A Nonsense Mutation in *PDE6H* Causes Autosomal-Recessive Incomplete Achromatopsia

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Achromatopsia (ACHM) is an autosomal-recessive retinal dystrophy characterized by color blindness, photophobia, nystagmus, and severely reduced visual acuity. Its prevalence has been estimated to about 1 in 30,000 individuals. Four genes, *GNAT2*, *PDE6C*, *CNGA3*, and *CNGB3*, have been implicated in ACHM, and all encode functional components of the phototransduction cascade in cone photoreceptors. Applying a functional-candidate-gene approach that focused on screening additional genes involved in this process in a cohort of 611 index cases with ACHM or other cone photoreceptor disorders, we detected a homozygous single base change (c.35C>G) resulting in a nonsense mutation (p.Ser12*) in *PDE6H*, encoding the inhibitory γ subunit of the cone photoreceptor cyclic guanosine monophosphate phosphodiesterase. The c.35C>G mutation was present in three individuals from two independent families with a clinical diagnosis of incomplete ACHM and preserved short-wavelength-sensitive cone function. Moreover, we show through immunohistochemical colocalization studies in mouse retina that Pde6h is evenly present in all retinal cone photoreceptors, a fact that had been under debate in the past. These findings add *PDE6H* to the set of genes involved in autosomal-recessive cone disorders and demonstrate the importance of the inhibitory γ subunit in cone phototransduction.

Achromatopsia (ACHM; synonyms: rod monochromatism, total color blindness; ACHM2 [MIM 216900], ACHM3 [MIM 262300], ACHM4 [MIM 613856], and ACHM5/COD4 [MIM 613093]) is an autosomal-recessively inherited disorder characterized by the inability to discriminate colors due to the loss of cone photoreceptor function. Affected individuals suffer from severely reduced visual acuity (<0.1 or 20/200) in daylight, nystagmus, and severe photophobia. Most affected individuals present with complete ACHM, but sometimes the phenotype is described as incomplete ACHM with milder symptoms and residual cone function. ACHM was thought to be a congenital and stationary disorder, but macular changes can appear with time, and recent retinal-imaging data provide evidence that a progressive degenerative process can occur.[1] To date, four genes have been shown to be associated with ACHM: *CNGA3* (cyclic nucleotide-gated cation channel alpha-3 [MIM 600053]),[2] *CNGB3* (cyclic nucleotide-gated cation channel beta-3 [MIM 605080]),[3,4] *GNAT2* (guanine nucleotide-binding protein G(t) subunit alpha-2 [MIM 139340]),[5,6] and *PDE6C* (cone 3′,5′-cyclic cyclic guanosine monophosphate [cGMP]-specific phosphodiesterase [PDE] subunit alpha′ [MIM 600827]).[7,8] The four encoded proteins are all crucial components of the phototransduction cascade in cone photoreceptors: light-excited cone visual-pigment molecules induce the exchange of guanosine diphosphate (GDP) to guanosine triphosphate (GTP) at the guanosine binding site of the transducin α subunit (GNAT2 = Gα) and its subsequent release from the inhibitory βγ subunits, thus constituting the activated form of the G protein (GαGTP). GαGTP induces a dramatic increase in PDE activity by sequestering the inhibitory γ subunit (PDE6H) of the PDE complex in cone photoreceptor outer segments. The catalytic core of the cone PDE is a homodimer composed of two α′ subunits (PDE6C) that hydrolyzes cGMP and effectively reduces its concentration in the outer segment. This results in the closure of the heterotetrameric cGMP-gated cation channels (CNGA3/CNGB3) and, subsequently, membrane hyperpolarization.[9] Mutations in *CNGB3* represent the most common cause of autosomal-recessive ACHM, accounting for ~40% of all cases, followed by *CNGA3*, which is mutated in about 25% of the achromats. Mutations in *GNAT2* and *PDE6C* are rare and are found in fewer than 2% of all achromats.[10] We report here the identification of the fifth gene implicated in ACHM, *PDE6H*, encoding the inhibitory γ subunit of the cone photoreceptor PDE (MIM 601190), as another rare cause of this condition.

