Received: 25 January 2022 | Revised: 23 March 2022 | Accepted: 9 April 2022

DOI: 10.1002/pd.6148

RESEARCH NOTE

PRENATAL DIAGNOSIS WILEY

Prenatal diagnosis of microcephaly as shown by plateauing of head circumference growth during the 3rd trimester in a fetus with a CCND2 inverse growth variant

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Key points

What's already known?

- Variants in CCND2 gene are known to cause syndromic macrocephaly. Recently inverse growth proximal variants were described in five individuals with microcephaly.

What does this study add?

- CCND2 loss of function distal variants can cause fetal microcephaly.

Prenatal diagnosis of neuronal proliferation disorders in fetuses with an otherwise normal US examination is challenging since most cases have normal head biometry until late in pregnancy or even during the first months of life.[1,2]

The patient, 37 years old woman G8P2 had an otherwise normal pregnancy, including normal chromosome micro array (CMA), until 23 weeks when fetal head measurements, were slightly smaller than expected leading to a recommendation for follow up. Repeated examinations showed head circumference (HC) within normal limits but its growth pattern was suboptimal (Figure 1). The HC of both parents as of their two children was within normal limits. At 33.4 weeks, the HC was found to be 1.9 SD below the norm, the corpus callosum measured 32 mm (percentile 5) and the weight estimation was 2182 gr. HC plateaued from this time on (Figure 1). At 37 weeks the HC was found to be 2.4 SD below the norm. The patient was referred for fetal MRI and genetic consultation before whole exome sequencing. The MRI showed non-specific brain findings and possible facial dysmorphism. The trio WES results came 5 days later (October 2021) and revealed a pathogenic heterozygous denovo splicing (loss of function) variant in CCND2 gene (c.720+1G>A – chr12–4398157G>A, NM0017594). The variant CCND2:c.720+1G>A is a splicing mutation based on PVS1, PM2, PS2, and PP4 [a denovo Null variant (within ±2 of splice site), in gene CCND2 for which loss-of-function is a known mechanism of disease (gene has 8 pathogenic LOF variants and gnomAD Loss-of-Function Observed/Expected = 0), associated with similar phenotype. Using strength Strong because the position is strongly conserved (phyloP100way = 9.38 is greater than 7.2), and this variant is predicted splicing (scSNV ADA Boost score = 1 is greater than 0.708). Variant not found in gnomAD exomes (with good gnomAD exomes coverage = 31.3). Variant not found in gnomAD genomes (with good gnomAD genomes coverage = 30.3)].

Based on these findings and accordingly with the genetic counseling the parents decide to apply for termination of pregnancy in accordance with Israeli law. A female fetus weighting 2675 gr (percentile 19 for Israeli females) was delivered. The stillborn had low set dysmorphic ears, wide nasal bridge, bowed upper lip and mild retrognathia, with an HC of 30 cm (−2.6SD).

