Response:

X-chromosome inactivation and autoimmunity

We thank Dr Ozcelik for his careful reading of our review and his thoughtful letter. Dr Ozcelik raises the issue of nonequivalence of monosomy X frequency and X-chromosome inactivation pattern (XCIP). The first refers to the proportion of cells with a single X chromosome, wherein transcription occurs from the lone X chromosome. The second refers to the ratio of inactivated maternal to paternal X chromosome, wherein transcription does not occur from the inactivated chromosome. We agree that although frequency of monosomy X and XCIP are different, both estimate the degree of inequality in X-chromosome dosage. Thus, while direct comparisons may not be possible, it is reasonable to use them as indices for processes inactivating the X chromosome.

Dr Ozcelik references 2 unpublished studies refuting XCIP skewing in primary biliary cirrhosis. These studies are unavailable to us and we are unable to comment on them.

Finally, our comments about age-related XCIP and the pathogenesis of certain autoimmune diseases have been misinterpreted by Dr Ozcelik. Certainly, many of these autoimmune diseases tend to be more prevalent in older rather than younger patients, and the increased prevalence of XCIP with age suggests there may be some relationship between the two. However, we clearly point out that “no studies have formally linked age related XCIP skewing with the development of autoimmune disease,” and that this topic “deserves further research.” Thus, we read with interest Dr Ozcelik’s further thoughts on unequal X-chromosome expression and autoimmune disease.

George L. Chen and Josef T. Prchal

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Josef T. Prchal, University of Utah, School of Medicine, 30 N 1900 E, Room 4C416, Salt Lake City, UT 84112; e-mail: josef.prchal@hsc.utah.edu.

References

To the editor:

Why the disorder induced by GATA1 Arg216Gln mutation should be called “X-linked thrombocytopenia with thalassemia” rather than “X-linked gray platelet syndrome”

GATA1 mutations induce 2 X-linked thrombocytopenias: dyserythropoietic anemia with thrombocytopenia (Online Mendelian Inheritance in Man [OMIM] 300367) and X-linked thrombocytopenia with thalassemia (XLTT; OMIM314050). The former has been described in 6 families with 5 different GATA1 mutations,1,2 whereas the latter has been identified in 3 pedigrees with the 216R>Q substitution.3,5 In both illnesses, patients present mild dyserythropoiesis, red cell hemolysis, severely defective maturation of megakaryocytes, macrothrombocytopenia with α-granule deficiency, and abnormalities of the cytoplasmic membrane system. Unbalanced globin-chain synthesis resembling β-thalassemia has been described only in patients with XLTT, whereas severe anemia and thrombocytopenia have only been observed in dyserythropoietic anemia with thrombocytopenia. These 2 disorders are therefore closely related and are the unique inherited thrombocytopenias that constitutively present abnormalities of red cell line.

Tubman et al4 identified a family with X-linked thrombocytopenia, large agranular platelets, and increased erythrocyte hemoglobin F (HbF) deriving from the 216R>Q mutation in GATA1 and recently reported it in this journal under the title “X-linked gray platelet syndrome due to a GATA1 216R>Q mutation.” Because genotype and phenotype of this pedigree are completely superimposable with those observed in previous patients with XLTT, their decision to classify them as “X-linked gray platelet syndrome” risks producing further confusion in the field of inherited thrombocytopenias, which is already per se complex and confusing. It is perfectly true that the large platelets with α-granule deficiency observed in XLTT are in some respects similar to those typical of Gray platelet syndrome6 (GPS; OMIM 139090), but it is also unquestionable that several other findings differentiate the former from the latter. For instance, the red cell defect of XLTT has never been described in GPS, whereas the bone marrow emperipolesis of GPS7,8 is not present in XLTT. Moreover, different expression and localization of α-granule proteins, such as differences in the spectrum of functional defects of platelets, distinguish these 2 disorders. Finally, the gene responsible for the classical GPS has not yet been identified, and it may be everywhere except in chromosome X, because an X-linked transmission has been never observed, whereas autosomal dominant inheritance has been well documented in some pedigrees. So GPS and XLTT are different disorders presenting the common finding of large platelets with α-granule deficiency. Furthermore, applying the term GPS to all conditions with pale platelets due to severe α-granule deficiency would also imply that other genetic thrombocytopenias with this finding (Medich giant platelet disorder, white platelet syndrome) have to be considered GPS. On the contrary, some affected members of GPS pedigrees who, due to the variable penetrance of this disorder, have very mild α-granule deficiency (despite full expression of other platelet defects)9 could no longer be classified as GPS.

