Whole Genome Sequencing Reveals a Chromosome 9p Deletion Causing DOCK8 Deficiency in an Adult Diagnosed with Hyper IgE Syndrome Who Developed Progressive Multifocal Leukoencephalopathy

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Abstract: PURPOSE A 30 year-old man with a history of recurrent skin infections as well as elevated serum IgE and eosinophils developed neurological symptoms and had T2-hyperintense lesions observed in cerebral MRI. The immune symptoms were attributed to Hyper IgE syndrome (HIES) and the neurological symptoms with presence of JC virus in cerebrospinal fluid were diagnosed as Progressive Multifocal Leukoencephalopathy (PML). The patient was negative for STAT3 mutations. To determine if other mutations explain HIES and/or PML in this subject, his DNA was analyzed by whole genome sequencing. METHODS Whole genome sequencing was completed to 30X coverage, and whole genome SNP typing was used to complement these data. The methods revealed single nucleotide variants, structural variants, and copy number variants across the genome. Genome-wide data were analyzed for homozygous or compound heterozygous null mutations for all protein coding genes. Mutations were confirmed by PCR and/or Sanger sequencing. RESULTS Whole genome analysis revealed deletions near the telomere of both copies of chromosome 9p. Several genes, including DOCK8, were impacted by the deletions but it was unclear whether each chromosome had identical or distinct deletions. PCR across the impacted region combined with Sanger sequencing of selected fragments confirmed a homozygous deletion from position 10,211 to 586,751. CONCLUSION While several genes are impacted by the deletion, DOCK8 deficiency is the most probable cause of HIES in this patient. DOCK8 deficiency may have also predisposed the patient to develop PML.

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Aaron Day-Williams, Chao Sun and Ilijas Jelcic have contributed equally to this paper.

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Electronic supplementary material

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Whole Genome Sequencing Reveals a Chromosome 9p Deletion Causing DOCK8 Deficiency in an Adult Diagnosed with Hyper IgE Syndrome Who Developed Progressive Multifocal Leukoencephalopathy

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Abstract
Purpose A 30 year-old man with a history of recurrent skin infections as well as elevated serum IgE and eosinophils developed neurological symptoms and had T2-hyperintense lesions observed in cerebral MRI. The immune symptoms were attributed to Hyper IgE syndrome (HIES) and the neurological symptoms with presence of JC virus in cerebrospinal fluid were diagnosed as Progressive Multifocal Leukoencephalopathy (PML). The patient was negative for STAT3 mutations. To determine if other mutations explain HIES and/or PML in this subject, his DNA was analyzed by whole genome sequencing.

Methods Whole genome sequencing was completed to 30X coverage, and whole genome SNP typing was used to complement these data. The methods revealed single nucleotide variants, structural variants, and copy number variants across the genome. Genome-wide data were analyzed for homozygous or compound heterozygous null mutations for all protein coding genes. Mutations were confirmed by PCR and/or Sanger sequencing.

Results Whole genome analysis revealed deletions near the telomere of both copies of chromosome 9p. Several genes, including DOCK8, were impacted by the deletions but it was unclear whether each chromosome had identical or distinct deletions. PCR across the impacted region combined with Sanger sequencing of selected fragments confirmed a homozygous deletion from position 10,211 to 586,751.

Conclusion While several genes are impacted by the deletion, DOCK8 deficiency is the most probable cause of HIES in this patient. DOCK8 deficiency may have also predisposed the patient to develop PML.

Keywords HyperIgE Syndrome · Dock8 deficiency · primary immune deficiency · Progressive Multifocal Leukoencephalopathy (PML) · JC virus

The hyper IgE syndromes (HIES) are rare primary immunodeficiencies characterized by elevated serum IgE, dermatitis and recurrent skin and lung infections [1, 2]. There are two forms of HIES that are characterized based on their inheritance patterns: autosomal-dominant HIES (AD-HIES) and autosomal-recessive HIES (AR-HIES). AD-HIES is caused by dominant mutations in STAT3 and is characterized in addition to the symptoms noted above by extra-immune manifestations including skeletal, connective tissue and vascular abnormalities [1, 2]. AR-HIES is caused by homozygous or compound heterozygous mutations in DOCK8, TYK2 or STK3, and these patients do not possess any of the extra-immune manifestations found in AD-HIES [3–6]. The major manifestations of DOCK8 deficiency leading to AR-HIES are recurrent viral and bacterial infections starting early in life, extreme eosinophilia, and elevated IgE levels. The causes of DOCK8 deficiency thus far described range from point mutations to large deletions involving this gene.
mutations and small indels to large deletions of portions of
DOCK8 preventing expression of the protein [3–6]. This
report adds to the growing body of knowledge about
DOCK8-deficient AR-HIES and discovers the largest pub-
lished deletion in the region around DOCK8. In addition, we
add to the literature showing the occurrence of Progressive
Multifocal Leukoencephalopathy in DOCK8 deficient
individuals.

