The First Purine Nucleoside Phosphorylase Deficiency Patient Resembling IgA Deficiency and a Review of the Literature

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ABSTRACT
Purine nucleoside phosphorylase (PNP) deficiency is a rare autosomal recessive primary immunodeficiency disorder characterized by decreased numbers of T-cells, variable B-cell abnormalities, decreased amount of serum uric acid and PNP enzyme activity. The affected patients usually present with recurrent infections, neurological dysfunction and autoimmune phenomena. In this study, whole-exome sequencing was used to detect mutation in the case suspected of having primary immunodeficiency. We found a homozygous mutation in PNP gene in a girl who is the third case from the national Iranian registry. She had combined immunodeficiency, autoimmune hemolytic anemia and a history of recurrent infections. She developed no neurological dysfunction. She died at the age of 11 after a severe chicken pox infection. PNP deficiency should be considered in late-onset children with recurrent infections, autoimmune disorders without typical neurologic impairment.

KEYWORDS
Purine nucleoside phosphorylase deficiency; combined immunodeficiency; IgA deficiency; autoimmune hemolytic anemia; chicken pox

Introduction
Purine nucleoside phosphorylase (PNP) deficiency is a rare autosomal recessive form of primary immunodeficiency disorders characterized by T-cell immunodeficiency (cellular immunity) and variable abnormalities of humoral (B-cell) immunity (Al-Herz et al., 2014). Patients with PNP deficiency present with recurrent infections, neurologic impairment (including ataxia, developmental delay, failure to thrive, mental retardation and spasticity), malignancies, and autoimmunity (especially autoimmune hemolytic anemia) (Markert, 1991; Tabarki et al., 2003; Watson et al., 1981). PNP is one of the enzymes involved in the purine salvage pathway which reversibly converts inosine to hypoxanthine and guanosine to guanine (Markert, 1991). PNP deficient-patients have increased amounts of deoxyguanosine and deoxyinosine in plasma and urine (Grunebaum et al., 2013). Intracellular accumulation of deoxyguanosine triphosphate has a toxic effect on thymocytes of the affected patients, resulting in
dysfunctional development and function of cellular immunity (Cohen et al., 1978). PNP deficiency is often fatal in the first two years of life (Fleischman et al., 1998) and hematopoietic stem cell transplantation (HSCT) is the only curative treatment for these patients (Classen et al., 2001). Herein, we report the third Iranian case with PNP deficiency with a tentative diagnosis of IgA deficiency without neurologic manifestations and a review of the literature of the previously reported patients.

Case presentation

The patient is an 11-year-old Iranian girl who was the only child of consanguineous parents. There was no family history of recurrent infections or immunologic disorders. She received all regular vaccinations according to the national vaccination schedule of Iran such as live vaccinations (Bacillus Calmette–Guérin, measles, mumps, rubella and oral polio vaccines) without any complications. At 24 months she was admitted due to the complaint of recurrent urinary tract infections and her urine culture was positive for *Escherichia coli*, which responded to antibiotic therapy. At 3 years, she underwent surgery for vesicoureteral reflux. She was healthy and had no complaint until 6 years of age when she was admitted due to pallor and fatigue. At this age, findings of bone marrow aspiration smears (hypercellular marrow with notable erythroid hyperplasia, dyserythropoiesis, karyorrhexis, binucleation, fragmentation of erythroid cells and detectable numerous mitotic figures of erythroid series and myeloid change) revealed autoimmune hemolytic anemia. After a diagnosis of autoimmune hemolytic anemia, intravenous immunoglobulin immunomodulation therapy, steroids and cyclosporine (Mastrandrea, 2015) were started for her and continued until the patient’s demise due to medical severity during withdrawal treatment phases. Beginning of episodic respiratory infections including pneumonia, otitis media and several hospitalizations for pansinusitis at 7 years, were all signs of immunodeficiency disorder. CT scan of the lung showed diffuse bronchiectasis. Laboratory tests revealed T-cell and B-cell lymphopenia (Table 1). Her serum immunoglobulin levels were all within normal limits except for IgA which was severely reduced. IgG4 was also diminished which was consistent with the autoimmune condition. At this time, she was diagnosed with late-onset combined immunodeficiency presenting with IgA-deficiency and placed on trimethoprim-sulfamethoxazole and amoxicillin antibacterial prophylaxis. Thus, the case was genetically evaluated by whole exome sequencing using a standard published method and pipeline analysis (Abolhassani et al., 2019). She had a novel homozygous missense mutation in exon 2 of the *PNP* gene (c.91T>C) and segregation analysis revealed that her parents were both heterozygous for this mutation. This variant results in a conversion of cysteine into an arginine at amino acid 31 (p.C31R, combined annotation dependent depletion score: 27.2, the mutation significance cutoff: 9.2) affecting the first β-strand in C terminal of the PNP protein (Figure 1).

