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Multisystem Inflammatory Disease in a Child with Multiple Heterozygous Variants: A Case Suggesting Oligogenic Interaction

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Abstract **Background:** The interpretation of multiple heterozygous Variants of Uncertain Significance (VUS) poses a significant challenge in clinical genomics, particularly in consanguineous pedigrees. **Case Presentation:** An example of a child with a severe multisystem disorder is that of a 10 year-old boy born out of a consanguinity relationship with manifested symptoms of chronic inflammatory bone pain (diagnosed with chronic non-bacterial osteomyelitis through biopsy), severe growth failure and chronic gastrointestinal symptoms. Whole-exome sequencing showed a heterozygous likely pathogenic variant in PAH (c.898G>T; p.Ala300Ser), a heterozygous likely pathogenic variant in PRKRA (c.796G>A; p.Ala266Thr), a heterozygous VUS in ALDH18A1 (c.1619A>G; p.Glu540Gly) and a compound heterozygote VUS in the SI gene. **Conclusion:** Variant prioritization was guided by ACMG/AMP classification, phenotypic concordance and pathway-level biological plausibility, with additional support from segregation analysis and functional correlation, including biochemical confirmation of sucrase-isomaltase deficiency. We suggest a hypothesis of a synergistic heterozygotic effect of PRKRA variants on inflammatory signaling, along with metabolic stress factors of the PAH and ALDH18A1 variants and nutritional deficiency of partial Sucrase-Isomaltase deficiency (SI) reduced the initiation threshold to severe CRMO.

Key Words Synergistic Heterozygosity, Variant of Uncertain Significance (VUS), Chronic Non-Bacterial Osteomyelitis (CRMO)

INTRODUCTION

Case reports are pivotal in delineating novel genotype-phenotype correlations, especially in the era of next-generation sequencing, which frequently uncovers Variants of Uncertain Significance (VUS) [1]. Specific diagnostic issue is observed in patients whose lineage is frequently consanguineous and who carry various heterozygous forms of genes linked with autosomal recessive dysfunction [2]. Synergistic heterozygosity is a theory that states that a combination of partial deficiencies of enzymes in multiple metabolic or cellular pathways may reach a critical threshold, leading to a complex clinical phenotype that is not consistent with a particular monogenic disease [3,4]. The model goes further than the traditional Mendelian models to consider oligogenic and polygenic factors on the expression of the disease [5]. We discuss a paradigm case of a 10 year-old boy who has a severe multisystem inflammatory and growth phenotype. Genetic examination demonstrated a cluster of heterozygous mutations in PAH, PRKRA, ALDH18A1 and SI. We propose the hypothesis that his condition is an interaction involving synergy between: (1) A PRKRA variant that predisposes the dysregulation of innate immune signaling, (2) PAH and ALDH18A1 variants that establish a chronic state of metabolic and connective tissue stress and (3) SI variants that cause nutritional deficiency and gastrointestinal inflammation. It is this accrued burden, we believe, which resulted in the emergence of the most serious acute chronic non-bacterial osteomyelitis (CRMO) and systemic growth retardation. This report will help shed light on the interpretive process of a variety of VUS and promote a systems-biology approach to complex pediatric genetics.

CASE PRESENTATION

Clinical History and Examination

The boy, aged 10, the son of first cousins, was referred to have the history of a two-year-old progressive and debilitating pain in the lower limbs, knees and ankles

investigated. It was mechanical pain, which increased with movement and mobility was severely affected. His past revealed that he had severe proportional short stature (height at 5th percentile) and underweight (weight at 3rd percentile) and a history of appetite loss. He had complained of abdominal pain on several occasions, occasional vomiting, chronic constipation and general symptoms such as pallor, night sweats and occasional dyspnea. No history of rash, morning stiffness or fever.

Family history played an important role in parental consanguinity and short stature of a cousin with growth hormone deficiency. Examination showed tenderness palpated in the metaphyseal areas of the distal femora and proximal tibiae on both sides without apparent joint swelling and warmth. Sensory Neurological No spasticity, dystonia or muscle weakness. Skin examination showed no evidence of cutis laxa or hyperextensibility.