On the basis of its role in cone phototransduction, we reasoned that *PDE6H*, encoding a small 83 amino acid protein, represents a prime candidate gene for cone

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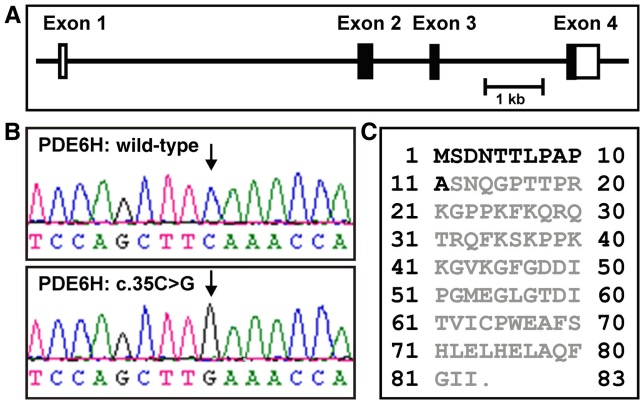

Figure 1. Genetic Analysis
(A) Genomic organization of *PDE6H* on chromosome 12q13.
(B) Sequence electropherograms displaying wild-type and c.35C>G (p.Ser12*) mutant sequences of exon 2 in *PDE6H*.
(C) Amino acid sequence of PDE6H. The shortened polypeptide that is predicted to result from the stop mutation is indicated in bold, black letters. However, the transcript is expected to undergo nonsense-mediated decay rather than translation into a truncated PDE6H polypeptide.

disorders, and we thus analyzed a cohort of 197 individuals with a clinical diagnosis of autosomal-recessive ACHM that had already been excluded for the known ACHM genes. The study was approved by the institutional review boards and followed the tenets of the Declaration of Helsinki. All genomic DNA samples underwent PCR amplification and Sanger sequencing of the three coding exons and flanking intron boundaries of *PDE6H*, followed by capillary electrophoresis on an automated sequencer (Figure 1A, Table S1 available online). Trace files were analyzed with Sequencing Analysis 5.2 (Applied Biosystems, Life Technologies, Carlsbad, CA, USA), and sequence variants were called with the use of SeqPilot (JSI Medical Systems, Kippenheim, Germany) software. Using this approach, we identified a male person (NL-II:1) with a homozygous nonsense mutation c.35C>G (p.Ser12*) (RefSeq NM_006205.2) who originated from the Netherlands (Figure 1B). The mutation was not observed in any database query (i.e., Exome Variant Server, 1000 Genomes project) and is predicted to result in a truncated protein of only 11 amino acid residues (Figure 1C), lacking all conserved domains relevant for transducin binding and inhibition of the catalytic activity of PDE. Thus, this mutation would produce a protein that is inactive, possibly representing a functional null allele. However, it is more likely that there will be a loss of this polypeptide, because the mutant transcript is predicted to undergo nonsense-mediated decay (Alamut version 2.0, Interactive Biosoftware, San Diego, CA, USA).

We then proceeded to analyze another 20 individuals with a clinical diagnosis of ACHM and 394 individuals with a clinical diagnosis of cone dystrophy. In this sample, we identified two siblings with the same homozygous mutation c.35C>G (p.Ser12*) in *PDE6H*. Segregation analysis showed heterozygosity for this mutation in both parents.

Apart from this clear-cut mutation, we observed three unpublished and three annotated sequence variants compared to the reference sequence NM_006205.2 (Table S2).

To define whether the occurrence of the nonsense mutation c.35C>G (p.Ser12*) in the Dutch and Belgian families arose independently or by a common founder, we performed haplotype reconstruction using microsatellite markers and SNPs flanking the *PDE6H* locus on chromosome 12p13. This identified a common haplotype of 301 kb flanked by rs111596034 (= D12S2210) and rs2430621 (Figure S1), supporting the hypothesis that the c.35C>G (p.Ser12*) mutation results from a common ancestral mutational event.

The clinical diagnosis was established via standard ophthalmologic examinations and electroretinographic testing (Figure 2). Two of the individuals were originally diagnosed with cone-rod dystrophy and one with incomplete achromatopsia. The Dutch individual NL-II:1 has been clinically evaluated in 1979, at the age of 45. He had reduced, but stable visual acuity and nystagmus since birth (Table 1). Slit-lamp biomicroscopy and funduscopy results showed no abnormalities at that time. Electroretinographic (ERG) recordings showed normal rod, severely reduced cone, and absent 30 Hz flicker responses. Color vision tests (pseudoisochromatic test and 100 Hue) showed a severe red-green color vision defect with relatively normal blue-yellow vision. The diagnosis was incomplete achromatopsia, however, with atypical features. We performed additional molecular genetic analyses to test for mutations and rearrangements in the red and green opsin gene cluster (*OPN1MW*, *OPN1LW*), excluding a differential diagnosis of X-linked blue cone monochromatism.

