Revisiting the craniosynostosis-radial ray hypoplasia association: Baller-Gerold syndrome caused by mutations in the *RECQL4* gene

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ABSTRACT

Background
Baller-Gerold syndrome (BGS - OMIM 218600) is a rare autosomal recessive condition with radial aplasia/hypoplasia and craniosynostosis. A small number of more than 20 cases reported thus far are atypical and have been eventually reassigned to other nosologic entities. This is true for Fanconi anemia, Roberts SC phocomelia and Pfeiffer syndromes after demonstration of corresponding cytogenetic or molecular abnormalities. However, most cases represent bona fide observations. Clinical overlap between BGS, Rothmund-Thomson (RTS - OMIM 268400) and RAPADILINO (OMIM 266280) syndromes is also noticeable. Because mutations in RECQL4 have been found in patients with RAPADILINO syndrome and in a subset of patients with RTS, we reassessed two previously reported families.

Results
We have found causal mutations in RECQL4 in both families. In the first family, there were four affected offsprings with craniosynostosis and radial defect and one of them developed poikiloderma. In this family compound heterozygosity for a R1021W missense mutation and g.2886delT frameshift mutation of exon 9 was found. In the second family, the affected male had craniosynostosis, radial ray defect, poikiloderma and short stature. He was found to have a homozygous splice site mutation (IVS17-2A>C). In both families affected offsprings had craniosynostosis, radial defects, growth retardation and two of them developed poikiloderma.

Conclusion
Our results confirm that a subgroup of patients with BGS are due to RECQL4 mutations, and could be integrated in a clinical spectrum that encompasses Rothmund-Thomson and RAPADILINO syndromes.
INTRODUCTION
Bilateral radial ray hypoplasia is found in a number of multiple malformation syndromes such as Fanconi anemia (OMIM 227650), Roberts SC phocomelia (OMIM 269000), thrombocytopenia-absent radius syndrome (OMIM 274000), Holt-Oram syndrome (OMIM 142900), and SALL4-related syndromes[1]. Craniosynostosis, when symmetrical and involving coronal and lambdoid sutures may be indicative for at least fifty syndromes[2]. However, association of these two distinctive clinical features is found in a limited number of syndromes but most constantly in Baller-Gerold syndrome (BGS;OMIM 218600). BGS was delineated after Baller[3] and Gerold[4] described the first patients with the association of radial hypoplasia and craniosynostosis. Interestingly, the first patient has (in the limits of what could be appreciated on the poor quality clinical photograph of the original paper) a skin appearance that seems compatible with poikiloderma.[3] (Fig 1).
A limited number of additional patients have been reported since then[5][6][7][8][9][10][11][12], and clinical overlap with other syndromes became more obvious when the clinical diagnosis of BGS was subsequently challenged by cytogenetic or molecular tests that revealed a diagnosis of Fanconi anemia[13][14][15][16][17][18], Roberts SC syndrome[19] or Saethre-Chotzen (OMIM 101400) syndrome. TWIST mutations are found in the latter condition, and they are usually associated with a broad fingers-receding forehead craniosynostosis phenotype, but anecdotal patients may also display radial hypoplasia [20][21]. Some patients with FGFR2 mutations may also mimick BGS but to a lesser extent, as exemplified by a patient who has in addition humero-ulnar synostosis [22]. The same holds true for SALL4-related syndromes[1]. Given the phenotypic overlap between these different conditions, additional studies, such as chromosome breakage assays or DNA sequencing of the FGFR or TWIST genes, may be useful to exclude other syndromes depending on the clinical findings. We hereby update the report of two previously published BGS families[11][12] and correlate the findings with the identification of mutations in the RECQL4 gene including two novel mutations, g.5428A>C and g.5435C>T.
Clinical histories

Family 1

Patient 1
The index patient has been described previously[11]. He was born at term after an uneventful pregnancy to unrelated parents. He had severe radial ray hypoplasia with oligodactyly, anus anteposition, pes talus, multiple cranial suture synostosis and a distinctive facial dysmorphia with a very small mouth, thin vermilion border, long upper lip and microretrognathism (fig 2 – middle panel). He died of unknown cause a few minutes after birth.

Patients 2 and 3
Subsequently, the parents had two other affected fetuses. Upper limb shortening, oligodactyly and severe brachycephaly were detected at ultrasound screening at 24 and 16 weeks respectively. Both pregnancies were terminated. Necropsy demonstrated in the first case (24w), a male with a normal weight (470 g), craniosynostosis of lambdoid and coronal sutures, large anterior fontanelle and radial ray hypoplasia with thumb aplasia (fig 2 – left panel). Necropsy of the second fetus at 16w, a female with a weight of 182 g, was similar in many respects: turricephaly, coronal craniosynostosis, large metopic and frontal sutures and wide fontanelles with a normal brain were observed. Arms were short and bowed. There was also radial aplasia, anus anteposition and hypoplasia of the great toe.

