Genetics of primary hypercalciuria

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Summary

Primary hypercalciuria is a highly heterogeneous complex metabolic disorder and it can be schematically represented by three general distinct clinical entities, such as absorptive hypercalciuria, renal hypercalciuria and resorptive hypercalciuria. In fact, other than absorptive hypercalciuria, hypercalciuria has been described in several monogenic syndromes such as Dent’s disease, Bartter’s Syndrome, Hereditary Hypomagnesaemia-Hypercalciuria Syndrome, hypercalciuric syndromes due to mutations of calcium sensing receptor gene such as Familial Hypocalcaemia with Hypercalciuria Syndrome and Familial Hypercalcemia and Hypercalciuria Syndrome and in a less common forms of hypophosphatemia with hypercalciuria. Of course, environmental factors influence hypercalciuria, but a strong genetic component has been clearly demonstrated. In fact, in many hypercalciuric conditions a familial trait has been observed indicating the existence of inherited predisposing gene mutations. Forty to 45% of patients with idiopathic hypercalciuria exhibit at least one family member with nephrolithiasis. An apparent autosomal inheritance of hypercalciuria has been reported as also a clear autosomal recessive transmission in individual kindreds. Up to date, several genetic defects have been already identified accounting for familial hypercalciuria, but others are still waiting for being unraveled. However, the genes responsible for inherited hypercalciuria might also account for sporadic forms as reported in literature, including isolated or incidental hypercalciuria. Here we will briefly review the more recent evidences accumulated in the international literature in this fascinating field of human pathophysiology.

KEY WORDS: family studies, gene polymorphisms, association studies.

Introduction

Primary hypercalciuria (PH) is a multifactorial disorder whose onset depends both on environmental and genetic factors. As for other complex diseases, such as diabetes, hypertension, osteoporosis, molecular technologies will be helpful to identify either the responsible genetic factors or subjects susceptible to develop such disorders, providing the opportunity for adequate clinical management and therapy. PH is a complex highly heterogeneous defect of calcium metabolism characterized by an elevated urinary excretion of calcium, in the absence of other alterations. According to Frick and Bushinsky, it can be caused by a “dysregulation of calcium transport at sites where large fluxes of calcium must be precisely controlled: these sites are the intestine, kidney and bone” (1). Generally, it is defined by the occurrence of a urinary calcium excretion exceeding the threshold values, established in 1957 by Hodgkinson and Pyrah, at 7.5 mmol/24 hours for men and 6.25 mmol/24 hours for women (2). Alternatively, urinary calcium may be normalized to body weight and hypercalciuria is considered as the calcium excretion above 100 µmol/kg per kg of body weight in both sexes (3). Hypercalciuric subjects represent the 5-10% of general population (2,3). Their presence causes a skewness to high values in the urinary calcium distribution curve, which is more evident in the stone forming (Figure 1) or osteoporotic populations. The frequency of hypercalciuria among these patients is higher than usually found in general population and may involve 20-50% of them (4,5). Analysis of the calcium excretion distribution curve in 471 stone formers indicates that it better fits a bimodal model (Figure 1). According to this model, stone formers appear to be composed by two different subsets of subjects (6). The first one is composed by 23% of patients, mostly hypercalciurics, whose calcium excretion can be estimated of 153±48 µmol/kg body weight in 24 hours. The other group, mainly composed by normocalciuric subjects, has an estimated calcium excretion of 86±33 µmol/kg body weight in 24 hours. Overlapping of calcium excretion curves, representing these subpopulations, reveals that PH may include subjects with different characteristics.
Genetic dissection of primary hypercalciuria

