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Mol Cell Endocrinol. Author manuscript; available in PMC 2012 December 5.

Published in final edited form as:
Mol Cell Endocrinol. 2011 December 5; 347(1-2): 90–96. doi:10.1016/j.mce.2011.05.045.

The Role of Vitamin D Receptor Mutations in the Development of Alopecia

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Abstract

Hereditary Vitamin D Resistant Rickets (HVDRR) is a rare disease caused by mutations in the vitamin D receptor (VDR). The consequence of defective VDR is the inability to absorb calcium normally in the intestine. This leads to a constellation of metabolic abnormalities including hypocalcemia, secondary hyperparathyroidism and hypophosphatemia that cause the development of rickets at an early age in affected children. An interesting additional abnormality is the presence of alopecia in some children depending on the nature of the VDR mutation. The data indicate that VDR mutations that cause defects in DNA binding, RXR heterodimerization or absence of the VDR cause alopecia while mutations that alter VDR affinity for $1,25(OH)_2D_3$ or disrupt coactivator interactions do not cause alopecia. The cumulative findings indicate that hair follicle cycling is dependent on unliganded actions of the VDR. Further research is ongoing to elucidate the role of the VDR in hair growth and differentiation.

The Metabolic Abnormalities in Hereditary Vitamin D Resistant Rickets

Vitamin D, the primary regulator of calcium homeostasis in the body, is particularly important in skeletal development and in bone mineralization (reviewed in Feldman et al., 2007). The active form of vitamin D, 1α, 25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$ or calcitriol], functions by binding with high affinity to the vitamin D receptor (VDR) (reviewed in Haussler et al., 2008). The VDR is a member of the steroid-thyroid-retinoid receptor gene superfamily of nuclear transcription factors that regulate the expression of specific target genes in response to hormone binding. Hereditary 1,25-dihydroxyvitamin D-Resistant Rickets (HVDRR), also known as Vitamin D Dependent Rickets type II (VDDR-II), is a rare genetic disease that is due to generalized resistance to $1,25(OH)_2D_3$ action (reviewed in Malloy and Feldman, 2010, Malloy et al., 1999, Malloy et al., 2011). HVDRR is caused by heterogeneous mutations in the VDR gene that cause loss of function of the receptor leading to complete or partial target organ resistance to $1,25(OH)_2D_3$ (reviewed in Malloy and Feldman, 2010, Malloy et al., 1999, Malloy et al., 2011). HVDRR is clinically manifested by a constellation of signs and symptoms caused by a loss of VDR-mediated actions. The main clinical features of HVDRR are severe rickets, hypocalcemia, secondary hyperparathyroidism, hypophosphatemia and elevated alkaline phosphatase (Marx et al., 1978, Rosen et al., 1979). The metabolic pathways are intact and the hypocalcemia, due to impaired intestinal calcium absorption, appropriately leads to secondary

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hyperparathyroidism and hypophosphatemia. However, the resulting high levels of $1,25(OH)_2D_3$ are unable to reverse the hypocalcemia or suppress the elevated PTH because of defective VDR in intestine and parathyroid glands. The hallmark of the disease is therefore hypocalcemia despite elevated $1,25(OH)_2D_3$ levels indicating resistance to even elevated levels of $1,25(OH)_2D_3$ (reviewed in Malloy and Feldman, 2010, Malloy et al., 1999, Malloy et al., 2011). Some patients also exhibit total or partial alopecia that will be extensively discussed in this review (Malloy and Feldman, 2010, Malloy et al., 1999, Malloy et al., 2011, Marx et al., 1986, Marx et al., 1978, Rosen et al., 1979).

In cases of HVDRR the first signs of rickets generally appear early in life, usually within months of birth. Characteristic bowing of the legs develops as the infant begins to walk. The rickets is usually severe and affected children suffer from bone pain, muscle weakness, and hypotonia. Children are often growth retarded and they frequently develop severe dental caries or exhibit enamel hypoplasia of the teeth (Balsan et al., 1983, Bliziotes et al., 1988, Kudoh et al., 1981, Laufer et al., 1987, Liberman et al., 1980, Rosen et al., 1979, Sockalosky et al., 1980). Some infants have died from pneumonia as a result of poor respiratory movement due to severe rickets of the chest wall (Balsan et al., 1983, Fraher et al., 1986, Liberman et al., 1980). In the most severe cases of hypocalcemia and metabolic disruption, convulsions due to the hypocalcemia have occurred.

