Deletion 16p13.11 Uncovers NDE1 Mutations on the Non-Deleted Homolog and Extends the Spectrum of Severe Microcephaly to Include Fetal Brain Disruption

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Manuscript Received: 21 January 2013; Manuscript Accepted: 14 March 2013

Deletions of 16p13.11 have been associated with a variety of phenotypes, and have also been found in normal individuals. We report on two unrelated patients with severe microcephaly, agenesis of the corpus callosum, scalp rugae, and a fetal brain disruption (FBD)-like phenotype with inherited deletions of 16p13.11. The first patient was subsequently found on whole exome sequencing to have a nonsense mutation (p.R44X) in NDE1 on the non-deleted chromosome 16 homolog. We then undertook copy number studies of 16p13.11 and sequencing of NDE1 in nine additional patients with a similar severe microcephaly, agenesis of the corpus callosum, and FBD-like phenotype. The second patient was found to have an inherited deletion of the entire NDE1 gene combined with a frameshift mutation.

Additional supporting information may be found in the online version of this article.

Conflict of interest: The authors have no conflicts of interest to declare.
Grant sponsor: NINDS; Grant number: RO1 NS41537; Grant sponsor: NINDS; Grant number: RO1 NS058721.
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How to Cite this Article:
Paciorkowski AR, Keppler-Noreuil K, Robinson L, Sullivan C, Sajan S, Christian SL, Bukshpun P, Gabriel SB, Gleeson JG, Sherr EH, Dobyns WB. 2013. Deletion 16p13.11 uncovers NDE1 mutations on the non-deleted homolog and extends the spectrum of severe microcephaly to include fetal brain disruption. Am J Med Genet Part A 161A:1523–1530.

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(c.1020-1021het_delGA) in the non-deleted NDE1. These observations broaden the phenotype seen in NDE1-related microcephaly to include FBD. These data also represent the second described syndrome, after Bernard-Soulier syndrome, where an autosomal recessive condition combines an inherited segmental duplication mediated deletion with a mutation in a gene within the non-deleted homolog. Finally, we performed informatics analysis of the 16p13.11 gene content, and found that there are many genes within the region with evidence for role(s) in brain development. Sequencing of other candidate genes in this region in patients with deletion 16p13.11 and more severe neurophenotypes may be warranted. © 2013 Wiley Periodicals, Inc.

Key words: deletion 16p13.11; NDE1; whole exome sequencing; fetal brain disruption; microcephaly; agenesis of the corpus callosum

INTRODUCTION

Chromosome 16 is rich in intrachromosomal segmental duplications [Martin et al., 2004] that recombine to cause several recurrent copy number variants and associated clinical syndromes. Among the more common of these are deletions and duplications of 16p13.11 (chr16:14.7–16.3 Mb) that contain a core set of genes including NDE1 [Ullmann et al., 2007; Hannes et al., 2009; de Kovel et al., 2010; Heinzen et al., 2010; Mefford et al., 2010; Williams et al., 2010; Ingason et al., 2011; Ramalingam et al., 2011; Sahoo et al., 2011]. Deletions of this region have been found in 1.34 per 1,000 individuals with schizophrenia and 4.9–6.0 per 1,000 individuals with various epilepsy syndromes as well as 4.4 per 10,000 controls [de Kovel et al., 2010; Heinzen et al., 2010; Ingason et al., 2011]. In addition to epilepsy and schizophrenia, deletion 16p13.11 has been associated with a wide spectrum of abnormalities including attention deficit hyperactivity disorder [Williams et al., 2010], autism [Ramalingam et al., 2011], intellectual disability, mild microcephaly, and congenital anomalies such as cleft lip, facial dysmorphism and even holoprosencephaly [Ullmann et al., 2007; Hannes et al., 2009].

During the course of a copy number variant study in our cohort of patients with agenesis of the corpus callosum (ACC), we discovered the common deletion 16p13.11 in a boy with severe congenital microcephaly, ACC, collapsed skull and prominent scalp rugae that overlap with the so-called “fetal brain disruption” (FBD) sequence [Russell et al., 1984; Bönemann and Meinecke, 1990; Moore et al., 1990; Alexander et al., 1995]. As his condition appeared very different from other patients with deletion 16p13.11, we performed whole exome sequencing (WES) to search for other genetic variants to explain his severe phenotype and identified a nonsense mutation in the non-deleted homolog of NDE1. We next performed quantitative PCR and sequencing of NDE1 in another nine patients with severe microcephaly and an FBD-like phenotype, and found a second unrelated girl with a compound heterozygous deletion 16p13.11 and NDE1 intragenic mutation. The phenotype in these children is intermediate between the few other individuals reported with homozygous mutations of NDE1 [Alkuraya et al., 2011; Bakircioglu et al., 2011; Guven et al., 2012].

