

## Case report

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# A case of familial isolated hemihyperplasia

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Published: 02 February 2004

Received: 18 November 2003

BMC Medical Genetics 2004, 5:1

Accepted: 02 February 2004

This article is available from: <http://www.biomedcentral.com/1471-2350/5/1>

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## Abstract

**Background:** Hemihyperplasia (hemihypertrophy) is defined as asymmetric body overgrowth of one or more body parts. Hemihyperplasia can be isolated or be part of well-defined syndromes such as in the case of Beckwith-Wiedemann syndrome (BWS). Isolated hemihyperplasia is usually sporadic, but a number of familial occurrences have been described.

**Case presentation:** We describe a Tunisian family in which three maternal cousins and their maternal grandfather present with isolated hemihyperplasia.

**Conclusions:** The etiology of isolated hemihyperplasia is unknown although in BWS, genomic imprinting has been shown to play a role in the asymmetric overgrowth. Given the similarity between these two conditions, it is possible that both may share a common pathogenesis. We also discuss the possible genetic mechanisms leading to the production of hemihyperplasia in this family.

## Background

Hemihyperplasia, formerly referred to as hemihypertrophy, is an asymmetric overgrowth involving one or more body parts [1-3]. Hemihyperplasia can be isolated or can occur as part of a syndrome. There have been several syndromes in which hemihyperplasia has been described, these include: Beckwith-Wiedemann syndrome (BWS), Proteus syndrome, Russell-Silver syndrome, Neurofibromatosis type I (NF I) and Klippel-Trénaunay-Weber syndrome (KTW) [2,3]. All of these conditions have well characterized features in addition to the hemihyperplasia. Isolated hemihyperplasia therefore must be differentiated from overgrowth that is part of a clinically recognized syndrome, since there are many prognostic implications for those individuals with an underlying syndromic diagnosis.

The prevalence of isolated hemihyperplasia is difficult to establish accurately, because many cases may be so mild as not to come to medical attention. The prevalence of hemihyperplasia has been estimated to be 1 in 13,200 live births [4]. This figure, however, may not be the most accurate since both isolated and syndromic forms of hemihyperplasia were included. Another large study [5] looked at 860,000 inpatient records and found a total of 10 cases with congenital asymmetry, suggesting that the prevalence for hemihyperplasia is approximately 1 in 86,000. However, several of the patients included in this survey had other congenital abnormalities, including BWS. Lastly, a study done in 1980 surveyed 14,430 consecutive live born infants delivered in a large maternity hospital in Tokyo and found only one newborn with hemihyperplasia [6]. These are the only epidemiological studies on hemihyperplasia published in the literature, and given

their limitations; it is difficult to estimate the real prevalence of this disorder in the general population.

When a clinician is faced with the evaluation of a patient with hemihyperplasia, it is very important to differentiate the isolated forms of hemihyperplasia from the syndromic ones, since the morbidity risks and follow up approaches could be significantly different. For example, Proteus syndrome, KTW and BWS carry different risks and have very different clinical management issues in comparison to isolated hemihyperplasia. All of these entities are usually sporadic cases and have a low recurrence risk. However, there have been several familial cases of BWS reported in the literature [7]. Isolated hemihyperplasia (likewise BWS) is usually sporadic with a low recurrence risk, however, there have been several reports of familial hemihyperplasia described in the literature with two or more affected relatives [8-16]. In this manuscript we describe a Tunisian family with several individuals affected with isolated hemihyperplasia. In addition, we have conducted a review of the literature specifically involving familial occurrences to evaluate the modes of inheritance that have been described previously, and comment on the possible molecular mechanisms leading to the occurrence of hemihyperplasia in this family.