Alopecia

Alopecia (sometimes called atrichia) is a clinical feature that is found in many children with HVDRR and can be quite variable in appearance and extent. As shown in Fig. 1, the pattern ranges from total absence of hair to generalized sparse hair, to patches of total alopecia adjacent to areas of dense hair, or in one case a single tuft of hair. Some patients have sparse body hair and some exhibit total scalp and body alopecia (Hochberg et al., 1984, Hochberg et al., 1985, Marx et al., 1986). Children with extreme alopecia often lack eyebrows and in some cases eyelashes, which may slowly develop as the child grows. Hair loss may be evident at birth or it develops during the first half year of life as some hair the child is born with falls out and is not replaced. In families with a prior history of the disease, the loss of scalp hair in newborns provides initial diagnostic evidence for HVDRR. During childhood, after the hair present at birth sheds, new hair regrowth does not occur (Hochberg et al., 1985). Examination of skin biopsies from patients with HVDRR and alopecia has shown that some hair follicles may be absent and contain follicular remnants and cysts (Bergman et al., 2005, Miller et al., 2001). On the other hand, when hair follicles were examined microscopically other investigators reported that the number of hair follicles were within the normal range but were empty of hair shafts (Hochberg et al., 1985). In some patients papular lesions develop on the face and shoulders, but usually not on the scalp. Both the clinical presentation and the hair histology are similar to the findings in the autosomal recessive disease total alopecia known as ‘Atrichia with Papular Lesions’ (APL) (Ahmad et al., 1998) that is due to mutations in the *hairless* (*hr*) gene (Ahmad et al., 1998, Zlotogorski et al., 1998, Zlotogorski et al., 2003, Zlotogorski et al., 2002). These findings have led investigators to conclude that the alopecia in HVDRR patients is a phenocopy of APL (Bergman et al., 2005, Miller et al., 2001). Evidence that the VDR directly interacts with HR has led to the hypothesis that the VDR and HR converge to regulate similar pathways in the hair cycle (Hsieh et al., 2003).

The Vitamin D Receptor

The human VDR gene is located on chromosome 12q13.11 and is composed of 14 exons spanning ~64 kbp of DNA. The human VDR protein contains either 427 or 424 amino acids depending upon the presence of a T to C polymorphism (ATG to ACG) in a translational

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start site (Gross et al., 1996, Saijo et al., 1991). The overall structure of the VDR protein is similar to the other members of the steroid-thyroid-retinoid receptor superfamily. At the N-terminus the VDR has a highly conserved DNA-binding domain (DBD) and in the C-terminal half of the protein a more variable ligand-binding domain (LBD). The VDR LBD contains 12 α-helices (H1–H12) and 3 β-sheets (S1–S3) (Rochel et al., 2000). Helix H12 forms a retractable lid that traps and holds the ligand in position. Ligand binding causes a conformational change in the VDR that promotes heterodimerization with RXR. VDR heterodimerization with RXR involves residues in H9, H10 and an E1 domain that overlaps H4 and H5 within the LBD. An activating function domain 2 (AF-2 domain) residues 416-424 of helix H12 and the region between amino acids 232-272 encompassing H3 and H4 are essential for transactivation (Rochel et al., 2000). The repositioning of helix H12 after ligand binding is critical for the formation of a hydrophobic groove that binds LxxLL motifs (where L is leucine and x is any amino acid) in the nuclear receptor interacting domains of coactivator proteins such as the g160 family of coactivators (SRC-1, SRC-2, SRC-3) and DRIP205 a member of the DRIP complex. Other regions of the VDR also act to recruit coactivator proteins or facilitate contact with proteins associated with the core transcriptional machinery such as TFIIB or the TAFs (Blanco et al., 1995, MacDonald et al., 1995). The VDR-complex together with the general transcription apparatus then drives the transcription of 1,25$(OH)_2$D-responsive genes that ultimately determine the cellular response to the hormone. Resistance to 1,25$(OH)_2$D can be caused by mutations in the VDR DBD that disrupt VDR binding to DNA or mutations in LBD that affect ligand binding, RXR heterodimerization or interactions with coactivators.

