Journal of Genetic Syndromes & Gene Therapy
ISSN: 2157-7412

Melloni et al., J Genet Syndr Gene Ther 2013, 4:10
DOI: 10.4172/2157-7412.1000190

Case Report Open Access

Autosomal Dominant Diseases are too Often Overlooked in the Parents of Affected Children: Report of Six Cases

Giulia Melloni, Maria Francesca Bedeschi, Claudia Cesaretti, Donatella Milani, Luisa Ronzoni, Barbara Gentilin, Vera Bianchi, Federica Natacci and Faustina Lalatta*

Fondazione IRCCS Cà Grande Ospedale Maggiore Policlinico Milano, Italy

Abstract

Clinical genetics is the discipline which deals with hereditary diseases and implies a strong diagnostic approach without which all information conveyed by the counselling process has insecure foundation and the estimation of recurrence risk within the family may be misinterpreted.

The ideal time for having a genetic counselling is before pregnancy. In this case the subsequent genetic evaluation and counselling may lead to the definition of a reproductive risk and thus to an early, even prenatal diagnosis in the offspring. However in some cases genetic conditions are under-recognized in the adult age and people are not referred to genetic services. This happens because of a variety of reasons both related to the health professionals (non-habit to the pre-conceptional genetic counselling, lack of attention/information on genetic themes, diagnostic difficulties related to the variability of gene expression, incomplete penetrance and late onset conditions) and to the patient's psychological status, for example denial mechanisms.

Six cases are presented in which a correct diagnosis in one parent was reached after the identification of a rare disease in the child with severe psychological and social consequences.

Obviously the lack of the correct diagnosis in the parent implied that he/she was not only uninformed about the presence of the increased reproductive risk, but also unaware of the clinical variability of the condition. Anger and frustration was present in all affected parents asking why their family doctors never suspected the condition which, afterwards, seemed quite obvious. Legal actions were started in two out of six cases.

Establishing the correct diagnosis, or at least the suspicion of a genetic disease, is therefore a priority that may be not considered an exclusive responsibility of the geneticist, but ideally involves other medical figures, for example primary care physician, pediatricians or other medical specialists who see a patient with a condition.

Keywords: Clinical genetic diagnosis; Rare diseases; Recurrence risk; Autosomal dominant; Precoceptional counselling; Clinical variability

Introduction

Genetic counselling-as defined by Harper [1] is "the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and of the ways in which this may be prevented, avoided or ameliorated". This process implies a strong diagnostic approach without which all information has an insecure basis and the estimation of risk may be wrong or misinterpreted.

Establishing the diagnosis, or even the suspicion of a genetic disease, isn't an exclusive responsibility of the clinical geneticist, but involves other medical professionals, especially the primary care physician. In the presence of clinical signs suggestive of a genetic condition a patient can be referred to a genetic service for a definitive diagnosis, counselling and follow up. Obviously, the ideal time for genetic counselling is before pregnancy in order to evaluate the reproductive risk and to develop an early, even prenatal, treatment plan in the offspring.

However, in some cases the genetic conditions are under-recognized because the same genetic condition had remained undiagnosed in one of the parents.

This happens because of a variety of reasons both related to the health professionals including lack of training in pre-conceptional genetic counselling; lack of attention to or information about genetic diseases; diagnostic difficulties related to the variability of gene expression, diseases with incomplete penetrance or late onset; and/or the patient's psychological status such as being in denial.

Obviously the lack of a correct diagnosis in a person with a genetic condition implies that he/she will not be informed about the presence of a reproductive risk with the increased likelihood of creating great difficulties for the person, the couple and their relatives.

We report here six representative cases to illustrate the consequences of the lack of an appropriate diagnostic process before conception. All of these families have been referred to our Unit during pregnancy or after birth of the affected child and, in all cases but one the clinical diagnosis has been validated by a molecular analysis.

