GATA2 null mutation associated with incomplete penetrance in a family with Emberger syndrome

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Introduction

GATA binding protein 2 (GATA2) is a zinc finger transcription factor associated with the development of different tissues including hematological, lymphatic, urogenital and neural. GATA2 mutations are associated with several conditions, including Emberger syndrome which is the association of primary lymphedema with hematological anomalies and an increased risk for myelodysplasia and leukemia. Incomplete penetrance may indicate that GATA2 haploinsufficiency is not enough to produce the phenotype of Emberger syndrome. It could be useful to perform whole exome or genome sequencing, in cases where incomplete penetrance or high variable expressivity is described, in order to probably identify specific gene interactions that drastically modify the phenotype. In addition, skewed gene expression by an epigenetic mechanism of gene regulation should also be considered.

Methods

A DNA sequencing of GATA2 gene was performed in the parents and offspring (five individuals in total). Three of them were affected (two of which were deceased) while two remained unaffected at the age of 40 and 13 years old. The three affected siblings (two boys and one girl) presented with lymphedema of the lower limbs, recurrent warts, epistaxis and recurrent infections. Two died due to hematological abnormalities (AML and pancytopenia). In contrast, the two other family members who carry the same mutation (the mother and one brother) have not presented any symptoms and their blood tests remain normal.

Results

The family consisted of 5 individuals with a GATA2 null mutation (c.130G>T, p.Glu44*); three of them were affected (two of which were deceased) while two remained unaffected at the age of 40 and 13 years old. The three affected siblings (two boys and one girl) presented with lymphedema of the lower limbs, recurrent warts, epistaxis and recurrent infections. Two died due to hematological abnormalities (AML and pancytopenia). In contrast, the two other family members who carry the same mutation (the mother and one brother) have not presented any symptoms and their blood tests remain normal.

Discussion

Incomplete penetrance may indicate that GATA2 haploinsufficiency is not enough to produce the phenotype of Emberger syndrome. It could be useful to perform whole exome or genome sequencing, in cases where incomplete penetrance or high variable expressivity is described, in order to probably identify specific gene interactions that drastically modify the phenotype. In addition, skewed gene expression by an epigenetic mechanism of gene regulation should also be considered.
Case report

Three siblings of the family were referred to the genetic service with hereditary lymphedema (Figure 1). The mother was 33 years old and the father 34 years old (at the first consultation), both with high school education. They were not consanguineous and apparently healthy. The mother had six pregnancies, all delivered normally (without complications) and there was no relevant family history of similar problems.

At the time of the first genetic consultation three of the six children presented with lymphedema of the lower limbs, aged 13 (boy, II-1), 12 (girl, II-2) and 8 (boy, II-4) years old. The unaffected siblings were aged 11 (boy, II-3), 6 (boy, II-5) and 5 (girl, II-6) years old (Figure 1). The oldest boy (II-1) had developed lymphedema of the right lower limb and genitalia at the age of 7 years old after a fall. He also exhibited recurrent warts, cellulitis in the right leg, epistaxis and pancytopenia episodes. He had 4 hospitalizations, one at age 18 months for a gastrointestinal infection and the second at 12 years for cellulitis of the right limb, where pancytopenia was detected. Two months later, he was hospitalized for a phimosis that did not require surgery. He was admitted a fourth time at 13 years old with cellulitis and septic shock. On that occasion, pancytopenia was accompanied by hypogammaglobulinemia (with normal IgA levels). Three days into his last hospitalization he was transferred to intensive care but, unfortunately, died of the septicemia.

His younger sister (II-2), presented with lymphedema of both lower limbs (mainly in the left leg) and genitalia since the age of 3 months. She presented with an unspecified hepatitis at 4 years old, chickenpox at 5 years old and was hospitalized at 8 years old for cellulitis in the legs. At 13 years old, she developed hyperkeratotic lesions in both legs; at 14 years old, she had an episode of chronic cough secondary to flu symptoms; and at 15 years old, she died of acute myelocytic leukemia (AML). The blood tests at the time of the AML diagnosis showed anemia, thrombocytopenia and leukocytosis. The family reported that she had chronic cellulitis of legs (four in a year), epistaxis and recurrent warts.

The youngest affected boy (II-4), who is currently 16 years old, developed lymphedema during the first year of life. Both feet (the left more prominently) and his left lower limb were affected. Later, in the adolescence, it extended to his genitalia. He has had recurrent episodes of cellulitis of his left limb requiring hospitalization, recurrent tinea pedis with erythema and peeling of the skin, and occasional epistaxis and warts. The hematological biometric tests in the rest of the family were normal, although all the siblings presented occasional epistaxis.