Analyses of VDR mutations in HVDRR patients with and without alopecia

Some HVDRR patients have been successfully treated with oral or intravenous calcium therapy, or in a few cases with high dose oral vitamin D therapy. These treatments correct the metabolic abnormalities of hypocalcemia and associated secondary hyperparathyroidism leading to healing of the rickets as assessed by X-ray and bone biopsy. However, despite the normalization of circulating calcium concentration, the correction of all serum biochemistries and reversal of the rickets, an important unresolved medical problem of HVDRR patients is persistent alopecia. The cumulative data indicate that a functional VDR is required for hair growth and that the alopecia is unrelated to the calcium or metabolic abnormalities that cause the rickets. In general, the presence of alopecia in HVDRR patients is correlated with the severity of rickets and the metabolic abnormality (Malloy et al., 1999, Malloy et al., 2011, Marx et al., 1986). HVDRR patients with alopecia are usually more resistant to treatment with vitamin D metabolites and usually require high doses of calcium, either administered intravenously or in some cases, success can be achieved with large oral doses (Ma et al., 2009, Malloy and Feldman, 2010, Malloy et al., 1999, Malloy et al., 2005, Malloy et al., 2011, Malloy et al., 2007, Malloy et al., 2010, Malloy et al., 2004).

The VDR is expressed in the hair follicle but mechanisms by which the VDR regulates hair growth are not well understood (Berger et al., 1988, Stumpf et al., 1979). However a number of insights have been gained from the molecular analysis of the VDR in HVDRR patients with and without alopecia. For example, patients with nonsense mutations that introduce premature stop signals and are totally hormone resistant all have alopecia. These findings indicate that the VDR is required for and is directly involved in hair growth. In addition, patients with missense mutations in the DBD or mutations that interfere with RXR dimerization also have alopecia indicating that DNA binding and heterodimerization are critical functions of the VDR to regulate hair growth. Mutations in the LBD that only reduce VDR binding affinity for 1,25$(OH)_2D_3$ are usually not associated with alopecia.

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Molecular analyses of the VDR from HVDRR patients that do not develop alopecia almost always have missense mutations in the LBD. Several of these mutations (Arg274Leu, His305Gln, Ile314Ser, and Trp286Arg) reduce the binding affinity of $1,25(OH)_2D_3$ for the VDR. Two of these amino acids Arg274 and His305 make direct contact with $1,25(OH)_2D_3$ (Rochel et al., 2000). Since the patients with the His305Gln (Malloy et al., 1997) and Ile314Ser (Whitfield et al., 1996) mutations were somewhat responsive to vitamin D therapy, it is reasonable to speculate that these VDRs, although exhibiting a 2–8 fold reduction in $1,25(OH)_2D_3$-binding affinity, are still able to exhibit enough activity to prevent the development of alopecia after birth. However, the patients with the Arg274Leu (Kristjansson et al., 1993) and Trp286Arg (Nguyen et al., 2002) mutations that resulted in more than a 1000-fold reduction in $1,25(OH)_2D_3$-binding also did not have alopecia. These findings led us to the hypothesize that $1,25(OH)_2D_3$-binding is not critical for the VDR pathway to regulate hair growth (Malloy et al., 2002). In further support of this hypothesis, alopecia is not found in patients with 1α-hydroxylase deficiency due to mutations in CYP27B1, the gene that encodes the 1α-hydroxylase enzyme that coverts $25(OH)D_3$ to $1,25(OH)_2D_3$ a condition of severe $1,25(OH)_2D_3$ deficiency, or in other forms of vitamin D deficiency (Kim et al., 2007). Thus alopecia appears to develop independently of the metabolic abnormalities due to defective $1,25(OH)_2D_3$ action and its presence or absence is instead dependent on the presence or absence of functional VDR, even if unliganded.

