Original Article

Primary antibody deficiency associated with ring chromosome 18

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ABSTRACT

Background: Patients with chromosome 18 abnormalities can present with an immune phenotype that resembles common variable immunodeficiency. Knowledge of the genes underlying the immune defects related to chromosome 18 aberrations could improve our understanding of the molecular basis of primary antibody deficiencies. Here we present a patient with ring chromosome 18 affected by primary antibody deficiency and autoimmunity.

Methods: Lymphocyte populations were determined by flow cytometry. Specific antibody response to protein vaccines and pneumococcal capsule antigen were measured by ELISA. Genome sequencing was performed using a PCR-free protocol.

Case: The patient was diagnosed with ring chromosome 18 for delayed growth and dysmorphic features at the age of 1 month. Array comparative genomic hybridization showed deletions of 18p11.21-pter and 18q21.31-qter. At the age of 10 months, she started having recurrent episodes of otitis media and pneumonia, as well as autoimmune arthritis. Serum immunoglobulins and specific antibody levels were low. The CD19+CD27+ memory B cell and CD45RO+ T cell populations were decreased. Recurrent infections were controlled with parenteral immunoglobulin and autoimmune arthritis was treated with systemic and intra-articular therapies.

Conclusions: Selective IgA deficiency is the most common form of immunodeficiency associated with chromosome 18 abnormalities, however patients with ring chromosome 18 may also be affected by specific antibody deficiency and require immunoglobulin replacement for optimal care. These patients might partially share the same genomic loss as in patients with non-syndromic primary antibody deficiency.

Statement of novelty: This report highlights an important teaching point about immune deficiency in a chromosomal anomaly that is not infrequently encountered in pediatric hospitals. Furthermore, our investigations provide more insight into the pathogenesis of immunodeficiency among patients with chromosome 18 abnormalities.

Introduction

Antibody deficiencies comprise the most common form of inborn errors of the immune system. Although some monogenic primary antibody deficiencies have been identified, the genetic basis is not yet clear for the majority of those patients (Conley 2009). This reflects the heterogeneous nature of immune system

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development and maturation. In addition to single gene defects, chromosomal structural abnormalities have been associated with primary antibody deficiencies (Cunningham-Rundles 2012; Schatorje et al. 2016). These include both autosomal and sex chromosome aneuploidies, duplication, deletions and ring chromosomes. Notably, defective humoral immunity has been described among the clinical findings of patients with different chromosome 18 abnormalities (Feingold and Schwartz 1968; Fischer et al. 1970; Michaels et al. 1971; Faed et al. 1972; Schinzel et al. 1974). Patients with deletions on both 18p and 18q have presented with selective IgA deficiency (SIgAD), hypogammaglobulinemia, impaired specific antibody responses, and loss of memory B cells (Browning 2010; Cody et al. 2014; Hasi-Zogaj et al. 2015; Calvo Campoverde et al. 2016). Additionally, deletions of chromosome 18 are often marked with severe forms of autoimmunity (Dacou-Voutetakis et al. 1999; Hasi-Zogaj et al. 2015). The combination of antibody deficiency and autoimmunity is a common feature of many patients with common variable immunodeficiency (CVID). Therefore, exploring the immunogenetics of patients with chromosome 18 abnormalities might help finding new insights into the yet-obscure genetics of primary antibody deficiencies in non-syndromic patients.

Ring chromosome 18 is characterized by dysmorphic features such as microcephaly, hypertelorism, epicanthal folds, micrognathia, and short tapering fingers. Additionally, the patients are affected by severe intellectual delay, hypotonia, seizures, white matter abnormalities, hearing loss, and growth hormone deficiency (Carter et al. 2015). Here, we report a case of ring chromosome 18 who presented with recurrent bacterial infections, low serum IgG and IgM levels, defective specific antibody responses, and severe autoimmunity. To further investigate this patient, we detected the breakpoints by array comparative genomic hybridization (aCGH) and performed genome sequencing (GS) to examine possible gene defects that could lead to the immune phenotype.

Materials and methods

Patient

The study was approved by the Research Ethics Boards (REBs) of the McGill University Health Center under the Canadian Primary Immunodeficiency Evaluation Study (CPRIMES). Written consent was obtained for the genetic and immunological investigations from the patient's parents.

Flow cytometry

Lymphocyte immunophenotyping was perform by standard flow cytometry using antibodies, all from BD Bioscience: CD45RA/CD45RO/CD3/CD4 (cat #340571) and CD45RA/CD45RO/CD3/CD4 (cat #340574), PerCp-Cy5.5 conjugated CD19 (cat #340951), FITC conjugated IgD (cat #555778), PE conjugated IgM (cat #55579), APC conjugated CD27 (cat #337169).