Our observations suggest that mutations (including deletion) of NDE1 may prove to be a relatively common cause of severe congenital microcephaly. Furthermore, the 16p13.11 deletion serves as the second paradigm for microdeletions uncovering mutations of genes on the non-deleted homolog—the other being Bernard-Soulier syndrome due to deletion 22q11.2 and mutation of GP1BB on the non-deleted homolog [Budarf et al., 1995; Ludlow et al., 1996]. Reports of single patients with novel and especially severe phenotypes should be considered provisional and likely to require more complex explanations. Finally, our informatics analysis of the gene content of the common 16p13.11 deletion provides insights into the contribution to neurologic development and function of other genes in the region.

METHODS

Patients

Patients were ascertained through the Molecular Genetic Studies of Developmental Disorders, and informed consent was obtained with approval of the Seattle Children’s Hospital Institutional Review Board. Retrospective clinical records and brain MRI scans were reviewed in a cohort of patients with severe microcephaly and FBD-like brain malformation. DNA was extracted from peripheral blood using the Gentra PureGene DNA isolation kit according to the manufacturer’s instructions.

Chromosomal Microarray

LP97-141a1, with severe microcephaly and FBD, was studied using the InfiniumII HumanHap610 BeadChip high-density single nucleotide polymorphism (SNP) array (Illumina, San Diego, CA). Data were analyzed using PennCNV [Wang et al., 2007] including for analysis only CNVs larger than 30 kb that contained at least 10 contiguous SNPs and at least 1 exon.

Whole Exome Sequencing

We performed WES of peripheral blood DNA from Patient LP97-141a1 to find other genetic variants to explain his severe phenotype. We used the Nimblegen whole exome capture kit, and sequence was generated on an Illumina GAII platform. Sequence was aligned to hg19 using BWA, and single nucleotide variants and indels were called using GATK 1.3. Mean coverage was calculated using GATK 1.3 DepthOfCoverageWalker. Annotation of variants was performed with SeattleSeq Annotation 134. Common variants were identified by filtering against the NHLBI Exome Variant Server. All tools are listed in the URLs cited.

Sanger Sequencing

Variants found by WES were confirmed with Sanger sequencing using standard methods. We also studied by direct Sanger sequencing the coding regions of NDE1 blood-derived DNA from products of conception (LP97-141a3, sibling of a1) from a pregnancy affected with severe microcephaly detected in utero at 14 weeks gestation, as well as eight additional patients with severe microcephaly and FBD-
like phenotype. Sequence chromatograms were analyzed using the Mutation Surveyor software version 3.97 (SoftGenetics, State College, PA). Sequences were compared with normal control samples and the reference sequences for NDE1 (NCBI reference number NM_017668).

**Quantitative PCR**

The nine additional patients with severe microcephaly and FBD-like phenotype were studied with qPCR of five probes (Supplementary Table SI—see supporting information online) flanking NDE1 on 16p13.11 using standard methods [Livak and Schmittgen, 2001].

**Informatics Analysis of 16p13.11 Gene Content**

The gene content of published deletion 16p13.11 patients was extracted and annotated using GEDI and UCSC TableBrowser. Tissue expression and developmental stage of expression in the mouse was evaluated by query of Allen Brain Atlas, BGEM, EMAGE, and MGI. All tools are listed in URLs cited.

**RESULTS**

**Clinical Phenotype**

LP97-141a1 had severe congenital microcephaly (Fig. 1), with birth occipital-frontal circumference (OFC) of $-7$ standard deviations (SD) below the mean. He had impaired gastric motility and required gastric bypass and placement of a gastrostomy tube at 8 months of age. He subsequently had a developmental disorder characterized by epilepsy, absence of speech and all non-verbal communication, and inappropriate laughter. Seizures appeared before the first year of life and were treated successfully with phenobarbital. Temperature instability began at age 14 years, with daily episodes of hypothermia requiring external warming. Brain MRI showed ACC and increased extra-axial space, a cortical dysplasia that appeared to be polymicrogyria-like, and a disproportionately small brainstem and cerebellum (Fig. 2A–C). The family had two subsequent pregnancies also affected with severe microcephaly and ACC, with OFC measurements at 14 weeks gestation consistent with 12 weeks gestation. A limited amount of DNA was available from the products of conception of LP97-141a3.

