centile), height was 135.2 cm (<3rd centile) and head circumference was 51.4 cm (5th centile). Besides Down syndrome facial features, he was noted to have an OD limbal dermoid in the inferior temporal quadrant (Fig. 2).

### Patient 5

The newborn female was first suspected to have Down syndrome in the presence of an AV canal defect noted at 20 week gestation. Subsequent karyotype from amniocentesis and post-natal peripheral blood revealed an abnormal 47,XX + 21. She was born at 36 weeks, and at two weeks of age, had a genetics consult because, in addition to Down syndrome, further concerns were raised. There was a family history of a mother and a maternal grandmother with cleft palates, and the infant had micrognathia, midface hypoplasia and hypotelorism. Given the family history and these features, testing for Stickler syndrome was sent and she was found to have a pathogenic *COL2A1* variant in exon 48:c.3535insG, which had been previously seen in other patients with Stickler syndrome. Testing of her mother and grandmother revealed the same mutation. She remained hospitalized in the NICU for two months mainly for breathing issues related to severe laryngomalacia and was also found to have hypothyroidism and moderate bilateral sensorineural hearing loss. She underwent successful repair of the atrioventricular canal defect at 5 months but continued to require 1 L nasal cannula oxygen at all times because of mild hypoxia. An ophthalmology exam at 12 months of age showed only mild myopia. At her last visit at 21 months, she weighed 8.81 kg (6th centile) and was 74.5 cm in length (<3rd centile). On physical exam, she showed stigmata of both Down and Sticker syndromes (family declined pictures).

### Patient 6

A six-day-old full-term infant was born following a pregnancy complicated by maternal history of HSV-1 controlled on Valcyclovir suppressive therapy. She first came to medical attention at 10 hr of life when she had a cyanotic event and an echocardiogram showed severe persistent pulmonary hypertension, a prolapsed and dysplastic tricuspid valve with moderate tricuspid valve regurgitation, a cleft mitral valve, a conoventricular ventricular septal defect, two small mid muscular ventral septal defects, and a patent ductus arteriosus. On examination, she had a weight of 3.040 kg (35th centile), length of 54 cm (greater than 90th centile; 50th centile for 1 month of age) and a head circumference of 34.5 cm (50th centile). On physical exam she was noted to have a weak cry, a third fontanelle, a high anterior hairline, downslanted palpebral fissures, and a flat midface. Tongue thrusting, excess nuchal skin, and striking arachnodactyly were also observed (family declined pictures). Postnatal metaphase cytogenetics confirmed Down syndrome with a karyotype 47, XX, + 21 in all cells. Given the possibility of Marfan syndrome, *FBN1* sequencing showed an IVS47 + 1G>A mutation. This is a previously reported pathogenic splice site mutation affecting an invariant nucleotide in the donor splice site.

At her last visit, she was three-months-old. Follow-up echocardiogram showed aortic dilatation in addition to her other cardiac anomalies. She had persistent pulmonary hypertension, requiring home oxygen use. She developed failure to thrive, with her weight centile dropping to 7th centile from the 35th centile on discharge from the NICU. The failure to thrive was attributed to developing heart failure. She had nystagmus on exam, but formal ophthalmology exam was normal.

## DISCUSSION

We present the clinical findings of a cohort of patients with primary chromosomal aneuploidies in whom unusual dysmorphic features, unreported birth defects, or more severe phenotypes led to further genetic testing with a second underlying condition identified in some cases. Molecular cytogenetic studies were performed in all cases, and further molecular studies, including sequencing of additional genes (and whole exome sequencing in one case), were performed to rule out a second condition given the clinician's suspicion that a coexistent diagnosis was possible. The six cases presented revealed clinical characteristics that deviate from the established description of two chromosomal aneuploidies, some of which have been previously reported. As both Down syndrome and Turner syndrome are common aneuploidies, co-occurrence with a second genetic condition could occasionally be seen, albeit rarely. For perspective, the overall frequencies of each primary chromosomal aneuploidy, the second suspected/known condition, and the combined frequencies expected just by chance are reviewed in Table II.

Patient 1 had mosaic Turner syndrome with ectodermal changes that included sparsity of scalp hair, eyelashes and eyebrows as well as a mosaic distribution of the sweat glands. The patient underwent *EDA1* gene analysis only showing the expected mosaic deletion of the entire gene suggesting that a different molecular mechanism is likely present. Alopecia areata, hypotrichosis, and reduced sweat gland activity has been reported only in a handful of cases with Turner syndrome, and a possible immune related mechanism has been suggested to mediate some of those changes [Tebbe et al., 1993; Rosina et al., 2003; Goldacre and Seminog, 2014].