Specific antibody response

Serum levels of anti-pneumococcal capsular antigen IgG for 14 pneumococcal serotypes (1, 3, 4, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19F, 23F, and 33F), were determined by ELISA as previously described (Lejtenyi and Mazer 2008). Intravenous immunoglobulin (IVIG) treatment was held for 6 months prior to immunization of the patient with a 23-multivalent pneumococcal polysaccharide vaccine. Post pneumococcal antibodies levels were measured 4 weeks after immunization.

Array comparative genomic hybridization (aCGH)

Genomic copy number variants were detected in a local diagnostic laboratory, by NimbleGen CGX-12 microarray, containing 135K oligos (Signature Genomic Laboratories, Spokane, WA, USA).

DNA extraction, whole genome sequencing and data analysis

DNA was isolated from peripheral blood monocytes using a commercially available kit (Qiagen, Toronto, ON, Canada) according the manufacturer's instructions. GS was performed on 1 μg of genomic DNA using a PCR-free protocol on an Illumina HiSeq X10 platform with 151-bp paired-end reads and a sequencing depth of >30X at the McGill University and Genome Quebec Innovation Center. Data analysis followed the Genome Analysis toolkit (GATK) best practices guidelines (https://software.broadinstitute.org/gatk/best-practices/). Copy number variants were detected using PopSV (Monlong et al. 2018).

Case summary

Our patient—who is currently 20 years old—was born at 36 weeks of gestation by breech vaginal delivery to non-consanguineous French-Canadian parents, after an

uncomplicated pregnancy. The Apgar score was 6 and 7 at 1 and 5 minutes of life, respectively. Growth parameters at birth were weight 2530 g, length 48 cm and head circumference 31.5 cm, all over 50th percentile for gestational age. She was treated with oxygen and antibiotics for meconium aspiration. She is the youngest of 3 and her older siblings are healthy. She was later re-admitted at the age of 1 month for failure to thrive and was found to have growth hormone deficiency. At that time, she had developed dysmorphic features including borderline low set ears, slightly protruding eyes, narrow palpebral fissures, prominent maxilla with Cupid's bow upper lip and mild micrognathia. She also had a protuberant abdomen, an umbilical hernia, and a sacral dimple. A brain MRI revealed delayed cerebral myelination that has been previously reported (Benini et al. 2012). A karyotype revealed ring chromosome 18. All metaphases exhibited 1 ring chromosome 18, and a small percentage of the cells had 2 ring 18 chromosomes. Results of aCGH showed a de novo interstitial deletion of 13q12.12 (23 544 669–24 109 193; UCSC 2009, GRCh37/hg19 Assembly), and deletions of 18p11.32p11.21 (141 491–14 117 537) and 18q21.31q23 (54 241 048–78 013 710; UCSC 2009, GRCh37/hg19 Assembly) (Figure 1).

At age of 10 months, she developed recurrent otitis media requiring bilateral pressure equalizing tube placement. The patient developed multiple bacterial infections including 2 *S. pneumoniae* pneumonia episodes with sepsis at age 15 and 21 months, cellulitis at age 16 months and a surgical granuloma with *S. aureus* superinfection at 17 months of age.

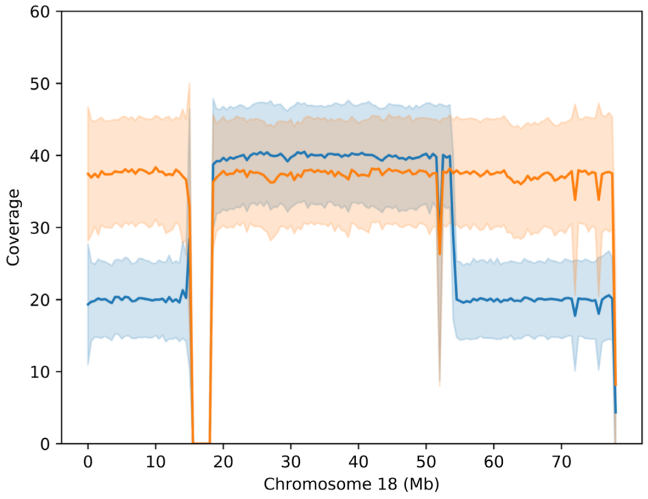

Figure 1: Schematic representation of the deleted regions on chromosome 18.