Patient LR01-271 was born with congenital microcephaly (birth OFC $-8$ SD). A single seizure was noted during infancy, but she had no further episodes. Gastroesophageal reflux disease (GERD) was treated with lansoprazole. She also subsequently had a severe neurodevelopmental phenotype that included absence of speech and all non-verbal language. She had similar hypothermic episodes that began at around 9 years of age. Brain MRI demonstrated ACC, a disproportionately small brainstem, and a large interhemispheric fluid space adjacent to the right lateral ventricle. This fluid space is also visible on coronal view and appears to communicate with the right lateral ventricle (Fig. 2D–F). She died of respiratory distress and cardiopulmonary arrest due to apparent sepsis at the age of 10 years. Both LP97-141a1 and LR01-271 were from non-consanguineous pedigrees, and the parents of both patients were phenotypically normal. The clinical findings of the patients are summarized in Table I.

**Copy Number Studies**

Patient LP97-141a1 was found by CMA to have a 0.83 Mb deletion of 185 probes on 16p13.11 (hg18 chr16:15369798-16195546x1). Quantitative PCR of proband and parental samples found this deletion to be inherited from the phenotypically normal father. The second patient, LR01-271, was found by qPCR to have a deletion of five markers flanking NDE1 on 16p13.11. The deletion was inher-
ied from her phenotypically normal mother. Due to limited DNA availability, copy number studies could not be performed in DNA extracted from LP97-141a3. The copy number studies are summarized in Figure 3.

Whole Exome Sequencing
In order to further understand the genetics of the severe disorder found in Patient LP97-141a1, we performed WES of blood cell-derived genomic DNA. We obtained a mean depth of coverage of 100× over the targeted exome. Our analysis identified a stop codon (chr16:15761189C/T, p.R44X) in NDE1 that was confirmed by Sanger sequencing (Fig. 4A).

Sanger Sequencing
We studied eight additional patients with severe microcephaly and FBD-like phenotype, and the products of conception of the affected sibling LP97-141a3. We identified the p.R44X mutation in NDE1 in LP97-141a3. In this patient, insufficient DNA was available for copy number studies, but the Sanger chromatogram showed only one allele suggesting deletion of the other allele. The p.R44X mutation is predicted to cause protein truncation in the homodimerization domain of NDE1. In Patient LR01-271, Sanger sequencing found a 2-bp deletion (c.1020-1021het_delGA) resulting in frameshift of NDE1. Sequencing of parental DNA demonstrated this mutation was inherited from the father (Fig. 4B).

Informatics Analysis of 16p13.11 Gene Content
Sixteen protein-coding genes were extracted from the 2 Mb 16p13.11 deletion region. The timing during development of gene expression, if known, and tissue(s) of expression are summarized in Supplementary Table SII—see supporting information online. Ten of the genes had evidence from at least one source of expression during brain development. Five of these genes (ABCC1, NDE1, NOMO1, NTAN1, and PDXDC1) had evidence from multiple sources, suggesting a role in brain development.

DISCUSSION
We describe two unrelated patients with severe microcephaly, ACC, and FBD-like cortical malformation, who have inherited deletions of 16p13.11 combined with truncating mutations in NDE1. In all patients reported to date with the homozygous NDE1 phenotype, severe congenital microcephaly was present with profound intel-
lectual disability and early onset seizures. In the first two reports, brain imaging showed severe microcephaly, extremely simplified gyral pattern, and ACC [Alkuraya et al., 2011; Bakircioğlu et al., 2011], as well as normal cortical ribbon thickness and small cerebellum. The malformation was designated microcephaly with lissencephaly or “microlissencephaly” [Alkuraya et al., 2011]. On our review, the published images suggest a dysplastic cortex and proportionate cerebellum. We prefer to restrict use of the term “lissencephaly” to malformations in which the cerebral cortex is abnormally thick, so would describe the published images as showing microcephaly with a simplified gyral pattern and polymicrogyria-like cortical malformation. The third report shows the same severe microcephaly, growth deficiency, simplified gyral pattern and ACC, but also scalp rugae, a striking loss of brain tissue described as “microhydranencephaly” and a polymicrogyria-like cortical dysplasia [Guven et al., 2012].

