Atypical, milder presentation in a child with CC2D2A and KIDINS220 variants
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Introduction

Cilia are hair-like organelles that are involved in a variety of important processes from embryonal development to cell signalling (Reiter and Leroux, 2017). They are found on virtually all cells. Due to their widespread presence, a disruption to their function leads to multisystem abnormalities from embryonal development to clinical manifestations associated with the two conditions. Clin Dysmorphol 29: 10–16 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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10 Original article

With the increasing availability and clinical use of exome and whole-genome sequencing, reverse phenotyping is now becoming common practice in clinical genetics. Here, we report a patient identified through the Wellcome Trust Deciphering Developmental Disorders study who has homozygous pathogenic variants in CC2D2A and a de-novo heterozygous pathogenic variant in KIDINS220. He presents with developmental delay, intellectual disability, and oculomotor apraxia. Reverse phenotyping has demonstrated that he likely has a composite phenotype with contributions from both variants. The patient is much more mildly affected than those with Joubert Syndrome or Spastic paraplegia, intellectual disability, nystagmus, and obesity, the conditions associated with CC2D2A and KIDINS220 respectively, and therefore, contributes to the phenotypic variability observed.

The number of causative genes associated with ciliopathies is nearing 200 (Reiter and Leroux, 2017). Coiled-coil and C2 domains-containing protein 2A (CC2D2A) is a protein which has been found to localise at the transition zone of cilia and has been demonstrated to form complexes with other proteins (known to cause ciliopathies) that influence ciliogenesis (Chih et al., 2011; Garcia-Gonzalo et al., 2011) and the movement of proteins between the ciliary and plasma membranes (Chih et al., 2012).

Variants in CC2D2A are associated with the autosomal recessive ciliopathy Joubert syndrome (Noor et al., 2008), Cerebellar vermis hypoplasia, oliophengia, congenital ataxia, ocular coloboma and hepatic fibrosis (COACH) syndrome (Doherty et al., 2010), and Meckel syndrome (Tallila et al., 2008). Joubert syndrome was first described in 1969 by Marie Joubert (Joubert et al., 1969). It is characterised by the presence of the molar-tooth sign (MTS) on brain imaging due to abnormal development of the cerebellar vermis and brainstem, hypotonia, and developmental delay (Maria et al., 1999). The diagnosis is, therefore, made on the grounds of imaging and clinical examination.

We are discovering that Mendelian disorders with well-defined phenotypes can be more variable and milder than originally described. This may be partly due to the fact that initial studies focused on severe developmental delay phenotypes but with wider access to next-generation sequencing, patients with non-distinctive, milder phenotypes are having more advanced genetic testing. Joubert syndrome and its associated genes are no exception (Irfanullah et al., 2016; Méjécase et al., 2019).

Here, we report a patient identified through the Deciphering Developmental Disorders (DDD) study (Wright et al., 2015) who is homozygous for a pathogenic variant in CC2D2A and heterozygous for a previously unreported pathogenic variant in KIDINS220. We provide a comprehensive review of the CC2D2A variants that have been published so far to add to the work previously published by Bachmann-Gagescu et al. (2012).

Materials and methods

The patient was referred to a UK clinical genetics centre and subsequently recruited to the DDD study. Trio-based exome sequencing was performed followed by analysis as per the DDD protocol described previously (Wright et al., 2015). Variants identified by the DDD study were validated using accredited UK NHS diagnostic genetics
laboratories prior to informing patients. Informed consent was obtained from the patient’s parents for inclusion in this report.

The Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) was searched for patients recruited to the DDD study who were found to have variants in CC2D2A (Firth et al., 2009).

A GeneMatcher request was created to identify other patients with Joubert Syndrome and CC2D2A variants (Sobreira et al., 2015).

**Results**

The DECIPHER database search identified a total of four patients from the DDD study with variants in CC2D2A. The pathogenicity of the variants was classified as uncertain in two patients, and one variant was not allocated a pathogenicity classification.

The GeneMatcher request did not identify any additional patients.

We, therefore, describe one patient who is homozygous for GRCh37(hg17) NM_001080522.2 c.2671G>A, p.(Glu891Lys) missense variant in the CC2D2A gene (DECIPHER ID 293170). This variant is biparentally inherited and has been previously reported in a compound heterozygous patient (Bachmann-Gagescu et al., 2015). A de-novo heterozygous nonsense variant in the KIDINS220 gene was also found; GRCh37(hg17) NM_020738.3 c.1369C>T, p(Gln457Ter). This truncating variant is likely to be pathogenic and has not been previously reported in the literature.