Table 1: **Major clinical findings in this patient with ring chromosome 18.**

Findings	Findings
Autism spectrum disorder	Pulmonary fibrosis and bronchiectasis
Intellectual disability	Nocturnal enuresis
Behavioral issues	Polyarthritis
Hypothyroidism	Low IgG and IgM
Growth hormone deficiency	Defective specific antibody responses
Delayed puberty	Decreased memory T and B cells
Premature ovarian failure	Ptosis, cataracts and anterior uveitis
Bilateral hearing loss	Pulmonary vein atresia

She developed hypothyroidism, anterior uveitis, and polyarthritis by the age of 2 years. She was seronegative for autoimmunity and the complement levels were normal. Her polyarthritis was controlled by systemic and intra-articular corticosteroids, Methotrexate and ultimately, Etanercept. Furthermore, she had frequent episodes of hemoptysis, secondary to complete atresia of the right upper pulmonary vein and a nearly atretic right lower pulmonary vein, which were surgically repaired. Her clinical features are summarized in Table 1.

Given the recurrent infections, her immune function was assessed at age 15 months. IgG and IgM serum levels were below the normal limits for age (1.1–3.92 µg/mL and 0.12–0.85 µg/mL, respectively). She was started on monthly infusions of IVIG (600 mg/kg) at the age of 21 months and there were no further episodes of sepsis (Figure 2). Furthermore, concurrent with starting IVIG

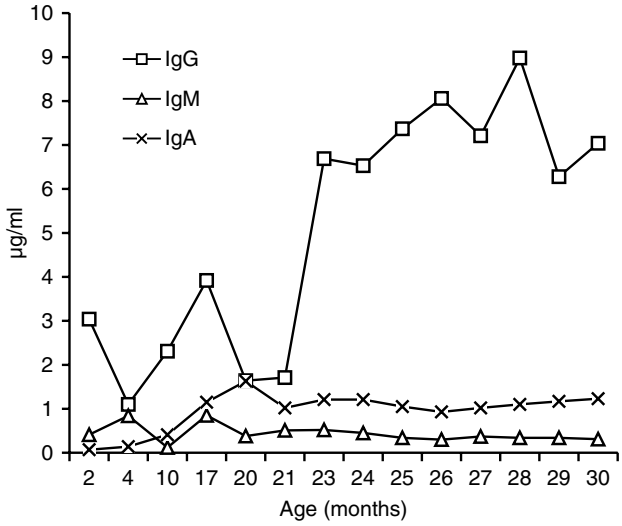

Figure 2: Serum immunoglobulin levels prior to and after IVIG administration at 21 mo of age.