Patients 2–6 had Down syndrome with significant phenotypic variation from what is expected for this chromosomal condition. Patient two had several phenotypic features suggestive of an acrocephalosyndacytly-like syndrome (bilateral toe syndactyly, shallow orbits with and convex nasal ridge, mandibular hypoplasia, cranial sutures diastasis) and a skeletal dysplasia (platybasia, metadiaphyseal widening of the long bones, multiple wormian bones, cone-shaped epiphyses, triphalangeal left thumb and bilateral halluces, accessory middle phalanx of the right third toe). Patients with Down syndrome are known to have a variety of craniofacial differences, and in very rare occasions, it can be associated with syndactyly or craniosynostosis [Conen et al., 1969; Di Luigi et al., 2011; Starbuck et al., 2013; Macho et al., 2014]. A single case of a concurrent skeletal dysplasia phenotype was previously reported [Ioan et al., 1993]. Our patient's phenotype appeared to be unique but unfortunately no pathogenic mutations were identified for known conditions through whole exome sequencing.

To the best of our knowledge, patients 3, 4, and 5 represent the first reported cases of documented Down syndrome with Prader-Willi, Craniofacial Microsomia, and Stickler syndromes, respectively. For patient 3, although the predominant facial profile and overall phenotype was that of Down syndrome, the concurrent Prader-Willi syndrome greatly contributed to the severity of her hypotonia, developmental delays, and feeding difficulties. In patient 4, the presence of the preauricular skin tag, an epibulbar dermoid, and vertebral anomalies allowed the clinical recognition of craniofacial microsomia but the predominant

phenotype was that of Down syndrome. In addition to typical findings seen in Down syndrome, patient 5 was diagnosed with Stickler syndrome given the positive family history of cleft palate in the setting of micrognathia, midface hypoplasia, and hypotelorism. The patient did have significant breathing difficulties that could have been attributed to the combination of severe laryngomalacia, the underlying atrioventricular canal defect, and the more severe cranial dysmorphology.

Lastly, patient 6 represents the second reported patient to have both Down syndrome and Marfan syndrome in the neonatal setting. In the previous case reported by Eayrs et al., only hypotonia and small ears were suggestive of Down syndrome in a patient that otherwise had more significant evidence of Marfan syndrome. Similar to our patient, that newborn also had large hands and feet with arachnodactyly, pulmonary hypertension, and a dysplastic tricuspid valve with tricuspid valve regurgitation [Eayrs et al., 2013].

While the clinical implications of having two confirmed coexistent genetic conditions like some of the cases here described are not fully known, modifications in surveillance guidelines and monitoring are likely to be needed. Besides the neuro developmental implications, the co-occurrence of Down syndrome and Prader-Willi syndrome is likely to also result in a higher aggregated risk for several other medical issues that are common in both syndromes such as obesity, short stature, sleep abnormalities, ophthalmologic issues, musculoskeletal problems, and hypothyroidism. Meanwhile, the concurrent presence of Down syndrome and Marfan syndrome would require ongoing cardiovascular, ophthalmologic, and musculoskeletal evaluations at a probably more frequent interval than typically recommended for either condition alone. Similarly, for the patient with Down syndrome and Stickler syndrome, additional ophthalmologic and musculoskeletal vigilance is likely to be needed given the possible additive effect of having both conditions concurrently.

In conclusion, we have presented six patients with primary aneuploidies that also had further phenotypic manifestations that in many cases made the immediate clinical recognition of the syndrome challenging. Published clinical reports have identified many individuals with chromosomal aneuploidies who clearly have clinical features that are atypical of the previously described phenotype. Due to the commonality of aneuploidies but the rarity of the combined associations, simply expanding the clinical phenotype of these conditions may not be the most appropriate conclusion. Therefore, it is suitable to consider an additional genetic diagnosis in these patients depending on their specific outlying clinical features and to pursue additional genetic testing as indicated.

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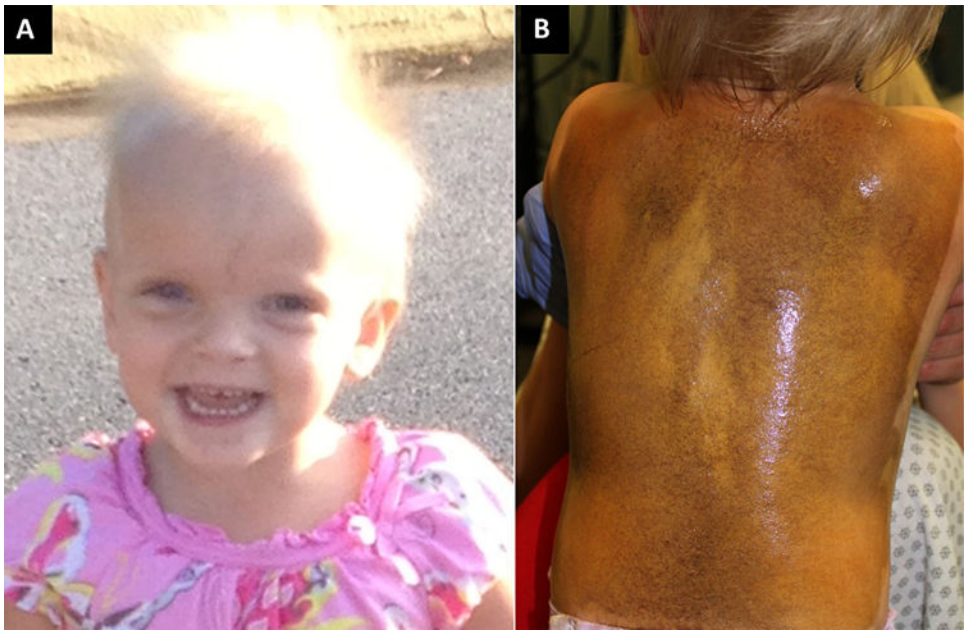


