Another Case of Galloway-Mowat Syndrome Associated With a Biallelic Mutation of the OSGEP Gene

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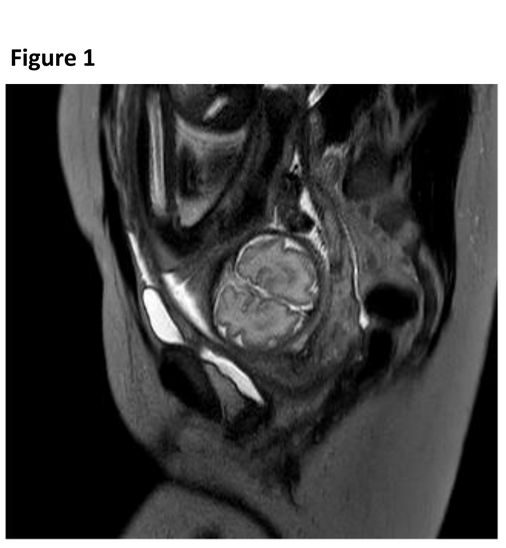
Introduction

Galloway-Mowat syndrome is a rare disease entity associating primary microcephaly and developmental delay with glomerular proteinuria rapidly progressing to cortico-resistant nephrotic syndrome and end-stage renal disease.
Due to its rarity (estimated frequency: 1/10.000.00) and its genetic heterogeneity, it has been proven difficult to identify the causal genes. Six genes are now known to be implicated in Galloway-Mowat syndrome including the OSGEP gene, recently published in 2017.
Here, we describe another case of Galloway-Mowat syndrome associated with a biallelic missense mutation of the OSGEP gene.

Case Presentation

At 30 weeks gestation, primary microcephaly was suspected in an otherwise uncomplicated pregnancy. Fetal MRI confirmed the presence of microcephaly associated with bilateral frontal pachygyria. Proteinuria was detected soon after birth (3g/l). At 6 months, the child presented a developmental delay; the neurological performances did not yet reach the milestones expected for a two month old baby. The child died at the age of 8 months from a respiratory infection complicated by overt nephrotic syndrome.
Our index case was the fifth child of consanguineous parents; the parents had one healthy child, two children were born with 'a very small head' and died before age one of terminal renal failure. A fourth fetus died during pregnancy. It was impossible to retrieve the medical records of these children due to geopolitical reasons.
SNP-array showed multiple regions of homozygosity including the 14q11.2 region where the OSGEP gene is located. Sequencing of the OSGEP gene revealed the presence of a homozygous c.953C>T missense mutation; both parents were healthy carriers.

Figure 1



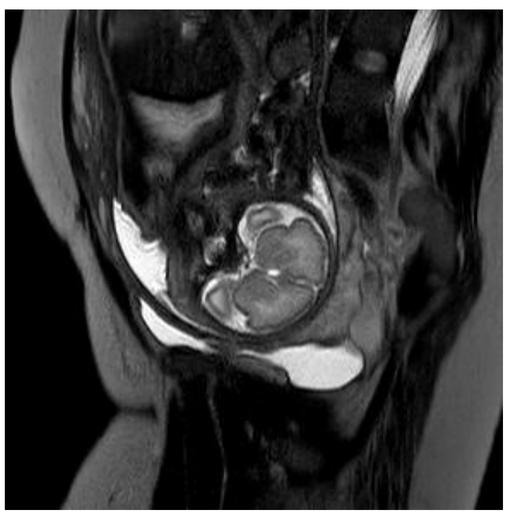
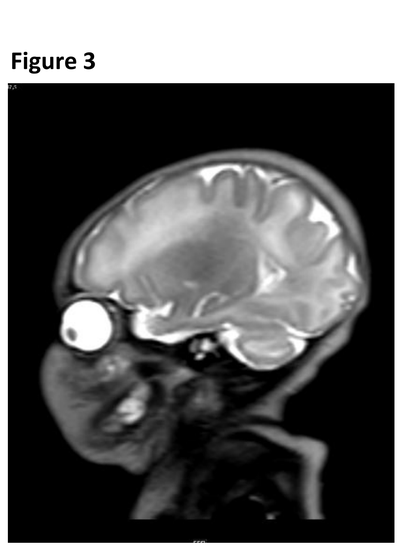


Figure 2

Figure 3



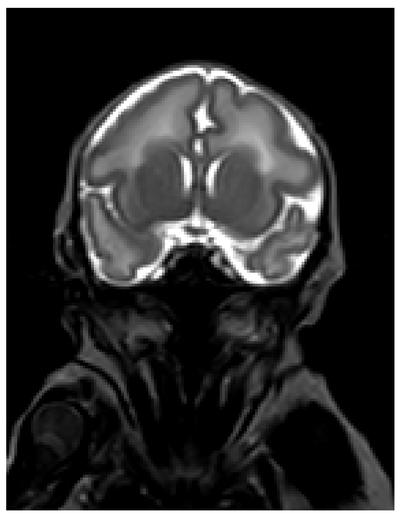


Figure 4

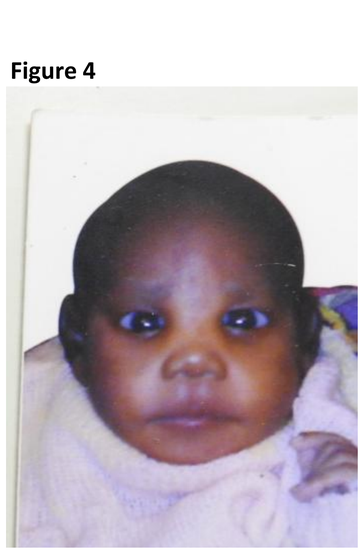


Figure 1: MRI during pregnancy showing bilateral frontal pachygyria
Figure 2: clinical pictures of the index case
Figure 3: postnatal MRI confirming the suspicion of bilateral pachygyria
Figure 4: clinical pictures of two deceased sibs of the index case demonstrating the presence of microcephaly

Conclusion

The OSGEP gene is one encoding the four subunits of the KEOPS-complex. Genes of the KEOPS complex are thought to be "essential" genes, required for the viability of the human cell lines.
Pathogenic mutations of OSGEP have been shown to induce defects in the cytoskeleton and to decrease the migration rate of podocytes, thus linking the two major manifestations of Galloway-Mowat disease, structural brain anomalies and nephrotic syndrome.
The index case also presented several dysmorphic features, as previously described associated with KEOPS-complex mutations (a small, narrow forehead, large ears, deep-set eyes and arachnodactyly (not shown)).
Hereby, we confirm the association of biallelic OSGEP mutations with nephrotic syndrome with primary microcephaly and brain anomalies, also known as Galloway-Mowat syndrome.

-Braun DA *et al*. Mutations in KEOPS-complex genes cause nephrotic syndrome with primary macrocephaly. Nat Genet. 2017;49:1529-1538
-Edvardson S *et al*.tRNA N6-adenosine threonylcarbamoyltransferase defect due to KAE1/TCS3 (OSGEP) mutation manifest by neurodegeneration and renal tubulopathy. Eur J Hum Genet. 2017;25:545-551

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