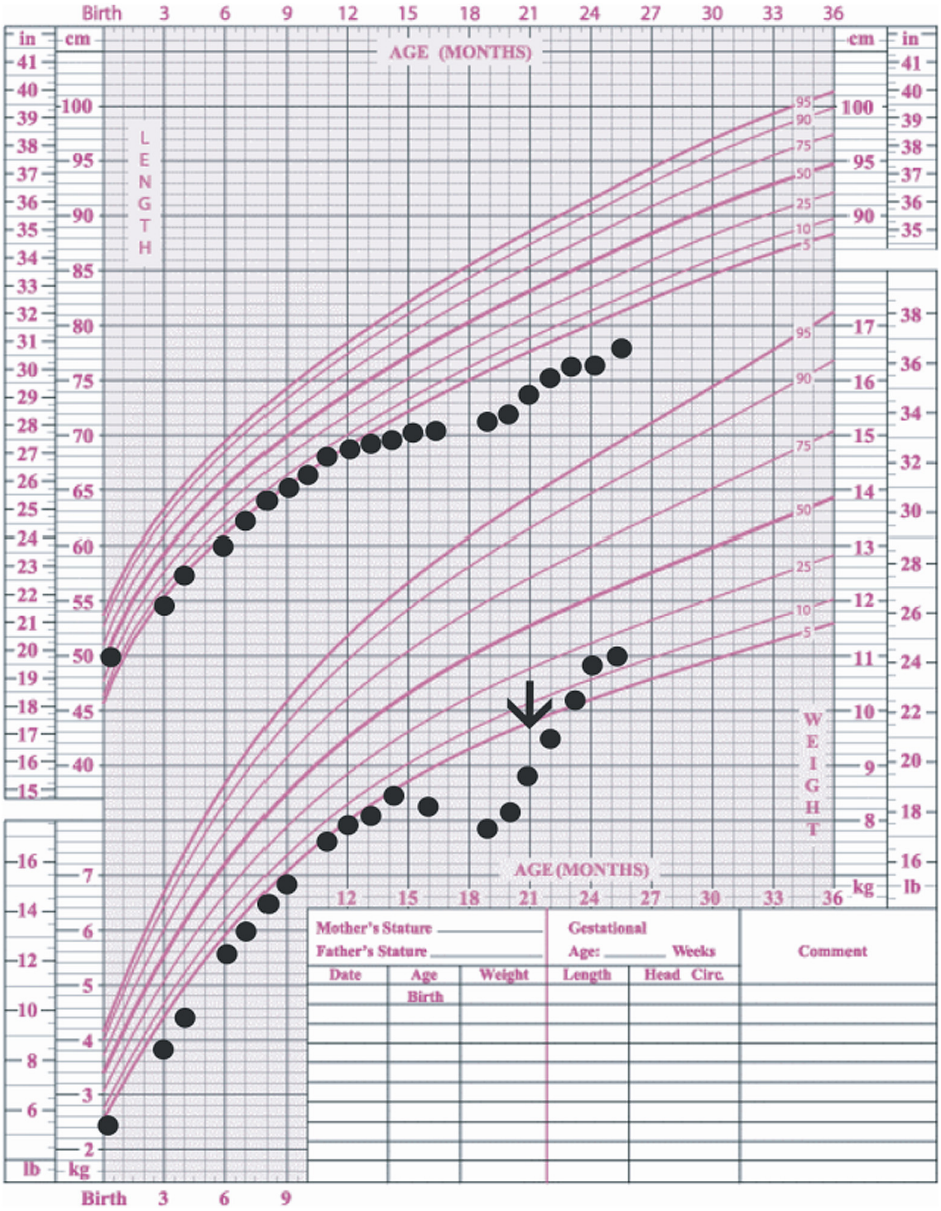

Figure 3: Improvement of weight gain after starting IVIG at 21 mo of age (arrow).

although, her height remained below the 5th percentile curve, after starting IVIG, she showed steady weight gain (Figure 3). She also received exogenous growth hormone (GH) as it had previously been shown to be beneficial in children with ring chromosome 18 and growth delay (Cody et al. 2015). A second assessment at the age of 11 years showed normal endogenous GH activity and GH was discontinued.

In the scenario of recurrent episodes of pneumococcal infection, antibody titers to diphtheria and tetanus were obtained and were initially borderline-lower-end normal at the age of 4 months (0.3 and 0.1 IU/mL, respectively), but 6 months after a booster vaccine the serum levels were protective (2.0 IU/mL). At the age of 9 years, antibody concentrations dropped to suboptimal levels for diphtheria, tetanus, *H. influenza*, Mumps, Varicella zoster virus (VZV), and Rubella. Nevertheless, booster doses for diphtheria and tetanus induced again appreciable concentrations of specific antibodies (Table 2). To determine if she should remain on IVIG, we assessed specific antibody response to the 23-multivalent pneumococcal polysaccharide vaccine. Unfortunately, due to her age, pre and post

Table 2: **Serum specific antibody titers against protein vaccines.**

Age	4 mo old	10 mo old (+ booster)	9 y old	9 y and 6 mo old (+ booster)
Diphtheria	0.3 IU/mL	2.0 IU/mL	0.01 IU/mL	4.8 IU/mL
Tetanus	0.1 IU/mL	2.0 IU/mL	0.07 IU/mL	1.6 IU/mL
H. influenzae	6 IU/mL	—	0.5 IU/mL	—
Mumps	—	—	—	Negative
VZV	—	—	—	Negative
Rubella	—	—	—	Negative

pneumococcal antibodies levels were not available prior to initiation of therapy, and stored sera were not available. At the age of 9 years, IVIG was held for 6 months prior to vaccination and we measured her response 4 weeks following 23-multivalent pneumococcal polysaccharide vaccine. Her poor response confirmed the clinical suspicion of SIgAD (Table 3). During the time off IVIG therapy, she developed episodes of sinusitis, streptococcal vulvitis, and fungal onycholysis. She was restarted on immunoglobulin therapy (subcutaneous) and was also given prophylactic azithromycin.

At age 13 and 18 years of age, immunophenotyping of T and B-lymphocytes revealed normal total CD4 and CD8 T cells and CD19+ B cells. However, the CD19+CD27+ memory B cell and CD19+CD27+IgD− switched memory B cell populations were decreased, compared to a health age-matched controls (Table 4). Additionally, analysis of CD45RA and RO subtypes revealed that both CD4+CD45RO+ and CD8+ CD45RO+ populations were significantly decreased (Table 4) with few single positive CD45RO+ cells and approximately 5% of T cells co-expressed CD45RA and RO (Figure 4). Nevertheless, T cell function tests including phytohemagglutinin-induced proliferation and V-beta repertoire were normal (data not shown).

