Background:
Frank-ter Haar syndrome is a rare disorder comprising cardiovascular, skeletal and craniofacial anomalies including hypertelorism, brachycephaly and a wide anterior fontanelle [1]. The ‘ter Haar’ syndrome was initially described in three related children, all of whom developed severe cardiovascular complications [2,3]. These patients appeared to share many of the craniofacial and skeletal features normally associated with Melnick-Needles Syndrome, an X-linked congenital disorder of skeletal dysplasia. However the autosomal recessive pattern of inheritance and congenital cardiac defects distinguished the syndrome as a separate entity [4,5]. The condition affecting this subgroup of patients was renamed Frank-ter Haar syndrome following the realisation that ter Haar’s three patients shared many of the features described previously by Frank in an 18 month old female with megalocornea, skeletal dysplasia and developmental delay [1,6].

A genetic basis for Frank-ter Haar syndrome has recently been established through homozygosity mapping studies in patients from 12 affected families, identifying homozygous mutations in the SH3PXD2B gene on chromosome 5q35.1 as the most common cause [7]. The analysis of patients from 13 families identified 4 different intragenic mutations, and one complete deletion of SH3PXD2B, accounting for the phenotype in 7 of the families [7]. Clinical features characterising this group of mutation positive patients include brachydactyly, megalocornea, hypertelorism, a prominent forehead, brachycephaly, a wide anterior fontanelle, micrognathia, a broad mouth and full cheeks [7]. Sh3pxd2b null mice appear to share many of the skeletal, craniofacial, cardiac and ocular defects described in Frank-ter Haar syndrome, supporting the link between this gene and the syndrome [7].

The craniofacial features of Frank-ter Haar syndrome are numerous however to our knowledge craniosynostosis has not been reported previously. Craniosynostosis refers
to the premature fusion of one or more of the calvarial sutures, affecting 1 in 2500 individuals [8]. The calvarial sutures arise where cranial ossification centres meet at approximately 18 weeks of embryonic development. From this stage onwards further skull growth is appositional, and deposition of new mineralised bone matrix occurs along the margins of the sutures [8]. Synchronised closure of these sutures during the postnatal period allows the calvarium to achieve its full size and shape, facilitating normal expansion and development of the underlying brain [9]. Growth restriction along a given margin may result in compensatory, excessive growth at other sutures leading to skull deformity [10]. Furthermore as the brain continues to develop and expand within a limited cranial capacity, raised intracranial pressure (ICP) may complicate craniosynostosis, with potential neurodevelopmental consequences [11].

Here we describe three siblings with the Frank-ter Haar syndrome phenotype, all of whom are homozygous for a complete deletion of exon 13 of the SH3PXD2B gene. They demonstrate many of the classic features associated with Frank-ter Haar syndrome, however two of them also have presented with non-scaphocephalic sagittal synostosis complicated by raised ICP.

**Case presentation**

We present a family of four children born to consanguineous (first cousin) parents originating from Kashmir, Pakistan. Three siblings (two males and one female) have Frank-ter Haar syndrome (Table 1, Figure 1) confirmed by genetic analysis. The youngest male sibling appears to be unaffected.

**Patient 1**

This male patient was the firstborn child, delivered by caesarean section for macrocephaly and cephalopelvic disproportion. Hypertelorism and dysmorphia were noted at birth, without evidence of fetal head constraint. He was referred to the Plastic Surgery Department for severe hypertelorism and forehead bossing. On examination at 20 months the head circumference was 49 cm (>99.6th centile), with marked hypertelorism, frontal at 20 months the head circumference was 49 cm severe hypertelorism and forehead bossing. On examination, no evidence of fetal head constraint. Facial features were normal (46,XY). Alternative clinical diagnoses considered included Winchester syndrome and geleophysic dysplasia, but genetic testing for these disorders was normal. The diagnosis was confirmed following the identification of the SH3PXD2B mutation at age 12 years and 4 months (Figure 2, Figure 3).