**FIG. 1.**

Patient 1 with Turner syndrome. (A, B). Patient 3 at two years of age. Sparsity of her scalp hair, eyelashes and eyebrows was seen. A sweat visualization test with iodine/starch preparation showed a clear pattern of sweat glands across the back in a mosaic distribution.

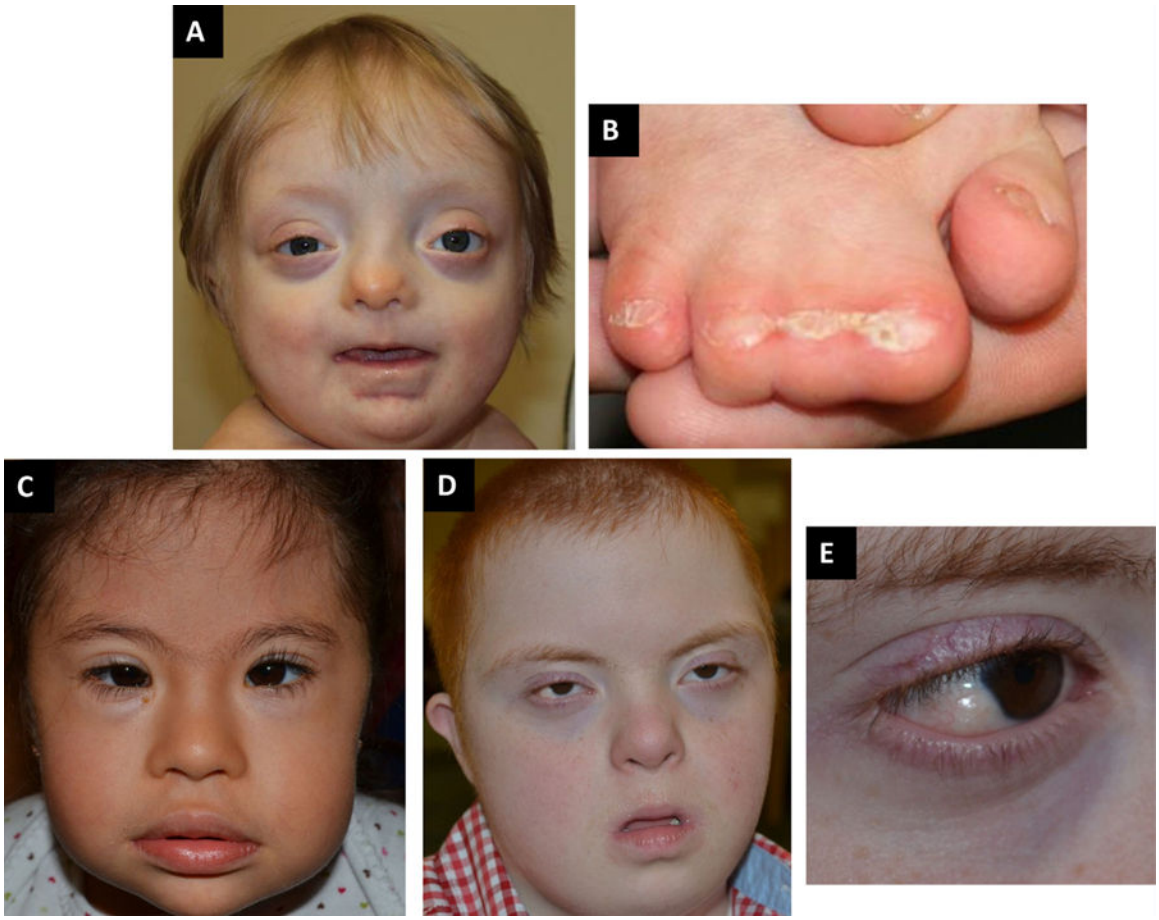


**FIG. 2.**

Patients 2, 3 and 4 with Down syndrome. (A, B). Patient 2 at two years of age. Dysmorphic features include shallow orbits and convex nasal ridge. Note sparse eyebrows and fine scalp hair, cutaneous 2–4 toe syndactyly, and angulated halluces. C. Patient 3 at four years of age. (D, E). Patient 4 at 12 years of age. Note the limbal dermoid in the inferior temporal quadrant of his right eye.