Diagnostic Investigations

Laboratory Studies revealed a profound inflammatory state: C-reactive protein (CRP) 48 mg/L (ref. <5), Erythrocyte Sedimentation Rate (ESR) 62 mm/hr. He was manifesting chronic transaminitis (ALT 85 U/L, AST 78 U/L). Extensive autoimmune serology (ANA, RF, ANCA) and celiac disease serology and infectious work-up (Brucella, tuberculosis) was negative.

Histopathology A bone biopsy of the left iliac crest revealed a lympho-histiocytic infiltrate and fibrosis and new bone formation, which is characteristic of chronic osteomyelitis. Bacterial and mycobacterial cultures and PCR were negative, which proved the diagnosis of chronic non-bacterial osteomyelitis (CRMO).

Genetic Analysis

Given the multisystem involvement and consanguinity, trio-based clinical whole-exome sequencing was performed. Sequencing achieved a mean coverage depth of ≥100×, with >95% of targeted regions covered at ≥20×, ensuring high sensitivity for variant detection. Raw sequencing reads were aligned to the human reference genome (GRCh37/hg19) using Burrows-Wheeler Aligner (BWA) and variant calling was performed using the Genome Analysis Toolkit (GATK) pipeline following best practice guidelines. Variant annotation and filtering were conducted using established bioinformatics pipelines. Variants with a minor allele frequency (MAF) >1% in population databases (gnomAD, 1000 Genomes) were excluded. Prioritization focused on rare coding and splice-site variants with predicted functional impact. Clinical relevance was assessed based on phenotypic concordance, gene function and pathway involvement. Variants were interpreted per ACMG/AMP 2015 guidelines [6,7]. Key findings are summarized in Table 1.

Table 1: Summary of Pathogenic and Uncertain Genetic Variants Identified by Whole-Exome Sequencing

Gene (Transcript)	Variant (Protein)	Zygosity	ACMG Classification	Associated Disorder (Inheritance)
PAH (NM_000277.3)	c.898G>T; p.Ala300Ser	Heterozygous	Likely Pathogenic	Phenylketonuria (AR)
PRKRA (NM_003690.5)	c.796G>A; p.Ala266Thr	Heterozygous	Likely Pathogenic	Dystonia 16 (AR)
ALDH18A1 (NM_002860.4)	c.1619A>G; p.Glu540Gly	Heterozygous	Uncertain Significance	AD Cutis Laxa / SPG9B (AD/AR)
SI (NM_001041.4)	c.3521A>T; p.Asp1174Val	Heterozygous (in trans)	Uncertain Significance	Congenital Sucrase-Isomaltase Deficiency (AR)
SI (NM_001041.4)	c.1996G>A; p.Gly666Arg	Heterozygous (in trans)	Uncertain Significance	Congenital Sucrase-Isomaltase Deficiency (AR)
LAMA2 (NM_000426.4)	c.307A>G; p.Ile103Val	Heterozygous	Uncertain Significance	LGMDR23 Muscular Dystrophy (AR)

Segregation Analysis and Preliminary Functional Correlation

Parental testing confirmed the SI variants were in trans (compound heterozygous). A sucrose hydrogen breath test was strongly positive, confirming functional carbohydrate malabsorption consistent with partial sucrase-isomaltase deficiency. Phenylalanine levels were within normal limits, excluding classic PKU.

DISCUSSION

This case presents a formidable interpretive challenge, moving beyond a simple monogenic diagnosis to a model of oligogenic interaction. We propose that synergistic heterozygosity best explains the severity and multisystem nature of the phenotype. PRKRA as an Inflammatory Instigator: PRKRA constructs PACT, which is an activator of protein kinase R (PKR). In addition to its effects in dystonia, the PACT/PKR axis is an essential controller of the innate immune response to cellular stress, which regulates NF-8586. PRKRA heterozygous mutations can result in haploinsufficiency, which entails an unregulated, hyper-inflammatory condition induced during stressful situations-an option of the likely primary cause of the severe CRMO [8,9].

SI Variants and the Gut-Inflammatory Axis: the established pathologic mechanism of the functional deficiency caused by compound heterozygous SI VUS lies in the development of chronic malabsorption and intestinal dysbiosis. This forms a chronic foci of systemic low grade inflammation and malnutrition and offers a continuous background stimulation to the immune system and leads to growth failure [10]. ALDH18A1 and Connective Tissue/Metabolic Stress: ALDH18A1 is the gene encoding P5CS which is necessary in the synthesis of proline and arginine. Heterozygous variants could lead to impairment of collagen synthesis (bone matrix integrity) and nitric oxide metabolism which could impair vascular and inflammatory regulation in bone [11,12]. This forms a skeletal substrate that is vulnerable.

