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Eyebrow anomalies as a diagnostic sign of genomic disorders

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Microdeletions and microduplications in the human genome, termed genomic disorders, contribute to a high proportion of human multisystemic neurodevelopmental diseases and are detected by array-based comparative genomic hybridization (aCGH). In general, most genomic disorders are associated with craniofacial and skeletal features and behavioural abnormalities, in addition to learning disability and developmental delay (LD/DD). Specifically, recognition of a characteristic 'facial gestalt' has been the key to distinguish one genomic disorder from the other. Here, we report our experience concerning the relevance of abnormal eyebrow pattern as a diagnostic indicator of specific genomic disorders.

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Clinical diagnosis of syndromes associated with congenital malformations and/or craniofacial dysmorphisms can be made by 'at glance' recognition of a specific pattern of anomalies or by an analytic search of subtle features. We have previously underlined the importance of hair distribution and microscopic morphology in the diagnosis of metabolic and malformation syndromes (1). Microdeletions and microduplications in the human genome, termed genomic disorders, contribute to a high proportion of human multisystemic neurodevelopmental diseases and are detected by array-based comparative genomic hybridization (aCGH) (2). In general, most genomic disorders are associated with craniofacial and skeletal features and behavioural abnormalities, in addition to learning disability and developmental delay (LD/DD). Specifically, recognition of a characteristic 'facial gestalt' has been the key to distinguish one genomic disorder from the other, for example, 'elfin-like' features in Williams' syndrome and 'Kabuki make-up' like features in Niikawa–Kuroki syndrome. Here, we report our experience concerning the relevance of abnormal eyebrow pattern as a diagnostic indicator of specific genomic disorders.

Eyebrow anomalies a diagnostic sign

Distribution of the frontal hairline and eyebrow pattern are determined in the embryo by the inhibition of hair growth produced by the developing eyes (3). Clinical evidence for this developmental pattern is the abnormal frontal hairline and aberrant eyebrows observed in several 'midline syndromes' associated with ocular hypertelorism or hypotelorism. Hypertelorism (widely spaced eyes) or hypotelorism (closely spaced eyes) is typical of cases with genomic disorders presenting with craniofacial features. An anomalous developmental pattern of the periorbital region results not only in abnormal positioning of the eyes but also disturbs the layout of the eyebrows. For example, in Fraser syndrome, an abnormal eyebrow pattern is often related to cryptophthalmos or 'hidden eyes', causing dysregulated growth of facial hair and eyebrows. A good review of the eyebrow morphology is available in a recent publication (4). We have made striking observations that a characteristic eyebrow pattern can represent a diagnostic sign for a number of genomic disorders, although some of the eyebrows configuration we describe can be occasionally found in normal individuals or in other malformation syndromes.