Case 1

At the 26th week of gestation of the first pregnancy of a non consanguineous couple multiple foetal rhabdomyomas were detected by ultrasound (Figure 1). The couple was counselled about the possible association of foetal multiple rhabdomyomas with tuberous sclerosis

***Corresponding author:** Faustina Lalatta, Medical Genetics Unit, Fondazione IRCCS Cà Grande Ospedale Maggiore Policlinico Milano, Via F. Sforza 35, 20122 Milano, Italy, Tel: +390255032941; E-mail: faustina.lalatta@policlinico.mi.it

Received August 22, 2013; **Accepted** October 28, 2013; **Published** November 10, 2013

Citation: Melloni G, Bedeschi MF, Cesaretti C, Milani D, Ronzoni L, et al. (2013) Autosomal Dominant Diseases are too Often Overlooked in the Parents of Affected Children: Report of Six Cases. J Genet Syndr Gene Ther 4: 190. doi:10.4172/2157-7412.1000190

complex (TSC) [2], a multisystem genetic disorder with an extreme interpersonal variability that carries an increased risk of developing CNS tumors and neurological impairment [3]. An examination of the mother by the clinical geneticist revealed the presence of facial angiofibromas and periungual fibromas (Figure 2). The same clinical features were noted in her sister and in her father. The presence of facial angiofibromas and periungual fibromas was sufficient to diagnose TSC in the mother and thus in the foetus, allowing for the appropriate counselling regarding fetal prognosis. The fetus underwent NMR at 32 weeks to look for cortical tuberous and to evaluate the risk of neonatal epilepsy. The child was born at a tertiary Centre so as to reduce neurological and cardiological risks. A recurrence risk of 50% for subsequent pregnancies as well as reproductive options were presented and discussed with the parents after identification of the familial mutation.

Case 2

This non consanguineous couple was referred to our Service because cleft palate had been diagnosed in their first child. Additional features were noted including microretrognathia, glossoptosis and left inguinal hernia, which had a spontaneous resolution. Echocardiography detected a minimum left-right shunt at the atrial septum level, that underwent spontaneous closure before the age of 9 months. In the neonatal period cerebral and abdominal ultrasound, ophthalmological evaluation, BAER and otoemissions, were performed without evidence of any additional signs. Growth parameters and psychomotor development were normal at the age of 6 (Figure 3).

Karyotype analysis revealed a normal female karyotype. In addition because of the presence of cleft palate and a minimal heart structural defect a FISH analysis for the 22q11.2 region was performed yieldind a normal result.

The mother's personal and familial history was uninformative. Conversely, the personal history of the father revealed the presence of myopia and cleft palate, surgically corrected at the age of 3 years. Facial dysmorphism at the clinical evaluation of the medical geneticist were quite evident (Figure 4).

The family tree of the child revealed other members of the family with the same characteristics in the the paternal branch: the paternal grandfather of the child had a retinal detachment at the age of 50 and

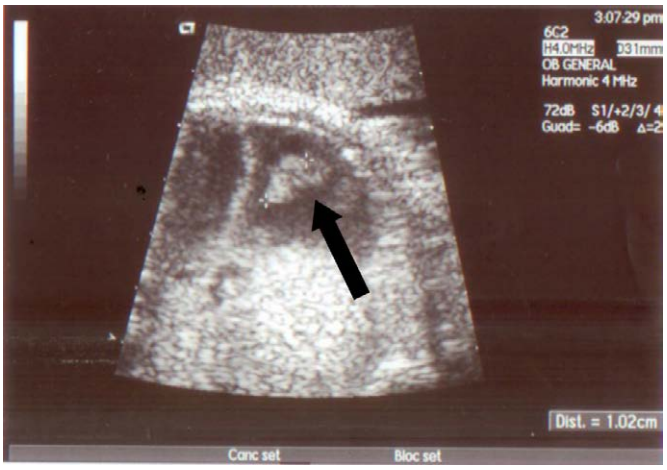

Figure 1: Multiple foetal rhabdomyomas (arrow) detected at 26 week gestation.

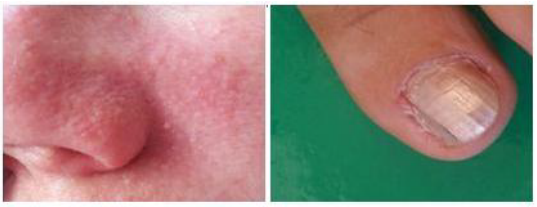

Figure 2: Facial angiofibromas and periungual fibromas of the mother.