Table 3: **Pre- and post-vaccination anti-pneumococcal antibody titers.**

Serotype	Pre-vaccination (μg/mL)	Post-vaccination (μg/mL)
1	0.11	<0.11
3	0.18	0.17
4	<0.08	0.10
6B	0.21	0.18
7F	0.56	0.49
9V	0.24	0.22
11A	0.31	0.19
12F	0.04	0.09
14	1.01	0.61
15B	0.62	0.5
18C	0.18	0.11
19F	0.52	0.40
23F	0.25	0.16
33F	0.52	0.43

Note: IVIG treatment was held for 6 mo before the patient was vaccinated with a 23-multivalent pneumococcal polysaccharide vaccine. Serum antibody titers for 14 serotypes were assessed 4 wk post-immunization.

Table 4: **Enumeration of CD4+CD45RA/RO+, CD8+CD45RA/RO+ and B cell subpopulations as a percentage of total CD4, CD8 and CD19 counts.**

Lymphocyte phenotype	Patient (%)	Reference (mean ± SD) %
CD19+sIgM+	68 (% CD19)	50 (34 ± 66)
CD19+CD5+	17 (% CD19)	39 (24 ± 54)
CD19+CD27+	4 (% CD19)	23 (11 ± 23)
CD19+CD27+IgD−	1 (% CD19)	>4
CD4+CD45RA+	57 (% CD4)	53 (33 ± 66)
CD4+CD45RO+	6 (% CD4)	28 (18 ± 38)
CD8+CD45RA+	42.5 (% CD8)	79 (61 ± 91)
CD8+CD45RO+	1 (% CD8)	23 (11 ± 23)

To investigate possible gene variants on the non-affected sister chromosome, we performed GS. This approach was chosen to find putative variants affecting coding or intronic sequences, splice sites, and regulatory regions. The results confirmed the breakpoints at chr18:5001–15 190 000 and chr18:54 215 001–78 020 000 (UCSC 2009, GRCh37/hg19 Assembly). No pathogenic or likely pathogenic variant of the genes in the deleted regions of chromosome 18 was filtered out. Meanwhile, we questioned whether a smaller intragenic copy number variant (CNV) on the regions corresponding to deletions had been missed on aCGH. Indeed, we did not observe any other CNV in the 2 regions of interest using PopSV. We, however, used the intermediate results of PopSV and looked at bins with z score ≤ -3. Using this method, we found a deletion of 4 kb (chr18:60,575,00160,579,000) deep in the middle of intron 8 of *PHLPP1* with almost