PAH and Metabolic Load

The heterozygous variant of PAH does not lead to hyperphenylalaninemia but can contribute to an overall increase in metabolic noise in the body, which manifests itself in stressful conditions and inadequate nutrition [13]. We hypothesize that the patient's CRMO did not result from a single cause but emerged from the confluence of these partial defects (Figure 1). The PRKRA variant primed his innate immune system for hyper-responsiveness. The chronic gastrointestinal inflammation and immune activation from SI deficiency, combined with the potential connective tissue vulnerability from ALDH18A1, created a permissive environment. This "multiple-hit" scenario lowered the threshold for an autoinflammatory bone response, triggering severe, multifocal CRMO. This model aligns with the emerging understanding of CRMO as a polygenic autoinflammatory disorder where multiple minor genetic hits influence disease penetrance and severity [14].

Figure 1 proposed synergistic threshold model. Schematic illustrating how partial deficiencies from heterozygous variants in multiple pathways (inflammatory signaling via PRKRA, gut barrier/nutrition via SI, connective tissue/metabolism via ALDH18A1) converge to lower the threshold for developing severe CRMO, exceeding a critical systemic "inflammatory load."

The management implications of this case are critical in that, (1) Active Management of CSID: Introducing a rigidly restricted diet based on sucrose/isomaltose (dietary interventions) is critical to suppress gastrointestinal inflammation and ameliorate nutritional condition, which will potentially adjust the overall disease burden [15], (2) Targeted Immunomodulation: The proposed PRKRA-PKR-NF-kB axis of action implies that biologics targeting this axis (e.g., IL-1 inhibitors, which are (3) VUS Re-classification: Phenotypic evidence of the pathogenicity of the SI and ALDH18A1 VUS based on a compound/cumulative model was good in this case. Formal re-classification should be sought through family studies and functional assays (e.g., P5CS enzyme activity) and (4)

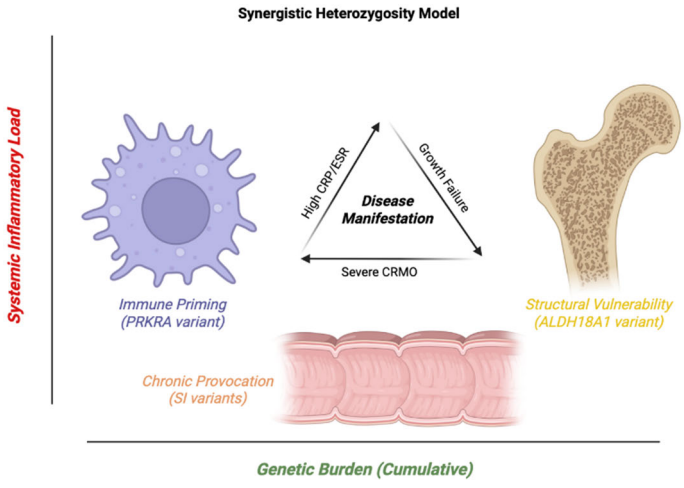

Figure 1: Proposed Synergistic Threshold Model

Oligogenic Counseling: The family needs to be educated about the complicated, possibly oligogenetic nature of the condition, where the chances of recurrence cannot be easily determined by a simple Mendelian ratio.

CONCLUSIONS

This case describes a child with a complex multisystem inflammatory phenotype in whom multiple heterozygous variants in PRKRA, SI, ALDH18A1 and PAH were identified. While no single variant fully explains the clinical presentation, the findings suggest the possibility of an oligogenic or synergistic interaction contributing to disease expression. However, in the absence of functional validation, these associations remain speculative. Importantly, this report highlights that in consanguineous populations, the presence of multiple variants of uncertain significance should not be dismissed outright but rather evaluated in the context of phenotype, biological plausibility and pathway-level interactions. At the same time, it must be emphasized that VUS, by definition, remain uncertain and may or may not have clinical relevance.

Patient Perspective

The patient's family provided informed consent for this publication.

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