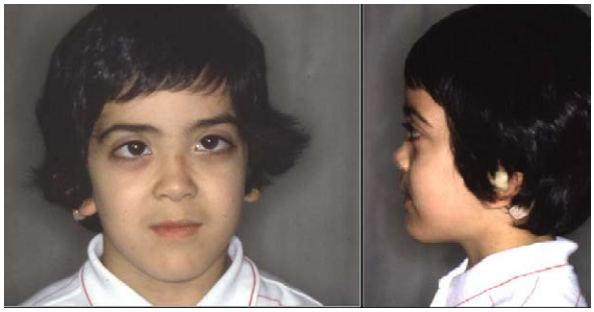

Figure 3: Frontal and lateral view of child with Stickler syndrome at 6 years of age. Hypertelorism, strabismus, malar hypoplasia, long filtrum.

Figure 4: Frontal and lateral view of the proband father affected by Stickler syndrome.

Wagner eye filaments were reported at ophthalmological evaluation; the sister of the paternal grandfather suffered from a retinal detachment and a great degree of myopia, while the father of the paternal grandfather was reported to have a bifid uvula and a lower degree of myopia.

Given the familiarity for cleft palate (the child and the father, bifid uvula in the paternal grandfather and eye problems, myopia and retinal detachment), we suggested the diagnosis of Stickler syndrome in the girl and her father.

Stickler syndrome is a genetic disorder characterized by the association of ocular signs (including myopia and retinal detachment), bone disorders, and sensorineural deafness with an estimated incidence of 1/7500, that is generally transmitted in an autosomal dominant manner. It is genetically heterogeneous [4] and has a high clinical variability [5]. COL2A1 is one of the most common genes implicated in Stickler syndrome and the molecular analysis of the gene detected a heterozygous mutation in the father and in the paternal grandfather confirming the diagnosis.

Case 3

This couple was sent to our clinic for assessment because of the presence of more then six café au lait spots (CALS) in their first son

(CALS Figure 5) and because of a suspicion that they might be due to Neurofibromatosis type 1 (NF1). NF1 is a multisistemic disorder characterized by the presence of cutaneous signs (CALS, freckling and neurofibromas), ocular signs (Lisch nodules and choroidal nodules) and other possible manifestations. During childhood CALS may be the only sign of the condition, but usually at least one additional sign appears before adulthood. However, by 17 months of age, no further signs of NF1 had developed.

The mother's personal and familial histories were uninformative while the father referred to the presence of more than 6 cafè au lait spots on his body (Figure 6). Clinical examination of the father revealed indeed the presence of 7 cafè au lait spots larger than 1.5 cm, an absence of neurofibromas but a macrocephaly (Head Circumference 58 cm, >97th percentile). After evaluation at our Service we obtained an ophthalmologic evaluation with slit lamp examination and fundus photography, which ruled out the presence of any of the signs of neurofibromatosis type 1. The presence of café au lait spots without additional signs of NF1 in the father led us to the diagnostic suspicion of Legius Syndrome rather than NF1. Legius syndrome is a recently described genetic condition characterized by the presence of multiple CALS and macrocephaly, without any other known clinical manifestations. This condition has an autosomal dominant pattern of transmission and is due to mutations in the SPRED1 gene [6,7].

Following the clinical and laboratory evaluations we performed a molecular analysis of the SPRED 1 gene on a peripheral blood sample from the father which identified a mutation known to be related to Legius Syndrome. Thus it was possible to establish a previously undetected diagnosis in the father and consequently in the son.