In contrast, some patients with missense mutations in the LBD have alopecia. In these cases the mutations (Phe251Cys, Gln259Pro and Arg391Cys) have little or no effect on ligand binding but interfere with RXR heterodimerization (Cockerill et al., 1997, Malloy et al., 2001, Whitfield et al., 1996). Although these mutations cause HVDRR in patients, in studies of cultured fibroblasts from patients *in vitro,* or in cells transfected with mutant VDR, the $1,25(OH)_2D_3$ resistance could be overcome by treatment with supra-physiological doses of $1,25(OH)_2D_3$ or by over-expression of RXR (Whitfield et al., 1996). These findings indicate that RXR heterodimerization is critical for VDR function in hair development. Furthermore, targeted inactivation of RXR in keratinocytes in mice also caused alopecia further supporting a role for RXR in hair growth (Li et al., 2001).

Perhaps the most interesting discovery providing a critical clue to which mutations cause alopecia came from a patient with HVDRR without alopecia who had a missense mutation that caused a Glu420Lys substitution in the VDR LBD. The mutation is located in the AF-2 domain that is important in binding the LxxLL motifs of coactivators. The Glu420Lys mutation had no effect on ligand binding or RXR heterodimerization but abolished binding of coactivators to the VDR and caused severe vitamin D resistance and all of the metabolic abnormalities associated with HVDRR but not alopecia (Malloy et al., 2002). These findings indicated that coactivator binding is not an essential function of the VDR for hair growth and although the mutation caused HVDRR and all of the metabolic abnormalities associated with a defective VDR, the presence of the defective VDR was sufficient to prevent alopecia. These finding led us to hypothesize that the VDR exhibits a ligand-independent action (that is, an action mediated by the VDR without hormone or by ‘unliganded VDR’) during hair follicle development that is critical for hair differentiation and growth (Malloy et al., 2002).

Findings in CYP27B1 and VDR knockout mice

The role of $1,25(OH)_2D_3$-binding and the VDR in the development of alopecia were also analyzed in mouse models of the human diseases. CYP27B1 knockout mice that are deficient in $1,25(OH)_2D_3$ production and two forms of VDR knockout mice, ones that express a VDR protein that has a deletion of the first zinc-finger module in the VDR DBD and in VDR knockout mice that do not express a VDR protein (Bouillon et al., 2008). In the CYP27B1 knockout mice, abnormalities develop in skeletal, reproductive and immune

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function (Panda et al., 2001). However, the CYP27B1 knockout mice do not develop alopecia. These results, along with the findings in patients with CYP27B1 mutations, support the conclusion that $1,25(OH)_2D_3$-binding to the VDR is not required for hair development. On the other hand, both forms of VDR knockout mice develop alopecia supporting the hypothesis that the VDR protein and particularly the DNA binding domain of the VDR, are essential for hair growth (Li et al., 1997, Yoshizawa et al., 1997). These VDR knockout mice also develop cysts suggesting an additional action of VDR function on sweat glands and sebum accumulation in skin, not just hair (reviewed in Luderer and Demay, 2010).

Analysis of VDR knockout mice and transgenic mice has led to a series of important findings about the role of the VDR in preventing alopecia (reviewed in Bouillon et al., 2008, Demay, 2006, Demay et al., 2007). It is of interest that many of these findings were also elucidated in the patients with HVDRR (reviewed in Malloy and Feldman, 2010, Malloy et al., 1999, Malloy et al., 2005, Malloy et al., 2011, Malloy et al., 2002). Importantly, Demay and colleagues showed that restricted expression of the intact VDR to keratinocytes was capable of preventing alopecia in the VDR null mice (Chen et al., 2001). Hair follicles reconstituted with keratinocytes from VDR knockout mice demonstrated a defective response to anagen initiation. Hence, alopecia in the VDR-null mice seems to be due to a localized defect within keratinocytes, perhaps involving epithelial-mesenchymal communication that is required for normal hair cycling (Chen et al., 2001). Further study was therefore focused on the keratinocyte as the cell of origin of alopecia and the findings continue to indicate that the alopecia is due to an absence of ligand-independent VDR function in this cell (Skorija et al., 2005).