Neurological examinations were all normal during her life and no organomegaly was observed. At the age of 11, autoimmune hemolytic anemia became severe and she frequently received blood transfusions. At the same age, she got a severe chicken pox infection and died 3 days later before finding an appropriate HLA-matched donor and HSCT performance. Unfortunately, no assessments were done for evaluation of T cell function or diversity. Other detailed laboratory findings of the patient during 5-year follow-up from the time of diagnosis of primary immunodeficiency until the patient’s
Table 1. Longitudinal laboratory and immunologic data of the patient in comparison to the age-appropriate reference value from healthy Iranian subjects during the 5-year follow-up.

| Laboratory tests                  | Patient (at age 7y) | Patient (at age 8y) | Patient (at age 9y) | Patient (at age 10y) | Patient (at age 11y) | Reference Intervals |
|-----------------------------------|---------------------|---------------------|---------------------|----------------------|---------------------|---------------------|
| WBC (10^3/μL)                    | 4.0l                | 4.0l                | 3.9l                | 4.15l                | 1.97l               | 5–13                |
| RBC (10^6/μL)                    | 3.4l                | 3.48l               | 2.18l               | 3.69l                | 2.25l               | 4–5.2               |
| Hb (g/dL)                        | 11.1l               | 11.1l               | 8.8l                | 12.1 (NL)            | 7.5l                | 11.5–15.5           |
| Hematocrit (%)                   | 33.8l               | 33.8l               | 25l                 | 37 (NL)              | 24.6l               | 35–45               |
| M.C.V (fL)                       | 97.1l (slightly ↑)  | 114.7l ↑            | 100.3l              | 109.3l ↑             | 11.6–14             |
| M.C.H (pg)                       | 3.19 (NL)           | 3.19 (NL)           | 40.4t               | 32.8 (NL)            | 33.3 (slightly ↑)   |
| M.C.H.C (g/dL)                   | 32.8 (NL)           | 32.8 (NL)           | 35.2 (NL)           | 32.7 (NL)            | 30.5 (slightly ↑)   |
| R.D.W (%)                        | 15.3l               | 15.3l               | 27.6l               | 14.9 (NL)            | 19.9l               |
| Platelets (10^5/μL)              | 3.3 (NL)            | 3.3 (NL)            | 3.11 (NL)           | 2.41 (NL)            | 1.96 (NL)           |
| ALC (cells/μL)                   | 520l                | 640l                | 702l                | 1494 (NL)            | 315.2l              |
| CD3 + T lymphocytes (cells/μL)   | 320l                | 406l                | 293l                | 1330 (NL)            | NA                  |
| CD4+ helper T lymphocytes (cells/μL) | 160l              | 196l                | 117l                | 448 (NL)             | NA                  |
| CD8+ cytotoxic T lymphocytes (cells/μL) | 165l          | 203l                | 136l                | NA                   | NA                  |
| CD19 + B lymphocytes (cells/μL)  | 32l                 | 39l                 | 56l                 | 45l                  | NA                  |
| IgG (mg/dL)                      | 1170 (NL)           | 1568 (NL)           | 1056 (NL)           | 1907l                | NA                  |
| IgA (mg/dL)                      | 7l                  | 2l                  | 5l                  | undetectable         | NA                  |
| IgM (mg/dL)                      | 139 (NL)            | 200 (NL)            | 95 (NL)             | 58 (NL)              | NA                  |
| IgE (IU/ml)                      | 49.2 (NL)           | 0 (NL)              | 101t                | 140 (NL)             | NA                  |
| IgG1-subclass (mg/dL)            | NA                  | 1082 (NL)           | NA                  | 964 (NL)             | NA                  |
| IgG2-subclass (mg/dL)            | NA                  | 348 (NL)            | NA                  | 821t                 | NA                  |
| IgG3-subclass (mg/dL)            | NA                  | 294t                | NA                  | 163 (NL)             | NA                  |
| IgG4-subclass (mg/dL)            | NA                  | 1l                  | NA                  | undetectable         | NA                  |
| Pneumonia Ab (IgG) (mg/L)        | 30.9 (+)            | 183 (+)             | NA                  | NA                   | NA                  |
| Pneumonia Ab (IgG2) (mg/L)       | 16.2 (+)            | 16.6 (+)            | NA                  | NA                   | NA                  |
| C3 (mg/dL)                       | NA                  | 95 (NL)             | NA                  | 86 (slightly ↑)      | NA                  |
| C4 (mg/dL)                       | NA                  | 15 (NL)             | NA                  | 19 (NL)              | NA                  |
| CH50 (U)                         | NA                  | 100 (NL)            | NA                  | 140 (NL)             | NA                  |
|                         | AST (U/l) | ALT (U/l) | Creatinine (mg/dl) | Urea (mg/dl) | Anti-Tetanus (IU/ml) | Anti-Diphtheria (IU/ml) |
|-------------------------|-----------|-----------|--------------------|-------------|----------------------|------------------------|
|                         | 36↑       | 19 (NL)   | 0.5 (slightly↓)    | 28 (NL)     | NA                   | NA                     |
|                         | 31 (slightly↑) | 37↑   | NA                 | NA          | <0.1                 | <0.1: Basic immunization recommended |
|                         | <31       | <31       | 0.5 (slightly↑)    | 24 (NL)     | NA                   | NA                     |
|                         | 15–36     | <0.1      | 0.6–1.2            | NA          | <0.1                 | <0.1: Basic immunization recommended |

WBC; white blood cell, RBC; red blood cell, Hb; hemoglobin, M.C.V; mean corpuscular volume, M.C.H; mean corpuscular hemoglobin, M.C.H.C; mean corpuscular hemoglobin concentration, R.D.W; Red blood cell distribution width, ALC; absolute lymphocyte count, CD; cluster of differentiation, Ig; immunoglobulin, Ab; antibody, C3; complement component 3, C4; complement component 4; CH50; 50% hemolytic complement, AST; aspartate aminotransferase, ALT; alanine aminotransferase, µL; microliter, dL; deciliter, fL; femtoliter, pg; picogram, IU; international unit, mg; milligram, U; units, U/l; units per liter, y; years, NL; normal, NA; not available.
death, are shown in Table 1. Since she was diagnosed with combined immunodeficiency presenting with IgA-deficiency and we had not primarily suspected to diagnosis of PNP deficiency in the patient, PNP activity and toxic metabolites' accumulation in patient's serum were not assessed until the age of 11 years when whole exome sequencing was

Figure 1. a: Mutations in PNP deficiency, frequency and types of reported variants (missense and loss of function) in the general populations according to genomAD database were compared with the distribution of mutations reported in PNP deficient patients. Type of mutations reported in PNP deficient patients within exons and introns of the PNP gene are depicted. b: The effect of currently identified mutation (p.C31R) in the index patient is illustrated on a ribbon protein structure of PNP.
performed for her and a novel missense mutation was found in PNP gene. Short time after diagnosis of PNP deficiency, she got a severe chicken pox and died 3 days later; thus we were unable to investigate further this case.