Patient 4
After birth of a normal boy, a fifth pregnancy was also carefully monitored by ultrasound. Upper limbs shortening and bilateral thumb agenesis was diagnosed at 15 weeks. The couple decided to continue the pregnancy. Patient 4 was born at term (fig 2 – right panel). Her birthweight was 2680 g, length 46 cm and OFC 36 cm. She had acrocephaly, temporal bulging, widely open anterior fontanelle, midface retraction with saddle nose, and bilateral agenesis of the thumbs. On X rays, ulna and radius were normally shaped. Anus was anteposed. Surgical correction of the craniosynostosis and pollicisation of the right index were successful. Patellar hypoplasia was noted at the age of six months. Erythematous skin lesions appeared progressively on the face and limbs during the first months of life, leading to a diagnosis of poikiloderma. Skin atrophy became more obvious over time but kept the same topographic pattern: almost absent on the trunk, mild on thighs, moderate on cheeks, nose and forehead, most prominent on forearms and hands, with fluctuating intensity of the erythema depending on sun exposure. Growth rate was abnormal since birth, leading to progressive dwarfism. At the age of nine months, she was 64 cm tall (-1.7 SD) and 5500 g (-3.2 SD). At the age of three years her height was 79 cm (-4.3 SD). At the age of six, she was 93.3 cm tall (-4.4 SD), her weight was 11 kg (-3.2 SD), and her OFC 48 cm (-3 SD). Endocrine workup included thyroid function and GH insulin test, as well as somatomedin C and IGF1 plasma concentrations which were all normal. She had chronic feeding difficulties requiring nasal tube feeding during the first months of life. Low appetite persisted during childhood. Early psychomotor development was normal. She walked unsupported at the age of 18 months. Absence of patellae induced an inward-rotated legs gait. Major voice problems related to her short, hypomobile velum were not improved by speech therapy. Despite her marked expressive problems, she participated in a regular classroom at the primary school level.

Family 2
This boy has been described previously[12] (fig 3). He was the second child of first cousins. The pregnancy was marked by severe intrauterine growth retardation. Clinical examination showed turribrachycephaly in relation with craniosynostosis of lambdoid and coronal sutures, short forearms with radial deviation of hands, missing left thumb and rudimentary thumb on the right, short stature and poikiloderma.
Molecular studies

Molecular studies were performed on DNA extracted from peripheral leucocytes. Sequencing of FGFR2 exons IIIa and c, FGFR3 exon IIIa and the TWIST gene was performed according to previously reported methods[23] and was normal in index patient of family 1. All exons and the short introns of RECQL4, except a small part of intron 12 were also sequenced, including the consensus splice sites, in both families[24].

In family 1 samples from parents and children one, four and five were available. Samples from the first and fifth children revealed compound heterozygosity for two mutations: a substitution and deletion mutation (g.2881G>C; g.2886delT) in exon 9 (also found in the maternal allele) and a missense mutation (g.5435C>T/R1021W) in exon 18 (also found in the paternal allele). The g.5435C>T mutation causes the arginine to tryptophan amino acid substitution R1021W. The unaffected brother was found to have only the g.2881G>C; g.2886delT mutation. The g.2881G>C/S523T change is likely a polymorphism which cosegregates with the g.2886delT mutation [25] [26]. No other pathogenic mutation was detected in the affected children.

In family 2 samples from the parents and affected male were available. The patient was homozygous for a g.5428A>C mutation which changes the splice acceptor site IVS17-2A>C probably affecting the correct splicing. Unfortunately RNA was not available to confirm the effect of the mutation at the transcript level.

The localization of these BGS mutations are presented in figure 4 together with the reported RECQL4 mutations causing RTS or RAPADILINO syndromes.

Discussion

When reviewing the published cases of BGS, the impression that prevails is that there is a core diagnosis consisting of lambdoid and coronal craniosynostosis in association with radial hypoplasia. The anecdotal reassignments of BGS published cases to other nosological entities were prompted by secondary haematological complications or atypical findings. Guided by clinical findings, one may therefore in specific circumstances ask, in addition to initial work-up, require special, chromosomal analysis after incubation with clastogens, or studies of DNA crosslinking sensitivity. Sequencing of FGFR1, FGFR2, FGFR3 or TWIST genes may also be required according to clinical findings.

Of note is the fact that poikiloderma is a skin manifestation that in RTS occurs after an interval of a few months. Caution should therefore be applied to BGS diagnoses made in the first few months of life and a follow-up evaluation is warranted

Rothmund-Thomson syndrome (RTS - OMIM 268400) and RAPADILINO syndrome (OMIM 266280) are two recessively inherited syndromes displaying some clinical overlap with BGS (fig 5). RTS is characterized by poikiloderma “congenita” (usually first manifested between 4 and 6 months of age), alopecia, skeletal defects, dystrophic nails, abnormal teeth, cataracts, and small stature. Photosensitivity is highly variable. Radial ray hypoplasia or absent thumbs occurs in a minority of cases. The clinical diagnosis rests on the poikilodermatous rash. If the onset or distribution of poikiloderma is atypical then two additional features such as bone abnormalities, cataracts or osteosarcoma are required for a diagnosis of probable RTS diagnosis[27]. Analysis of 33 RTS patients suggests that approximately 60% of patients with definite or probable RTS carry mutations in RECQL4[28] with the remainder of RTS due to mutations in gene(s) that have not yet been identified.