The mitral valve function subsequently deteriorated resulting in ventricular dilatation and requiring mitral valve repair at 12 years and 5 months. Examination at age 12 years and 11 months revealed a progressive lower limb oedema, which had been developing over a 2 year period, and was initially suspected to be a complication of his cardiac condition. Originally affecting the right leg only, it had progressed to involve the left groin, left leg and genitalia, and appeared to be lymphatic in origin. Lymphoscintigraphy studies at age 13 years and 10 months demonstrated profound lymphatic abnormalities in both lower legs and functional hypoplasia of the main draining lymphatics.

This patient has a left-sided astigmatism and meibomian gland dysfunction; however he does not have any of the ocular complications classically associated with Frank-ter Haar syndrome, such as megalocornea and glaucoma [7,16]. Intraocular pressures have been within the normal range, without clinical evidence of glaucoma. He has been attending a mainstream school with learning support, and is under occupational therapy for difficulties with fine motor skills, washing and dressing as a result of the severe hand contractures and deformity.

**Patient 2**

This is the second affected sibling in the family, delivered by caesarean section for maternal proteinuria without evidence of fetal head constraint. Facial features including hypertelorism were noticed at birth. Examination on presentation to the craniofacial department at age 6 years and 6 months demonstrated hypertelorism, brachycephaly (cephalic index 89%), a flat nasal bridge, prominent ears, a class III malocclusion and hypoplastic teeth. Her fingers and toes appeared shortened and exostoses on the dorsal aspect of the radius and ulna were visible on examination of the arms.

CT head and 3D studies were carried out at age 6 years and 10 months to further delineate the craniofacial features. This demonstrated sagittal synostosis, however the skull...
Table 1 Comparison of clinical features in patients 1–3 with previous cases with proven SH3PXD2B mutations

| Clinical features                                      | Patient 1 | Patient 2 | Patient 3 | Other 10 Frank-ter Haar cases with confirmed SH3PXD2B mutation [7] |
|--------------------------------------------------------|-----------|-----------|-----------|-------------------------------------------------------------------|
| **General**                                            |           |           |           |                                                                  |
| Gender                                                 | M         | F         | M         | M:F 8:2                                                           |
| Consanguinity                                          | +         | +         | +         | 9/10                                                              |
| **Craniofacial**                                       |           |           |           |                                                                  |
| Prominent forehead                                    | +         | +         | +         | 10/10                                                             |
| Hypertelorism                                          | +         | +         | +         | 9/9                                                               |
| Brachycephaly                                          | +         | +         | +         | 10/10                                                             |
| Wide anterior fontanelle                               | +         | -         | +         | 10/10                                                             |
| Prominent ears                                         | +         | +         | -         | 5/7                                                               |
| Flat nasal bridge                                      | +         | +         | -         |                                                                  |
| Micrognathia                                           | +         | -         | -         | 9/10                                                              |
| Class III malocclusion                                 | -         | +         | -         | †                                                                 |
| Anterior open bite                                     | -         | -         | +         | †                                                                 |
| Open metopic suture                                    | +         | -         | -         | †                                                                 |
| Sagittal synostosis                                    | -         | +         | -         | †                                                                 |
| Raised intracranial pressure                           | -         | +         | -         | †                                                                 |
| Hypoplasia of teeth                                    | +         | +         | -         |                                                                  |
| Broad mouth                                            | +         | +         | -         | 10/10                                                             |
| Broad alveolar ridges                                  | NR        | NR        | NR        | 6/8                                                               |
| Anteverted nostrils                                    | -         | -         | -         | 6/9                                                               |
| Full cheeks                                            | +         | +         | +         | 10/10                                                             |
| **Skeletal**                                           |           |           |           |                                                                  |
| Talipes                                                | +         | -         | -         | 5/8                                                               |
| Size discrepancy in feet                               | -         | +         | -         | †                                                                 |
| Exostoses                                              | +         | +         | -         | †                                                                 |
| Subcutaneous nodules                                   | +         | +         | -         | †                                                                 |
| Contractures/flexion deformity fingers/clawing         | +         | -         | -         | 3/10                                                              |
| Short hands/digits, brachydactyly                      | +         | +         | -         | 10/10                                                             |
| Kyphosis                                               | -         | -         | +         | 5/8                                                               |
| Bowing of long bones                                   | NT        | NT        | NT        | 7/10                                                              |
| Prominent coccyx                                       | +         | -         | -         | 8/10                                                              |
| **Cardiac**                                            |           |           |           |                                                                  |
| Aortic regurgitation/prolapse                          | AVR       | AVR       | -         | 1/6                                                               |
| Tricuspid regurgitation                                | +         | -         | -         |                                                                  |
| Mitral valve prolapse/regurgitation                    | MVP/MVR   | MVP/MVR   | MVR       | 3/6                                                               |
| Ventricular septal defect                              | -         | -         | -         | 5/7                                                               |
| Double right outlet                                    | -         | -         | -         | 2/3                                                               |
| **Ocular**                                             |           |           |           |                                                                  |
| Megalocornea                                           | -         | -         | -         | 9/9                                                               |
| Congenital glaucoma/raised IOP                         | -         | -         | -         |                                                                  |
was not scaphocephalic in shape, but instead appeared brachycephalic in keeping with the clinical examination findings. There was evidence of limited space within the supratentorial compartment, and small ventricles. Although neurological development had previously been within normal limits, difficulties with literacy and recurrent headaches were reported at this time, also suggestive of raised ICP. ICP monitoring (Codman Microsensor, Codman and Shurtleff Inc., Raynham, Mass.) demonstrated elevated pressures with a mean of 22 mmHg and 5 significant