**Clinical report**

Our patient is a male born to consanguineous parents. He has a brother and two cousins who have been diagnosed with autism spectrum disorder. The pregnancy was uncomplicated. He was delivered at 38 weeks gestation weighing 2.77 kg (11th centile). There were no immediate complications after delivery. He is developmentally delayed; he walked after the age of two and had only one to two words at the age of three and a half.

At the age of six and a half, when he was assessed by the clinical genetics team, he was in mainstream school with one-to-one support. He had been diagnosed with an autism spectrum disorder. There were no reports of seizure activity. Parents mentioned that tantrums were a problem, and he is particular with food. On examination, his height was 119 cm (53rd centile), weight was 21 kg (36th centile), and he had an occipital frontal circumference of 52 cm (57th centile). He was not dysmorphic. He had poor horizontal saccadic eye movements which he has had since infancy and a typical head thrust associated with this. An MRI scan of the brain and ultrasound scans of the liver and kidneys were unremarkable. The MTS was absent.

**Published variants**

CC2D2A variants, with and without available phenotypic information, published after the work by Bachmann-Gagescu and colleagues can be found in Tables 1 and 2, respectively. Variants that have been described in a heterozygous state can be found in Table 3.

In Table 2, Ben-Salem et al., (2014) identified a novel variant c.4258G>A, (p.Arg1528His), however, following a review of the variants we noted that the nucleotide at position 4258 is cytosine. We, therefore, believe that this variant should be c.4583G>A which would then result in p.Arg1528His. The senior author in this paper was contacted to clarify this variant and they have confirmed that it should read c.4583G>A.

**Discussion**

A number of CC2D2A variants have been described in the literature since the last summary a few years ago (Bachmann-Gagescu et al., 2012) (see Tables 1–3). The majority of variants have been identified in a compound heterozygous state in individuals who have a diagnosis of Joubert syndrome or Meckel syndrome. We would like to highlight from these summary tables an interesting variant that was described in an individual with Meckel syndrome. Meckel syndrome is a CC2D2A allelic disorder with a more severe phenotype. In general, missense variants lead to Joubert syndrome and null alleles lead to MKS (Mougou-Zerelli et al., 2009). Takenouchi et al. (2017) described a transposable element insertion in CC2D2A; a novel mutation type associated with ciliopathies. This along with a maternally inherited frameshift variant was thought to be the cause of Meckel syndrome in this individual. Transposable element insertions have also been described in Alström syndrome and Bardet Biedl Syndrome (Taşkesen et al., 2011; Tavares et al., 2018) suggesting that this type of variant may be important to bear in mind for cases where only one variant has been identified with the usual analytical pipelines.