RAPADILINO is a rare autosomal recessive malformation syndrome[29]. The acronym refers to the main clinical features (radial ray defect; patellae hypoplasia or aplasia and cleft or highly arched palate; diarrhea and dislocated joints; little size and limb malformation; nose slender and normal intelligence). Fourteen patients have been reported in Finland and only three in other countries[29][30][31][32][24]. One of the non-Finnish patients was later re-
diagnosed as an RTS case[33]. It has recently been identified that RAPADILINO syndrome is caused by mutations in RECQL4[24].

RECQL4 encodes a member of the RecQ helicase family based on sequence conservation[34]. However, few functional studies have been performed. Recently, it has been reported that the RECQL4 proteins interacts in the cytoplasm with ubiquitin ligases UBR1 and UBR2 proteins of the N-end rule pathway[35]. The physiologic significance of this interaction is unknown. The Fin-major mutation[24] is a splice site mutation causing in-frame skipping of exon 7. All the Finnish patients are either homozygotes or heterozygotes for this mutation (fig 3).

Similarities between Rothmund-Thomson and BGS have already been pointed-out by one of us[12]. RAPADILINO syndrome also fits the BGS clinical spectrum since radial hypoplasia is one of the hallmarks of RAPADILINO syndrome, and one non-Finnish case was rediagnosed as RTS after poikiloderma-like rash appeared at the age of 21 months. An intermediate phenotype with craniosynostosis, poikiloderma and anteriorly placed anus has also been reported recently[36]. The fact that clinical course of patient four from family 1 and index patient from family 2 had poikiloderma prompted us to investigate a possible continuum between these apparently distinct entities by searching mutations in RECQL4 gene. In both families, mutations in RECQL4 were found to be the cause of the BGS phenotype. In conclusion, we have demonstrated in two unrelated families that RECQL4 mutations cause BGS. These results bring the number of clinical syndromes attributable to RECQL4 mutations to three: RTS, RAPADILINO and BGS. The genotype-phenotype correlations in these syndromes need to be studied further. It is interesting to see whether certain mutations always lead to distinct phenotypes or if the correlation is more complex. Since a BGS phenotype has already been associated with FA, Roberts SC phocomelia, TWIST and FGFR2 mutations, careful clinical delineation will assist in defining this nosological entity. Radial defects are a variable feature associated with otherwise classical craniosynostosis gene mutations. This feature also belongs to cytogenetically defined disorders, as Fanconi or Roberts syndrome, and in some cases of VATER association. In these two subsets cutaneous manifestations are found only in Fanconi anemia patients in the form of pigmentary changes. We provide here evidence that a third subgroup of BGS patients have a RECQL4-related phenotype with eventual developmental skin lesions (not present at birth). In this context, the consistent presence of sutural anomalies in 4/4 affected patients from family 1 may be a mutation-specific manifestation perhaps relating to the specific domain of the protein altered by the missense mutation. Study of intrafamilial variability and genotype-phenotype correlations within the RECQL4 spectrum, based on a larger set of patients will be necessary to determine whether the apparently distinctive phenotypes breeds true and are linked to distinct mutations. Also, multiple malformation syndromes that include craniosynostosis and/or radial ray aplasia and/or poikiloderma should be investigated for RECQL4 mutations.
References


Legend to figures

Fig. 1: Clinical photograph of original Baller's patient retrieved from German literature (see reference [3]). Note brachycephaly and skin appearance of her forearm. Since the photograph is more than 50 years old, there is no need to obtain a permit for publication.

Fig. 2: Family 1: Note clinical findings in a 16 w-old fetus (patient 3) displaying mild brachycephal, radial aplasia and oligodactyly (left panel). These have to be compared with the newborn (patient 1) who has marked brachycephaly and facial dysmorphia that includes small mouth, short nose, short palpebral fissures with telecanthus and a bulging forehead where a W-shaped upper furrow points to widely opened anterior fontanelle (middle panel). At an older age (patient 4 at 2 years), dysmorphia is less pronounced but failure to thrive is obvious. On a 3-D tomodensitometric reconstruction of the skull, one can see the sharp contrast between coronal and lambdoid craniosynostosis and skull ossification defect with wide fontanelles (right panel). We have obtained written authorisations from the legal tutors to publish these clinical photographs.

Fig. 3: Index patient from family 2. Note similarities with patient 4 of family 1. We have obtained written authorisations from the legal tutors to publish these clinical photographs.

Fig. 4: Schematic structure of RECQL4 gene. Note the three new mutations (ringed) and compare with the previously reported mutations in RTS (normal characters) and RAPADILINO syndrome (in bold).

Fig. 5: Venn diagram of the paramount features of the three entities. If we hypothesize a continuum between them, then the core (overlapping) criteria would include growth deficiency, facial dysmorphia and GI disturbance.

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