Author's response to reviews

Title: Bilateral radial agenesis with absent thumbs, complex heart defect, short stature, and facial dysmorphism in a patient with pure distal microduplication of 5q35.2-5q35.3

Authors:

Aleksander Jamsheer (jamsheer@wp.pl)
Anna Sowinska (sowka7@wp.pl)
Malgorzata Jamsheer-Bratkowska (mjamsheer@pzh.gov.pl)
Tomasz Trzeciak (trzeciak@orsk.ump.edu.pl)
Anna Latos-Bielenska (anna.latosbielenska@gmail.com)
Dorota Simon (dorotasimon@poczta.onet.pl)

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Author's response to reviews: see over
RE: “Bilateral radial agenesis with absent thumbs, complex heart defect, short stature, and facial dysmorphism in a patient with pure distal microduplication of 5q35.2-5q35.3.”

November 20th, 2012

Dear Editor,

We would like to thank you and the reviewer for your helpful comments. We have revised the manuscript, and hope it is significantly improved. Please find the detailed responses to the reviewer’s comments below.

We would be grateful for your further consideration.

With Kind Regards,

Aleksander Jamsheer, MD, PhD, MSc

Reviewer’s report:
This manuscript reports on a patient with clinical features similar to reported individuals, but with additional findings that have not previously been identified. In addition, the patient that is being reported did not include the MSX2 gene which has been shown to be important during developmental. Therefore, the authors propose that there may be other genes or regulatory elements that may also be playing a role in the phenotype of individuals with a duplication involving distal 5q. I recommend acceptance of the manuscript, pending inclusion of the following information.

Compulsory revisions:
1) This study was based on laboratory findings including aCGH, karyotype and FISH analysis; however, none of this data was shown. To strengthen the paper, the authors should add a figure that includes all of the above results. Also, was the karyotype really normal for this patient? It was stated that FISH was performed on the abnormal chromosome 5, so was it actually abnormal and just not detectable by chromosome analysis? The figure would help to clarify this.

An additional image (Figure 2) has been introduced. The image combines the data from aCGH, karyotype, FISH, and qPCR assays. Since visual presentation of aCGH results performed on Agilent’s platform has been lost, we decided to repeat the analysis with our current platform, i.e. Roche NimbleGen (CGX 12-plex chips). Therefore, only the latter data is shown.
Initial GTG banding did not show any chromosomal abnormality. However once we got back to karyotype after identification of the microaberration upon aCGH, we could see a tiny gain on 5q. This tiny gain could only be seen retrospectively. Figure of partial karyotype has been shown.

2) Absent thumbs was previously reported as a clinical feature in a patient with increased copies of distal 5q, so why are having additional clinical findings such as bilateral radial aplasia important when on average you see this in approximately 1/30,000 live births without 5q duplications?

Absent thumbs and radial ray agenesis both belong to the spectrum of radial ray deficiency. Thus, we suggest that this kind of malformation did not occur only by chance in two different patients carrying a gain on 5q. On the other hand, such possibility cannot be excluded.

Minor Essential Revision:
1) A good deal of the numbers listed are showing with a comma between, eg) 7,8 kg instead of 7.8 kg and 9,5 years.

Corrected

2) In the methods section, there is little to no information on the additional participants that were used for sequencing and MLPA. In the discussion section the authors mention that 8 patients were studied with bilateral radial agenesis, but no additional information was provided. Was chromosome analysis, aCGH, FISH studies normal for these patients? What were there ages, background?

Information about additional participants included in this study has been introduced in the method section:

"Additional probands with bilateral radial aplasia
To identify further probands and test the frequency of 5q35 duplication we screened a cohort of another 8 unrelated sporadic patients (6 males and 2 females) with bilateral radial agenesis and absent thumbs. All patients were of Polish ethnicity and were seen in our genetic clinic at different ages varying from 3 months to 31 years. Four cases manifested isolated limb malformation, whereas the other four presented with additional features comprising congenital heart defect (3 cases), and mental retardation (1 case). The patients were prescreened by bi-directional sequencing and MLPA for TBX5 and SALL4 mutations and turned out to be negative. Additionally, a patient affected by mental retardation was analyzed by means of GTG banding, which showed normal result."

3) There are some misspellings throughout the paper which should be corrected.

Corrected

With Kindest Regards,
Aleksander Jamsheer, MD, PhD, MSc