A 30 year old, male, Caucasian patient suffering from
eczematoid dermatitis developed impetiginization of the skin
with Klebsiella pneumonia and group A β-hemolytic strepto-
coccus species in July 2008. The patient was diagnosed with
HIES based on elevated serum IgE (26,800 kU/L) and elevat-
ed eosinophils (1.6×10⁹ /L). The patient had atopic dermatitis
that was treated with topical corticosteroids and recurrent
herpesviral skin infections from the age of 6 years. There were
no reports of any other immunosuppressive agents. The pa-
tient history revealed that his parents were first cousins, how-
ever, no immunological diseases, opportunistic infection or
childhood diseases were reported in the parent’s siblings or
their children. In September, 2008 the patient developed a left-
sided sensory hemisyndrome, which progressed to a spastic-
atactic hemiparesis within a few weeks. A cerebral MRI
showed a large confluent T2-hyperintense lesion in the frontal
parietal central region of the right cerebral hemisphere, a small
T2-hyperintense lesion in the right temporal cortex, and small
T2-hyperintense lesions in the right cerebellar hemisphere. In
October, 2008 the cerebrospinal fluid (CSF) of the patient was
positive for JC polyoma virus DNA (500 copies/mL) leading
to the diagnosis of Progressive Multifocal Leukoencephalopathy (PML). Peripheral blood analysis showed repeatedly highly increased numbers of IgE
(12,166–26,800 kU/l) and eosinophils (3,066–6,068/ul) and
decreased levels of lymphocytes (296–770/ul), CD3+ T cells
(130–265/ul), CD4+ T cells (71–169/ul), CD8+ T cells (29–
109/ul), CD19+ B cells (173–262/ul) and NK cells (10–81/ul)
(Table S1). After stimulation of lymphocytes with phyto-
agglutinin, CD3+ T cells responded adequately as shown by
intracellular production of interferon-γ (24 % of cells),
tumor necrosis factor-α (11.2 %).

A screen for STAT3 mutations in April, 2009 was negative.
The family history of first cousin parents and the absence of
STAT3 mutations lead to the refined diagnosis of AR-HIES of
unknown etiology. In August 2009, antiepileptic treatment
with 3,000 mg levetiracetam and 100 mg pregabaline daily
was started because of focal sensory epileptic seizures in the
left hemibody. MRI follow-up showed a reduced size of the
T2-lesion within the right cerebral central region, but CSF
JCV DNA copy number had increased tenfold (5,200 JCV
genomic copies/mL). Until December 2010, neurological def-
icits had progressed only mildly, but MRI showed dissemina-
tion and enlargement of the PML lesions in the left thalamic
region, left hemisphere, pons, and the right cerebellar
pedunculus. The patient’s DNA was sent for whole-genome

Fig. 1 Deletion of DOCK8 in a
patient with HIES and PML. A.
Telomeric region of chromosome
9p showing the deleted region and
the impacted genes. B. Hypothetical ploidy observed in
whole genome sequence. Note
apparent single copy coverage
near the telomere, then nearly
500 kb with no coverage, and
then diploid coverage starting at
approximately 586,000 bases.
The letters a,b,c and d show the
approximate location of PCR
primers used to confirm the nature
of the deletion. C. Results of PCR
using the primers shown in 1B.
Gel a: lanes 1,2, and 4 are
controls, lane 3 is the HIES
subject. Gels b, c and d: lane 1 is
the HIES subject, lanes 2 and 3
are control subject, lane 4 is a no
template control. Primer sets a, b,
and c produce bands from the
controls but not from the HIES
subject, and primer set d only
produces a band from the HIES
subject.
SNP analysis and sequencing in April, 2012. After this the patient was not available for follow-up of the disease course. The patient’s DNA was whole genome sequenced (WGS) by Complete Genomics Incorporated (CGI; software version 2.0) \[7, 8\] and was analyzed on the Illumina Omni 1 quad genome-wide SNP array. The WGS approach used short (31–35 base) sequence reads at >30X coverage mapped to the reference genome using methods previously described \[7\] to identify single nucleotide, copy number, and structural variants. Relative to the reference genome, the sequence of this individual included 19435 missense variants, 178 nonsense variants, 470 frameshift variants, and >100 copy number and structural variants. Single nucleotide variants (SNVs) were analyzed using the ENSEMBL Variant Effect Predictor v2.8 \[9\] on the ENSEMBL v70 database, and variant effects on the annotated canonical transcripts for all genes were assessed via PolyPhen2 \[10\] and SIFT \[11\]. A variant was considered possibly damaging if it was determined to be either ‘probably damaging’ or ‘possibly damaging’ by PolyPhen2 or ‘deleterious’ by SIFT. We examined known genes associated with immune deficiency, including the HIES genes STAT3, TYK2, STK3 and DOCK8, and observed no damaging mutations in STAT3 or STK3, heterozygosity for a possibly damaging missense variant in TYK2 (rs147991080, R448W, MAF <0.01 (http://browser.1000genomes.org/); Table S2), and large deletions on both copies of chromosome 9p in the region that includes DOCK8. The SNP array data also suggested a large deletion on chromosome 9p, with mostly non-called SNPs from approximately 194,000 to 600,000 bases (Table S3). Given the heterozygosity and ambiguous function of the TYK2 variant and the obvious deletions around DOCK8, it is clear that the DOCK8 mutation(s) contribute to the patient’s disease.