Case 4

This healthy and non consanguineous couple came to our attention during its second pregnancy. The first pregnancy ended with a stillbirth. The fetus showed bilateral anotia, atresia of the external auditory canal and severe micrognathia. She had a normal female karyotype. These signs did not suggest a specific diagnosis to the pathologist who performed the autopsy. Family history revealed that an aunt of the proband (sister of her mother) died at 1 year because of respiratory tract stenosis. Mother's history revealed that she was born with a preauricular fistula, surgically corrected at the age of 8 years, and that she was affected by conductive hearing loss. These clinical features suggested the diagnosis of Treacher Collins syndrome, previously

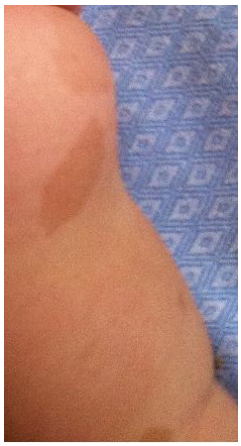

Figure 5: Café au lait spots (CALS) of the proband at 17 months of age.

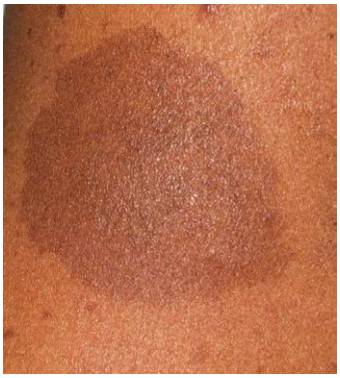

Figure 6: Café au lait spots larger than 1.5 cm, of the father.

unsuspected, with variable expression in the mother and first child (Figure 7 and 8).

Treacher Collins Franceschetti syndrome ("TCS") is a congenital condition with an incidence of 1/50,000 live births, characterized by external ear abnormalities, hypoplasia of the zygomatic bones and mandible associated with several head and neck defects but without abnormalities of the extremities. TCS is generally transmitted with an autosomal dominant pattern of inheritance and in the majority of cases is caused by mutations in TCOF1 gene, although heterogeneity has been demonstrated. The couple was counseled accordingly [8].

A molecular analysis of the TCOF1 gene was performed in the mother but did not reveal any genetic mutation causative of TCFS. Subsequently, the couple gave birth to a second girl. CVS sampling revealed a normal female karyotype. At birth, cleft palate, downslanting eyelids, malar hypoplasia and bilateral small ears (Figure 9) were noted. Cardiac examination showed an interventricular septal defect. Ophthalmologic examination, cerebral and abdominal ultrasound was normal.

Once again Treacher Collins syndrome was suspected. By that time the additional genes (POLR1D and POLR1C) were identified as being associated with TCS. Molecular analysis of these latter genes was performed on the child and on her mother and a heterozygous mutation of POLR1D was detected in both the child and the mother, thus confirming the diagnosis of TCS in the family [9].

Case 5

The first son of a non -consanguineous couple came to our attention following the diagnosis of generalized hypotonia during the first days of life. Vital parameters were normal. Clinical examination revealed: broad and prominent forehead, bulbous nasal tip, anteverted nostrils, long philtrum, micrognathia, low set ears with convoluted antelix, joint hyperlaxity, especially at the limb's extremity (Figure 10a).

A family history revealed that joint hyperlaxity was present in the father too. The father also remembered his own neonatal hypotonia, recurrent infections and joint laxity in infancy, mitral valve prolapse, Inter Atrial Defect, lumbar hernia, myopia and strabismus. In addition it was reported that the paternal grandfather of the baby was affected by joint laxity as well. These individuals were never diagnosed and had suffered for years being limited in their ability to work and complaining of recurrent unexplained pain.

Because of the overlap of some of the clinical signs present in the son and the father, the father underwent a clinical genetic evaluation

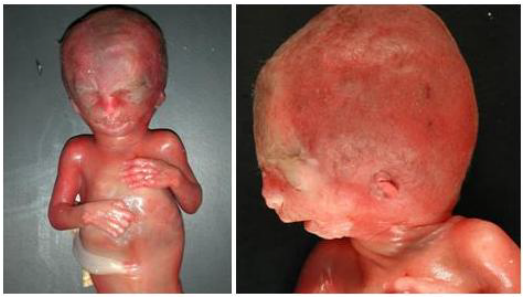

Figure 7: Frontal and lateral view of the fetus showing bilateral anotia, atresia of the external auditory canal and severe micrognathia.