**Discussion**

We herein describe a novel missense mutation within exon 2 of *PNP* gene in a girl presenting with normal neurological function, recurrent infections and autoimmune hemolytic anemia. To date, 72 PNP-deficient cases have been reported which we reviewed and summarized these patients in Table 2 and Figure 1. Our case was the third reported PNP-deficient patient in Iran and the first one in the north of Iran. Among the previous cases, one of them was a 7-year-old boy who died due to pulmonary infections and the other was a 9-year-old boy with progressive multifocal leukoencephalopathy (Parvaneh et al., 2008).

PNP deficiency is characterized by impaired cellular immunity and variable humoral immunity abnormalities (Cohen et al., 2000). In total, 22 of the 72 reported cases have had decreased T-cell immunity and intact B-cell immunity, however, 26 cases have been reported with combined immunodeficiency as well as both abnormal T-cell and B-cell immunity similar to our patient (Alangari et al., 2009; Al-Saud et al., 2009; Aytekin et al., 2010, 2008; Brodzski et al., 2015; Celmeli et al., 2015; Classen et al., 2001; Delicou et al., 2007; Girit et al., 2012; Kiykim et al., 2016; Madkaikar et al., 2011; Markert et al., 1987; Myers et al., 2004; Parvaneh et al., 2007, 2008; Rich et al., 1979; Rijken et al., 1987; Sasaki et al., 1998; Somech et al., 2013, 2012; Stoop et al., 1976; Yamamoto et al., 1999; Yeates et al., 2017).

Reported PNP-deficient patients have presented different immunoglobulin profiles including: agammaglobulinemia (Markert et al., 1987; Myers et al., 2004; Parvaneh et al., 2008; Somech et al., 2012; Yeates et al., 2017), Hyper IgM (Rijken et al., 1987; Stoop et al., 1977; Watson et al., 1981), hypergammaglobulinemia (Alangari et al., 2009; Moallem et al., 2002; Tsuda et al., 2002), normal immunoglobulin levels (Al-Saud et al., 2009; Baguette et al., 2002; Brodzski et al., 2015; Celmeli et al., 2015; Classen et al., 2001; Delicou et al., 2007; Gelfand et al., 1978; Giblett et al., 1975; Girit et al., 2012; Hallett et al., 1994; Hamet et al., 1977; Kiykim et al., 2016; Kumar et al., 2012; Markert et al., 1987; Martin et al., 2016; Ozkinay et al., 2007; Rich et al., 1980; Simmonds et al., 1987; Somech et al., 2012; Soutar and Day, 1991; Tabarki et al., 2003; Virelizier et al., 1978) and increase or decrease in one or two immunoglobulin subclasses (Alangari et al., 2009; Aytekin et al., 2010, 2008; Dror et al., 2004; Gelfand et al., 1978; Kiykim et al., 2016; Parvaneh et al., 2008; Rich et al., 1979; Rijken et al., 1987; Somech et al., 2013; Stoop et al., 1976, 1977; Van Heukelom et al., 1977; Watson et al., 1981; Zabay et al., 1982). To the best of our
Table 2. Clinical and Immunologic presentation of 72 previously reported PNP-deficient patients.