### Case presentation

The proband in this family (Patient 1, III:1) is a 2 year-old Tunisian male who was diagnosed with right-sided hemihyperplasia. He was being followed by periodic abdominal ultrasounds every six months to screen for abdominal tumors. One month prior to our examination of the patient, three nodules were noted on his kidney by ultrasonography. Further evaluation revealed he had unilateral Wilms tumor with a negative metastatic work-up. The patient underwent tumor resection followed by chemotherapy with good outcome. His medical history was significant for the diagnosis of hemihyperplasia a few months after birth. He had no other medical problems until the development of the Wilms tumor. His birth weight was 3.6 kg (75<sup>th</sup> centile). His development has been normal for age. His physical examination at 2 years of age revealed: weight 20.9 kg (>95<sup>th</sup> centile), height 97 cm (>95<sup>th</sup> centile) and head circumference 55 cm (>95<sup>th</sup> centile). His clinical exam revealed hemihyperplasia involving both his right upper and right lower extremities. He had a leg-length discrepancy with his right leg being 3 cm longer than the left measured on clinical examination. His right calf circumference was 26 cm while his left calf circumference was 23 cm. He had no dysmorphic features or other abnormal findings on his physical examination. The neurological exam was normal. Specifically, he had no macroglossia, history of abdominal wall defects, ear lobe creases, café-au-lait macules or vascular abnormalities. G-band chromosome analysis performed on periph-

eral blood lymphocytes at approximately 550-band resolution level was reported as normal. No cytogenetic abnormalities were detected in the 11p15 region.

Patient 2 is the 5 year-old male maternal first cousin of the proband (III:3). He also has been diagnosed with hemihyperplasia and is undergoing tumor screening by serial abdominal ultrasounds. He has had no signs, symptoms or radiographic findings suggestive of a neoplasm. His birth history is non-contributory. His development has been normal for age. He has hemihyperplasia of the right upper and lower extremities with a 3.5 cm leg length discrepancy (Figure 1) also recorded on the clinical exam. Otherwise his physical examination is normal. His neurological exam was normal as well. G-band chromosome analysis performed on peripheral blood lymphocytes, at approximately 550-band resolution level, was also reported as normal. Like in our previous case, no cytogenetic abnormalities were detected in the 11p15 region. Both patients 1 and 2 were examined by the authors.

There are reportedly two additional individuals in this family affected with hemihyperplasia. One is a maternal first cousin to both patients 1 and 2 who is currently in Tunisia (III:7), whom by report has hemihyperplasia affecting the left leg. She is currently 10 years old and said to have no other manifestations besides her limb asymmetry. She also has normal development. She has no history of neoplasm and is currently undergoing abdominal ultrasound screening. Unfortunately she is unavailable for examination. The maternal grandfather (I:1), also unavailable for direct examination, is reported to have hemihyperplasia of the extremities on the right leg with no other obvious manifestations. He is currently 50 years old and lives in Tunisia. There is no consanguinity in this family. The family pedigree is shown in Figure 2.

### Conclusions

We have identified a family with four individuals affected with isolated hemihyperplasia. We have examined two members of the family while the two other are not available for direct physical examination. The transmission of the hemihyperplasia in this family could be compatible with autosomal dominant inheritance with incomplete penetrance, but given what we know about BWS, we propose that the hemihyperplasia in this family could also be the result of an imprinting defect. Of the familial cases of hemihyperplasia in the literature, seven had direct parent to child transmission [9,11,12,14-16]. However, in many of these families additional findings were also reported. Scott [9] described a family in which the mother and daughter were affected with hemihyperplasia but, in addition, the daughter had congenital heart disease and nevi. Morris and MacGillivray [12] also described a family in which both the mother and daughter were affected with



**Figure 1**  
Patient 2 with hemihyperplasia involving the upper and lower right extremities. The leg length discrepancy can be noted by the pelvic tilt.