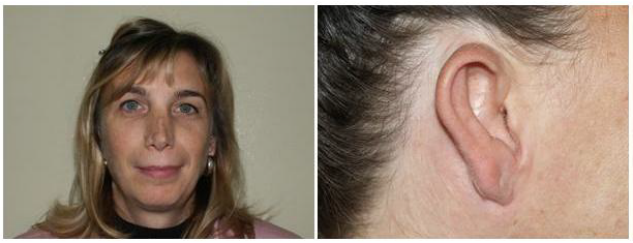

Figure 8: Facial phenotype of proband's mother. Small ears and micrognathia are the only signs besides conductive hearing loss.

Figure 9: Facial phenotype of proband: minor facial anomalies are evident including downslanting eyelids, malar hypoplasia and bilateral small ears.

that revealed macrocephaly, hypertelorism, long face, prominent frontal bossing, thick eyebrows, prominent nasal root and tip high arched palate, micrognathia, smooth and silky skin, especially at the trunk, elastic skin at the knees, hands, elbows, neck and inner arms and small white scars at the chin. Joint laxity especially at the knees, hands, feet and shoulders was noted as well as scoliosis and rotation of the pelvis (Figure 11). The signs suggested the diagnosis of Ehlers-Danlos Syndrome. Ehlers-Danlos syndromes are a group of hereditary connective tissue diseases characterized by joint hyperlaxity, cutaneous hyperelasticity and tissue fragility, that are transmitted in an autosomal dominant manner [10,11]. Its diagnosis is based on clinical findings. Recurrence risk was identified as 50%.

Case 6

A non consanguineous couple was referred at the 15th week of gestation of her first dichorionic diamniotic twin pregnancy by means of in vitro fertilization, because a cardiac anomaly was suspected in one foetus. Ultrasound examination at the 17th week, performed at our Institution confirmed a conotruncal cardiac anomaly which as appeared to be a Tetralogy of Fallot (Figure 12). The other foetus seemed morphologically normal with foetal biometry appropriate for the gestational week. The couple was counselled about the possible association of cardiac defects with 22q11.2 deletion syndrome, a common microdeletion syndrome clinically characterized by an extreme variability and multisystemic features including congenital heart defect, a typical facial appearance, immune deficiency, palatal cleft, velofacial dysfunction, hypoparathyroidism and developmental and behavioural problems [12,13]. CGH-array analysis of the foetus with the cardiac anomaly revealed the presence of a 2.5 Mb deletion in the 22q11.2 region. The CGH-array analysis done in the mother on the basis of her particular facial appearance and developmental problems detected during the collection of her family history (Figure 13), confirmed the presence of the same 22q11.2 deletion. Considering the 50% risk of transmitting the deleted chromosome to each fetus, the FISH and array-analysis were extended to the second apparently normal foetus, confirming the presence of the same deletion in the second twin. Pregnancy was terminated and autopsy identified features of 22q deletion in both fetuses. Psychological disturbances in the mother become evident after the unexpected diagnosis which involved her own person, as well as her two fetuses, and forced her into an unexpected and difficult choice.

Discussion

Retrospective diagnosis progressing from child to parent is not rare in clinical genetics and usually happens when a child receives a diagnosis of a recessive condition then the parents are diagnosed as otherwise healthy carriers. In these cases, since the parents are clinically

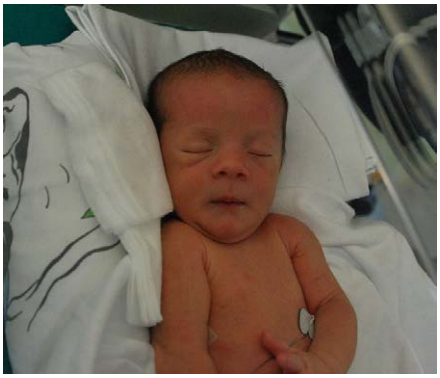

Figure 10: Neonatal phenotype of proband with Ehlers-Danlos. Broad and prominent forehead, bulbous nasal tip, anteverted nostrils, long philtrum, micrognathia, low set ears with convoluted antelix, joint hyperlaxity, especially at the limb's extremity