| N  | Origin              | AOD | AOD | Sex | Consanguinity | Lymphocyte (x10^3) | T-cells (x10^3) | CD4 (x10^3) | CD8 (x10^3) | B-cell (x10^3) | IgG (mg/ml) | IgA (mg/ml) |
|----|---------------------|-----|-----|-----|---------------|-------------------|----------------|-------------|-------------|--------------|-------------|-------------|
| P 1| Bahamian            | 8 m | 12 m| F   | No            | 328               | 75              | 59          | 61          | 100          | 15.08       | 2.64        |
| P 2| Palestinian         | 6 m | 12 m| F   | Yes           | 185               | 37              | 15          | 28          | 1            | 12.81       | 0.3(NL)     |
| P 3| Iranian             | 4 y | 6 y | M   | Yes           | 300               | 66              | 25          | 40          | 130          | 25           | 0.55(NL)    |
| P 4| Turkish             | 6 m | 2 y | M   | Yes           | 300               | 66              | 46          | 11          | 10           | 4.53(NL)    | 0.26(NL)    |
| P 5| Swedish             | 9 m | 2 y | M   | Yes           | 600               | 390             | 130         | 150         | 70           | NL          | NL          |
| P 6| Turkish             | -   | 13 m| F   | No            | 400               | 11               | 0.9         | 0.1         | 35           | 2.47        | 0.25(NL)    |
| P 7| -                   | 2 y | 13 y| F   | No            | 560               | 185             | 79          | 84          | 90           | 7.13        | 0.5(NL)     |
| P 8| -                   | 6 m | 7 m | F   | Yes           | 520               | 161             | 202         | 157         | 139          | 7.18        | 0.38(NL)    |
| P 9| -                   | 1 y | 7 y | F   | Yes           | 200               | 46              | 24          | 33          | 12           | 15.3        | 0.83(NL)    |
| P 10| Turkish            | 2 y | -   | F   | Yes           | 520               | 261             | 15.6        | 15.6        | 130          | NL          | NL          |
| P 11| -                   | 3 y | 3.5 y| F   | Yes           | 600               | 132             | 30          | 60          | 11           | 7.56(NL)    | 0.371       |
| P 12| Saudi Arabian       | 9 m | 2 y | F   | Yes           | 420               | 385             | 106         | 263         | 311          | 18.77       | 2.97        |
| P 13| Iranian             | 7 y | 9 y | M   | Yes           | 410               | 220             | 137         | 64          | 55           | 51          | undetectable|
| P 14| mixed Caucasian     | 26 m| 4.5 y| M   | -             | 280-4301          | 44.8-68.81      | 36.4-55.91  | 5.6-86.1    | 92.4-141.9(NL)| 5.9(NL)     | 3.71        |
| P 15| Arabian             | 2 m | 9 y | M   | Yes           | 680               | 272             | 143         | 95          | 2110         | NL          | NL          |
| P 16| -                   | 2 m | 7 m | F   | Yes           | 364               | 116             | 109         | 71          | 153          | 8.19(NL)    | 1.751       |
| P 17| Indian              | 15 d| 22 m| F   | Yes           | 520               | 161             | 109         | 71          | 153          | 8.19(NL)    | 1.751       |
| P 18| -                   | 2 m | 5 y | F   | Yes           | 495               | 91              | 91          | <0.01       | <0.01        | 0.84(NL)    | undetectable|
| P 19| Arab                | 4 m | 9 m | F   | Yes           | 420               | 261             | 15.6        | 15.6        | 130          | NL          | NL          |
| P 20| Japanese            | 2.7 m| 7 y | F   | Yes | 1008           | 6991            | -           | -           | -            | 1.1         | 1           |
| P 21| -                   | 1 y | 3 y | M   | Yes           | 400               | 601             | 70           | 701         | 71           | 16.07(NL)   | -           |
| P 22| -                   | 10 m| -   | F   | Yes           | 624              | 1451           | 231         | 1171        | -            | NL          | NL          |
| P 23| -                   | 22 m| -   | F   | Yes           | 1350             | 13000          | -           | -           | -            | 1.91        | 1.31        |
| P 24| -                   | 3 m | 2.8 y| M   | Yes           | 504              | 504            | -           | -           | -            | 5.6(NL)     | 1.08(NL)    |
| P 25| Tunisian            | 6 m | -   | F   | Yes           | 132              | 13000          | -           | -           | -            | 1.91        | 1.31        |
| P 26| -                   | 3 m | 2.9 y| M   | Yes           | 504              | 504            | -           | -           | -            | 5.6(NL)     | 1.08(NL)    |
| P 27| Irish               | 2.7 m| 7 y | F   | Yes           | 1350             | 13000          | -           | -           | -            | 1.91        | 1.31        |
| P 28| Dutch               | 2 m | 2.7 y| F   | Yes           | 306              | 306            | -           | -           | -            | NL          | NL          |
| P 29| Post-mortem         | 1 y | -   | M   | No            | 432              | 432            | -           | -           | -            | 19.66       | 0.52(NL)    |
| P 30| Post-mortem         | 1 y | -   | M   | No            | 570              | 570            | -           | -           | -            | 2.28        | 0.36(NL)    |
| P 31| -                   | 1 m | 10.5 y| M   | -             | <750             | 13000          | -           | -           | -            | NL          | NL          |
| P 32| -                   | 3 y | 7 y | M   | -             | 282              | 132            | 130         | 130         | 130          | NL          | NL          |
| P 33| -                   | 4 m | 4.5 y| M   | -             | 130              | 130            | 130         | 130         | 130          | NL          | NL          |
| P 34| Caucasian           | 4 m | 5.5 y| M   | No            | 260-9501         | 46.3-256.51    | -           | -           | -            | 0.014       | 0.1(NL)     |
| P 35| -                   | 13 m| -   | M   | Yes           | 300              | 41.7           | 32.7         | 207         | 16.05        | 5.51        | 0.738(NL)   |
| P 36| -                   | 15 m| 15 m| M   | No            | 1500             | 406           | 130         | 130         | 130          | 1.17        | 0.041       |
| P 37| -                   | 3 m | 6.5 y| F   | No            | 864              | 216           | 78          | 130         | 300          | 5.04        | 0.034       |
| P 38| -                   | 2 y | 3 y | M   | No            | <500             | 200-275        | 100-250     | 50-90       | 50-95        | 6.1         | 1.1(NL)     |
| P 39| -                   | 13 m| 2 y | M   | -             | 1200             | 560           | 120         | 420         | 190          | NL          | 0.9(NL)     |
|   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P40 | Saudi Arabian |   | 2 y | F | Yes | 618 | 314 | 167 | 18 | 58 | 10(NL) | 0.14(NL) |
| P41 |   |   |   |   |   |   |   |   |   | 7.5(NL) | 0.6(NL) |
| P42 |   |   |   |   |   |   |   |   |   | NL | NL |

IMMUNOLOGICAL INVESTIGATIONS

|   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P43 |   | 15 m | 15 m | F | No | 319 | 83 | 1 | 1 | NL | 7.5(NL) | 0.72(NL) |
| P44 |   | 6 m | 22 m | F | No | 96 | 70 | 17 | 61 | NL | NL |
| P45 |   | 3 m | 5 y | M | No | 500 | 1 | 1 | 1 | NL | NL |
| P46 |   | 1 y | 3 y | F | No | 120 | 400 | Trace | 20 | - | - |