Joubert syndrome is genetically heterogeneous and phenotypically very variable. Genotype-phenotype correlations exist which is helpful in informing patients and clinicians about the potential development of complications in the future and guiding monitoring (Bachmann-Gagescu et al., 2015). Joubert syndrome patients with CC2D2A variants seem to have much lower chances of developing organ-specific complications compared to other genes such as TME,M67 where patients are highly likely to have colobomas and develop liver disease (Bachmann-Gagescu et al., 2012). From an ophthalmological perspective, CC2D2A has been shown to be associated with oculomotor apraxia in almost all cases with a high proportion also having nystagmus (Brooks et al., 2018). There have been very few reports of retinal disease in CC2D2A patients with only one patient in two series of patients being identified (Bachmann-Gagescu et al., 2015; Brooks et al., 2018).
| Reference          | Identification       | Allele 1                  | Allele 2                  | Diagnosis | MTS | ENC | DD/ID | OA/N | RCD | Renal | Liver | PD | Other                                  |
|--------------------|----------------------|---------------------------|---------------------------|------------|-----|-----|-------|------|-----|-------|-------|----|-----------------------------------------|
| Srour et al., 2012  | 161.0572             | c.2181+1G>A               | c.4667A>T, p.(Asp1556Val) | JS         | +   | ?   | +     | +    | −   | −     | −     | −  | Hypotonia, ataxia                       |
| Xiao et al., 2017  | Proband              | c.2848C>T, p.(Arg950*)    | c.2581G>T, p.(Asp861Asn)  | JS         | +   | ?   | +     | ?    | ?   | −     | −     | ?  | Hypotonia                               |
| Srour et al., 2017  | UW262-2              | c.3347C>T, p.(Thr1116Met) | c.4741A>G, p.(Thr1581Ala) | JS         | +   | ?   | +     | −    | −   | −     | −     | −  |                                          |
| Srour et al., 2015  | 1342.488             | c.3347C>T, p.(Glu126Lys)  | c.4667A>T, p.(Asp1556Val) | JS         | +   | ?   | +     | −    | −   | −     | −     | −  |                                          |
| Srour et al., 2015  | 1343.488             | c.3347C>T, p.(Glu126Lys)  | c.4667A>T, p.(Asp1556Val) | JS         | +   | ?   | +     | −    | −   | −     | −     | −  | Hypotonia, ataxia, autism, ADHD          |
| Srour et al., 2015  | 1356.492             | c.3347C>T, p.(Glu126Lys)  | c.4667A>T, p.(Asp1556Val) | JS         | +   | ?   | +     | −    | −   | −     | −     | −  | Hypotonia, ataxia, autism, ADHD          |
| Srour et al., 2015  | 39-31-483            | c.3452C>T, p.(Val1151Ala) | c.248-4_248-3insAAGTTTT   | JS         | +   | ?   | +     | −    | −   | −     | −     | −  |                                          |
| Syzmanska et al., 2012 | 158                | c.3540delA, p.(Arg1180Serfs*7) | c.3540delA, p.(Arg1180Serfs*7) | MKS/MKS-like | ?   | +   | +     | +    | +   | +     | +     | +  | Cleft lip/palate + other malformations, see paper for further details |
| Syzmanska et al., 2012 | 180                | c.3540delA, p.(Arg1180Serfs*7) | c.3540delA, p.(Arg1180Serfs*7) | MKS/MKS-like | ?   | +   | ?     | ?    | ?   | PC    | −     | +  | Dandy-Walker malformation                |
| Bachmann-Gagescu et al., 2015 | UW088-3          | c.3989G>A, p.(Arg1330Gln) | c.3743_3746dupTGGT, p.(Pro1250Glnfs*11) | JS         | +   | ?   | +     | −    | −   | −     | −     | −  |                                          |
| Bachmann-Gagescu et al., 2015 | UW088-4         | c.3989G>A, p.(Arg1330Gln) | c.3743_3746dupTGGT, p.(Pro1250Glnfs*11) | JS         | +   | ?   | +     | −    | −   | −     | −     | −  |                                          |
| Al-Hamed et al., 2016 | FT26               | c.4437+1G>A               | c.4437+1G>A               | JS         | ?   | ?   | +     | ?    | ?   | −     | ?     | ?  | Ascites                                 |
| Inciçek et al., 2012 | 1                   | c.4452C>T, p.(Arg1518Trp) | c.4452C>T, p.(Arg1518Trp) | JS         | +   | ?   | +     | −    | −   | −     | +     | +  | Episodic hyperpnoea, coloboma, hypotonia, cerebellar vermis aplasia, vermian cleft |
| Inciçek et al., 2012 | 10                  | c.4452C>T, p.(Arg1518Trp) | c.4452C>T, p.(Arg1518Trp) | JS         | +   | ?   | +     | −    | −   | −     | +     | +  | Episodic hyperpnoea, ataxia, hypotonia, cerebellar vermis aplasia, vermian cleft |
| Jones et al., 2014  | Proband              | c.4550C>G, p.(Thr1517Ser) | c.3774dupT, p.(Glu1259*)  | MKS         | ?   | +   | ?     | ?    | ?   | PC    | ?     | −  |                                          |
| Shaheen et al., 2013 | MKS_F8              | c.4531T>C, p.(Trp1511Arg) | c.4531T>C, p.(Trp1511Arg) | MKS         | ?   | +   | ?     | ?    | ?   | PC    | ?     | +  | See paper for further details           |
| Shaheen et al., 2013 | MKS_F14             | c.4531T>C, p.(Trp1511Arg) | c.4531T>C, p.(Trp1511Arg) | MKS         | ?   | +   | ?     | ?    | ?   | PC    | ?     | +  | See paper for further details           |
| Srour et al., 2015  | 994.385              | c.4559A>G, p.(Asn1520Ser) | c.3376G>A, p.(Glu1126Lys) | JS         | +   | ?   | +     | −    | −   | −     | −     | −  |                                          |
| Srour et al., 2015  | 1033.385             | c.4559A>G, p.(Asn1520Ser) | c.3376G>A, p.(Glu1126Lys) | JS         | −   | ?   | +     | −    | −   | −     | −     | −  |                                          |
| Kroes et al., 2016  | 1                   | c.4577C>A, p.(Thr1526Asn) | c.3289delG, p.(Val1097Phelps*2) | JS         | +   | ?   | +     | ?    | +   | RI    | −     | ?  |                                          |
| Bachmann-Gagescu et al., 2015 | UW287-3           | c.4600T>G, p.(Leu1534Val) | c.1017 + 1G>A             | JS         | +   | ?   | +     | −    | −   | −     | −     | −  |                                          |
| Srour et al., 2012  | 1223.447             | c.4667A>T, p.(Asp1556Val) | c.3376G>A, p.(Glu1126Lys) | JS         | +   | ?   | +     | −    | −   | −     | −     | −  | Oromotor apraxia                         |
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There is recent evidence to suggest that the phenotype associated with CC2D2A variants could be milder than classic Joubert syndrome. From the literature search, three brothers from a consanguineous family have been described. They underwent whole-exome sequencing for rod-cone dystrophy and were found to be compound heterozygous for variants in CC2D2A (Méjécase et al., 2019). Similar to our patient, they all have normal brain imaging with absence of the MTS. Our patient, therefore, provides further support of a milder phenotype associated with CC2D2A; he presents with normal imaging of the brain, kidneys, and liver but with oculomotor apraxia and a homozygous variant in CC2D2A which has been previously reported in a compound heterozygous state in a patient with classic Joubert syndrome (Bachmann-Gagescu et al., 2015). There is, unfortunately, no phenotypic information available about the latter patient other than a diagnosis of Joubert syndrome (see Table 2).