So, to avoid confusion, we suggest that (1) the disorder deriving from GATA1 216R>Q mutation is not an “X-linked gray platelet syndrome” but rather XLTT, and (2) the term GPS should be used
to indicate the illness (or the syndrome) that several reports and reviews have well described in the past.

**Response:**

**What's in a name?**

Balduini and colleagues characterized the platelets with GATA1 mutation Arg216Gln, which leads to a subtle beta thalassemic phenotype plus large, agranular platelets, a condition designated “XLTT.” In their letter, these authors now propose that our phenotype plus large, agranular platelets, a condition designated XLTT by Balduini et al or the distinctions drawn between GATA1 and XLTT “lumping” versus “splitting” in the characterization of these naming controversy and a different philosophical outlook about features). However, we have a different view of this specific mutation by a different route, namely by linkage analysis and candidate gene sequencing in a kindred with what appears to be an X-linked form of “gray platelet syndrome” (GPS), will add confusion and imprecision to the field. They suggest that “X-linked GPS” is an inaccurate name. We have no important disagreement with either the rationale for the name XLTT by Balduini et al or the distinctions drawn between GATA Arg216Gln mutation and autosomal GPS (which lacks thalassemia features). However, we have a different view of this specific naming controversy and a different philosophical outlook about “lumping” versus “splitting” in the characterization of these platelet disorders.

The question is fundamentally one of nosology (how medical syndromes get their names), a subject with a rich history. We believe this Arg216Gln mutation disorder could be classified in any of the following ways: (1) as a member of the broad spectrum of congenital GATA1 disorders, which presently includes dyserythropoiesis, transient myeloproliferative disease of trisomy 21, porphyria, and macrothrombocytopenia with granule defects; (2) as a unique kind of GPS, inherited in X-linked fashion, with platelets indistinguishable by experts from autosomal GPS (at the light microscope and ultrastructure level); or (3) as its own unique syndrome, “XLTT.” Each classification teaches us something different; none is more “wrong” or “right” than the others. Although we chose the second option, we endorse all 3.

There are biologic and practical reasons not to discard the idea of X-linked GPS, despite the critique of Balduini et al. Biologically, because GATA1 is a master regulator in megakaryopoiesis, it is likely that the autosomal GPS gene(s) (when discovered) will prove to be downstream targets of GATA1. In this hypothetical pathway, it seems to us unreasonable to consider giving different mutations different disease names. This is true of any genetically heterogeneous disorder (for example, the Fanconi anemia pathway, with more than a dozen members, including the BRCA2 gene). We need look no further than thalassemias for evidence of nonconfusion because the name XLTT itself causes no confusion with thalassemias linked to the globin genes on chromosomes 11 and 16. Practically, some of the distinctions between XLTT and autosomal GPS are out of reach of clinical hematologists, whereas GATA1 sequencing for large, agranular platelets is easy to obtain.

Globin-chain ratios are infrequently assessed in any clinical setting. Marrow evaluation for emperipolesis is not standard in our platelet function evaluations. Several percent of the world’s population has a thalassemia trait, so the coincidental appearance of microcytosis with absent alpha granules does not necessarily spell XLTT. Thus, we stand by the name X-linked GPS with a nod of gratitude to the prior work of Balduini et al, and we predict that some fraction of males with sporadic or familial GPS will prove to have GATA1 mutations.

**Reference**


**References**

Why the disorder induced by GATA1 Arg216Gln mutation should be called "X-linked thrombocytopenia with thalassemia" rather than "X-linked gray platelet syndrome"

Carlo L. Balduini, Erica De Candia and Anna Savoia