| Table 1 Comparison of clinical features in patients 1–3 with previous cases with proven SH3PD2B mutations (Continued) |
| --- |
| **Other** |
| Recurrent UTIs/duplex system | NT | + | NT |
| Bilateral lymphoedema legs | + | - | - | + |

Comparison is made with features in other previously-reported confirmed cases of Frank-ter Haar syndrome with known SH3PD2B mutations [7].

- Features not described in any previous report or Frank-ter Haar syndrome, regardless of whether or not genetic analysis was performed to confirm the diagnosis [1-3,5,7,12-15].
- NR - not recorded.
- NT - not tested.
- AVR - aortic valve regurgitation.
- MVR - mitral valve regurgitation.
- MVP - mitral valve prolapse.

**Figure 1** A-D: Patient 1. A: Antero-posterior (AP) view showing facial features including hypertelorism. B: Lateral view showing brachycephaly and micrognathia. C: X-ray (XR) right radius/ulna showing broad appearance of the radius at the junction between the proximal and middle thirds. D: XR left hand showing crowding of the carpal bones, broad metacarpals, proximal and middle phalanges, and flexion at the MCP and PIP joints. E: Patient 2. E: AP view showing facial features including hypertelorism. F: Lateral view showing brachycephaly. G: 3D CT scan showing absence of the sagittal suture. H: Patient 3. H: AP view showing facial features including hypertelorism. I: Lateral view showing class III malocclusion and brachycephaly. J: 3D CT scan showing absence of the sagittal suture.
Figure 2 Genome and sequence context of deletion in SH3PXD2B. The upper panel shows a schematic representation (not to scale) of SH3PXD2B around the deleted region. Exons are shown as rectangles with coding sequence filled black and the 3' UTR unfilled. Affected individuals were homozygous for a 7,625 bp deletion (double-headed red arrow). The breakpoint (dotted red lines) occurred at the position shown in the sequence chromatogram from patient 2, with an ambiguity of one nucleotide because a cytosine is located at both breakpoints. The lower panel shows the results of PCR with the primer pairs indicated. Individuals homozygous for the deletion failed to amplify using primer pair 12F/13-8R (upper gel image, 2,268 bp product); all family members yielded a truncated product using primer pair 12F/13-7R (lower gel image; non-deleted product would be 11,464 bp) indicating that unaffected family members are heterozygous for the deletion. C: control DNA from an unaffected, unrelated individual. N: negative control. The hg19 co-ordinates of the deleted region are chr5:171,763,754-171,771,378.

