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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Paroxysmal Nocturnal Haemoglobinuria (PNH) Arising from Non-Canonical Mutations

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Introduction
Acquired somatic mutations in the X-linked *PIGA* gene are the most commonly described pathological mutations found in the serious haematopoietic disorder paroxysmal nocturnal haemoglobinuria (PNH), though incidental cases of mutations in *PIGT*, *PIGB* and *PIGV* have been reported. Mutations in the family of 20 PIG (phosphatidylinositol glycan) genes can disrupt biosynthesis of glycosylphosphatidylinositol (GPI) anchors, critical for tethering many important proteins, including the vital complement regulators CD55 and CD59, to the cell membrane. Their absence in PNH leads to complement dysregulation and complications including potentially life-threatening haemolysis and thrombosis, which may be mitigated by lifelong anti-complement therapy.
From the cohort of 273 PNH patients currently on complement inhibitor therapy at the Leeds National PNH Centre we have identified 37 patients whose diagnostic flow cytometry report or clinical course differs significantly from expectation, particularly with evidence of inflammatory presentations, which may be indicative of an alternative, non- *PIGA*, aetiology.
Methods
Patients consented to the Leeds PNH Research Tissue Bank with unusual clinical and laboratory presentations were identified, genomic DNA was extracted from peripheral blood and initially screened by targeted high sensitivity NGS of the *PIGA* gene. From the first ten patient samples sequenced, three lacked any evidence of *PIGA* mutations and so whole exome sequencing (WES) was carried out.
Results
Patient 1:An 80 year old man, diagnosed with MDS with rearrangement of chromosomes 3 and 7 resulting in a dicentric chromosome and loss of chromosome 20q, was diagnosed with PNH following an increase in transfusion requirement. In addition to classical symptoms of PNH he was diagnosed with seronegative rheumatoid arthritis. Flow cytometry showed an unusual PNH phenotype with a large population of partially GPI-anchor deficient cells only (Table 1). Symptoms improved on eculizumab but he remained transfusion dependent and the disease later transformed to acute myeloid leukaemia. WES: exonic frameshift insertion in *PIGT* (figure1), pathogenic variant rs760395465.
Patient 2:A 34 year old woman presented with a 13 year history of intermittent episodes of generalized urticaria associated with nausea, vomiting, general malaise and myalgia, increasing in intensity and latterly being associated with haemoglobinuria, lethargy and jaundice leading to a PNH diagnosis. Episodes were triggered by pregnancy or infections, but she remained asymptomatic between attacks. Flow cytometry revealed a PNH clone with a majority of cells being partially GPI deficient. She responds well to C5 inhibition with no further symptoms, including urticaria. WES: exonic frameshift insertion in *PIGT* (figure 1), pathogenic variant rs760395465.
Patient 3: A 14 year old girl presented with intermittent episodes of urticaria and severe lethargy and was diagnosed with symptomatic significant transfusion-dependent PNH, with completely GPI-deficient cells. Diagnosis followed an episode of massive haemolysis resulting in transient acute renal failure requiring haemodialysis. She commenced anticoagulation initially

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until eculizumab was approved 2 years later; despite occasional episodes of breakthrough haemolysis she displays no further urticaria. She has also had symptoms of diffuse arthralgia. WES: stopgain mutation in *PIGV* (figure1), pathogenic variant rs145160045.

Conclusions

These cases add to the emerging picture of non- *PIGA* associated PNH cases and suggest that the presence of joint problems and episodic urticaria may be sufficient indication to prompt screening for alternative causative mutations. Similar to the previously reported *PIGB* mutated case, the patients with *PIGT* mutations only had partially deficient cells. It is important to fully characterise these emerging non-canonical variants in order to improve our understanding of the pathophysiology of this disorder and to provide more individualised care.

Disclosures Pike: *Sobi:* Honoraria. **Arnold:** *Florio:* Honoraria; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sobi:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Munir:** *AstraZeneca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BeiGene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Muus:** *Novartis:* Other: Advisory board member; *Sobi:* Other: Travel support and lecture fees. **Hillmen:** *Apellis Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Griffin:** *Sobi:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion, AstraZeneca Rare Disease:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Regeneron Pharmaceuticals:* Consultancy; *Amgen:* Membership on an entity's Board of Directors or advisory committees; *Biocryst:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Apellis:* Other: educational grant support . **Kelly:** *Astellas:* Honoraria, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Pfizer:* Honoraria, Speakers Bureau; *Jazz:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Biologix:* Honoraria, Speakers Bureau; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Honoraria, Research Funding, Speakers Bureau.