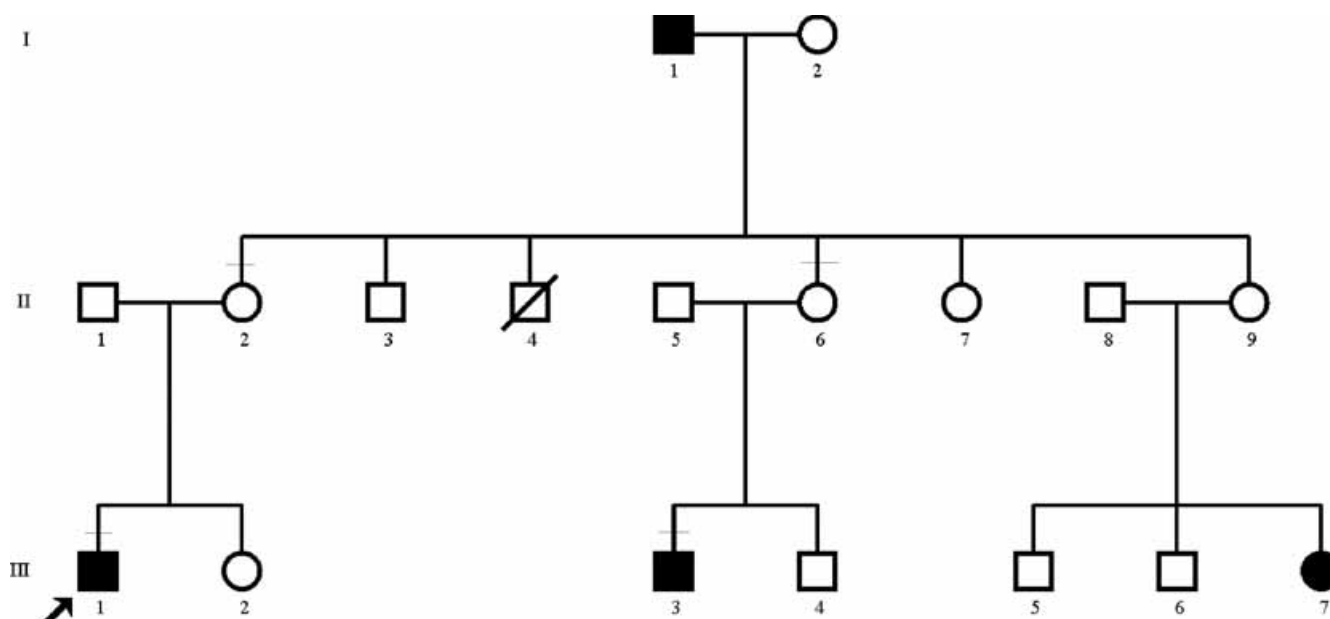
hemihyperplasia but both individuals had mental retardation in addition as well as a psychiatric disorder. The mother was noted to have pigmented lesions while the daughter had pes cavus. Slavotinek et al. [17] reported a mother and son with apparent isolated hemihypertrophy. The presentation was unusual, however, in that the chest asymmetry in the son and the leg length discrepancy in the mother were not noted until adolescence. Stoll et al. [15] reported a mother and daughter with hemihyperplasia

and in addition the daughter was noted to have an extra nipple. There have been three families reported with parent to child transmission of hemihyperplasia involving the face only. Rudolph and Norvold [11] reported a child, mother and grandmother each with facial asymmetry. Bencze et al. [16] described a three-generation family with apparent autosomal dominant transmission of facial hemihyperplasia and strabismus. Burchfield and Escobar [14] reported a family with father to son transmission of facial asymmetry and severe malocclusion. Several other family members were also affected. The family described by Burchfield and Escobar is unique in that it is the only family described with known male-to-male transmission, in all other families the affected individuals were related through the maternal lineage.

In addition to the families described with parent to child transmission, there have been three reports of siblings with hemihyperplasia. One case reported two sisters with complete left-sided hemihyperplasia, however they additionally had significant mental retardation [12]. In this family, their maternal grandmother apparently had left facial hemihyperplasia but did not have mental retardation therefore it is unclear if the retardation was an unrelated finding. One other reported family showed a brother and sister with complete right-sided hemihyperplasia [8]. The brother had a history of seizures and the sister had mental retardation, nevi and strabismus. Fraumeni et al. reported a family in which a female presented with right-sided hemihyperplasia of the arm, leg and tongue as well as a Wilms tumor of the left kidney [13]. Her brother had right-sided hemihyperplasia of the leg. Furthermore, a maternal uncle was reported as having his right leg longer than his left leg. Lastly, Arnold [10] reported a nephew and uncle with possible hemihyperplasia. The male child had right-sided hemiacromegaly with early eruption of several permanent teeth and his maternal uncle was also said to have an "enlarged right cheek", the authors state that he was not evaluated clinically.