Figure 3 Schematic plan of SH3PXD2B (TKS4) protein showing all mutations identified to date and their location in relation to domains defined by PROSITE (prosite.expasy.org). Note the extent of the deletion identified in this family. A deletion of the entire encoding SH3PXD2B gene has also been reported in another affected family [7].
associated B-waves. Calvarial expansion was successfully undertaken. She made a good post-operative recovery, and the headaches subsequently resolved.

This sibling has also developed cardiac complications but has been less severely affected than her older sibling. Echocardiography at age 7 years and 6 months demonstrated mild-moderate mitral regurgitation with mitral valve prolapse, and minimal aortic regurgitation. Left ventricular function is currently stable. The diagnosis of Frank-ter Haar syndrome was made at age 7 years and 7 months following genetic analysis of the family (Figure 2).

This patient has not developed any of the ocular complications classically associated with Frank-ter Haar syndrome and intraocular pressures and appearance of the retina have been within normal limits. She has been attending a mainstream school, but has experienced some difficulties with literacy.

Patient 3
Patient 3 is the younger affected male sibling. He was delivered by caesarean section following a normal pregnancy, without evidence of fetal head constraint. Facial features in keeping with Frank-ter Haar syndrome were noticed soon after birth including hypertelorism, a broad nose, and skeletal features including short fingers and toes, and a mild positional talipes. The cephalic index was 88% in keeping with the clinical appearance of brachycephaly. Calvarial expansion was performed at age 7 years and 7 months.

Cardiac complications have also been documented, but have been less severe than the other affected siblings, with evidence of mild mitral regurgitation on echocardiography. No ocular complications have been reported, and intraocular pressures have been within the normal range. He has required some learning support for literacy and numeracy, but developmental progress and performance at school have been within normal limits.

Genetic analysis
We genotyped DNA samples from three affected patients, one unaffected sibling and their parents using the Affymetrix GeneChip Human Mapping 250K Sty Array. Linkage analysis was performed assuming autosomal recessive inheritance, full penetrance, consanguinity and a disease allele frequency of 0.0001. Multipoint LOD scores were calculated using the program ALLEGR0 [17]. We identified three regions of shared homozygosity on chromosomes 5 (150943995–173861414; bg18 coordinates), 8 (134041593–146264218) and 12 (115552170–123960781). Following the identification of mutations in Frank-ter Haar syndrome [7], it was noted that the region of homozygosity on chromosome 5 included the SH3PXD2B gene. All coding exons of SH3PXD2B were therefore PCR amplified in samples from the family (primer sequences available on request). As exon 13 failed to amplify (using primers 13F, 5′-AACATCTCCATTGTTGCTCC-3′ and 13R, 5′-GATGTTTGGCTGCGATC-3′, positions of primers are shown in Figure 2) in the affected individuals, an alternative primer pair (13-2F, 5′-CATGTAAGATATCCGCCGGAACATGGT-3′; 13-2R, 5′-CCCATGTCATTTTTCACGTGGAAAC-3′) was designed to rule out the possibility of a SNP underlying the primer and preventing annealing. This also failed to amplify in the 3 affected individuals, confirming a homozygous deletion of exon 13 of SH3PXD2B. Further primer pairs were designed throughout the 3 untranslated region (UTR) to identify the extent of the deletion (primer sequences available on request), primer pair near the end of the 3′ UTR successfully amplified in the affected individuals (13-7F, 5′-TACCTTATCCACAGTTGCTGA-3′; 13-7R, 5′-GCGTGGCCTTGTTGAGAGGTTTAAATGAC-3′), the reverse primer of which was then used in a long PCR with the 12F primer (5′-ATACCAACTAGTGGCTCCACGC-3′). This yielded a truncated product of ~3.5 kb rather than the normal 11,464 kb, which was sequenced to identify the exact breakpoint. All family members produced this smaller PCR product, demonstrating that unaffected members are heterozygous carriers of the allele bearing the deletion, which preferentially amplifies during PCR. The non-deleted allele was demonstrated by PCR between 12F and 13-8R (5′-CATACACATCGTGGAAATACACCGGATC-3′). The complete deletion of the coding part of exon 13 is predicted to abolish over half of the protein, including the SH3 domains and a proline-rich domain (Figure 3).