P47 Irish At birth At birth M Yes 13001 ↓↓ ↓ ↓ ↓ 105-2801 20-64 ↓ ↓ ↓ |

P48 -   - 18 y M - ↓ 191 ↓ 921 ↓ 71 ↓ - NL NL |

P49 -   - 3 y F - - ↓ 1 ↓ 1 ↓ 1 NL 5.97(NL) 1.07(NL) |

P50 -   - 1 y 3 y M - 492 ↓ 1 ↓ 1 ↓ 1 - - 11(NL) 0.8(NL) |

P51 -   - 21 m F - 180 ↓ 1 ↓ 1 ↓ 1 NL - - |

P52 Tunisian 1 y - F Yes - - - - - - - - |

P53 -   - 6 m - F No - - - - - - - - |

P54 -   - 2 y F - - - - - - - - - - |

P55 -   - 1 m F - - - - - - - - - - |

P56 -   - 19 y M - - - - - - - - - - |

P57 -   - 2 m M - - - - - - - - - - |

P58 -   - 1 y M - - - - - - - - - - |

P59 -   - 3 y M - - - - - - - - - - |

P60 -   - 1 m F - - - - - - - - - - |

P61 -   - 2 y - M - <370 - - - - - - - |

P62 Arab 11 m - M Yes - ↓ (We do not have further information, as only limited investigations were permitted.)
| P 1 | 1.551 | 118.96 (at the lower limit of normal) | Homozygous | Exon 5 | c.467G>A | p.Gly156Ala | + | + | + | - | failure to thrive | Moallem et al. (2002) |
| P 2 | 5.51  | 118.96 (at the lower limit of normal) | Homozygous | Exon 5 | c.649G>A | p.Val217Ile | + | + | + | - | diarrhea | Somech et al. (2013) |
| P 3 | 0.35 l | 34.51 | Homozygous | Exon 3 | c.212G>A | p.Gly71Glu | + | + | - | - | chronic diarrhea | Parvaneh et al. (2008) |
| P 4 | 0.84 (NL) | 5.95 l | Homozygous | Exon 5 | c.393 C>T | p.Pro198Leu | - | + | - | - | fever and respiratory distress | Brodzski et al. (2016) |
| P 5 | NL | 12 l | 16 l | compound | Exon 6 | c.729C>G | p.Asn243Lys | + | + | - | - | obesity | Kyykim et al. (2015) |
| P 6 | 0.25 l | 11.9 l | 30.5 l | Homozygous | Exon 5 | c.593 C>T | p.Pro198Leu | + | + | - | - | persistent fever | Gelmeli et al. (2015) |
| P 7 | 1.83 (NL) | 107.06 | Homozygous | Exon 4 | c.349G>A | p.Ala117Thr | + | + | + | + | vision loss due to herpes zoster infection | Aytekin et al. (2010) |
| P 8 | 0.49 (NL) | <29.74 l | Homozygous | Exon 5 | c.593C>T | p.Pro198Leu | + | + | - | - | intermittent hematuria | Girt et al. (2012) |
| P 9 | 1.19 (NL) | 35.69 | 42.4 l | Homozygous | Exon 4 | c.349G>A | p.Ala117Thr | + | + | + | - | fever abscess by Aspergillus | Aytekin et al. (2010) |
| P 10 | NL | 49.37 l | 1.4 l | Homozygous | Exon 4 | c.349G>A | p.Ala117Thr | + | + | - | - | pulmonary tuberculosis | Ozkinay et al. (2007) |
| P 11 | 0.32 l | 23.79 l | 2 l | Homozygous | Exon 4 | c.349G>A | p.Ala117Thr | + | - | + | - | progressive multifocal leukoencephalopathy | Aytekin et al. (2010) |
| P 12 | 3.66 l | 62.6 l | 324 l | Homozygous | Exon 4 | c.437C>T | p.Pro146Leu | + | + | - | - | chronic diarrea | Alangari et al. (2009) |
| P 13 | undetectable l | 59.48 l | - | - | Exon 5 | c.475T>G | p.Ala159Val | + | + | + | - | progressive multifocal leukoencephalopathy | Parvaneh et al. (2007, 2008) |
| Exon | Position | Mutation | p.Amino Acid | State | Disease Description |
|------|----------|----------|--------------|-------|---------------------|
| 2    | c.172C>T | p.Arg57Ter | + + + - | Compound heterozygous | Dror et al. (2004), Dalal et al. (2001) |
| 3    | c.244C>T | p.Gln82Ter | - + + - | Homozygous | parvovirus infection which induced pure red cell aplasia requiring multiple blood transfusions-severe marrow dysplasia |
| 5    | c.285+1G>A | splicing site mutation | + + + - | Homozygous 1 | acute respiratory illness |
| 5    | c.265G>A | p.Glu89Lys | - - - - | Homozygous 2 | diarrhea-bronchiolitis |
| 3    | c.487T>C | p.Ser163Pro | - - - - | Homozygous 3 | |
| 2    | c.59A>C | p.His20Pro | + + - - | Homozygous 4 | |
| 5    | c.497A>G | p.Tyr166Cys | + + - - | Homozygous 5 | |
| 2    | c.70C>T | p.Arg24Ter | + + - - | Homozygous 6 | |
| 3    | c.218T>C | p.Leu73Pro | + + + + | Homozygous 7 | |
| 2    | c.161G>T | p.Leu54Val | + + + + | Homozygous 8 | |
| 3    | c.203A>G | p.Lys68Asn | + + + + | Homozygous 9 | |
| 4    | c.383A>G | p.Asp128Gly | + + - - | Homozygous 10 | |
| 4    | c.383C>G | p.Asp128Asp | + + + + | Homozygous 11 | |
| 5    | c.468delA | p.Gly156fsX170 | + + - - | Homozygous 12 | |
| 5    | c.468del | p.Gly156fsX170 | + + - - | Homozygous 13 | |
| 4    | c.349G>A | p.Ala117Thr | + + - - | Homozygous 14 | |
| 5    | c.385G>A | p.Asp128Glu | + + - - | Homozygous 15 | |
| 6    | c.385C>A | p.Asp128Asp | + + - - | Homozygous 16 | |
| 4    | c.383A>G | p.Asp128Gly | + + - - | Homozygous 17 | |
| 4    | c.383C>G | p.Asp128Asp | + + + + | Homozygous 18 | |
| 5    | c.468delA | p.Gly156fsX170 | + + - - | Homozygous 19 | |
| 5    | c.468del | p.Gly156fsX170 | + + - - | Homozygous 20 | |
| 4    | c.349G>A | p.Ala117Thr | + + - - | Homozygous 21 | |
| 5    | c.385G>A | p.Asp128Glu | + + - - | Homozygous 22 | |
| 6    | c.385C>A | p.Asp128Asp | + + + + | Homozygous 23 | |
| 4    | c.383A>G | p.Asp128Gly | + + - - | Homozygous 24 | |
| 4    | c.383C>G | p.Asp128Asp | + + + + | Homozygous 25 | |
| 5    | c.468delA | p.Gly156fsX170 | + + - - | Homozygous 26 | |
| 5    | c.468del | p.Gly156fsX170 | + + - - | Homozygous 27 | |