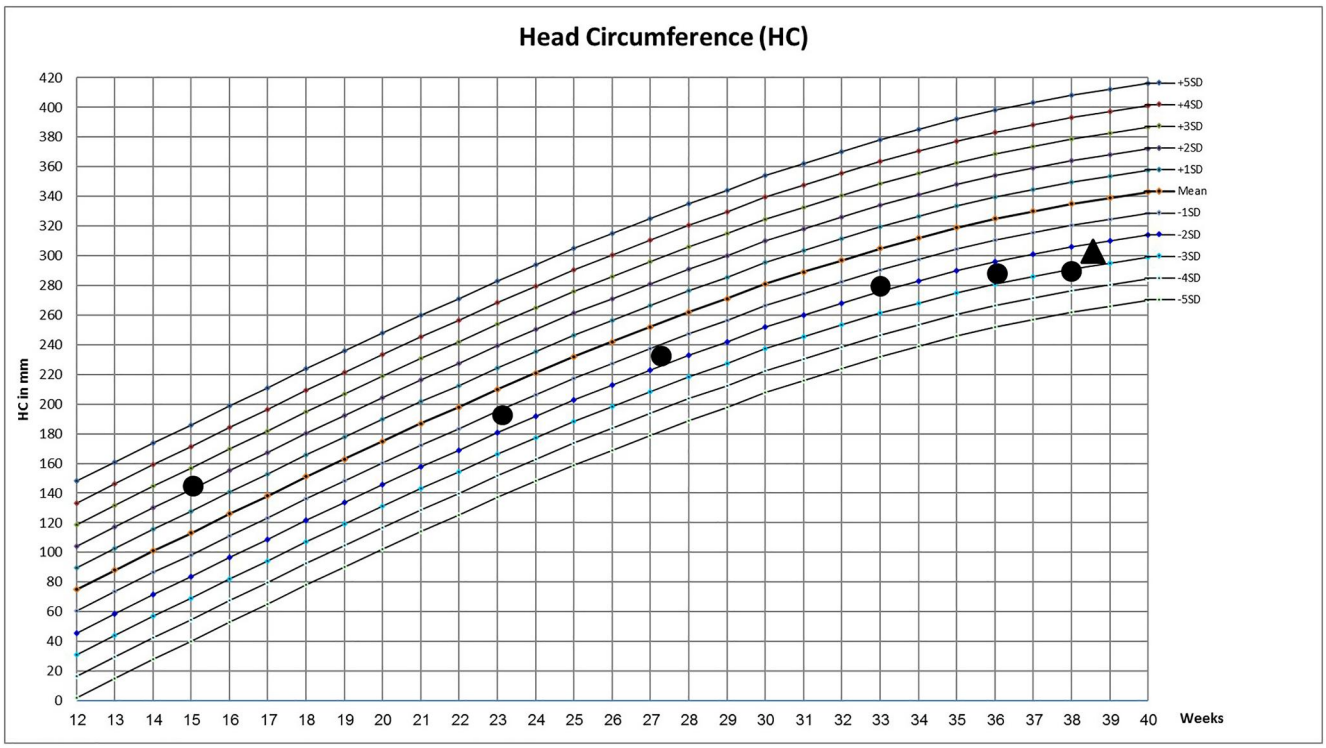

FIGURE 1 Development of head circumference through pregnancy (adapted from Chervenak et al.[7]) Black circles, HC through pregnancy. Black triangle, HC at birth [Colour figure can be viewed at wileyonlinelibrary.com]

In the absence of associated anomalies, fetal primary microcephaly is rarely diagnosed, and when suspected the diagnosis should be made with caution, because of two different reasons. On one side the definition of fetal microcephaly requires a HC measurement three standard deviations below the norm due to the fact that the accepted definition in children, two standard deviations, includes 2.3% of the normal population; on the other side approximately nine out of 10 children diagnosed by the age of 12 months with this disorder had a normal head circumference at birth. As previously reported by Schwarzler et al.[3] and Le Ray et al.,[4] in our patient, the diagnosis was suspected based on the performance of repeated HC measurements showing a clear deficient HC growth (Figure 1).

The present case demonstrates the significant value of WES for the diagnosis of genetic microcephaly syndromes, this is critical late in pregnancy when confronted with a low head size in the absence of familial history or associated anomalies. In our patient, there was a clear plateau in HC growth staring at 33 weeks that by himself was indicative of developing microcephaly but only in conjunction with the NGS result reached diagnostic certainty.

The case series reported by Pirrozi et al. although accepted in May 2021 was published only in September 2021; **in our patient WES was performed on the stored DNA from the amniocentesis in October 2021**, should the amniocentesis performed early than **this date** most probably the denovo mutation would be classified as of unknown significance due to the lack of previous reported cases.

Mutations causing gain of protein function in the CCND2 gene are known to produce megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 3 (MPPH3) (OMIM # 615938).[5] But as mentioned, the month before the WES was performed in our patient, it was shown, in a case series by Pirozzi et al.[6] including 5 individuals from 3 different families, that mutations causing loss of protein function in this gene are associated with microcephaly, growth restriction and neurodevelopmental disorders. In their report three out of five newborns were IUGR, but only one presented with microcephaly.

Since the mutations causing microcephaly in the mentioned study have been reported in the first two exon and the mutation causing megalencephaly in the 5th exon, it was concluded that the proximal variants in CCND2 are associated with reciprocal effect on human brain growth (microcephaly and megalencephaly due to possible loss or gain of protein function, respectively), adding to the growing paradigm of inverse phenotype due to segregation of key brain growth genes. In our case the splicing mutation was located at the end of exon 4, which can imply that variants in the first four (out of five) exons of the CCND2 gene are associated with microcephaly and only mutations in the 5th exon causes macrocephaly. If this observation is confirmed in the future, it may indicate the point according to which we can predict the outcome of variants in this gene.

ACKNOWLEDGMENT

None.

CONFLICT OF INTEREST

No conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request when permitted by Law.

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How to cite this article: Malinger G, Haratz Krajden K, Brinbaum R, Tsur E, Berger R, Shohat M. Prenatal diagnosis of microcephaly as shown by plateauing of head circumference growth during the 3rd trimester in a fetus with a CCND2 inverse growth variant. *Prenat Diagn*. 2022;42(10):1343-1345. https://doi.org/10.1002/pd.6148