Both siblings of the Belgian family (BE-II:1 and BE-II:2) are affected children of nonconsanguineous parents and presented with moderate photophobia and normal night vision (Table 1). Only BE-II:2 presented with nystagmus. Myopia was diagnosed at 3 years of age. ERG was performed under anesthesia in both children at the ages of 3 years and 5 years, respectively, and the results were suggestive of cone dysfunction with absent photopic 30 Hz flicker responses. There has been no deterioration in vision in either sibling over the last 15 years, suggesting that the cone dysfunction is stationary. Color-vision testing via Hardy-Rand-Rittler plates, the Farnsworth 100 Hue test, and the Panel D-15 test in both siblings at the ages of 22 years and 20 years, respectively, showed mainly deutan color defects with normal tritan color discrimination (Figure S2). Visual fields in both siblings showed normal peripheral limits, and funduscopy revealed optic discs of normal color with large temporal myopic crescents (Figure 2A). The retinae presented with irregular atrophic depigmentation in the posterior pole with sparing of the macula (Figures 2A and 2B). Autofluorescence (AF) fundus imaging revealed normal diffuse and homogeneous AF in the posterior pole and a normal macular region (Figure 2C).

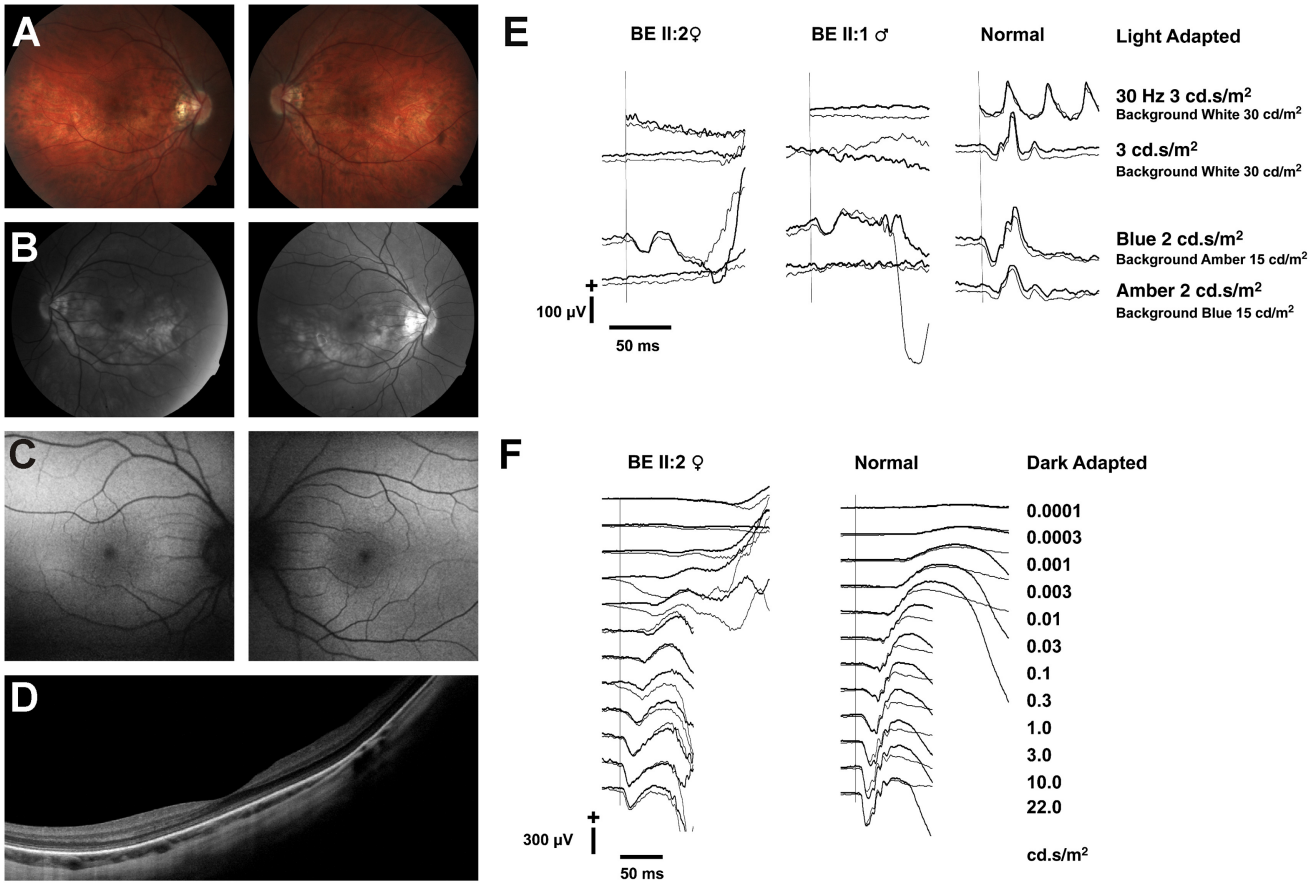

Figure 2. Clinical Presentations of the Siblings in Family BE
(A–D) Proband BE-II:2.
(A) Fundus photography showed depigmentation of the posterior pole with sparing of the macula and large myopic crescent of the optic disc.
(B) Red-free fundus photography.
(C) Autofluorescence imaging revealed normal diffuse and homogeneous AF in the posterior pole and macula.
(D) In OCT of the right eye, all retinal layers could be identified and appeared to be continuous, but IS/OS junction of the cone photoreceptors could not be clearly distinguished.
(E) Photopic ERG of both siblings, BE-II:2 and BE-II:1, in comparison to a normal control. Note the absence of photopic response to 30 Hz flicker, white, and amber light stimulation. Stimulation with blue light with amber background elicited a blue cone response in both siblings.