Nearly 14,000 children and their parents were recruited to the DDD study, however, only two patients with variants in CC2D2A were identified (Firth et al., 2009); one of which is not thought to be significant in terms of molecular finding and phenotypic fit. This may suggest that either patients with CC2D2A variants present with a recognisable phenotype, such as Joubert syndrome, and therefore were not recruited to the study, or the phenotype is mild and therefore the patients did not meet eligibility criteria for recruitment. With the increasing availability of next-generation sequencing, those with milder phenotypes will have genetic testing and the latter group of patients may come to light following reverse phenotyping.

There may be several reasons as to why these patients are less severely affected than one would normally expect with biallelic variants in other Joubert syndrome genes. The first reason may just be the phenotypic variability associated with the gene which is becoming more apparent with reverse phenotyping. This has been described in other ciliopathy genes such as INPP5E (de Goede et al., 2016). INPP5E variants usually lead to Joubert syndrome, however, de Goede et al. (2016) describe two branches of a consanguineous family who presented with developmental delay and learning difficulties for assessment. The family phenotype was variable but the authors concluded that all were within the spectrum of INPP5E-related ciliopathies.

The second is the possibility that modifier genes play a part in the more subtle phenotypes of these families, however, further investigations will be required to determine this possibility in our case. The intricacies surrounding ciliopathy phenotypes and variation have been previously well described (Reiter and Leroux, 2017).

Our patient was also found to be heterozygous for a likely pathogenic variant in KIDINS220 (Kinase D-interacting
Table 2  Case reports with no phenotype information in the NM_001080522.2 CC2D2A gene

| Reference          | Identification | Allele 1 | Allele 2 | Diagnosis |
|--------------------|----------------|----------|----------|-----------|
| Ben-Salem et al., 2014 | MTL-127       | c.1412delG, p.(His471Leufs*40) | c.4258G>A, p.Arg1528His | JS or JSRD |
| Bachmann-Gagescu et al., 2015 | UW271-3       | c.1503_1505delAGA, p.(Lys501_Asp502delinsAsn) | c.2875del, p.(Glu998Asnfs*3) | JS |
| Bachmann-Gagescu et al., 2015 | UW301-3       | c.2875del, p.(Glu998Asnfs*3) | c.2875del, p.(Glu998Asnfs*3) | JS/MKS |
| Watson et al., 2016   |                | c.2875del, p.(Glu998Asnfs*3) | c.2875del, p.(Glu998Asnfs*3) | JS/MKS |
| Bachmann-Gagescu et al., 2015 | UW265-3       | c.2875del, p.(Glu998Asnfs*3) | c.2875del, p.(Glu998Asnfs*3) | JS/MKS |
| Bachmann-Gagescu et al., 2015 | UW265-4       | c.2875del, p.(Glu998Asnfs*3) | c.2875del, p.(Glu998Asnfs*3) | JS/MKS |
| Bachmann-Gagescu et al., 2015 | UW320-3       | c.3594 + 5G>A | c.1558C>T, p.(Arg520*) | JS/MKS |
| Watson et al., 2016   |                | c.3594 + 5G>A | c.1558C>T, p.(Arg520*) | JS/MKS |
| Bachmann-Gagescu et al., 2015 | UW265-3       | c.3594 + 5G>A | c.1558C>T, p.(Arg520*) | JS/MKS |
| Bachmann-Gagescu et al., 2015 | UW308-3       | c.4491A>C, p.(Gln1497His) | c.3594 + 5G>A | JS/MKS |
| Bachmann-Gagescu et al., 2015 | UW309-3       | c.4491A>C, p.(Gln1497His) | c.3594 + 5G>A | JS/MKS |
| Bachmann-Gagescu et al., 2015 | UW301-3       | c.4491A>C, p.(Gln1497His) | c.3594 + 5G>A | JS/MKS |
| Bachmann-Gagescu et al., 2015 | UW320-3       | c.4491A>C, p.(Gln1497His) | c.3594 + 5G>A | JS/MKS |