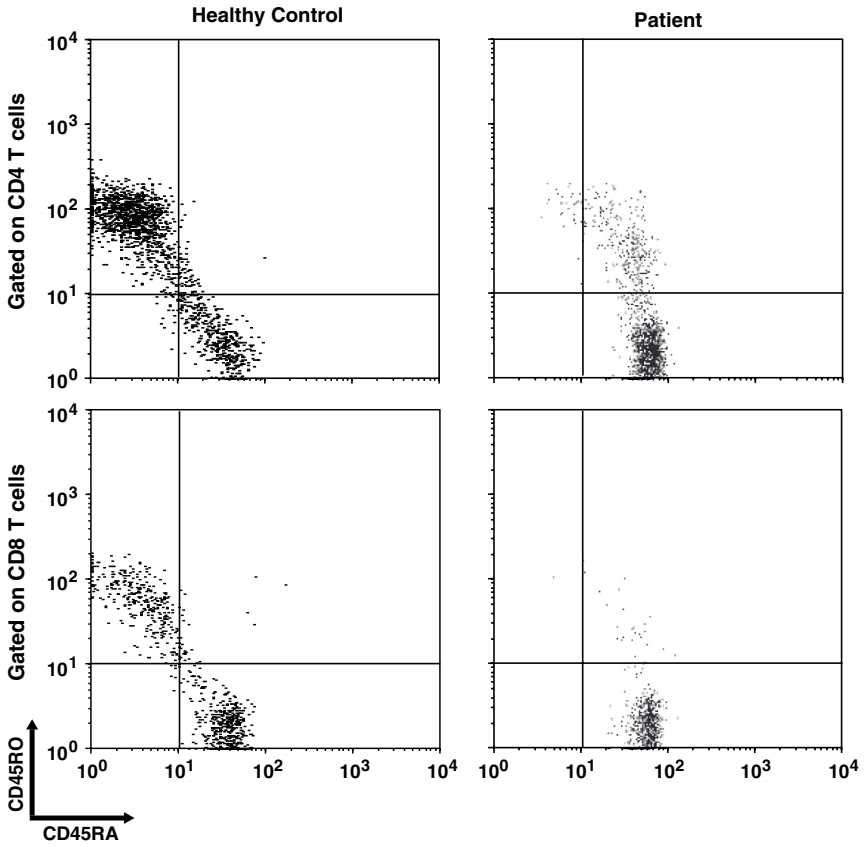

Figure 4: Loss of CD45RO+ memory T cell subpopulations in our patient with ring chromosome 18. Peripheral blood mononuclear cells from the patient and healthy control were stained and analyzed as described.

2.5–3 kb distance from 5′ and 3′ splicing sites. GS further excluded known monogenic defects associated with primary antibody deficiencies.

Discussion

The phenotype of individuals with a given ring chromosome can simply resemble those with terminal deletions, but without ring formation. Nevertheless, given the secondary genomic instability, clinical presentations can be highly variable (Guilherme et al. 2011). Chromosome 18 was among the first chromosomes found in humans to be affected by ring formation (Carter et al. 2015). Although deletions of 2 regions on 18q (17 000 000–19 667 062 and 45 578 734–46 739 965) are reportedly fatal, large deletions of chromosome 18 are thought to be less lethal due to the low gene density per Mb (Cody et al. 2015). Deletions of 18q are thought to have a more variable and unpredictable phenotype compared to 18p deletions. This is likely due to the high variability of hemizygosities as well as other factors such as duplications, somatic mosaicism and ring instability (Cody et al. 2009; Carter et al. 2015; Hasi-Zogaj et al. 2015). Our patient also has a 500 kb hemizygous deletion on chromosome 13 that does not encompass any UCSC genes.

13% of patients with 18p- have low serum immunoglobulin levels. SIgAD is the most common immune defect in any type of chromosome 18 abnormality (Cody et al. 2015; Hasi-Zogaj et al. 2015). Distal hemizygosity of 18q22.3-q23 has been also shown to be associated with SIgAD (Dostal et al. 2007). However, normal serum IgA levels in our patient could be due the variable penetrance of this locus that has been estimated to be between 33% and 50% (Cody et al. 2015). Additionally, the fact that SIgAD also affects patients with 18p-, suggests that more than 1 single locus on chromosome 18 regulates IgA. Indeed, there is evidence that there is a common genetic basis for SIgAD and CVID as the occurrence of both diseases in the same family or progression of SIgAD to CVID has been observed (Aghamohammadi et al. 2008). The conversion of SIgAD to CVID has also been previously

reported in a female patient with 18q-syndrome (Slyper and Pietryga 1997). Linkage analysis has failed to show any loci on chromosome 18 associated with SIgAD (Vorechovsky et al. 1999). Nonetheless, given the technical limitations at the time of those earlier studies, a re-assessment of patients using recently developed technologies such as arrays or next generation sequencing might help to discover novels gene defects or genomic variations implicated in SIgAD or CVID.

In our patient, both IgM and IgG serum levels were low and treatment with immunoglobulin was associated with reduction in the frequency of infections, elimination of septic episodes, and improved weight gain. She failed to develop a protective response to unconjugated pneumococcal capsule antigens despite adequate post-vaccine responses to tetanus and diphtheria, suggesting the diagnosis of specific antibody deficiency. The lack of specific polysaccharide antibodies has been previously reported in a patient with 18p- who only responded once immunized with a conjugated vaccine (Browning 2010). Meanwhile, a recent report of a patient with ring chromosome 18 depicted a different vaccine response: while all immunoglobulin isotypes, including IgA, were low, he had a good responses to unconjugated pneumococcal vaccination and booster doses of diphtheria and tetanus vaccines (Calvo Campoverde et al. 2016). Therefore, it is likely that, at least for protein vaccines, a booster dose can augment the specific antibody response in patients with chromosome 18 abnormalities and the use of conjugate vaccines should be prioritized.

Impaired homeostasis of memory T and B cells has been documented in CVID patients with autoimmunity (van de Ven and Warnatz 2015). We observed decreased CD19+CD27+ switched memory B cells and CD45RO+ memory T cell populations, as has been shown in 1 other patient with ring chromosome 18 (Calvo Campoverde et al. 2016). CVID patients with reduced number of CD45RO+ T cells might be affected with severe viral infections (Narula et al. 2007).