(F) Single-flash mixed rod-cone ERG responses in BE-II:2 and in a normal subject. Normal rod responses were recorded in both siblings. ERG was performed according to the ISCEV extended protocol for the full-field ERG (ERG, rod- and cone b-wave series). Stimuli were produced with a Ganzfeld stimulator (Standalone ColorDome system, Diagnosys, Impington, UK). In addition, a red-flash ERG was measured under scotopic conditions. Furthermore, S cone-specific ERG testing was performed with an amber stimulus of 2 cd.s/m^2 after adaptation to a blue background of 15 cd/m^2 and with a blue stimulus of 2 cd.s/m^2 after adaptation to an amber background of 15 cd/m^2. All ERG responses were recorded with Dawson Trick Litzkow (DTL) fiber electrodes.

Upon optical coherence tomography (OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany), all retinal layers could be identified and appeared to be continuous, but inner segment (IS)-outer segment (OS) junction of the cone photoreceptors could not be clearly distinguished (Figure 2D). Recent ERGs in both siblings that were in accordance with the ISCEV (International Society for Clinical Electrophysiology of Vision) extended protocol showed absent photopic responses to a single bright, white flash and absent 30 Hz flicker responses (Figure 2E). Short-wavelength-sensitive (S) cone-specific testing showed absent responses to the amber stimulus but recordable responses to the blue stimulus (Figure 2E). In both siblings, the scotopic ERG was normal (Figure 2F). Responses to a red flash under dark adaptation were reduced with long implicit time, indicating contribution of the rod system component only. Color vision testing, as well as the ERG results of the siblings with the *PDE6H* mutation, indicates severe L and M cone dysfunction but relatively preserved S cone function. Upon reevaluation of the two cases, a clinical diagnosis of incomplete achromatopsia with preserved S cone function was finally established.