Familial studies display that calcium excretion is correlated between sib-pairs, brothers and sisters, parents and children, but not between spouses (Figure 2) that do not share a common genetic background. Thus, a great portion of calcium excretion variability appears to be explained by hereditary factors. The proportion of calcium excretion variance is indicated by the correlation coefficient in offspring-parents (7). In the considered families, approximately 50% of the calcium excretion variance is justified by additive effect of genes \( r=0.474, n=63, p=0.0001 \), Figure 2. In human pedigrees, hypercalciuria can be detected at each generation, with a sex independent transmission and no concordance for hypercalciuria in wives and husbands (8,9). These familial studies considered urinary calcium as a qualitative trait with hypercalciuria/normocalciuria as the only possible phenotypes. In these studies hypercalciuria inheritance was regarded as an autosomal dominant Mendelian trait with high penetrance (8,9). However, calcium excretion is a quantitative trait and its phenotypes are distributed on a continuous scale (10). Variance of a quantitative trait is a multigenic parameter involving many alleles singularly exerting a small effect, and hypercalciuria has to be considered as a polygenic trait with a heterogeneous genetic substrate and complex pattern of hereditary transmission (11,12). The complexity of this picture is increased by gene-gene and gene-environment interactions with reciprocal influences, able to change substantially the effect of a gene on a phenotype (13). The search for genetics of hypercalciuria has been aimed to identify both candidate genes and genetic polymorphisms underlying the genetic susceptibility for this disorder. Although it cannot be excluded that polymorphisms in a single gene may be sufficient to cause hypercalciuria, it is more likely that PH arises when predisposing alleles, at different loci, together concur to regulate urinary calcium excretion. The number of involved loci and the effect size of alleles may vary according to the role of candidate genes in calcium metabolism, to the activity of their different variants and to the gene-s-gene/s interactions (13). A different genetic substrate may be present in the two subpopulations of stone formers identified by the analysis of calcium excretion distribution: they may be distinguished by the presence of allele variants at one locus or, more likely, at few loci having remarkable effects on the phenotype, shifting the mean of the calcium excretion distribution curve toward higher values (10). Genetic causes of PH have been approached with different strategies. A strain of spontaneously hypercalciuric rats has been obtained, but the gene/s responsible for the defect has not been yet found (14). Furthermore, at least three strains of knockout rats have been selected, respectively not expressing sodium-phosphate co-transporter, paracellin or caveolin 1, and they are under investigation (15-17). In humans, familial studies revealed the association between polymorphisms of soluble adenilate-cyclase (sA C) gene, located onto chromosome 1q23.3-q24, and hypercalciuria and low bone mass (18), while the study of calcium sensing receptor (Ca S R) gene exhibited conflictual results (19, 20). Moreover, other genes have been taken into account, like those of epithelial calcium channel (EcaC1) or vitamin D receptor (VDR) gene (9,21), but no significant association with hypercalciuria has been observed. All these genetic studies tested a single gene and, due to this limitation, their results cannot be considered definitive in the presence/absence of a genotype-phenotype correlation (13). Positive or negative results have to be reconsidered in function of gene-gene and gene-environment interactions.
Several genes accounting for Mendelian forms of PH, with or without nephrocalcinosis, have been identified, such as Dent’s disease, Bartter’s syndrome, familial hypomagnesemia hypocalciuria, familial hypercalcaemia hypercalciuria, familial hypercalcaemia hypercalciuria, and some hypophosphatemic syndromes. Unfortunately, their role in the pathogenesis of sporadic forms of PH has to be clearly elucidated.

Candidate genes in familial and sporadic idiopathic renal calcium stones/hypercalciuria

After identification of chromosomal localization of disease-gene by linkage approach in kindreds affected by hypercalciuria and/or calcium nephrolithiasis, many Authors also identified the respective responsible genes, namely, polymorphisms of the same genes have been analyzed in sporadic cases of PH. Hence, disease-causing mutations and functional variants, namely, polymorphisms, of these genes have also been evaluated in sporadic cases of PH. Hence, disease-causing mutations and functional variants, namely, polymorphisms, of the same genes have been analyzed in order to detect the PH susceptibility genotype. Due to no homogeneity of patients suffering from PH and idiopathic PH and to find no case of Dent’s disease, subsets of sporadic cases might be due to mutations or polymorphic variants in different candidate genes. However, up to now available results do not support the hypothesis that the described gene mutations and polymorphisms have a significant role in the majority of sporadic PH and ICN cases.