Association of primary antibody deficiencies and autoimmunity has been well characterized (van de Ven and Warnatz 2015). In addition to humoral immunodeficiency, patients with chromosome 18 abnormalities have been affected with rheumatoid arthritis, lupus, thyroiditis, vitiligo and type I diabetes mellitus (Dacou-Voutetakis et al. 1999; Hasi-Zogaj et al. 2015). In a patient with a terminal deletion of 18q (18q21.32-q23) and low serum IgA and IgG4 levels, autoimmune thyroiditis and type 1 diabetes mellitus, regulatory T cell (Treg) counts were low (Hogendorf et al. 2016). Our patient has severe polyarthritis, uveitis, and hypothyroidism. Unfortunately, we do not have data on Tregs in our patient.

The lack of efficient B cell and T cell interplay has been proposed to affect the development of memory T cells (Martini et al. 2011). Our understanding of the genetics of B cell deficiencies over the past decade has largely advanced. None of those genes is located on chromosome 18. In fact, patients with proximal interstitial deletions of 18q do not show any abnormal immune phenotype (Kato et al. 2010; Imataka et al. 2015). Therefore, it is probable that the candidate genes for antibody defects on 18q are located distally. In fact, homozygous pathogenic variants of Mucosa-Associated Lymphoid Tissue Lymphoma Translocation 1 gene (*MALT1*), that resides on 18q21.32, has been reported in patients with both CVID phenotypes with reduced switched memory B cells and autoimmunity with decreased Foxp3+ T cells (McKinnon et al. 2014; Charbit-Henrion et al. 2017). To examine if our patient's immune dysregulation was due to a gene variant on the regions of deletion, including *MALT1*, and to exclude other known monogenic causes of immunodeficiency and autoimmunity, we performed WGS. However, we could not find any variant that could explain the immunological phenotype, nor could we find any pathogenic variant, including CNVs, of *MALT1*. To our knowledge, *MALT1* haploinsufficiency has not been reported in humans as yet.

Indeed, few genes on chromosome 18 have been predicted to be haploinsufficient (Cody et al. 2009), among which only *TCF4* falls into the deleted region in our patient. Heterozygous mutations of *TCF4*, however, are associated with Pitt-Hopkins syndrome with no well-established immunological presentation. We ranked the genes on the deleted regions, using the probability of being loss-of-function (LoF) intolerant (pLI), described by the Exome Aggregation Consortium (ExAC; exac.broadinstitute.org) (Lek et al. 2016). Genes with pLI $\geq$ 0.9 are considered as an extremely LoF intolerant, meaning haploinsufficient.

We reviewed published studies in Pubmed.com and further shortlisted genes of interest based on their

Table 5: **List of the genes located on the deleted region of chromosome 18 in our patient with pLI score of ≥0.90.**

Chr	Gene_start	Gene_end	Gene	pLI
chr18	52889562	53332018	*TCF4*	0.999
chr18	12785477	12929642	*PTPN2*	0.995
chr18	56338618	56417371	*MALT1*	0.994
chr18	77155856	77289325	*NFATC1*	0.969
chr18	60382672	60647666	*PHLPP1*	0.918
chr18	55102917	55158529	*ONECUT2*	0.903
chr18	59992520	60058516	*TNFRSF11A*	0.879

Note: pLI, probability of being loss-of-function intolerant.

possible involvement in immunological processes (Table 5). Interestingly, both *TCF4* and *MALT1* ranked on the top of the list (Table 5). This observation suggests that the phenotypical consequence of genetic variants of those genes might not have been recognized, including possible digenic conditions.

We also examined other genes in the deleted region, determined from the literature, that could contribute to the lack of memory cells and SIgAD. *PTPN2* is a negative regulator of Jak1 and Jak3 and deficient lymphocytes show increased STAT1 and STAT5 signaling (Simoncic et al. 2002). *Ptpn2*$^{-/-}$ mice show impaired B cell lymphopoiesis, as well as impaired T and B cell response to mitogens. However, T cell development in the thymus is not affected (You-Ten et al. 1997). On the other hand, PTPN2 expression is enhanced in B cell lymphomas (Lu et al. 2007). Importantly, it has been shown that early maturation of B cells in the bone marrow of *Ptnp2*$^{-/-}$ mice was blocked due to enhanced IFNγ-STAT1 signaling (Bourdeau et al. 2007). STAT1 activation is known to be upregulated in autoimmune disorders (Domeier et al. 2016). Also, gain-of-function (GOF) mutations of *STAT1* have been shown in patients with CVID and autoimmunity (Al Rushood et al. 2013; Toubiana et al. 2016). Given the direct effect of PTPN2 on STAT1 phosphorylation (ten Hoeve et al. 2002), loss of PTPN2 might contribute to a similar phenotype as of STAT1 GOF mutations.