Conclusions
Frank-ter Haar syndrome is a rare, autosomal recessive disorder. We present three siblings born to consanguineous parents, who are homozygous for a deletion of exon 13 of the SH3PXD2B gene. These three children share many of the characteristic physical features of the
Frank-ter Haar phenotype, however two of the three siblings also developed non-scaphecephalic sagittal synostosis, both cases being complicated by raised ICP. Craniosynostosis and raised ICP have not been described in previous reports of Frank-ter Haar syndrome.

The sagittal suture is involved in 50-60% of cases of craniosynostosis, and is therefore the most common suture to be synostosed [8,10]. Familial or genetic factors are less significant in sagittal synostosis than in other forms of craniosynostosis. In a large study of over 500 patients with isolated sagittal synostosis familial factors were identified in only 6% [18]. Most such cases are likely to be multifactorial, as causative genetic mutations are only rarely identified [19-21]. In comparison genetic factors comprising chromosomal abnormalities and gene mutations appear to account for at least 21% of cases of craniosynostosis overall [22]. Intrauterine fetal head constraint has been implicated as an important causative factor in sagittal synostosis [23], however to our knowledge neither of our two Frank-ter Haar siblings with sagittal synostosis had a history of intrauterine fetal head constraint.

It is widely acknowledged that premature fusion of the calvarial sutures may restrict normal growth and development of the underlying brain especially in syndromic cases. This can be complicated by raised ICP [10]. Raised ICP may be defined as an elevated baseline of function mutations have been described. The first is a spontaneous nee mutation resulting from the deletion of a single base pair in exon 13 of the Sh3pxd2b gene (1303delA), which is thought to encode a truncated protein lacking part of the third and all of the fourth SH3 domains [16,26]. The second is an engineered null mutation created by the insertion of a gene trap vector between exons 3 and 4 of the Sh3pxd2b gene, which appears to result in a complete loss of gene expression [7]. Mice with the engineered null mutation appear to share many of the craniofacial, skeletal and cardiac features described in patients with Frank-ter Haar syndrome including mitral valve defects, hypertelorism and micrognathia [7,26,27]. Significantly, abnormal cranial proportions were described in these Sh3pxd2b null mice, which had a short snout, brachycephaly and hypertelorism, associated with persistently open sagittal sutures [7]. Both Sh3pxd2b null and Sh3pxd2b nee mice appear to develop ocular features including corneal opacities and anterior segment dysgenesis resulting in early-onset glaucoma. Sh3pxd2b nee mice also have abnormal craniofacial features including a short snout, brachycephalic skull, and Eustachian tube dysmorphology [16,26,27]. Surprisingly the ocular features associated with Frank-ter Haar syndrome were not identified in any of the three affected siblings, which contrasts both with the occurrence of megalocornea in all previous patients with identified SH3PD2B mutations and with the ocular abnormalities described in both mouse models.