These reported families do not point to a clear inheritance pattern of transmission in hemihyperplasia. In all but one reported family [14], the transmission of hemihyperplasia occurred through maternal relatives. It must be noted though that in several cases there were other abnormalities present besides the body asymmetry, suggesting that these families may not truly qualify for isolated hemihyperplasia. In the family we present, there are clearly two maternal cousins with isolated hemihyperplasia presenting in infancy. One cousin developed Wilms tumor. Both individuals were examined and clearly did not fit diagnostic criteria for any syndromic form of hemihyperplasia.

It has been suggested that isolated hemihyperplasia may be part of the BWS spectrum [3]. BWS is a syndrome of pre

**Figure 2**

Pedigree. III-1, III-3, II-2, and II-6 were examined by the authors.

and post-natal overgrowth, macroglossia, omphalocele, neonatal hypoglycemia and hemihyperplasia. The etiology of BWS is complex and thought to be the result of a genomic imprinting defect [7,18,19]. Genomic imprinting refers to an epigenetic phenomenon characterized by monoallelic expression of a gene depending on its parent of origin [20]. The mechanisms leading to imprinting are complex and consist of a parental specific mark or imprint that is established in gametogenesis. This imprint mark must be switchable when transmission occurs through members of the opposite sex, for example from a mother to her son. Although the exact molecular mechanisms for BWS still remain elusive, several genetic mechanisms have been postulated as probable cause [19,21,22]. BWS appears to be associated with abnormal expression of a gene/s on chromosome 11p15, which is one of the few imprinted regions of the human genome. The paternally expressed genes on 11p15 include: Insulin Growth Factor 2 (*IGF2*) that is a growth promoter, and *KCNQ1*-overlapping transcript 1 (*KCNQ1OT1* or *LIT1*). Some of the maternally expressed genes include cyclin-dependent kinase inhibitor 1C (*CDKN1C*) a cell cycle inhibitor also known as p57(*KIP2*); *KCNQ1*, a potassium channel, voltage-gated gene also known as *KvLQT1*, and *H19* that codes for an untranslated RNA [20]. The region is further divided into two distinct domains. Domain 1 contains *IGF2* and *H19*, and Domain 2 contains *CDKN1C*, *KCNQ1OT1*, and *KCNQ1*. In addition, these two domains are apparently regulated by two distinct imprinting cent-

ers. The imprinting centers are thought to maintain the imprints in somatic cells but also play a role in resetting the imprint in the germline [23]. The genetic lesions described thus far in BWS include paternal duplications of 11p15, maternal translocations that disrupt the 11p15 region and mutations of *CDKN1C*. However, the majority of BWS cases have no identifiable genetic alteration. It is believed that most cases of BWS are caused by epigenetic factors. One such situation is paternal uniparental disomy of 11p15 that occurs in 10–20% of BWS cases [21]. Even though the genetic and epigenetic mechanisms involved in BWS are quite complex and not fully understood, it is widely accepted that BWS results from dysregulation of several closely linked genes on 11p15 which are involved in cell cycle regulation and growth control. Further supportive evidence can be surmised from evaluation of maternal duplications of 11p15. Recently, Fisher *et al.* [24] reported the first three cases of maternal duplications of the BWS region. The phenotype in these three patients included growth retardation, in contrast to the characteristic overgrowth seen in paternal duplications of this region (BWS). Another study looked at epigenetic alterations of *H19* and *LIT1* in BWS patients [25]. In this particular cohort of patients, 92 children with BWS were studied molecularly showing some interesting results. 39 out of the 92 children studied (42%) had an altered methylation pattern of *LIT1* with normal *H19* methylation, 10 out the 92 (11%) had an abnormal methylation pattern of *H19* with normal *LIT1*, and 12 out of the 92 (13%) had altered

methylation on both *H19* and *LIT1*. From this last group, only 9 have paternal UPD, which was somehow expected, but the remaining 3 had biparental inheritance for the 11p15 region. This result strongly suggests the role of epigenetic mutations in BWS. Interestingly, in this group with abnormal methylation for both *H19* and *LIT1*, as well as in those cases with paternal UPD for the 11p15 region, there was a higher incidence for hemihyperplasia. The association of UPD and hemihyperplasia in BWS has also been supported but previous clinical-molecular studies.