**CLCN5 gene**

CLCN5 gene encodes for a chloride channel protein, expressed in several human cells and in particular localized to the S3 segment of the proximal tubule and to medullary thick ascending limb (mTAL). Subsequent subcellular fractionation studies indicate that CLCN5 is localized to endosomes (22) and it is important for tubular reabsorption of low molecular weight proteins (1). Several Mendelian CLCN5 gene mutations depending phenotypes have been described: X-linked hypercalciuria nephrolithiasis, Dent’s disease, X-linked recessive rickets, and renal osteodystrophy (27). Including PH (23), Frymoyer et al. (24) described a man with an inactivating mutation in the CLCN5 gene who did not have low molecular weight proteinuria (together with the other features of the Dent’s disease) and whose unique biochemical abnormality was hypercalciuria (25). This raised the question as to whether mutations in CLCN5 gene might contribute to the phenotype in patients with the diagnosis of PH, a condition that is twice as common in males as in females suggesting that a subset of patients may have an X-linked transmission. Scheinmann et al. (25) looked for CLCN5 gene mutations in a group of 32/107 unrelated individuals (12 adults and 25 children) with PH. However, PH was defined in a broad sense; this is meaningful in the Dent’s condition where the mechanism of hypercalciuria includes both excessive intestinal absorption of dietary calcium and fasting hypercalciuria (26). No CLCN5 gene mutation was observed in this study and it is likely that Dent’s disease accounts for no more than 3% of patients with sporadic form of PH. Gambaro et al. recently performed CLCN5 gene mutation analysis in 158 patients with a personal history of calcium or radiopaque stones/hypercalciuria. No CLCN5 mutations were identified in this study (33). It should be over-represented (Gambaro et al., unpublished).

**NKCC2, ROMK, and CLCNKB genes**

Mutations of these genes account for the highly genetic heterogeneous disorder represented by Bartter’s syndrome. This disorder consists of a set of renal tubular disorders, inherited as autosomal recessive trait, clinically characterized by chronic hypokalemia, metabolic alkalosis, hyperreninism and hyperaldosteronism with normal values of blood pressure: Antenatal (with hyperproduction of type E Prostaglandins) and Classical forms of Bartter’s syndrome. PH is presented on both these forms. Other additional biochemical and clinical features determine a different tubulopathies phenotype classification (27). Antenatal form consists of type I, II and IV Bartter’s syndrome while Classical form is also indicated as type III Bartter’s syndrome (28). Mutations of the responsible genes created a severe disturbance in maintaining the electric driving force at tubular level regulating the paracellular reabsorption (from lumen to blood) of calcium.

**NKCC2 gene**

It encodes for the Na+/K+/2Cl− co-transporter, a membrane protein expressed on the lumen side of tubular cells at TAL level, that physiologically determines the entry of the above-described ions from lumen within the cell. Its mutations have been reported in Antenatal Bartter’s syndrome preventing the entry of Na+/K+/Cl− from the luminal side (1).

**ROMK gene**

The encoded product of this gene is a potassium channel protein whose function consists of recycling of K+, entered through NKCC2 from intracellular store to the tubular lumen. It is essential for the function of NKCC2 itself. It has been found mutated in Antenatal Bartter’s syndrome. Transfection experiments with mutated ROMK-cDNA in COS-7 cells are able to reduce or destroy the electrophysiological properties of the channel protein, preventing the K+ recycling (29).

**CLCNKB gene**

It encodes for the human Chloride channel (hClC-KB) (28) and its mutations alter the transportation, at the basolateral membrane level, of the Chloride reabsorbed through hClC-KB in the distal part of nephron (30, 31).

**PCLN-1 gene**

**gene-dependent hypercalcemic diseases**

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHN) is a rare disorder of calcium and magnesium homeostasis. Other additional biochemical and clinical features determine a decrease of calcium and magnesium reabsorption (32, 33). A striking incidence of hypercalciuria, and nephrolithiasis among family members not affected by FHHNC was observed by Weber et al. in 13 of 23 families (33) and 11 cases (42%) out of 26 family members not affected by FHHNC was observed by Weber et al. (33) (33) and 11 cases (42%) out of 26 members of 4 affected families. In this study (33) most of the non-FHHNC subjects presenting with hypercalciuria and/or nephrolithiasis were obligate carriers of heterozygous PCLN-1 mutations. It seems therefore reasonable to propose a relationship between sporadic hypercalciuria or stone disease and mutations in the PCLN-1 gene. It might be expected that mutation analysis of kindreds affected by familial hypercalciuria with nephrocalcinosis and/or nephrolithiasis (with an apparently dominant mode of inheritance) would demonstrate heterozygous mutations in the PCLN-1 gene in some of them. Unfortunately, this kind of study has yet to be performed.