Subsequent studies were performed to determine which regions of the VDR were required for actions that would prevent alopecia (reviewed in Bouillon et al., 2008, Demay, 2006, Demay et al., 2007). Investigation of mice engineered to lack the first zinc finger of the VDR demonstrated that they express a truncated receptor containing an intact LBD and AF2 domain (Bula et al., 2005). These mice demonstrated the critical requirement of an intact DBD for hair follicle homeostasis and for the prevention of alopecia. These findings in mice mirror the results from HVDRR patients with mutations in the DBD (reviewed in Malloy and Feldman, 2010, Malloy et al., 1999, Malloy et al., 2005, Malloy et al., 2011). Even a single point mutation in a critical amino acid of the DBD can cause HVDRR and alopecia (Malloy et al., 2010).

Skorija et al then developed transgenic mice that expressed VDRs with mutations in either the LBD or the AF2 domain (Skorija et al., 2005). These investigations demonstrated that mutant VDRs, even though incapable of ligand-dependent transactivation, were still able to prevent the development of alopecia (Skorija et al., 2005). Again, these mouse studies recapitulate the findings in HVDRR patients (Malloy et al., 2002). Mutations in children that prevent DNA binding, or VDR-RXR dimerization exhibit alopecia while patients with VDRs that are defective in ligand binding or co-activator binding do not develop alopecia although they do exhibit the metabolic abnormalities of hypocalcemia and rickets (reviewed in Malloy and Feldman, 2010, Malloy et al., 1999, Malloy et al., 2011). Investigation is currently underway to define the mechanisms by which the unliganded VDR maintains hair follicle homeostasis and prevents alopecia.

Role of the Hairless protein (HR) in regulating unliganded VDR actions in the hair follicle

The alopecia associated with HVDRR is clinically and pathologically indistinguishable from the generalized atrichia with papules found in patients with mutations in the *hr* gene (Ahmad

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et al., 1998, Bergman et al., 2005, Miller et al., 2001, Zlotogorski et al., 2003). But *hr* mutations do not cause the metabolic abnormalities or rickets of HVDRR. The *hr* gene is expressed in many tissues especially in the skin and brain (Cichon et al., 1998). The *hr* gene product, HR acts as a corepressor and directly interacts with the VDR and suppresses $1,25(OH)_2D_3$-mediated transactivation (Hsieh et al., 2003, Malloy et al., 2009, Wang et al., 2007). Like the VDR, HR is a zinc finger protein suggesting that it interacts with DNA. It has been hypothesized that the role of the VDR in the hair cycle is to repress the expression of a gene(s) in a ligand-independent manner (Hsieh et al., 2003, Malloy and Feldman, 2003, Malloy et al., 2004, Malloy et al., 2002, Skorija et al., 2005, Wang et al., 2007). The ligand-independent activity requires that the VDR heterodimerize with RXR and bind to DNA even if it failed to activate gene transcription (Malloy and Feldman, 2003, Malloy et al., 2002). The corepressor actions of HR may also be required in order for the unliganded VDR to repress gene transcription during the hair cycle.

Studies of naturally occurring mutations in the *hr* gene that cause alopecia in humans have shown that they do not affect HR association with the VDR but do disrupt association with histone deacetylase 1 (Wang et al., 2007). In addition, mutant HRs with alteration of residues in the Jumonji C domain abolishes or reduces HR transrepressor activity also retain association with VDR (Hsieh et al., 2010, Malloy et al., 2009). The Jumonji C domain is thought to confer lysine demethylase activity that may be important in chromatin remodeling and repress the transcription of VDR target genes that control the hair cycle (Hsieh et al., 2010, Malloy et al., 2009, Wang et al., 2007).

Mutations in the VDR that disrupt the ability of the unliganded VDR to suppress gene transcription are hypothesized to lead to the derepression of a gene(s) whose product, when expressed inappropriately, disrupts the hair cycle that ultimately leads to alopecia (Hsieh et al., 2003, Malloy and Feldman, 2003, Malloy et al., 2004, Malloy et al., 2002, Skorija et al., 2005, Wang et al., 2007). Potential candidates include inhibitors of the Wnt signaling pathway (Beaudoin et al., 2005, Thompson et al., 2006) and PTHrP (Holick, 1985, Hsieh et al., 2003, Hsieh et al., 2010, Peters et al., 2001, Wysolmerski et al., 1994). Overexpression of PTHrP causes alopecia indicating its involvement in the regulation of the hair cycle (Cho et al., 2003, Wysolmerski et al., 1994). Since the VDR is a negative regulator of the PTHrP gene expression (Ikeda et al., 1989), loss of VDR regulation of the PTHrP gene due to mutations in the VDR may lead to the development of alopecia in HVDRR patients.