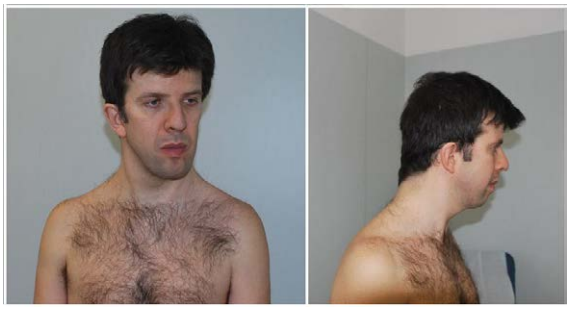

Figure 11: Father with Ehlers-Danlos syndrome: macrocephaly, hypertelorism, long face, prominent frontal bossing, thick eyebrows, prominent nasal root and tip, micrognathia, sloping shoulders.

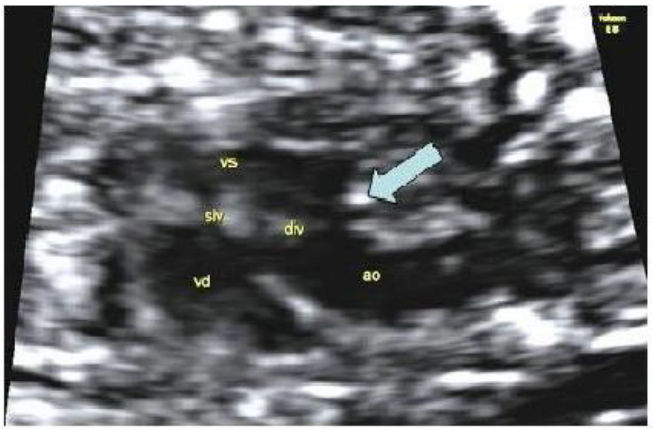

Figure 12: Ultrasound picture of cardiac anomaly of one twin (Tetralogy of Fallot). VS: left ventricle; VD: right ventricle; AO: aorta; SIV: interventricular septum; DIV: interventricular defect (Arrow).

Figure 13: Facial phenotype of the Parent's mother characterized by long face, short palpebral fissures, prominent nasal bridge, prominent mandible.

healthy, there is no reason a priori to suspect that they might be at risk of bearing an affected child.

In our cases we focused on autosomal dominant inheritance in families in which the affected parent had never been diagnosed with the genetic condition identified in the child. The main reasons for the missed diagnoses are one or a combination of the following: i) some patients do not seek health services despite suffering from some clinical signs because of denial or other psychological defenses; ii) Conditions which can now be diagnosed in young children that are still under-recognized in the adult. iii) Professionals who come across families requesting reproductive services, rarely collect a family history which may hint at the vertical transmission of abnormal clinical features.

Moreover several genetic conditions are expressed to a different extent in different individuals ("variable expressivity"). Since milder cases do not limit the individual's ability to reproduce, it is easier to find a subclinical form in one of the parents of a severely affected child and not vice versa.

Even "anticipation" may play a role. This phenomenon implies that offspring show an earlier onset and that the appearance of the symptoms in the son/daughter may precede the diagnosis in the affected parent.

Considering all of the above reasons it perhaps may be a little clearer why, in a number of cases, dominant genetic conditions remain undiagnosed before conception. Preconception counselling should therefore be encouraged and practised much more under all circumstances (taking the opportunity during other examinations or even as an adjunct during a gynaecologic visit when suspending a contraceptive prescription).

In addition, it is important that all medical specialists and general practitioners become more aware that malformations (heart abnormalities, cleft lip/palate, clubfoot, hydrocephalus, spina bifida), skin lesions (CALS, hypo-pigmented patches, periungual fibromas, benign tumors), dysmorphisms, excessive height or short stature, skeletal disproportion, neurological symptoms, hearing or visual impairment, borderline IQ or multiple symptoms in the same individual may be the indicators of an underlying genetic condition. Accurate family medical histories and physical examinations are essential so as to confirm or rule out the genetic significance of these signs.