**CaSR gene-dependent hypercalcemic diseases**

CaSR gene activating mutations of the extracellular domain, resulting in a gain of function, have been originally described to be associated with hypocalcemia in kindreds (34-36). Carling et al. (37) recently described a kindred with 20 affected individuals in whom the hypercalciemic trait segregated, in an autosomal recessive manner.
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nal dominant manner, with inappropriately higher serum PTH and magnesium levels and urinary calcium levels than in unaffected members. Presumably, the hypercalcuria in this family may be secondary to the presence of hypercalcaemia due to primary hyperparathyroidism.

Sequencing analysis identified an inactivating mutation with substitution of phenylalanine to leucine at codon 881, located in the cytoplasmic tail of the receptor and functional studies demonstrated an inactivation of the receptor (37), probably with a different functional capacity, in parathyroid and renal cells, determining a more severe derangement in extracellular with a different functional capacity, in parathyroid and renal cells, determining a more severe derangement in extracellular calcium renal stones derive from the possibility that a mild activation of the CaSR could cause (in association with mild hypercalcaemia) both the increased intestinal calcium absorption and calcium renal loss. Recently, a mechanism described by Hebert et al (40) suggests that when at basolateral level calcium concentrations are elevated, condition minimizing the reabsorption, CaSR activation induces the inhibition of the Na+/K+/Cl- co-transporter, then inhibiting the electric force gradient driving the paracellular transportation of Ca++ from lumen to blood (40). However, association studies in general populations have not corroborated this hypothesis. Indeed, Petrucci et al (41) in a sib-pairs analysis in 359 French-Canadian stone former subjects showed no significant association between genetic variants of the CaSR gene and PH and ICN traits. Furthermore, Lerolle et al (42) failed to detect any mutation in the seven coding exons of the CaSR gene in 9 families with PH, renal stones and with a familial transmission consisting of autosomal dominant inheritance. It is not possible to rule out that mutations of the CaSR gene could be found in some other families or other populations, or that mutations of regulatory regions of the gene may exist; nevertheless these findings indicate that CaSR gene mutations do not represent a common cause of familial PH. More recently, Vezzoli et al (43) in an Italian population case-control study, analyzing three shotgun Single Nucleotide Polymorphisms (SNPs) at exon 7 of CaSR (G/T at codon 986, G/A at codon 990 and C/A at codon 1011), hypothesized a role for such variants in the physiological modulation of the CaSR gene transcriptional levels, thus identifying patients with increased relative risk for hypercalciuria/renal stones, according to specific clinical-chemical phenotypes. Such SNPs determine the conservative amino acid changes, which functional effects are still unknown, although the importance of the allele 996Gly and of the allele 990Gly has been previously suggested according to lower plasma levels of calcium in healthy people (44) and of PTH in uremic patients (45), respectively. Thus, Vezzoli et al. (43) suggested that the 990Gly allele may increase the CaSR sensitivity or response to calcium ions, increasing inhibition of PTH secretion leading to lower calcium serum levels, increased calciuria and bone turnover. According to this hypothesis, this gene variant should be associated to a variant phenotype, CaSR gene cannot be considered as a major gene involved in the pathogenesis of PH, representing only one of the genetic components modulating the calcium excretion.

The minor contribution of the CaSR gene to calcium excretion could explain why no linkage was shown in the sib-pair study carried out in Canada (41).