(Continued)
|   |  IgM (mg/ml) |  Uric acid (μmol/L) | PNP activity (nmol/l/mg Hb) | Zygosity | Location | cDNA change | Protein change | Infections | Neurological impairment | Autoimmune phenomena | Eventful chicken pox infection | Other clinical manifestations | Reference |
|---|-------------|--------------------|-----------------------------|----------|----------|-------------|---------------|------------|----------------------|----------------------|-----------------------------|---------------------------|-----------|
| P 27 | 8.51 | Partially | Undetectable | - | - | - | - | + | + | - | - | Aseptic meningitis-malignant lymphoma of the B immunoblastic type | Watson et al. (1981), Simmonds et al. (1987) |
| P 28 | 2.05 (NL) | - | 01 | - | - | - | - | + | - | - | - | Diarrhea | Zabay et al. (1982) |
| P 29 | 1.29 (NL) | 30i | 0.11 | - | - | - | - | + | - | - | - | Lymphosarcoma | Van Heukelom et al. (1977), Stoop et al. (1976) |
| P 30 | 0.57 (NL) | I | I | - | - | - | - | + | - | - | - | Pyruvate-toxic epidermal necrolysis | Gelfand et al. (1978) |
| P 31 | 1.2 (NL) | - | I | - | - | - | - | + | + | - | - | Progressive pulmonary insufficiency | Rich et al. (1980) |
| P 32 | NL | 101.12I | Undetectable | - | - | - | - | + | + | + | - | Influenza-like illness-persistent ear infections | Simmonds et al. (1987) |
| P 33 | 1.1 (NL) | Trace | I | - | - | - | - | + | + | + | - | Died of complication related to immunosuppression of graft versus host disease | Aytekin et al. (2008) |
| P 34 | 21 | 107.06I | 1.5I | - | - | - | - | + | + | + | - | Right preauricular and left axillary lymphadenitis due to disseminated BCG infection | Rich et al. (1979) |
| P 35 | 0.147I | 5.95I | 01 | - | - | - | - | + | + | + | - | Right preauricular and left axillary lymphadenitis due to disseminated BCG infection | Myers et al. (2004) |
| P 36 | 0.18I | 88.7I | 56.4I | - | - | - | - | + | + | - | - | Right preauricular and left axillary lymphadenitis due to disseminated BCG infection | Boume et al. (1996) |
| P 37 | NL | 77I | 95.8I | - | - | - | - | + | + | - | + | Right preauricular and left axillary lymphadenitis due to disseminated BCG infection | Rijken et al. (1987) |
| P 38 | 1.61 | 20I | 30I | - | - | - | - | + | + | - | - | Right preauricular and left axillary lymphadenitis due to disseminated BCG infection | Hallett et al. (1994) |
| Page | Value | Expected Value | Comparison | Significance | Reference |
|------|-------|----------------|------------|--------------|-----------|
| 40   | 0.2 i | undetectable   | -          | +            | Alangari et al. (2009) |
| 41   | 0.8 (NL) | 1560 i     | -          | +            | Vrelizer et al. (1978) |
| 42   | 1.4 (NL) | i         | -          | +            | Gefland et al. (1978) |
| 43   | 2.76 i | undetectable | -          | +            | Stoop et al. (1977) |
| 44   | NL    | 31 i        | -          | +            | Glassen et al. (2001) |
| 45   | NL    | 630 i       | -          | +            | Delicou et al. (2007) |
| 46   | NL    | undetectable| -          | +            | Soutar and Day (1991) |
| 47   | NL    | 71 i        | -          | +            | Pannicke et al. (1996) |
| 48   | NL    | i           | -          | +            | Kumar et al. (2012) |
| 49   | 1.64 (NL) | 0 i       | -          | +            | Martin et al. (2016) |
| 50   | 1.5 (NL) | i         | -          | +            | Hamet et al. (1977) |
| 51   | -     | 214.12 (NL) | undetectable | +          | Blatt (1990) |
| 52   | -     | 184 (NL)    | Homozygous | +            | Tabarki et al. (2003) |
| 53   | -     | Compound heterozygous | Exon 4 c.349G>A p.Ala117Thr | + | Parmicke et al. (1996) |
| 54   | -     | Compound heterozygous | Exon 5 c.575A>G p.Tyr192Cys | + | - |
| 55   | -     | Compound heterozygous | Exon 6 c.199C>T c.730delA (1-bp deletion at position +730) | - | - |