Transient gene expression assays have demonstrated that the cooperative transcriptional effects of β-catenin and Lef1 are abolished in keratinocytes isolated from VDR-null mice, suggesting a role for the unliganded VDR in canonical Wnt signaling (Cianferotti et al., 2007). Thus, absence of the VDR impairs canonical Wnt signaling in keratinocytes and may be the defect in keratinocyte stem cells that leads to the development of alopecia (Cianferotti et al., 2007). Teichert et al compared the gene expression profiles in the hair follicle of the VDR knockout mice, the CYP27B1 null mice that have no 1α-hydroxylase and are unable to synthesize $1,25(OH)_2D_3$ and the Rhino mice that have alopecia due to the absence of the hairless protein caused by a nonsense mutation in the hairless gene (Teichert et al., 2010). In the VDR knockout and Rhino mice a number of genes were down-regulated in the hedgehog, WNT, FGF and TGFβ pathways, but not in CYP27B1 knockout mice. When the VDR knockout mice were treated with an agonist that activates the hedgehog pathway hair follicle cycling was partially restored, suggesting a role for the hedgehog pathway in the regulation of hair follicle cycling by the unliganded VDR (Teichert et al., 2010).

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VDR Gene analysis in wild-type, HVDRR and APL fibroblasts

We also examined gene expression in fibroblasts from normals, from patients with HVDRR with alopecia and patients with APL having a mutation in *hr*. In a first analysis, in the absence of calcitriol, we compared the gene expression profiles of normal fibroblasts to fibroblasts that are devoid of VDR due to a premature stop mutation (Y295X) from an HVDRR patient with alopecia. Genes that were de-repressed in the mutant fibroblasts that do not express VDR *vs*. normal fibroblasts with WT VDR are candidates for ligand-independent silencing by the VDR. Table 1 shows a partial list of the genes that exhibited elevated expression in HVDRR fibroblasts compared to normal fibroblasts in the absence of calcitriol. There were 57 genes that were elevated in the HVDRR mutant fibroblasts *vs*. normal fibroblasts. These genes represent potential targets for silencing by the unliganded VDR. Interestingly, expression of the Wnt pathway inhibitor, SFRP1, was substantially elevated in the mutant cells. This finding is highly significant since Wnt signaling is critical for many developmental processes including hair. It is worth noting that SFRP1 is also an important regulator of osteogenesis (Gaur et al., 2005) and some APL patients exhibit delayed bone growth (Kruse et al., 1999). The expression of the nuclear receptors, Nurr-1 and Nor-1, were also elevated in the HVDRR mutant fibroblasts. These nuclear receptors belong to a set of early response genes that have been shown to be involved in bone homeostasis and brain development (Maruyama et al., 1998).

In a second microarray analysis, we compared the gene expression profile of fibroblasts from an APL patient (HR null) to normal fibroblasts. Approximately 112 genes were elevated in the HR null *vs*. normal fibroblasts. This list of genes was then compared to the list of genes identified in the VDR null fibroblasts from an HVDRR patient with alopecia to identify genes that were common to both APL and HVDRR with alopecia. This list contained 37 genes in common. Table 2 shows a partial listing of the potential targets for gene silencing by VDR and HR. TRα is particularly interesting because of its role in development and as a partner for HR. Also of special interest were FABP5, SOX9 and FGF13 that are important in hair growth and skin regeneration (Kawano et al., 2004, Madsen et al., 1992, Vidal et al., 2005). SOX9 is also important in chondrogenesis and sexual development (Marshall and Harley, 2000).