**TABLE I**

Clinical Description of Six Patients with Primary Chromosomal Aneuploidies and a Second Suspected or Confirmed Second Diagnosis

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| **Chromosomal Diagnosis** | **Turner syndrome** | **Down syndrome** | **Down syndrome** | **Down syndrome** | **Down Syndrome** | **Down Syndrome** |
| Age (years) | 2.5 years | 2 years | 4 years | 12 years | 1.8 years | 6 days |
| Development | Moderate global delay | Moderate global delay | Severe global delay | Moderate global delay | Moderate global delay | – |
| Other features outside expected primary chromosomal diagnosis | Hypopigmented macules, ectodermal changes | Multiple skeletal anomalies, toe syndactyly, mandibular hypoplasia, choanal stenosis, oligodontia, peg-shaped incisors, sparse hair | Persistent severe hypotonia, growth deficiency | Gray matter heterotopias, ocular dermoid, cleft palate, C6-C2 partial fusion | Positive family history of cleft palate, infantile myopia | Arachnodactyly, mitral valve cleft, tricuspid valve dysplasia, aortic dilatation |
| Dysmorphic Facial Features | None reported | Shallow orbits, proptosis, convex nasal ridge, Down syndrome facies | Down syndrome facies | Down syndrome facies | Down syndrome facies, midface hypoplasia, hypotelorism, micrognathia | Down syndrome facies |
| Microarray results | arr[hg19] Xp22.3p21.1 (0–34,974,003) ×1,Xp21.1q21.31 (34,924,162–88,536,964) ×1~2,Xq21.31q28 (88,536,966–155,220,560) ×1 | arr[hg19][a] 21q11.2q22.3 (15,446,711–48,073,143) ×3 | arr [hg19] 15q11.2q13.1 (22,220,421–28,823,222) ×1,21pterqter (15,006,452–48,092,322) ×3 | arr[hg19] 21q11.2q22.3 (14,368,320–48,100,155) ×3 | arr[hg19][*] 21q11.2q22.3 (14,402,064–48,094,803) ×3 | arr[hg19]21q11.2q22.3 (14,338,286–48,112,896) ×3 |
| Additional Molecular Testing | TSC1/TSC2, EDA1 | CREBBP, whole exome sequencing | Prader-Willi syndrome Methylation | – | COL2A1 | FBN1 |
| Second Diagnosis suspected | Ectodermal Dysplasia | Skeletal dysplasia, syndactyly, ectodermal Dysplasia | | | | |
| Second Diagnosis confirmed | | | Prader-Willi syndrome | Craniofacial Microsomia | Stickler syndrome (c.3535insG) | Marfan syndrome (IVS42 + 1G>A) |

[a]Converted from hg18.

**TABLE II**

Overall Frequencies of Each Primary Chromosomal Aneuploidy, the Second Suspected/Known Condition or Birth Defect, and the Combined Frequencies Expected Just by Chance

| | Chromosomal aneuploidy | Estimated frequency in live births | Suspected/confirmed second condition | Estimated Frequency in live births/a priori risk | Highest expected combined frequency just by chance |
|---|---|---|---|---|---|
| Patient 1 | Turner syndrome | 1/15,000[a] Jacobs et al. [1997] | Ectodermal dysplasia | 1/5,000–1/10,000[b] Wright et al. [1993] | 1/75,000,000 |
| Patient 2 | Down syndrome | 1/691Parker et al. [2010] | Skeletal dysplasia | 1/5000Krakow and Rimoin [2010] | 1/3,455,000 |
| Patient 3 | Down syndrome | 1/691Parker et al. [2010] | Prader Willi syndrome | 1/15,000–1/25,000 McCandless and Committee on [2011] | 1/10,365,000 |
| Patient 4 | Down syndrome | 1/691Parker et al. [2010] | Craniofacial Microsomia | 1/5600–1/26550 Heike et al.[1993] | 1/3,869,600 |
| Patient 5 | Down syndrome | 1/691Parker et al. [2010] | Stickler syndrome | 1/2 | 1/1382 |
| Patient 6 | Down syndrome | 1/691Parker et al. [2010] | Marfan syndrome | 1/5,000Judge and Dietz [2005] | 1/3,455,000 |

[a]Assuming an overall frequency of 1/2500 of Turner syndrome and 16% relative frequency of 45,X/46,X,r(X).

[b]Frequency for hypohidrotic ectodermal dysplasia.