Chromosome 1p36.33 microdeletion is a relatively common genomic disorder associated with intractable seizures, LD/DD and by a recognizable facial gestalt including deep-set eyes and horizontal eyebrows extending straight from medial to the lateral side (5) (Fig. 1a). Microdeletion of chr2q21–23, including the *ZEB2* gene, causes the Mowat–Wilson phenotype characterized by a syndromic form of Hirschsprung disease associated with a peculiar facial dysmorphism and eyebrow pattern (6). The patients with this syndrome have a unique eyebrow pattern characterized by medial flaring and sparseness in the lateral portion that becomes more prominent with age (Fig. 1b). A 1-Mbp deletion on chr3q26.3–q27 that includes the *SOX2* gene was reported in a patient with anophthalmia/microphthalmia, DD and failure to thrive (7). Absence of normal eye development is reflected by the presence of sparse and broad-based eyebrows (Fig. 1c). We also identified a novel 1.4-Mbp chr7p15.3 duplication in a 13-month-old female, with a neonatal tentative diagnosis of Noonan syndrome. This clinical suspicion was made at birth on the basis of intrauterine echographic detection of pulmonary valve stenosis associated with septal hypertrophy, early neonatal growth retardation, Noonan-like facial features, and a short neck. A subsequent molecular analysis of the *RAS-MAPK* pathway genes was negative. A further clinical follow-up documented distinctive bitemporal narrowing, puffy cheeks and a unique eyebrow anomaly with sparseness of the lateral aspect, giving an impression of an 'interruption' of the eyebrow at the middle of the supraorbital ridge (Fig. 1d). Clinical signs of chr9q34.3 terminal deletion are hypothesized to be related to the haploinsufficiency of the *EHMT1* gene mapping within the deleted region (8). The phenotype is characterized by LD/DD, hypotonia, seizures and distinctive facial dysmorphisms consisting of hypertelorism, epicanthal folds, depressed nasal bridge, broad/bifid nasal tip, open mouth with cupid-bowed upper lip and downturned corners. The eyebrows are arched in the midportion with synophrys (Fig. 1e). A 10-Mbp chr10p11.22–p12.31 deletion, not previously described, was the genomic rearrangement observed in a patient with LD/DD, intractable seizures, cerebellar vermis agenesis, bilateral enophthalmia and microphthalmia, pulmonic stenosis, adducted thumbs. In this case, a medially sparse but laterally wide eyebrow characterized the facial phenotype (Fig. 1f). Duplication of chr10q22.3–23.2 is a rare chromosomal imbalance, associated with microcephaly, prominent supraorbital ridge, deep-set eyes, square chin and bow-shaped mouth (9). Eyebrows in a patient with this microduplication are laterally broad but exhibit medial flaring (Fig. 1g). Smith–Magenis syndrome is a well-known microdeletion syndrome caused by a chr17p11.2 microdeletion characterized by LD/DD, self-injurious behaviours, severe sleep disturbances and a facial dysmorphism consisting of a broad nasal bridge, midface hypoplasia, prominent supraorbital ridge, and prognathism. The eyebrows are laterally extended with synophrys (or unibrow) (10) (Fig. 1h). A 470-kbp chr17q21.31 microdeletion, recently emerging as a phenotypically recognizable genomic disorder characterized by mild to severe LD/DD, deep-set eyes, wide nasal bridge and bulbous tip of the nose (11), was identified in a 4-year-old boy. His eyebrows were broad, arched and they extended beyond the lateral orbital wall (Fig. 1i). A previously undescribed 9-Mbp chr19q13.33 duplication, resulting from a (4:19) balanced paternal translocation one, was found in an 18-year-old boy presenting with LD. Typical facial features include hypertelorism, long and down-slanting palpebral fissures, wide nasal bridge, bulbous nose, long philtrum and thick lower lip. The eyebrows are high and wide set, with a downward slant parallel to that of the palpebral fissures (Fig. 1j). A 500-kbp *de novo* microduplication chr22q11.23 was detected in a 3-month-old girl referred for severe hypotonia, associated with microcephaly, intractable seizures, ophthalmoplegia. Dysmorphic