Conclusions

The data on the VDR mutations in HVDRR patients combined with the findings in the 1α-hydroxylase and VDR knockout mouse models, suggest that the role of the VDR in the hair cycle is to represses the expression of some gene(s) in a ligand-independent manner. This activity requires RXR heterodimerization and DNA binding but not interaction with coactivators. HR may also be required as a co-repressor for this negative regulatory activity of the VDR. The VDR is a negative regulator of a number of genes and the loss of its suppressor activity by the unliganded VDR could potentially lead to the derepression of those genes that could ultimately lead to alopecia. Some of the genes with suspected involvement in the process include Wnt inhibitors such as SFRP1 and inhibitors of PTHrP.

Although HVDRR is a rare disease, studies of these cases and the VDR knock out and transgenic animal models have revealed many aspects of vitamin D biology including its roles in calcium metabolism, bone homeostasis and hair differentiation. The children with HVDRR, so-called “experiments of nature” have furthered our knowledge of VDR function and led to advances in the understanding of vitamin D action in humans. The molecular and metabolic analyses of the consequences of mutations in the VDR have helped to elucidate the structure and function of the VDR and have led to advances in the therapy of HVDRR, a complicated and severe disease of childhood. Further study of the cases of HVDRR as they

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mature and get older will no doubt continue to shed light on the role of the VDR in the development or prevention of various human diseases considered to be related to vitamin D deficiency (Malloy et al., 2011).

Acknowledgments

We thank Lihong Peng for her assistance in performing the gene arrays comparing the VDR and HR mutant cells and normal cells. We are grateful to the physicians from around the world who have collaborated with us and allowed us to study their HVDRR patients. We are indebted to the families affected by this disease who have consented to our involvement in the diagnosis and treatment of their abnormalities.

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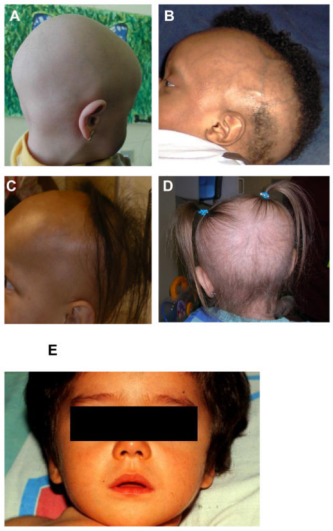

Figure.

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Table 1

Partial Microarray Data Comparing HVDRR Mutant ($VDR^{-/-}$) Vs. Wildtype Fibroblasts ($VDR^{+/+}$) in the Absence of Calcitriol.

De-repressed Genes In The HVDRR Mutant Fibroblasts		**Fold Increase**
Gene Name	**Gene Symbol**	**VDR null**
Nurr-1	NR4A2	14.0
Fibroblast growth factor 7 (keratinocyte growth factor)	FGF7	11.4
Nor-1	NR4A3	10.8
Parathyroid hormone like hormone (also known as PTHrP)	PTHLH	6.2
Involucrin	IVL	6.0
Secreted frizzled-related protein 1	SFRP1	5.6
Prostaglandin-endoperoxidase synthase 2 (COX-2)	PTGS2	4.0

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Table 2

Partial Microarray Data of Differentially Regulated Genes in Fibroblasts From Patients With HVDRR with Alopecia ($VDR^{-/-}$) and Patients with APL ($HR^{-/-}$) Compared To Wildtype Fibroblasts ($VDR^{+/+}$, $HR^{+/+}$).

Genes Elevated In Common In HVDRR And APL Fibroblasts		**Fold Increase**	
Gene Name	**Gene Symbol**	**VDR null**	**HR null**
Thyroid hormone receptor, alpha (TRα)	THRA	9.8	8.8
Phospholipase A2, group IVA (cytosolic, calcium-dependent)	PLA2G4A	9.2	6.6
Synaptotagmin XIV	SYT14	6.2	5.8
Matrix metalloproteinase 3 (stromelysin 1, progelatinase)	MMP3	6.2	4.6
Fatty acid binding protein 5 (psoriasis-associated)	FABP5	6.2	4.4
SRY (sex determining region Y)-box 9 (campomelic dysplasia)	SOX9	5.4	6.4
Fibroblast growth factor 13	FGF13	4.4	4.0