The cone photoreceptor PDE complex was initially isolated from bovine retinal lysates, including the deduced inhibitory γ subunit with a molecular weight of 13 kDa.[11] Subsequently, *PDE6H* was cloned from a bovine cDNA

Table 1. Clinical Characteristics of the Three Individuals with Homozygous *PDE6H* Mutation c.35C>G (p.Ser12*)

Proband	Year of Birth	Sex	Year and Age at Last Examination	Best-Corrected Snellen Visual Acuity	Refraction	Color Vision	Photophobia	Nystagmus	Rod ERG	Cone ERG
NL-II:1	1934	male	1979 45 years	OD 20/125 OS 20/125	OD −7.5 OS −6.5	severely disturbed red/green axes, normal blue/ yellow axes	since birth	since birth	scotopic responses normal	severely reduced cone ERG and absent 30 Hz flicker response
BE-II:1	1989	male	2012 22 years	OD 20/63 OS 20/63	OD −13.75 OS −14.25	D-15: sat: no confusions; desat: multiple confusions, disturbed red/green axes, normal blue axes	moderate	no	scotopic responses normal	severely reduced cone ERG; 30 Hz flicker absent
BE-II:2	1991	female	2012 20 years	OD 20/200 OS 20/100	OD −8.25 OS −8.25	D-15: sat: no confusions; desat: multiple confusions, disturbed red/green axes, normal blue axes	moderate	yes	scotopic responses normal	severely reduced cone ERG; 30 Hz flicker absent

The abbreviations used are as follows: ERG, electroretinography; OD, right eye; OS, left eye; D-15, Panel D-15 test; sat, saturated; desat, desaturated.

library[12] and was also later identified through comparative studies in other species, including humans.[13] Although *PDE6H* has already been cloned more than 20 years ago, there is surprisingly little known about the spatial and temporal distribution of the cone PDEγ in the retina. Using antibodies specific for the rod and cone γ subunits, Hamilton and Hurley provided evidence that PDE6H might only be present in a subset of cones, notably S cones.[12] To date, this has neither been substantiated nor contradicted by any further functional or immunohistochemical studies. We therefore used a PDE6H-specific antibody that was purified from rabbit antiserum raised against a amino acid synthetic 20 amino acid peptide derived from the N terminus of the murine protein. (C.B. and P. Ruth, unpublished data) for immunohistochemistry on mouse retinal sections. This antibody specifically stained all cone photoreceptors, as indicated by colabeling with peanut hemagglutinin (Figure 3A) and anti-blue opsin antibodies (Figure 3B). Appropriate negative controls are presented in Figure S3. This confirmed that PDE6H is located in all cone types, arguing against the above-mentioned finding that PDE6H in mouse retina is restricted to S cones.

In a prior publication, a heterozygous sequence variant of unknown significance in the 5′ untranslated region (UTR) of *PDE6H* had been hypothesized as the cause of autosomal-recessive cone dystrophy with supernormal rod response (CDSRR).[14] This finding could not be further corroborated; instead, CDSRR was shown to be caused by mutations in *KCNV2*.[15,16] The identification of mutations in *PDE6H* in individuals affected by incomplete ACHM, as reported here, is in line with the function of the known genes associated with ACHM—*GNAT2*, *PDE6C*, *CNGA3*, and *CNGB3*—all of which encode crucial components of the cone phototransduction cascade. However, it has to be emphasized that the phenotype of individuals with the PDE6H mutation is different, in that S cone function is more preserved than L and M cone function. It remains to be elucidated how the inactivation of the cone PDE holoenzyme takes place in the absence of PDE6H—maybe by recruiting other inhibitory PDEγ subunits, such as the rod photoreceptor PDE6G or others.

The lack of PDE6H in cones would functionally imply a constantly high PDE activity, low levels of cGMP in the cone outer segment, and permanent closure of cGMP-gated channels, a scenario analogous to permanent light stimulation that has been described as the equivalent-light hypothesis in retinal degeneration.[17] However, studying gene-targeted *Pde6g*^{tm1Goff} knockout mice revealed that the ablation of the inhibitory PDE6G subunit in rods causes reduced rather than increased PDE6 activity.[18]

The clinical phenotype of individuals with ACHM caused by mutations in *PDE6H* supports the clear distinction between the inhibitory PDE6G subunits in rod and PDE6H in cone photoreceptors, as cone function is severely impaired and essentially absent in standard photopic and 30 Hz flicker ERG recordings, whereas rod function is within normal limits. This specificity of PDE6H for cone function is explained by its exclusive presence in cone photoreceptors, as shown by our immunohistological staining in the murine retina. Prior reports about the presence of PDE6H in only a subset of cones could not be corroborated in our study. However, color vision testing revealed residual color discrimination in all investigated persons, along with more preserved S cone function, implying that other mechanisms must exist to inactivate PDE6C. In the inverse situation, a mutation in *PDE6G*, the gene encoding the rod PDE6G subunit, results in specific impairment of rod function that eventually progresses into retinal degeneration. This has been observed in mouse mutants and most recently in humans diagnosed with autosomal-recessive retinitis pigmentosa (MIM 180073 and MIM 613582).[18,19]