TNFRSF11A, also known as Receptor Activator of Nuclear Factor Kappa-B (RANK), encodes the receptor for RANK ligand (RANKL) that together make the master signaling pathway for osteoclast differentiation. Patients with Autosomal-Recessive Osteoporosis (ARO) are affected by homozygous mutations of *RANK* and *RANKL*. Additionally, these patients are unable to produce antibodies in response to tetanus vaccination (Guerrini et al. 2008). Interestingly, patients with homozygous mutations of *TNFRSF11A* (*RANK*), but not *TNFSF11* (*RANKL*) show decreased switched memory B cells (IgD−CD27+), but did not show T cell abnormalities (Guerrini et al. 2008).

PHLPP1 is a phosphatase that in parallel with PTEN regulates the PI3K/AKT pathway (Chen et al. 2016). Heterozygous mutations of *PTEN* cause Hamartoma Tumor Syndromes (PHTS). Patients with PHTS have defective antibody responses and autoimmune manifestations (Driessen et al. 2016). While absolute numbers of transitional peripheral B cells are elevated in these patients, the CD27+ memory B cell population is decreased. Moreover, class switch recombination and somatic hypermutation are impaired in PHTS patients (Driessen et al. 2016) as well as in PTEN deficient mice (Suzuki et al. 2003). The effect of loss of PTEN on B cells has been attributed to increased PI3K/AKT signaling. In fact, in patients with dominant GOF mutations of P110δ (a subunit of PI3K electively expressed in lymphocytes) show impaired class switch recombination, defective antibody responses and increased transitional B cells (Angulo et al. 2013). Notably, although loss of PTEN in humans does not affect Treg development, inhibitors of PHLPP1 block in vitro Treg differentiation (Chen et al. 2016). Collectively, absence of PHLPP1 in patients with 18q- could putatively replicate the immunological phenotype of PTEN deficiency in association with defective Treg responses. We found a deep intronic 4 kb deletion in intron 8 of *PHLPP1* in our patient. However, this deletion is very unlikely to be deleterious as it is quite far from flanking splice sites. Further functional studies will be required to assess whether haploinsufficiency of *PHLPP1* is could lead to this immunological phenotype.

NFATC1, encoding the nuclear factor of activated T cell c1 (NFATc1), is a member of NFAT family of transcriptional factors that are regulated via Ca^{2+}/Calcineurin (Medyouf and Ghysdael 2008). Based on animal models, it has been suggested that NFATc1 deficiency might cause immunodeficiency in human patients with 18q- (Li et al. 1995). Loss of *Nfatc1* in mice affects development and survival of both peritoneal and splenic B1-a cells (Berland and Wortis 2003). Moreover, even though NFATc1 does not affect the development and maturation of B cells, it plays a critical role in their function and fate. It has been shown

that *Nfact1*$^{-/-}$ B cells in mice show impaired proliferation and survival in response to BCR stimulation, Ig class switching and can suppress T cell activation (Bhattacharyya et al. 2011). These findings were in association with impaired Ca^{2+} influx resembling defective BCR signaling (Bhattacharyya et al. 2011). On the other hand, loss of NFATc1 in T cells impaired homing of follicular regulatory T cells in B cell follicles via transactivation of CXCR5. This was associated with an exacerbated lupus-like phenotype in mice (Bhattacharyya et al. 2011).

Conclusion

The association of hypogammaglobulinemia and abnormal chromosome 18 was recognized over 50 years ago (Feingold and Schwartz 1968). However, despite the advancement of our understanding of the genetics of the immune system, the responsible gene(s) for this phenotype are not yet known. In this case, in addition to low serum immunoglobulin levels, we found that both T and B memory cells and specific polysaccharide antibody responses were defective in our patient with ring chromosome 18. These data suggest that although the underlying defective mechanisms are not yet elucidated, it might be beneficial to attempt booster doses of protein or conjugate vaccines to patients with chromosome 18 abnormalities and defective humoral immunity. Further investigations on patients with chromosome 18 aberrations using new technologies could help discover novel genes involved in primary immunodeficiency and autoimmunity.

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