**NPT2a gene-dependent hypercalciuric diseases**

Disorders of renal phosphate wasting may lead to hypophosphatemia, increase of 1,25(OH)2D3 and consequent excess of intestinal calcium absorption and hypercalciuria. A clear example is represented by Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH) (46), a phenotype similar, except for bone, to that of mice with deletion of the kidney-specific sodium-phosphate co-transporter gene, Npt2a. Mutational analysis of human Npt2a gene has been performed by Prie et al (47) identifying two patients (2 out of 20) carrying NPT2a mutations, exhibiting uratiolithiasis or osteoporosis and persistent idiopathic hypophosphatemia, associated with a decrease in maximal renal phosphate reabsorption. Npt2a gene located at chromosome 5q35. One of the 2 subjects was a man with recurrent renal stones, hypophosphatemia, and reduced renal phosphate reabsorption; the second patient was a 7-year-old woman with idiopathic bone demineralization, hypophosphatemia, and reduced renal phosphate reabsorption. Her only daughter, who also had the mutation, had spinal deformity and a history of arm fractures, with hypophosphatemia and low maximal renal phosphate reabsorption. NPT2a is a renal proximal tubular, brush-border membrane Na+/phosphate co-transporter. Both NPT2a gene mutations (V147M and A48F) had a dominant negative effect on the phosphate-induced current in oocytes co-transfected with the wild and mutant RNAs. These findings were consistent with a dominant negative effect of the mutant proteins on the function of the wild type carrier, leading to a substantial renal phosphate losses in heterozygous patients. However, as correctly pointed out by Scheinman and Tenenhouse (53), this is at odds with the model with the targeted inactivation of Npt2 gene, where the heterozygous animals have neither hypercalciuria nor nephrocalcinosis (54). The reason why renal phosphate leak leads to either calcium stones or bone demineralization is still unknown, although it might be due to gender, environmental factors, or other genetic differences. Although they did not search for mutations in introns or regulatory regions of the NPT2a gene, other genes may also be involved in the renal phosphate leak in patients who did not display NPT2a gene mutations. The reported mother to daughter mutation segregation suggests an autosomal dominant inheritance, but up to date no systematic analysis of kindreds with similar clinical phenotype has been performed.

**“New” putative candidate genes**

**ECA1 gene**

Although no kindreds with familial hypercalciuria and/or renal stones linked to the Epithelial Ca++ channel 1 (ECA1) locus have been reported so far, Muller et al (55) have looked for ECA1 gene mutations in 9 families in which hypercalciuria dominantly segregated. This channel has been recently identified: it allows the apical calcium entry step facilitating tran-scellular calcium transport of the apical membranes of 1,25(OH)2D3-responsive epithelia in the kidney and small intestine (56). It is a high selective channel that might play a crucial role in Ca++-related disorders (57). The gene is on chromosome 7q35. The results from the Muller’s study were negative and they did not support a primary role for the HECAC1 in the pathogenesis of PH, but ECA1 cannot be excluded as a candidate gene in other families with PH as the pathogenesis of the disease is heterogeneous.
Mutations in the genes responsible for distal renal tubular acidosis (dRTA)

It is known that subtle forms of dRTA can occur only with hypercalciuria and recurrent calcium nephrolithiasis. Thus, it is possible that the same molecular defects responsible for the full range of dRTA are also causative of cases of familial and sporadic forms of PH and ICN. As yet, both the s1 subunit of the vacuolar H+–ATPase (ATP6B1) and the carbonic anhydrase II genes have not been investigated in sporadic and familial forms of ICN. On the contrary the possible existence of a linkage between the Anion Exchanger (AE1) locus and familial ICN was the working hypothesis of a previous study of Gambard et al. They formerly described the association of an anomalous erythrocyte oxalate self-exchange with ICN, dependent on an abnormal phosphorylation of the AE1-band 3 exchanger (58, 59). Physiological and clinical studies showed the relevance of this defect on ICN, and interestingly subclinical acidification defects were disclosed in stone patients with the erythrocyte anomaly (59). In a family study, the abnormal erythrocyte oxalate self-exchange appeared to be genetically determined, segregating as a Mendelian autosomal dominant trait, although polygenic inheritance could not be excluded (60). However, a linkage analysis between the 17q21-qter loci, containing the AE1 gene and the normal oxalate self-exchange, in 2 of three-generation families with renal stones was negative (61). Thus, the suggested hypothesis is that the erythrocyte oxalate self-exchange is an intermediate phenotype, possibly with a polygenic determination.