Mutational analysis

DNA was extracted and screened for GATA2 mutations by Sanger sequencing for all the family members (Figure 1). A heterozygous GATA2 mutation (c.130G>T, p.Glu44*) leading to a premature stop codon in amino acid 44 was detected by two independent laboratories in two affected siblings (the oldest had already died), the unaffected mother and one unaffected son (I-1, II-5), who now is 13 years old. The resulting messenger RNA would encode a truncated GATA protein, but the mRNA may be degraded via the non-sense mediated mRNA decay (NMD) pathway. Mendola et al. [14] previously reported the mutation of the two affected siblings (II-2 and II-4) in a mutational screening report, without the clinical data.

Discussion

Emberger et al. [15] first described the association of lymphedema of the lower limbs, sensorineural deafness and hematological anomalies (MIM#614038) as an autosomal dominant trait. Later, Mansour et al. [16] further delineated the phenotype in seven unrelated cases. Finally, Ostergaard et al. [8] described the genetic alterations in GATA2.

In this report, we describe a family with a null mutation in GATA2 associated with Emberger syndrome. Three siblings were symptomatic (two are deceased) but two additional family members are unaffected carriers. Although the presence of lymphedema has been reported as a low-penetrant phenotype in families with the same genetic mutation in GATA2 [3,12,13], this is one of the few cases that exemplify a highly variable expressivity, including the possibility of incomplete penetrance in a family with Emberger syndrome. In this report, although the youngest affected brother (II-4) has not had documented hematological anomalies yet, the presence of recurrent infections and epistaxis episodes are suggestive. Considering the ages of the unaffected family members, it is likely that some clinical manifestations associated with GATA2 mutations may arise in the future. This has, indeed, been observed in other mutation carriers who presented with hematologic symptoms only after 70 years of age [12,13], in agreement with the age-dependent penetrance in GATA2 mutation carriers. Lymphedema can also have a late-onset appearance.

Previous work has shown a wide clinical variability in individuals with GATA2 mutations [3,12,13]. Non-penetrance for any condition associated with GATA2 mutations had a frequency of 7% (n = 4) in a series of 57 individuals with these mutations [12]. Lymphedema is one of the least frequent manifestations (found in 11%) and hematological abnormalities the most frequent (>80%) [12]. This high variability, even within the same family, accompanied with cases of
incomplete penetrance \[3,10\] supports the notion that GATA2 haploinsufficiency is not enough to produce any of the clinical manifestations. Thus, many genes with their respective variants, as well as some environmental factors, may interact to produce the phenotype. Considering the high number of phenotypes associated with hematological abnormalities, and its high penetrance in GATA2 mutation carriers, GATA2 seems to play a more preponderant role in the hematological development and function than in the development of the lymphatic, urogenital or neural tissues. A poorly explored mechanism involved in variable expression and incomplete penetrance is the epigenetic regulation of gene expression, as reported in homozygous twins discordant for multifactorial diseases \[17,18\]. Interestingly, epigenetic regulation of GATA2 leading to skewed allele-specific expression (ASE) has been reported in patients with acute myeloid leukemia and normal karyotype \[19\]. Although this ASE was not observed in normal tissues, we cannot exclude its potential role in this family and other similar cases.

Considering the high inter-individual variability within the same family in earlier reports and the current family, it appears that a precise genotype-phenotype correlation cannot be established \[12\]. Because all the syndromes previously described as produced by GATA2 mutations can present clinical overlap, these should be considered as part of the phenotypic spectrum of the same genetic deficiency. Nevertheless, as previously observed \[10,12\], the type of mutation (null mutation) in this family was associated with the presence of lymphedema in the three affected members.

In this particular genetic condition, familial screening is essential for a correct genetic counseling of risk and for the early detection of suitable hematopoietic stem cell donors in order to perform bone marrow transplantation, which has been reported as an effective treatment for patients with GATA2 mutations \[20\]. However, the precise moment in which this should be done remains to be determined particularly in cases with intermittent immunodeficiency and pancytopenia. Therefore, a close surveillance of hematological alterations is needed in GATA2 mutation carriers.

In conclusion, we report a family with a null mutation in GATA2 and Emberger syndrome with variable expressivity and incomplete penetrance. This case emphasizes the need of genetic interactions to produce specific phenotypes in the clinical spectrum of GATA2 deficiency, where no precise genotype-phenotype correlation has been found. This and other cases, where incomplete penetrance or a highly variable expressivity is described, are good candidates for whole genome sequencing in order to identify specific gene interactions that drastically modify the phenotype; these genomes could be submitted in an electronic database that allow worldwide users to access it.

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**Figure 1.** The family tree showing the affected members (with filled quadrants), the carriers (black circle inside) and the death members (with a transversal line).
Disclosure statement

No potential conflict of interest was reported by the authors.

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