Our two patients also had prominent loose scalp skin with scalp rugae. Brain MRI showed changes intermediate between the prior reports, including severe microcephaly, enlarged extra-axial fluid surrounding the brain that communicated with the lateral ventricles medially, severe simplified gyral pattern with obvious polymicrogyria-like cortical malformation, and ACC. The scalp rugae suggest late fetal loss of brain volume, and combined with the dramatic increased extra-axial space, resembles an FBD-like phenotype.

FBD refers to severe congenital microcephaly with a collapsed skull and prominent scalp rugae, increased extra-axial space, and cortical clefting. This combination of features has been previously regarded as occurring secondary to intrauterine brain disruption [Russell et al., 1984; Bönnermann and Meinecke, 1990; Moore et al., 1990; Alexander et al., 1995; Schram et al., 2004], and thus not genetic with a low recurrence risk. Our observations show that FBD can result from genetic causes with a high recurrence risk, although we still believe that some forms of FBD are indeed secondary to intrauterine brain disruption.

The malformations shown in the homozygous NDE1 reports most closely resemble the pattern associated with mutations of WDR62 [Bilguvar et al., 2010; Yu et al., 2010], while the associated growth deficiency resembles the pattern seen with severe microcephaly due to mutations of CENPJ [Al-Dosari et al., 2010]. Both WDR62 and CENPJ appear to be rare causes of severe congenital microcephaly reported in few pedigrees. Our data suggest that homozygous loss of NDE1 function may be a more common cause of autosomal recessive severe microcephaly, and may be present in outbred families. As the most common forms of severe congenital microcephaly are autosomal recessive, many clinicians do not order CMA to investigate them. We obtained an array in our proband because of the presence of ACC. We now prefer to order SNP microarrays in children with severe congenital microcephaly both to detect this microdeletion and to detect stretches of homozygosity that may represent loci harboring pathogenic mutations.

This is the second segmental duplication-mediated deletion associated with a recurrent autosomal recessive phenotype. The first is the bleeding disorder Bernard-Soulier syndrome, which is caused by homozygous or compound heterozygous mutations of the GP1BB gene encoding the platelet glycoprotein GPIb/IX recep-
tor. At least four patients have been reported in which the common 22q11.2 deletion served as one of the two mutations [Budarf et al., 1995; Ludlow et al., 1996; Lascone et al., 2001; Nakagawa et al., 2001].

The inherited 16p13.11 deletions in our patients are additionally interesting because of the disparate phenotype reports associated with copy number variations at this locus. Many of the patients published have had relatively mild phenotypes such as ADHD, treatment-responsive epilepsies without cognitive impairment, mild microcephaly (OFC −3 SD), and isolated dysmorphic findings such as cleft palate. It has been difficult to then reconcile the association of the same 16p13.11 deletion with the more severe neurodevelopmental findings of autism, intellectual disability, and schizophrenia. Our data suggest that

**FIG. 3.** A: Deletion of 185 probes (0.83 Mb) on 16p13.11 found by chromosomal microarray in Patient LP97-141a1. B–F: Quantitative PCR of five probes flanking NDE1 demonstrated the 16p13.11 deletion in LP97-141a1 to be inherited from the father. The deletion of NDE1 in Patient LR01-271 was shown by qPCR to be inherited from the mother.
these more severe phenotypes may be indicative of second genomic events—such as mutations of genes within the non-deleted 16p13.11 homolog.

Haploinsufficiency of NDE1 has been suggested as a possible cause for the developmental and neurologic phenotypes associated with 16p13.11 deletions [de Kovel et al., 2010; Heinzen et al., 2010; Mefford et al., 2010], although all parents carrying heterozygous mutations of the gene were reported to be normal [Alkuraya et al., 2011; Bakircioglu et al., 2011; Guven et al., 2012]. Our informatics analysis of the gene content of the 16p13.11 region found evidence that several of the genes in the region, such as ABCC1, NOMO1, NTAN1, and PDXDC1 have expression during brain development—as does NDE1. These may be candidate genes for second-hit mutations in patients with deletions of 16p13.11 and more severe disorders of cortical connectivity such as autism, intellectual disability, and schizophrenia. Sequencing of these candidates in patients with severe neurodevelopmental phenotypes may yield more compelling explanations for these disorders.

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ACKNOWLEDGMENTS
We are grateful for the participation of the families described in this research. J.G.G. is supported by NINDS RO1 NS41537; W.B.D. is supported by NINDS RO1 NS058721.

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