Conclusions

As discussed, the frequencies of dominant and recessive renal-stone-related conditions are uncommon to rare, reflecting the rarity of mutated genes producing them. In these disorders, the inheritance of one or a couple of defective alleles is necessary and sufficient to induce the disease in the absence of any particular environmental factors. In polygenic diseases, the individual genes by per se are not capable to cause the disease; but individual environmental factors are also incapable to determine the disease. However, individual genes and environmental factors, in various combinations, account for common types of calcium nephrolithiasis. We have already discussed that mutations of genes involved in monogenic disorders were not found in sporadic idiopathic stone formers. However, a possible explanation is that some of candidate, and still unknown genes, have to be analyzed in this regard; alternatively, only a small subset of PH and ICN patients has a Mendelian disorder. Similar considerations suggest the possibility that mutations in the AE1 gene or the ATP6B1 gene which have been described in recessive forms of dRTA are responsible for sporadic PH and ICN. Subtle defects in renal acidification, and hypocitraturia, in some cases markers of mild form of dRTA, are too much frequently observed in idiopathic patients. On the contrary, familial dRTA, particularly the recessive forms, are extremely rare conditions. An autosomal dominant inheritance has also been suggested in families with PH (both the absorptive and renal types) and calcium renal stone forming subjects (62). However, since in as high as 55-60% of index cases (proband) no other case can be recognized in the family, under the hypothesis that hypercalciuria is an autosomal disorder it is very unlikely that a mutation occurs in 50% of hypercalciuric subjects. That possibility would require a new mutation rate greater than observed in humans. On the other hand, by excluding probands from the analysis of these observations, the proportion of hypercalciuric siblings decreases to value as low as 10%, a proportion very far from expected in a case of an autosomal dominant inheritance (63). A polygenic model of inheritance of renal stones was proposed by Resnick et al (64) based on the observation that there is a higher proportion of affected younger siblings in which one of two oldest siblings is affected than when both are unaffected. Several Authors have already noted that some of the quantitative traits encountered in idiopathic calcium stone formers have a normal distribution with no evidence for bimodal distribution; as observed for the renal phosphate threshold and hypophosphatemia and hypercalciuria. These findings suggest that the biochemical phenotypes encountered in PH and ICN are complex traits of both multiple factors (social, cultural, environmental, dietary, etc.), and multiple genes. The complexity of this apparent simple and clear statement is huge and generated by difficulties in dissecting non-hereditary from hereditary factors. This is the real gamble in grasping complex diseases. The genetic component of complex, polygenic diseases as PH and ICN may become evident only through a careful control of non-hereditary factors. Dietary habits of stone formers compared with nonstone formers are very similar (63), indirectly suggesting that part of the variability in stone-related diseases is genetically raised; moreover, investigation of a 17q21 normal subjects under self-selected, controlled and formula diets provided the development of a computer model showing that with only three genes a pattern of inheritance is generated, simulating the observed inheritance in ICN in the population and among relatives of stone formers. This could be an oversimplification, but it is a clear demonstration that the idiopathic renal stone disease is a polygenic disorder. Indeed, we have no idea about the number of genes predisposing to hypercalciuria and calcium stone formation. Furthermore, we do know neither whether among several genes one or few genes play a major role, nor whether different degrees of risk are associated with each locus. Larger population studies have to be performed, and environmental factors, particularly nutrients, have to be accurately evaluated together with complex genotyping in order to establish their importance in masking/unmasking functional variants correlated to specific genetic background and to create more effective preventive strategies for PH and ICN. Accurate standardized phenotype definitions are needed to add a more powerful statistical value to family-base studies. Comparative genetics will add informations on potentially interesting genes in humans once quantitative traits in animal models are identified. Great results are expected from development of new DNA microarray and bioinformatic technologies not only for gene variants detection, but also for “proteomic and metabolomic” aspects of the pathogenesis of PH and ICN, providing new opportunities to identify individuals at risk for these disorders and to develop new tailored therapies by newly designed clinical trial involving less genetically unselected individuals, creating also the opportunity of avoiding/reducing severe side effects.

References


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