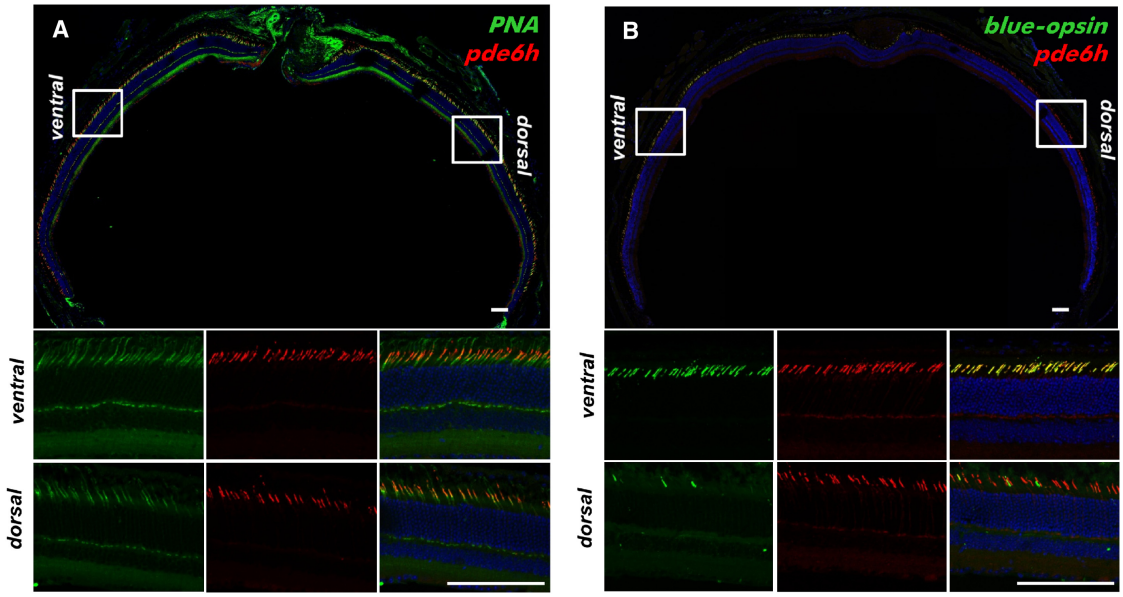

Figure 3. Double Immunofluorescence Labeling of Mouse Retina with Antibodies Specifically Staining Cone Photoreceptors
(A) Colabeling with a Pde6h-specific antibody (red, 1:500) and peanut hemagglutinin (PNA, green, 1:50). An overview of a retina slice and magnifications of the ventral and dorsal parts (single- and multichannel panels) are displayed.
(B) Colocalization with S opsin (green, 1:200) and Pde6h (red, 1:500) antibodies. Again, an overview of a retina slice and magnifications of the ventral and dorsal parts are shown.
The colocalization experiments shown in (A) and (B) confirmed that Pde6h is exclusively located in cone photoreceptors, but is present in all three cone types, including the S cone. DAPI (1:10,000) was used as a nucleus-staining fluorochrome. Scale bars represent 100 μm.

To summarize, we identified *PDE6H* as the fifth gene associated with ACHM, with very low prevalence. Indeed, extrapolating the frequency of *PDE6H* mutations in the comprehensive Tuebingen ACHM cohort, comprising over 680 independent families and 860 achromats in total, we estimate that mutations in *PDE6H* account for only ~0.3% of all autosomal-recessive ACHM cases.

Supplemental Data

Supplemental Data include three figures and two tables and can be found with this article online at http://www.cell.com/AJHG/.

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Web Resources

The URLs for data presented herein are as follows:

1000 Genomes, http://www.1000genomes.org/
Exome Variant Server, http://evs.gs.washington.edu/EVS/
ISCEV, http://www.iscev.org/standards
Online Mendelian Inheritance in Man (OMIM), http://www.omim.org

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