Table 3  Case reports with a single heterozygous variants in the NM_001080522.2 CC2D2A gene

| Reference          | Identification | Allele 1 | Allele 2 | Diagnosis |
|--------------------|----------------|----------|----------|-----------|
| Kroes et al., 2016 |                 | c.949G>A, p.(Glu317Arg) | c.949G>A, p.(Glu317Arg) | JS |
| Kang et al., 2016  |                 | c.4202G>C, p.(Thr1401Ser) | c.4202G>C, p.(Thr1401Ser) | JS |
| Kroes et al., 2016 |                 | c.4553G>A, p.(Arg1518Gln) | c.4553G>A, p.(Arg1518Gln) | JS |
| Méje case et al., 2019 |               | c.3182+355_3825del*6 | c.2774G>C, p.(Arg925Pro) | Simplex RCD |

DD/ID, developmental delay/intellectual disability; ENC, encephalocoele; JS, Joubert syndrome; JSRD, Joubert syndrome-related disorder; MKS, Meckel syndrome; NPHP, nephronophthisis; OA/N, oculomotor apraxia/nystagmus; PC, polycystic; PD, polydactyly; RCD, rod-cone dystrophy; RI, renal insufficiency; ?, no information available; +, present; −, absent.

*Variant may be in cis or trans.

substrate of 220kDa). The protein was first identified nearly 20 years ago (Iglesias et al., 2000) as a substrate of protein kinase D which has been found to be important in the development of the neural and cardiovascular systems (Cesca et al., 2011; Cesca et al., 2012).

Heterozygous truncating variants in KIDINS220 have been associated with spastic paraplegia, intellectual disability, nystagmus, and obesity (SINO – OMIM 617296) (Josifova et al., 2016; Yang et al., 2018). Pathogenic homozygous variants seem to be associated with a more severe phenotype with limb contractures and hydrocephalus (Mero et al., 2017).

In comparison to the other cases described in the literature, our patient is phenotypically milder. The three cases reported by Josifova et al. (2016) were dysmorphic with abnormal brain MRI. All had spastic paraplegia and had weights over the 80th centile; our patient had none of these features. Due to the small number of published cases, it is difficult to know whether our patient expands the phenotype associated with variants in KIDINS220 or whether this is a reflection of patient ascertainment bias; two out of the three patients described by Josifova et al. (2016) were identified from their phenotype before functional work performed, the associated pathogenic mechanism of disease remains unclear. One might conclude from the current reports in the literature that complete loss of KIDINS220 expression leads to a severe phenotype, while monoallelic expression of this protein leads to a mild phenotype, such as in our case. However, this conclusion is not supported by population data. In addition, the reported truncating variants associated with possible expression of a shorter protein could support a gain of function mechanism in this gene (Josifova et al., 2016; Mero et al., 2017; Yang et al., 2018), again however, this is also not supported by population data in gnomAD. When examining this data (data last accessed 20 February 2019), three heterozygote truncating variants were identified within the last exon or the 50 nucleotides in the penultimate exon, predicting the translation of a shortened protein. Also, 12 heterozygote truncating variants were seen which are predicted to result in protein haploinsufficiency. The KIDINS220 gene has a low probability of loss-of-function (LoF) intolerance (PLI of 0.03). Therefore, we alternatively propose that incomplete penetrance is likely to be associated with pathogenic variants in this gene. We do not recommend the use of PVS1 (ACMG classifier) in the interpretation of LoF variants within this gene but to instead consider the other available evidence in a case by case basis. In our patient, the KIDINS220 c.1369C>T, p.(Gln457Ter) was de novo (PS2 strong) and it was not present in control populations in gnomAD (PM2_moderate), giving a likely pathogenic classification.
In summary, we describe a 7-year-old boy, who is an example of the ever growing cohort of patients who are being ‘reversed phenotyped,’ who present with an atypical phenotype with pathogenic variants in CC2D2A and KIDINS220. Further phenotype-genotype studies in these two genes may give further information regarding their associated phenotypic spectrums.

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Conflicts of interest

The authors report no conflicts of interest.

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