Our cases show multiple positive consequences of a correct diagnosis for the perspective parent, well behind mere information and the increased awareness of genetic risks. For example improvement of prenatal and neonatal care as shown by cases 1 and 4. The chance for several family members to be correctly informed after diagnosis as in case 2; modification of clinical care (case 3) or even a better adaptation to everyday life after understanding the consequences of the clinical expression of the disease. Retrospective diagnosis, from a child to a parent may indeed be very useful for a parent, who may now choose to begin regular follow visits (case 5). Case 6 is indeed the most dramatic, showing the unexpected painful discovery of a well known condition which had been overlooked in the young woman.

An inability to carry out a clinical diagnosis can also have legal consequences and may even lead to detrimental effects on a couple's stability because of the shame and guilt connected with the late recognition of genetic risk.

In conclusion we have demonstrated how our intervention at multiple levels (prenatal, paediatric, adult) permits an accurate diagnosis for each family member.

Biographical Note

Giulia Melloni, Claudia Cesaretti, Maria Francesca Bedeschi, Barbara Gentilin, Vera Bianchi, Federica Natacci are clinical geneticist working in the Medical Genetics Unit at IRCCS Cà Granda, Ospedale Maggiore Policlinico Foundation, Milan, Italy.

Faustina Lalatta is the chief of the Medical Genetics Unit at IRCCS Cà Granda, Ospedale Maggiore Policlinico Foundation, Milan, Italy. All Authors have read and approved the manuscript.

Acknowledgements

We thank Dr. Tint GS for language supervision and active support.

References

1. Harper PS (2010) Practicals Genetic Counselling. (7thedn) Hodder Arnold UK: 3-5
2. Chao AS, Chao A, Wang TH, Chang YC, Chang YL, et al. (2008) Outcome of antenatally diagnosed cardiac rhabdomyoma: case series and a meta-analysis. Ultrasound Obstet Gynecol 31: 289-295.
3. Curatolo P, Bombardieri R, Jozwiak S (2008) Tuberous sclerosis. Lancet 372: 657-668.
4. Snead MP, Yates JR (1999) Clinical and Molecular genetics of Stickler syndrome. J Med Genet 36: 353-359.
5. Liberfarb RM, Levy HP, Rose PS, Wilkin DJ, Davis J, et al. (2003) The

Stickler syndrome: genotype/phenotype correlation in 10 families with Stickler syndrome resulting from seven mutations in the type II collagen gene locus COL2A1. Genet Med 5: 21-27.

6. Brems H, Chmara M, Sahbatou M, Denayer E, Taniguchi K, et al. (2007) Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. Nat Genet 39: 1120-1126.
7. Denayer E, Chmara M, Brems H, Kievit AM, van Bever Y, et al. (2011) Legius syndrome in fourteen families. Hum Mutat 32: E1985-1998.
8. Marszałek B, Wójcicki P, Kobus K, Trzeciak WH (2002) Clinical features, treatment and genetic background of Treacher Collins syndrome. J Appl Genet 43: 223-233.
9. Dauwerse JG, Dixon J, Seland S, Ruivenkamp CA, van Haeringen A, et al. (2011) Mutations in genes encoding subunits of RNA polymerases I and III cause Treacher Collins syndrome. Nat Genet 43: 20-22.
10. Malfait F, Wenstrup RJ, De Paepe A (2010) Clinical and genetic aspects of Ehlers-Danlos syndrome, classic type. Genet Med 12: 597-605.
11. Gawthrop F, Mould R, Sperritt A, Neale F (2007) Ehlers-Danlos syndrome. BMJ 335: 448-450.
12. Molesky MG (2011) Chromosome 22q11.2 microdeletion syndrome. Neonatal Netw 30: 304-311.
13. Bretelle F, Beyer L, Pellissier MC, Missirian C, Sigaudy S, et al. (2010) Prenatal and postnatal diagnosis of 22q11.2 deletion syndrome. Eur J Med Genet 53: 367-370.

This article was originally published in a special issue, **Genetic Disorders** handled by Editor(s). Dr. Xiaobo Li, Yeshiva University, USA