(Continued)
| N   | IgM (mg/ml) | Uric acid (μmol/L) | PNP activity (nmol/h/mg Hb) | Zygosity | Location | cDNA change | Protein change | Infections | Neurological impairment | Autoimmune phenomena | Eventful chicken pox infection | Other clinical manifestations | Reference       |
|-----|-------------|-------------------|-----------------------------|----------|----------|-------------|---------------|------------|-----------------------|-----------------------|-----------------------------|-----------------------------|------------------|
| P56 | -           | 100(at the lower limit of normal) | -                           | Compound heterozygous | Exon 2   | c.172C>T    | p.Arg57Ter   | -          | -                     | -                     | -                           | -                           | Walker et al. (2011) |
| P57 | -           | 144(NL)           | 142I                         | Compound heterozygous | Exon 4   | c.383A>G    | p.Asp128Gly  | -          | -                     | -                     | -                           | -                           | Walker et al. (2011) |
| P58 | -           | 152(NL)           | 1631I                        | Compound heterozygous | Exon 2   | c.172C>T    | p.Arg57Ter   | -          | -                     | -                     | -                           | -                           | Walker et al. (2011) |
| P59 | -           | 15I               | 0I                           | Compound heterozygous | Exon 3   | c.569G>T    | p.Gly190Val  | -          | -                     | -                     | -                           | -                           | Walker et al. (2011) |
| P60 | -           | 110(NL)           | 0I                           | Compound heterozygous | Exon 3   | c.257A>G    | p.His86Arg   | -          | -                     | -                     | -                           | -                           | Walker et al. (2011) |
| P61 | -           | 11.9I             | -                            | Compound heterozygous | Exon 3   | c.257A>G    | p.His86Arg   | -          | +                     | +                     | -                           | Encephalitis            | McGinniss et al. (1985) |
| P62 | -           | 5I                | 0.1I                         | -          | -          | -            | -             | -          | +                     | -                     | -                           | Meningitis-paregenerative anemia-pneumopathy | Simmonds et al. (1987) |
| P63 | -           | 17I               | 0I                           | -          | -          | -            | -             | +          | -                     | -                     | -                           | -                           | Chantin et al. (1998) |
| P64 | -           | TraceI            | 0.1I                         | -          | -          | -            | -             | +          | +                     | -                     | -                           | -                           | Simmonds et al. (1986, 1987) |
| P65 | -           | -                 | -                            | Compound heterozygous | IVS 3    | c.286-18 G>A | splice site mutation | p.Arg234Pro | -                     | -                     | -                           | -                           | Markert et al. (1997) |
| P66 | -           | -                 | -                            | Compound heterozygous | Exon 4   | c.385C>386C  | 387delATC    | p.Lle129del | -                     | -                     | -                           | -                           | Markert et al. (1997) |
| P67 | -           | -                 | -                            | Compound heterozygous | Exon 6   | c.701G>C     | p.Arg234Pro   | -          | -                     | -                     | -                           | -                           | Markert et al. (1997) |
| P68 | -           | -                 | -                            | Compound heterozygous | Exon 5   | c.520G>C     | p.Ala174Pro   | -          | -                     | -                     | -                           | -                           | Markert et al. (1997) |
| P69 | -           | -                 | -                            | Compound heterozygous | Exon 3   | c.701G>C     | p.Arg234Pro   | -          | -                     | -                     | -                           | -                           | Markert et al. (1997) |
| P70 | -           | -                 | -                            | Compound heterozygous | Exon 6   | c.769C>G     | p.His257Asp  | -          | -                     | -                     | -                           | -                           | Grunebaum et al. (2004) |
|    |    |    | Exon 6 | c.700C>T | p.Arg234Ter |    |    |    |    | Grunebaum et al. (2004) |
|----|----|----|--------|----------|-----------|----|----|----|----|------------------------|
| P 71 | - | - | - | - | - | - | - | - | - | - |
| P 72 | - | - | - | - | - | - | - | - | - | - |

N; number, AOO; age at onset of disease, AOD; age at diagnosis of disease, M; male; F; female, P; patient, NL; normal, n.d.; not determined.
knowledge, no cases of PNP-deficiency associated with IgA deficiency have been reported and this is the first case with low serum IgA levels.

Neurological impairments are typical clinical manifestations among PNP-deficient patients. Since PNP is essential for removing metabolites of DNA breakdown and induces recycling of purine bases, the lack of PNP leads to accumulation of metabolites which are toxic and cause lymphopenia and impaired cell-mediated immunity as well as neuronal cell apoptosis. Up to now, almost 70% of the reported cases have suffered from neurological dysfunction including ataxia, disequilibrium, developmental delay, hyper/hypotonia, spastic paresis, behavioral problems and mental retardation (Camici et al., 2010). In contrast, our case showed no neurological involvement during the life. In almost 1/3 of the cases similar to our patient, neurological involvements have not been detected (Aytekin et al., 2010; Blatt, 1990; Cohen et al., 1976; Gelfand et al., 1978; Hamet et al., 1977; Markert et al., 1987; Stoop et al., 1976; Virelizier et al., 1978; Zabay et al., 1982). Based on these data, it is suggested that although neurological deficits are an important feature of PNP deficiency, the severity and presentation vary significantly between patients and some of these patients may not manifest any neurologic complication. However, it is important not to rule out PNP deficiency in immunodeficient children with normal neurologic conditions.