A variety of specific SH3PD2B gene mutations have been reported in families with the Frank-ter Haar syndrome phenotype, but none so far have reported specific involvement of exon 13, the region of the gene affected in this family (Figure 3). However deletion of the entire SH3PD2B gene has been described in one family [7]. Our three children have many features classically associated with Frank-ter Haar syndrome however they also have additional features which to our knowledge have not been described in previous reports (Table 1). These include lymphoedema, class III malocclusion, anterior open bite, open metopic suture, and non-scaphecephalic sagittal synostosis. Although we cannot completely exclude the possibility that these novel phenotypes are related to the two other regions of shared homozygosity identified on chromosomes 8 and 12 in this family, the involvement of the sagittal suture and additional craniofacial features in mouse models of the disease provides a precedent. The clinical features of craniosynostosis and raised ICP in this family therefore expand the clinical spectrum of Frank-ter Haar syndrome.

Consent
Written informed consent was obtained from the family for publication of this case report and any accompanying
images. A copy of the written consent is available for review by the Series Editor of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
CLB collected the clinical data and wrote the paper. ALF performed the mutation analysis. JAH made the clinical diagnosis in the patients. GN and PN performed the homozygosity mapping. SAW supervised the clinical study. AOWM supervised the genetic studies and wrote the paper. DJ supervised the clinical study and wrote the paper. All authors read and approved the final manuscript.

Acknowledgements
The family for their cooperation.

Wellcome Trust (078666) for funding (AOMW).

Author details
1Oxford Craniofacial Unit, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford OX3 9DU, UK. 2Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK. 3Department of Clinical Genetics, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, UK. 4Cologne Centre for Genomics, University of Cologne, Cologne, Germany. 5Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany. 6Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany. 7Current address: Department of Clinical Genetics, Great Ormond Street Hospital NHS Foundation Trust, WC1N 3BH, UK.

Received: 19 May 2012 Accepted: 29 October 2012 Published: 9 November 2012

References
1. Maas SM, Kayserili H, Lam J, Apak MY, Hennekam RC: Autosomal recessive Melnick-Needles syndrome or ter Haar syndrome? Report of a patient and reappraisal of an earlier report. Am J Med Genet 1997, 65(3):312–316.
2. ter Haar B, Hamel B, Hendriks J, de Jager J: Disruption of the podosome adaptor protein TKS4 (SH3PXD2B) causes scaphocephaly: a series of eight cases. J Anat 2003, 202(3):139–148.
3. Millán JL, Hennekam R, Hamel B, Courtneidge SA, van Bokhoven H: Atypical Crouzon Syndrome with a Novel Cys62Arg Mutation in FGFR2 Presenting with Sagittal Synostosis. Cleft Palate Craniofac J 2012, 49(3):373–377.
4. Renier D, Sainte-Rose C, Marchac D, Renier D: Genetic study of scaphocephaly. Am J Med Genet A 1996, 55(2):282–285.
5. Neelova M, Schaefer C, Rentrop J, Hentschel N,的商品名,商品名,商品名,商品名,商品名,商品名,商品名: Inclusion in PubMed, CAS, Scopus and Google Scholar
6. Neelova M, Schaefer C, Rentrop J, Hentschel N,商品名,商品名,商品名,商品名,商品名,商品名,商品名: No space constraints or color figure charges
7. Neelova M, Schaefer C, Rentrop J, Hentschel N,商品名,商品名,商品名,商品名,商品名,商品名,商品名: Thorough peer review
8. Neelova M, Schaefer C, Rentrop J, Hentschel N,商品名,商品名,商品名,商品名,商品名,商品名,商品名: Convenient online submission
9. Neelova M, Schaefer C, Rentrop J, Hentschel N,商品名,商品名,商品名,商品名,商品名,商品名,商品名: Inclusion in PubMed, CAS, Scopus and Google Scholar
10. Neelova M, Schaefer C, Rentrop J, Hentschel N,商品名,商品名,商品名,商品名,商品名,商品名,商品名: Research which is freely available for redistribution