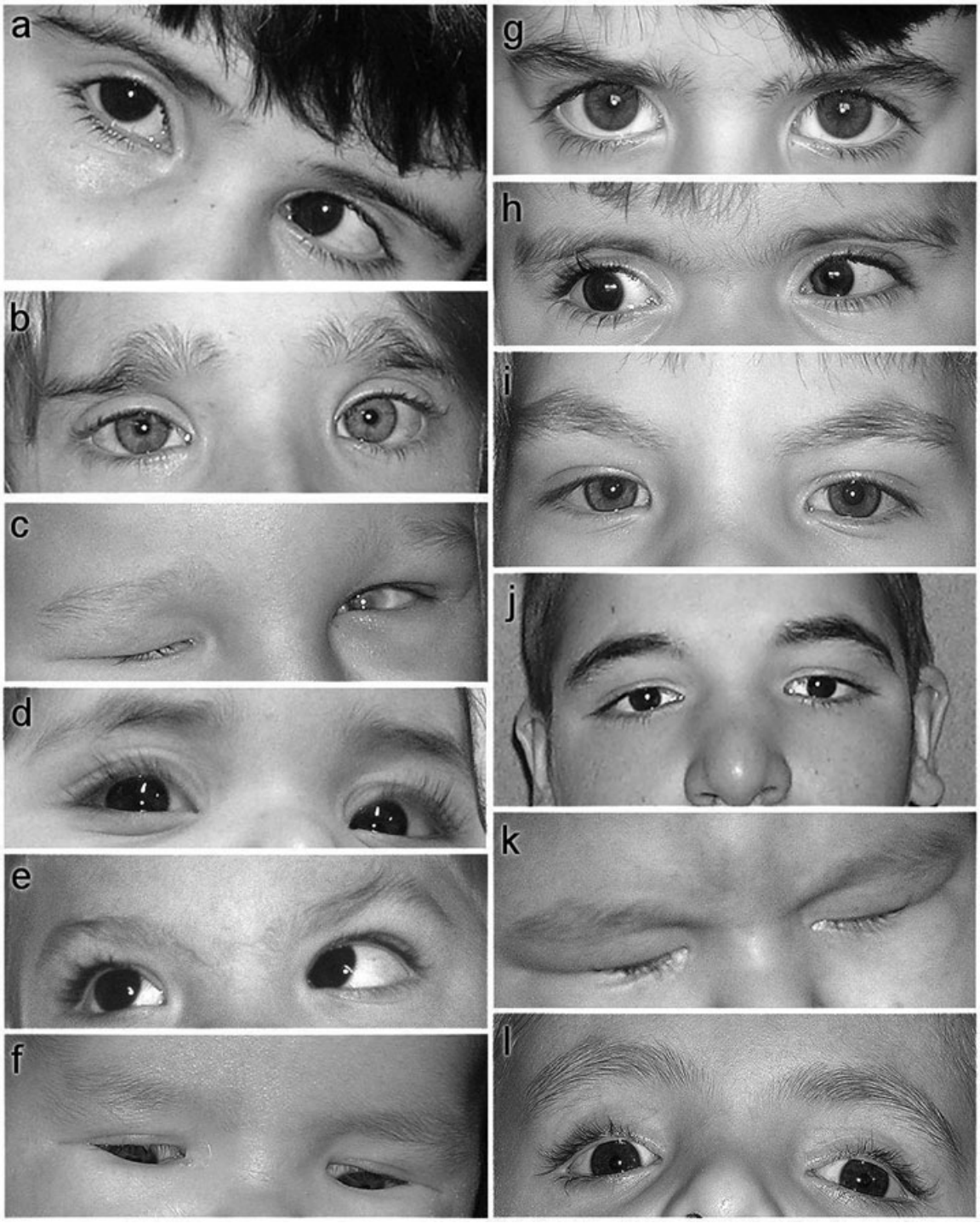

Fig. 1. Eyebrow anomalies detected in patients with genomic anomalies. (**a**) Chr1p36.33 microdeletion syndrome: deep-set eyes and horizontal eyebrows extending straight from the medial to the lateral side. (**b**) Chr2q21–23 microdeletion, Mowat–Wilson syndrome: pathognomonic eyebrows pattern characterized by medial flaring and sparseness in the lateral portion. (**c**) Chr3q26.3–q27 microdeletion: anophthalmia/microphthalmia with sparse and broad-based eyebrows. (**d**) Chr7p15.3 duplication: extreme sparseness of the lateral portion of the eyebrows. (**e**) Chr9q34.3 terminal deletion: arched eyebrows and synophrys. (**f**) Chr10p11.22–p12.31 deletion: bilateral enophthalmia/microphthalmia, medially sparse but laterally wide eyebrows. (**g**) Chr10q22.3–23.2 duplication: prominent supraorbital ridge, deep-set eyes, laterally broad with medial flaring eyebrows. (**h**) Chr17p11.2 microdeletion, Smith–Magenis syndrome: prominent supraorbital ridge, laterally extended eyebrows, thick and bushy in the lateral portions, synophrys. (**i**) Chr17q21.31 microdeletion syndrome: deep-set eyes, broad and arched eyebrows. (**j**) Chr19q13.33 duplication: hypertelorism, long and down-slanting palpebral fissures, with high and wide set eyebrows, with a downward slant parallel to that of the palpebral fissures. (**k**) Chr22q11 microduplication: thin eyebrows with synophrys, broad-based and sparse in the lateral portions. (**l**) Complex genomic rearrangement chr12p12.1–p12.2 deletion/chr16q23.3 duplication: hypertelorism, thick eyebrows.

features consisted of a bulbous nose, thin upper lip, cupid-bowed mouth, microstomia, micrognathia and prominent cheeks. The eyebrows displayed a peculiar pattern, being thin with synophrys medially but broad-based and sparse in the lateral portions (Fig. 1k). A complex genomic rearrangement consisting of chr12p12.1–p12.2 deletion and chr16q23.3 duplication was found in a 2-year-old boy with DD with an initial diagnosis of acrocallosal syndrome. The phenotype was characterized by multiple malformations including a Morgagni-type diaphragmatic hernia, corpus callosum agenesis, spatulated thumbs and halluces. His facial dysmorphism consisted of hypertelorism, downward slant of the palpebral fissures and widening of the middle and lateral portions of the eyebrows (Fig. 1l) The eyebrow pattern contributes greatly to the clinical recognition of the facial phenotype in a large number of malformation syndromes.

Widespread use of aCGH has allowed to define subtle genomic phenotypes recognizable either by a synthetic approach ('gestaltic' diagnosis) or by an analytic (or anthropometric) evaluation of the facial dysmorphisms. We suggest that eyebrow abnormalities are a useful indicator of a chromosomal phenotype in patients with syndromic LD/DD (12). As a number of our patients have previously undescribed very rare chromosomal rearrangements, obviously more cases are needed to confirm a valid association between specific chromosomal anomalies and specific eyebrow pattern.

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