Although the pathogenicity of p.C31R mutation was re-evaluated using the updated guideline for interpretation of molecular sequencing by the American College of Medical Genetics and Genomics (Richards et al., 2015), considering the allele frequency in the population database, computational data, immunological profile, familial segregation and parental data, atypical clinical phenotyping of the patient may suggest a hypomorphic mutation given the normal uric acid and the lack of neurological defects and severe cellular immunodeficiency. Recently, another study has reported a 13-year-old patient with a homozygous missense pathogenic variant with a late-onset PNP deficiency (p. A117T) diagnosed with hypogammaglobulinemia at the age of 10 (Celmeli et al., 2015), suggesting that residual PNP activity in patients with hypomorphic pathogenic variants can show atypical presentation like in adenosine deaminase deficiency, another enzyme important for purine degradation and salvage (Grunebaum et al., 2013).

Autoimmune phenomena including hemolytic anemia, idiopathic thrombocytopenic purpura, autoimmune neutropenia, systemic lupus erythematosus, sclerosing cholangitis, pericarditis and arthritis are another clinical manifestations among PNP-deficient patients (Buckley, 1994). Our patient was diagnosed with autoimmune hemolytic anemia. Similar to our patient, 13 other cases have been reported with hemolytic anemia (Dalal et al., 2001; Delicou et al., 2007; Dror et al., 2004; Kiykim et al., 2016; Moallem et al., 2002; Parvaneh et al., 2007; Rich et al., 1979, 1980; Simmonds et al., 1987; Somech et al., 2013, 2012; Walker et al., 2011). Thus, the presence of autoimmune disorders especially hemolytic anemia in immunodeficient patients with impaired cellular and humeral is an important clue for considering PNP deficiency.

PNP gene is located on chromosome 14q13.1 encoding PNP enzyme consisting of 289 amino acids (Williams et al., 1984). In our patient, sequence analysis revealed a novel mutation within the PNP gene. She inherited a novel missense mutation, putatively leading to a disruption of first β-stand and adjacent DNA binding site (polynucleotide binding region) composition in the PNP enzyme. So far, 37 unique mutations have been reported among the PNP-deficient patients (Table 2). Majority of
identified variants were missense (71.9%) reflecting the intolerance of the enzyme to the biallelic mild mutations as the most frequent mutations found are also missense (A117T and R234P, Figure 1). Moreover, mutations spread around different exons constituting the main functional domain of the protein, but the exon 2 (the exon affected in our index patient, 3.5 mutation/100 bp) is less affected compared to other exons (exons 4 and 5 contain almost 60% of the reported mutations, 11.7 mutation/100 bp). The rarity of the disease and the small number of reported mutations has limited the possibility to appraise the presence of hot spots within the gene. Mutation analysis in the affected patients will help to determine the genetic defects responsible for the disease.

Varicella-zoster virus (VZV) is the microorganism causing chicken pox. Previous investigations have demonstrated that recovery from varicella is associated with the development of VZV-specific T-cell mediated immunity (Arvin et al., 1986; Kumagai et al., 1980). The T-cell immunity against VZV-infected is related to CD4 and CD8 T-cells (Diaz et al., 1988; Frey et al., 2003; Hayward, 1990; Hayward et al., 1989), thus defective cellular immunity predisposes the affected immunodeficient patients to VZV infection and patients with an abnormality in T-cells manifest more severe disease than normal hosts (Arvin et al., 1986; Webster et al., 1988). PNP-deficient patients are at high risk of Varicella infection due to defective cellular immunity, as observed in our patient who died 3 days after a severe chicken pox infection and eight other reported PNP-deficient cases suffering from severe and even lethal varicella infection (Baguette et al., 2002; Broome et al., 1996; Celmeli et al., 2015; Gelfand et al., 1978; Hallett et al., 1994; Markert et al., 1987; Simmonds et al., 1987). In HIV-infected children with CD4 deficiency, it has been demonstrated that vaccination against VZV resulted in the prevention of varicella infection (Levin et al., 2006). Except for Japan, the United States, Canada, the United Kingdom, some parts of Australia and some European countries, vaccination against VZV is not routinely performed. Since children are not vaccinated against VZV in our country, individuals with PNP deficiency are predisposed to a higher risk of morbidity and mortality. On the other hand, cautious is required when live VZV attenuated vaccine is considered for a T cell immunodeficient patients. Since vaccine-associated varicella infections have been previously reported in patients with combined immunodeficiency (Bayer et al., 2014; Dalal et al., 2001), physicians must be aware of potential adverse effects of VZV vaccination and the early management. These data demonstrate that delayed diagnosis could be fatal for patients with PNP deficiency. Taken together, further investigations are needed to clarify the effectiveness of varicella vaccination in PNP deficiency and the feasible procedures for reducing the severity of varicella infection in the affected PNP-deficient patients.

In conclusion, it is important to confirm the diagnosis of PNP deficiency by genetic analysis, even in children with immunodeficiency who may not present with neurological abnormalities or autoimmune phenomena. Newborn screening, especially in families with the history of immunodeficiency disorders and earlier diagnosis of these patients, could help to better manage affected patients before the presentation of neurologic impairment and irreversible phenomena by means of supportive care and enzyme replacement therapy and HSCT, leading to lowering the mortality rate among the affected patients.
**Conflict of interest**

The authors declare no conflict of interest.

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