The WGS and SNP data were not clear on the exact deletion breakpoints or whether the patient was homozygous for the same deletion or had inherited two different deletions.

### Table 1

| Gene Symbol | GO biological process | GO function | OMIM phenotypes (MIM number) |
|-------------|-----------------------|-------------|-----------------------------|
| DDX11L5     | None                  | None        | None                        |
| WASH1       | GO:0006810:transport  | GO:0003779:actin binding | None          |
|             | GO:0016197:endosomal transport | GO:0005515:protein binding | None          |
|             | GO:0034314:Arp2/3 complex-mediated actin nucleation | GO:0031625:ubiquitin protein ligase binding | None          |
|             | GO:0042147:retrograde transport, endosome to Golgi transport | GO:0043014:alpha-tubulin binding | None          |
| FAM138C     | None                  | None        | None                        |
| FOXD4       | GO:0006351:transcription, DNA-templated | GO:0003700:sequence-specific DNA binding transcription factor activity | None          |
|             | GO:0006355:regulation of transcription, DNA-templated | GO:0008301:DNA binding, binding | None          |
|             | GO:0043565:sequence-specific DNA binding | GO:0043565:sequence-specific DNA binding | None          |
| CBWD1       | None                  | GO:0000166:nucleotide binding | None          |
|             | GO:000524:ATP binding | None        | None                        |
| C9orf166    | None                  | None        | None                        |
| Dock8       | GO:0001771:immunological synapse formation | GO:0005085:guanyl-nucleotide exchange factor activity | Hyperimmunoglobulin E recurrent infection syndrome, autosomal recessive (243700) |
|             | GO:0007264:small GTPase mediated signal transduction | GO:0005515:protein binding | Mental retardation, autosomal dominant 2 (614113) |
|             | GO:0007596:blood coagulation | GO:00061485:memory T cell proliferation | None          |
|             | GO:003633:dedritic cell migration | GO:00070233:negative regulation of T cell apoptotic process | None          |
| KANK1       | None                  | None        | Cerebral palsy, spastic quadriplegic, 2 (612900) |
The WGS CNV analysis estimated that the patient was homozygous null for DOCK8 and some of KANK1, but could be hemizygous towards the telomere encompassing CBWD1, FOXD4, FAM138C, WASH1, and DDX11L5 (Fig. 1 panels A,B), and was consistent with the hypothesis that the patient had some DNA telomeric to DOCK8. The WGS analysis of the p-arm from the telomere to the DOCK8 locus is complicated by a segmental duplication that results in extremely high sequence similarity to Chromosome 2 [12, 13] and ambiguous sequence assembly. To resolve the breakpoints for the individual’s deletion(s) we designed targeted PCR around SNPs rs12353065, rs7853676 and rs11794423 which the WGS SNP analysis called high confidence SNPs, the WGS CNV analysis estimated to be hemizygous, and PCR primers unique to chromosome 9 could be designed (Fig. 1 panels B,C). Figure 1 panel C shows that the PCR with primers for the 3 SNPs (gels a, b and c) are all negative illustrating that the patient is in fact homozygous null from around the telomere into KANK1. To resolve the exact breakpoints we designed PCR primers close to the telomere and in KANK1 (PCR pair d Fig. 1 panel B,C).

Upon the successful amplification of this fragment we cloned the DNA and Sanger sequenced the fragment. We performed a global gapped alignment with the Needleman-Wunsch algorithm of the resulting DNA fragment to chromosome 9 from bases 1-700,000 (NC_000009.11) and it revealed the alignment in Supplementary Figure 1. The alignment shows a massive homozygous deletion from position 10,211 to 586,751 that makes the patient homozygous null for the genes WASH1, FAM138C, FOXD4, CBWD1, C9orf66, DOCK8 and most of KANK1.

DOCK8 deficiency is the most likely cause of HIES in this subject, and may have predisposed him to the development of PML. Among the genes in the deletion interval none of the other genes are so obviously connected to the phenotype (Table 1), and elsewhere in the genome there are no mutations consistent with known inheritance patterns for HIES. Notably, this is not the first case report of PML in DOCK8 deficiency [14]. PML has been observed in a limited subset of PID’s that includes DOCK8 deficiency, Wiskott-Aldrich Syndrome, STAT1 gain of function mutations and CD40L deficiency [15–20]. This observation highlights a new pathway by which the ubiquitous JC virus causes PML in a small fraction of individuals and further demonstrates the utility of whole genome sequencing for diagnosing diseases of unknown etiology. DOCK8 deficiency can be treated by bone marrow transplantation [21–23], and the possibility of PML in these individuals is a reason to consider early and accurate diagnosis of suspect cases by genetic analysis and treatment by transplantation.

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