Although BWS usually is sporadic, there have been several families described with autosomal dominant inheritance. *CDKN1C* mutations account for a larger portion of familial cases of BWS than sporadic cases, but the mechanism for the majority of cases is still unknown. Viljoen et al. [7] described a family with BWS, and reviewed 27 kindreds with familial BWS reported thus far in the literature and in all but four cases; the inheritance pattern was potentially consistent with an imprinting defect.

The transmission pattern of hemihyperplasia in the family presented here could also be consistent with a similar imprinting mechanism. The maternal grandfather (I-1) of the two male cousins discussed here (III-1 and III-3), is reported to have hemihyperplasia. If we assume that I-1 has an imprinting abnormality (such that of *IGF2* itself or of its imprinting center) of his maternally derived allele that allows over expression of a growth-promoting factor such as *IGF2*, this could lead to hemihyperplasia. His maternal allele should normally be silent and now is active secondary to an epigenetic defect. This individual will also have his paternal copy that would result in functional duplication and over expression of the *IGF2* genes. If this mutated allele was then transmitted from the grandfather to his daughters (II2, II6 and II9), it would behave normally, since a paternal allele would normally express *IGF2*. These individuals would not be affected but would be potential carriers. They have now the paternal "active" allele and the maternally silent allele. These individuals would then have a 50% chance of passing this abnormally imprinted allele to their offspring. During gametogenesis in individuals II2, II6 and II9 the imprinting mark on this allele should be changed to a maternal, "silent" pattern. However, if a particular epigenetic change renders this allele unable to be reverted back to its silent form, it will continue to have a paternal pattern of expression. In this case the offspring that inherit this allele will now have a net gain overexpression of a growth promoter such as *IGF2* therefore leading in this case to hemihyperplasia. Certainly, loss of *IGF2* imprinting is not the only possibility in this family, as the molecular mechanisms and interactions of the imprinted genes on 11p15 are quite complex, but the molecular mechanism (abnormal

imprinting) proposed in this family, could be consistent with the paternal imprint model as proposed for familial BWS. The other families reported in the literature with hemihyperplasia showing autosomal dominant inheritance and maternal transmission could also be consistent with an imprinting mutation as well, (although they could be more consistent with a maternal imprint) [9,11,12,15]. Cytogenetic analysis was performed in three of these families [15] ruling out the possibility of maternal translocations, however, this cannot be completely ruled out in the other families. Moreover, it is unclear whether some of the other families reported in the literature can be considered as isolated hemihyperplasia as there are other abnormalities found in these individuals. Not all the reported families however would fit with an imprinting pattern of inheritance [13], but as the majority cases for BWS and hemihyperplasia remains unknown, these families could represent different molecular mechanisms caused by disturbance of balance between growth promoters and suppressors. Similarly, the reported families with isolated facial hemihyperplasia [14,16] do not fit with an imprinting pattern of inheritance. In summary, hemihyperplasia and similarly to what is seen BWS, is a heterogeneous group of disorders possibly caused by different molecular mechanisms. In the family presented in this paper is certainly interesting to hypothesize a paternal imprint defect. This additional family also raises caution when counseling is done to these individuals. A good family history with particular attention to overgrowth is warranted in these patients. We believe that clinicians should continue quoting a low recurrence risk for hemihyperplasia, however, the rare possibility of familial recurrences needs to be reported in our opinion as part of the routine counseling.

### Competing interests

None declared.

### Authors contributions

HH evaluated the patients and prepared the manuscript.

CB evaluated the patients and edited the manuscript.

All authors have read and approved the final version of the manuscript.

### Acknowledgements

We have been unable to obtain written consent for this publication since the family presented here was unfortunately lost to follow up.

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