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Table 1. Patient information

Patient	Gender	Age at diagnosis (years)	Diagnosis	Co-morbidities	PNH flow cytometry at presentation	Symptoms and signs prior to complement inhibitor therapy	Indication for anticomplement therapy	Outcome	Mutation (VAF)
Case 1	Male	80	MDS-Haemolytic PNH	Seronegative rheumatoid arthritis Lemierre's syndrome Ischaemic heart disease Atrial fibrillation Type 2 diabetes Gallstones Skin infections	Granulocyte PNH clone (type II cells) = 92.49%. Monocyte PNH clone (type II cells) = 90.88%. Red cell PNH clone = 5.47% (5.46% type II cells and 0.01% type III cells).	Abdominal pain, fatigue, haemoglobinuria, erectile dysfunction, fatigue, dyspnoea, chest pain, diarrhoea, dysphagia	Transfusion dependent haemolysis	Died (acute myeloid leukaemia)	Chr20 *PIGT* exonic frameshift insertion (0.791)
Case 2	Female	34	Haemolytic PNH	Nil	Granulocyte PNH clone = 42.81%. Monocyte PNH clone = 43.88%. Red cell PNH clone = 30.44% (30.39% type II cells and 0.05% type III cells).	Episodes of urticaria, nausea, vomiting, malaise, myalgia, haemoglobinuria, lethargy, jaundice	Episodes of transfusion dependent haemolysis	Alive	Chr20 *PIGT* exonic frameshift insertion (0.652)
Case 3	Female	14	Haemolytic PNH	Migraine Addison's disease Appendicitis Arthralgia Cholelithiasis Splenomegaly	Granulocyte PNH clone = 94.3%. Monocyte PNH clone = 93.2%. Red cell PNH clone = 12.84% (2.64% type II cells and 10.2% type III cells).	Severe lethargy, malaise, haemoglobinuria, renal impairment, urticaria, dysphagia, dyspneoa	Episodes of transfusion dependent haemolysis	Alive	Chr1 *PIGV* stopgain (0.967)

Figure 1. Location of mutations within *PIGT* and *PIGV*

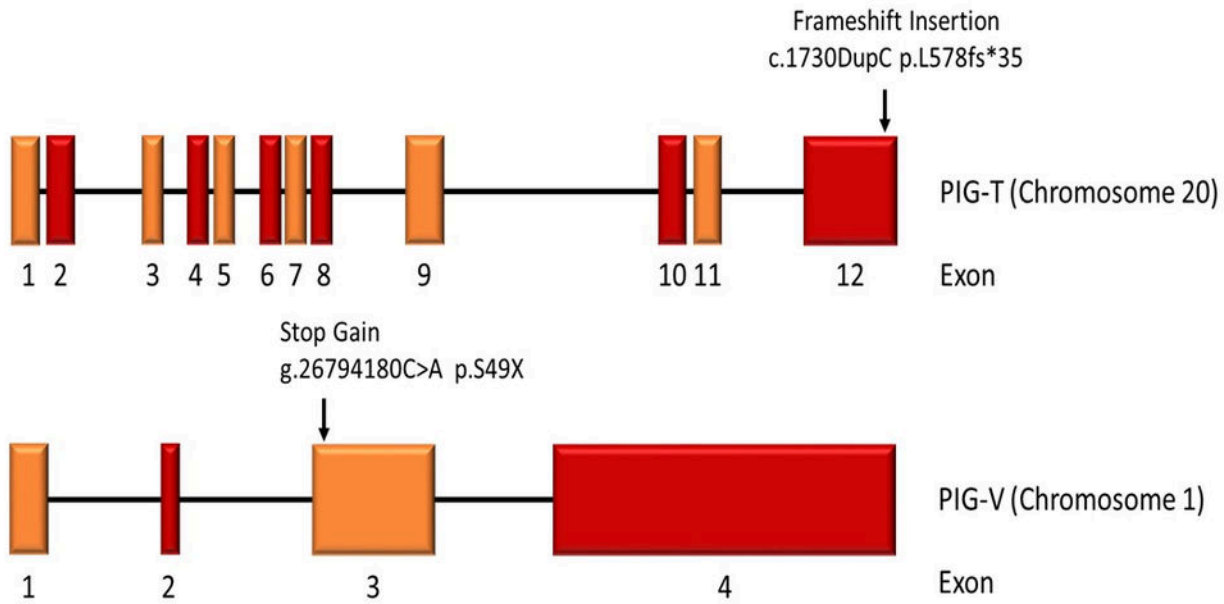

Figure 1